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Cicle XXIX

COMBINATION OF ACTIVE INGREDIENTS IN A SINGLE SOLID FORM FOR ORAL ADMINISTRATION: STUDY OF FORMULATION AND CRITICAL COMPRESSION PARAMETERS

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Sunto

Il lavoro di tesi di dottorato è stato condotto nella prima metà presso l'Università degli Studi di Parma, Dipartimento di Farmacia, e successivamente presso l'Università di Bordeaux (FR), Dipartimento di Meccanica e Ingegneria, in accordo alla Convenzione di dottorato in co-tutela.

Il progetto di dottorato ha riguardato lo studio dei parametri critici di compressione di una compressa tristrato per il rilascio immediato di due farmaci in combinazione. Le compresse multistrato sono progettate per la fabbricazione di prodotti di combinazione a dose fissa che semplificano il regime terapeutico e potenzialmente aumentare la compliance del paziente. In particolare, i farmaci utilizzati per la produzione della compressa multistrato sono stati un farmaco antiinfiammatorio non stereoideo, ibuprofene lisina, e un citoprotettore, sucralfato. Ibuprofene lisina è efficace nel trattamento di stati infiammatori, ma un'assunzione cronica del farmaco può dare luogo, come effetto collaterale, a lesione della mucosa gastrointestinale e formazione di ulcere. Il sucralfato è un protettore della mucosa gastrointestinale e quindi l'utilizzo dell'ibuprofene lisina in combinazione con sucralfato può prevenire la comparsa di ulcere.

La compressa tristrato doveva essere costituita da uno strato centrale contenente 342 mg di ibuprofene lisina e due strati esterni contenenti ciascuno 100 mg di sucralfato.

Le compresse multistrato di sucralfato/ibuprofene lisina sono state realizzate mediante l'utilizzo di un simulatore di compressione, che permette di produrre queste compresse in condizioni di stretto controllo delle forze e dello spostamento dei punzoni. Il controllo dei parametri critici di compressione è di particolare importanza nel caso della produzione di compresse multistrato, che sono sistemi eterogenei in cui due o più strati di polveri compattate sono separati tra loro da una interfaccia discreta. La resistenza alla rottura della compressa e la tendenza alla separazione degli strati delle compresse multistrato

dipendono non solo dalla composizione dello strato, ma anche dalla proprietà di deformazione di ogni strato durante il processo di compressione.

Durante il periodo di tesi di dottorato svolto presso l'Università degli Studi di Parma, la ricerca ha riguardato inizialmente lo sviluppo formulativo per l'ottenimento degli strati singoli di sucralfato e di ibuprofene lisina. Successivamente, è stato eseguito uno studio dei parametri critici di precompressione e di compressione di una compressa bistrato, ottenuta mediante precompressione di un strato di sucralfato e successiva compressione dello strato di ibuprofene lisina. Sono state prodotte due tipologie di compresse bistrato di sucralfato/ibuprofene lisina, che si differenziavano in termini di composizione della formulazione utilizzata per la produzione dello strato di sucralfato. In un caso, il sucralfato è stato granulato con cellulosa microcristallina mentre nel secondo caso il sucralfato è stato granulato con una miscela di cellulosa microcristallina e lattosio. Le compresse bistrato contenenti solo cellulosa microcristallina nello strato di sucralfato hanno mostrato il fenomeno di separazione degli strati, durante la fase di espulsione della compressa dalla matrice, all'aumentare delle forze di precompressione e di compressione applicate. Al contrario, le compresse bistrato in cui era presente anche il lattosio nello strato di sucralfato, non si è osservato separazione degli strati indipendentemente dalle forze di precompressione e di compressione applicate.

La separazione dello strato è dovuta alla presenza di cellulosa microcristallina, che si comporta come materiale plastico. La rugosità superficiale della cellulosa microcristallina nel primo strato diminuisce all'aumentare della forza di precompressione, diminuendo i punti di adesione tra i due strati adiacenti. Invece, il lattosio, materiale fragile, tende a fratturarsi aumentando l'area superficiale disponibile e quindi l'adesione tra gli strati.

Sulla base dei risultati ottenuti dalla compressione delle compresse bistrato di sucralfato/ibuprofene lisina, si è passato alla produzione delle compresse tristrato utilizzando, per gli strati di sucralfato, la formulazione contenente come eccipienti la

microcristallina cellulosa e il lattosio. Come nel caso delle compresse bistrato, la presenza di lattosio ha permesso l'ottenimento delle compresse tristrato senza osservare il fenomeno di separazione degli strati al termine del processo di compressione.

Il periodo di dottorato svolto presso l'Università di Bordeaux si è concentrato su tre aspetti differenti. Il primo è stato quello di valutare se il test riportato nella Farmacopea Europea per la misura della resistenza alla rottura delle compresse potesse essere utilizzato anche nel caso di compresse multistrato. Tale test consiste nell'applicare una forza diametrale sulla compressa e misurare tale forza al punto di rottura. Dal confronto di questo test con altri due diversi test, il test a indentazione (che applica forza tramite un punzone posizionato tra gli strati) e il test a ghigliottina (che consiste nel tenere fermo uno strato mediate una struttura apposita e nell'applicare forza sull'altro strato), si è concluso che il test di rottura diametrale non è idoneo nel caso di compresse multistrato, in quanto misura esclusivamente la forza di rottura di uno dei due strati, anziché quella di delaminazione.

Il secondo aspetto è stato quello di valutare l'influenza della forma dell'interfaccia sull'adesione di due strati in una compressa multistrato. Si sono prodotte diverse compresse multistrato con soli eccipienti con interfacce differenti mediante l'uso di punzoni appositi (cilindrici, convessi, con diverso raggio di curvatura della convessità) e si è misurata la resistenza alla rottura delle compresse bistrato mediante l'uso di un test idoneo, il testo a indentazione, convalidato durante la prima parte del lavoro eseguito presso l'Università di Bordeaux. Dai risultati si è evinto che le interfacce fabbricate con punzoni con curvature tendono ad essere meno resistenti rispetto a compresse bistrato aventi un'interfaccia completamente piatta. Si è notato come la forza di precompressione influisce sulla creazione della curvatura dell'interfaccia, infatti a basse forze di precompressione tutte le compresse prodotte avevano un'interfaccia piatta, quindi un'alta resistenza alla rottura, mentre ad alte forze di precompressione i punzoni ricurvi producevano compresse con

un’interfaccia curva e meno resistenti e di conseguenza si osservava la separazione degli strati in fase di espulsione dalla matrice.

Il terzo aspetto è stato quello di eseguire un disegno sperimentale basato sulla produzione di una compressa bistrato di sucralfato e ibuprofene lisina. Il disegno sperimentale ha incluso i fattori di produzione (*drying time*) delle formulazioni di sucralfato, ottenute durante il periodo di dottorato presso l’Università degli Studi di Parma, di conservazione delle compresse prodotte (in particolare il grado di umidità presente durante il periodo di conservazione) e dei parametri di compressione. Dall’analisi del disegno sperimentale si è evidenziato che il contenuto di acqua residuo nel granulato di sucralfato sia un fattore importante nell’ottenimento della compressa bistrato. A valori alti di contenuto di acqua residua (circa 30%) si sono ottenute compresse bistrato con bassi valori di resistenza alla rottura. Inoltre, è stata riscontrata una correlazione tra il grado di umidità residua del sucralfato e l’umidità dell’ambiente in cui la compressa bistrato è conservata. Infatti, quando la differenza tra i valori di umidità residua dello strato di sucralfato e di umidità dell’ambiente di conservazione è grande, la compressa tende ad avere una bassa resistenza alla rottura. Viceversa, nei casi in cui la differenza tra grado di umidità presente nello strato di sucralfato e l’umidità dell’ambiente di conservazione è ridotta, la compressa bistrato risulta avere una maggiore resistenza alla rottura.

Résumé

Le travail de thèse de doctorat a été mené dans la première moitié auprès de l'Università degli Studi di Parma, Dipartimento di Farmacia, et successivement auprès de l'Université de Bordeaux (FR), Département de Mécanique et Ingénierie, conformément à la Convention de co-tutelle de thèse de doctorat.

Le projet de doctorat a concerné l'étude des paramètres critiques de compression d'un comprimé à trois couches pour le relâchement immédiat de deux médicaments en combinaison. Les Comprimés multicouches sont projetés pour la fabrication de produits de combinaison à dose fixe qui simplifient le régime thérapeutique et potentiellement augmenter l'observance du patient.

En particulier, les médicaments utilisés pour la production du comprimé multicouche ont été un médicament anti-inflammatoire non-stéroïdien, ibuprofène lysine, et un cytoprotecteur, sucralfate. Ibuprofène lysine est efficace dans le traitement d'états inflammatoires, mais un emploi chronique du médicament peut provoquer, comme effet indésirable, la lésion de la muqueuse gastro-intestinale et la formation d'ulcères. Le sucralfate est un protecteur de la muqueuse gastro-intestinale et donc l'emploi de l'ibuprofène lysine en combinaison avec le sucralfate peut prévenir l'apparition des ulcères.

Le comprimé à trois couches devait être constitué d'une couche centrale contenant 342 mg d'ibuprofène lysine et deux couches extérieures contenant chacune 100 mg de sucralfate.

Les comprimés multicouches de sucralfate/ibuprofène lysine ont été réalisés avec l'utilisation d'un simulateur de compression, qui permet de produire ces comprimés dans des conditions de strict contrôle des forces et du déplacement des poinçons. Le contrôle des paramètres critiques de compression est de grande importance dans le cas de la production de comprimés multicouches, qui sont des systèmes hétérogènes dans lesquels deux ou plus couches de poussières compactes sont séparées parmi eux par une interface

discrète. La résistance à la rupture du comprimé et la tendance à la séparation des couches des comprimés multicouches ne dépendent pas seulement de la composition de la couche, mais également de la propriété de déformation de chaque couche pendant le procès de compression.

Pendant la période de thèse de doctorat déroulée auprès de l'Università degli Studi di Parma, la recherche a concerné initialement le développement de la formule pour l'obtention des couches individuelles de sucralfate et d'ibuprofène de lysine. Successivement, l'on a effectué une étude des paramètres critiques de pré-compression et de compression d'un comprimé à deux couches, obtenu par la pré-compression d'une couche de sucralfate et la compression successive de la couche d'ibuprofène de lysine. L'on a produit deux types de comprimés à deux couches de sucralfate/ibuprofène lysine, qui se diversifiaient en termes de composition de la formulation utilisée pour la production de la couche de sucralfate. Dans un cas, le sucralfate a été granulé avec de la microcrystalline cellulose, pendant que dans le deuxième cas le sucralfate a été granulé avec un mélange de microcrystalline cellulose et lactose. Les comprimés à deux couches contenant seulement de la microcrystalline cellulose dans la couche de sucralfate ont montré le phénomène de séparation des couches, pendant la phase d'expulsion du comprimé de la matrice, avec l'augmentation des forces de pré-compression et de compression appliquées. Au contraire, dans les comprimés à deux couches où il y avait même le lactose dans la couche de sucralfate, l'on n'a pas observé de séparation des couches indépendamment des forces de pré-compression et de compression appliquées.

La séparation de la couche est due à la présence de cellulose microcristalline, qui se comporte comme matériel plastique. La rugosité superficielle de la cellulose microcristalline dans la première couche diminue avec l'augmentation de la force de pré-compression, en diminuant les points d'adhésion entre les deux couches adjacentes. Par contre, le lactose,

matériel fragile, tend à se fracturer en augmentant l'aire superficielle disponible et donc l'adhésion parmi les couches.

Su la base des résultats obtenus de la compression de comprimés à deux couches de sucralfate/ibuprofène lysine, l'on a procédé à la production de comprimés à trois couches en utilisant, pour les couches de sucralfate, la formulation contenant comme excipients la microcristalline cellulose et le lactose. Comme dans le cas de comprimés à deux couches, la présence de lactose a permis l'obtention des comprimés à trois couches sans observer le phénomène de séparation des couches à la fin du procès de compression.

La période de doctorat déroulée auprès de l'Université de Bordeaux s'est concentrée sur trois aspects différents. Le premier aspect a été celui d'évaluer si le test rapporté dans la Pharmacopée Européenne pour la mesure de la résistance à la rupture de comprimés pouvait être utilisé même dans le cas de comprimés multicouches. Ce test consiste à appliquer une force diamétrale sur le comprimé et mesurer telle force au point de rupture. De la comparaison de ce test avec deux autres tests différents, le test à indentation (qui applique la force par un poinçon positionné parmi les couches) et le test à guillotine (qui consiste à maintenir une couche immobile avec une structure appropriée et à appliquer une force sur l'autre couche), l'on a conclu que le test de rupture diamétrale n'est pas correct dans le cas de comprimés multicouches, parce qu'il mesure exclusivement la force de rupture d'un des deux couches, plutôt que celle de délamination.

Le deuxième aspect a été celui d'évaluer l'influence de la forme de l'interface sur l'adhésion de deux couches dans un comprimé multicouche. L'on a produit plusieurs comprimés multicouches seulement avec des excipients avec des interfaces différentes à travers l'emploi de coinçons appropriés (cylindriques, convexes, avec un rayon différent de courbure de la convexité) et l'on a mesuré la résistance à la rupture des comprimés à deux couches par l'emploi d'un test correct, le test à indentation, validé pendant la première partie du travail effectué auprès de l'Université de Bordeaux. Des résultats, l'on a observé que les

interfaces fabriquées avec des poinçons avec des courbures tendent à être moins résistantes par rapport à des comprimés à deux couches ayant une interface complètement plate. L'on a remarqué comme la force de pré-compression influence la création de la courbure de l'interface, en effet à des basses forces de pré-compression tous les comprimés produits avaient une interface plate, donc une haute résistance à la rupture, alors que avec des hautes forces de pré-compression les poinçons courbes produisaient des comprimés avec une interface courbe et moins résistants et par conséquent l'on observait la séparation des couches dans la phase d'expulsion de la matrice.

Le troisième aspect a été celui d'élaborer un dessin expérimental basé sur la production d'un comprimé à deux couches de sucralfate et ibuprofène lysine. Le dessin expérimental a inclus les facteurs de production (drying time) des formulations de sucralfate, obtenues pendant la période de doctorat auprès de l'Università degli Studi di Parma, de conservation de comprimés produits (en particulier le degré d'humidité présent dans la période de conservation) et des paramètres de compression. De l'analyse du dessin expérimental l'on a remarqué que le contenu d'eau restant dans le granulé de sucralfate est un facteur important dans l'obtention de comprimé à deux couches. Avec des valeurs hautes de contenu d'eau restant (environ de 30%) l'on obtient des comprimés à deux couches avec des basses valeurs de résistance à la rupture. En outre, l'on a constaté une corrélation entre le degré d'humidité restant du sucralfate et l'humidité de l'environnement dans lequel le comprimé à deux couches est conservé. En effet, là où la différence entre le degré d'humidité du sucralfate et l'humidité de l'ambient de conservation est plus elevée, le comprimé tend à avoir une basse résistance à la rupture. Vice-versa, dans les cas où la différence entre le degré d'humidité de sucralfate et l'humidité de l'environnement de conservation est faible, le comprimé à deux couches résulte avoir plus de résistance à la rupture.

Thesis Introduction

1 Introduction

1.1 Inflammation

Inflammation is a biological automatism that occurs at the level of a vascularized tissue in response to a damage. It is basically a protective response on the part of the body in order to eliminate the initial cause of cell injury; in some cases, the inflammation, if not properly controlled, can cause damage and disease [1]. Each stimulus can give rise to a response. At the macro level, it is manifested by the cardinal signs of inflammation: *rubor, tumor, calor, dolor and functio laesa* [2, 3].

The inflammatory response is characterized by three distinct phases [4]:

1. *erythematous acute* phase, in which there is an increase in capillary permeability, vasodilation and release of chemical mediators, such as histamine, serotonin, eicosanoids, cytokines;
2. *delayed subacute* phase, in which infiltration of leukocytes and phagocytes in the site of inflammation is mainly observed;
3. *chronic proliferative* phase, characterized by tissue degeneration and fibrosis.

The chemical mediators, released during the inflammatory process, induce the biosynthesis of eicosanoids (main mediators of inflammation) by interacting with receptors of the plasma membrane associated proteins. As a result of this interaction, the activation of phospholipase A_2 and C occurs. The phospholipase A_2 is able to hydrolyze the ester bond existing between the arachidonic acid and phospholipids of the membrane; the acid is released and metabolized by multiple pathways, in which the most important involves two different enzyme systems, cyclooxygenase and lipoxygenases [5].

The term “eicosanoid” references to three different classes of chemical mediators: prostaglandins, leukotrienes and thromboxane. Each of them is synthetized from the arachidonic acid (5,8,11,14-eicosatetraenoic acid, Figure 1).

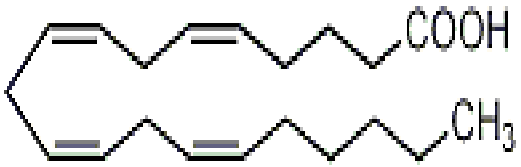

Figure 1: Chemical structure of arachidonic acid

The synthesis of prostaglandins and thromboxanes occurs through the mediation of ubiquitous enzymes, the cyclo-oxygenase, of which three isoforms exist:

1. cyclooxygenase-1 (COX-1), isoform expressed in many tissues (gastric and intestinal mucosa, kidneys, platelets and vascular endothelium), responsible of the production of prostanoids;
2. cyclooxygenase-2 (COX-2), produced by the inflammatory process and expressed constitutively in the brain and liver; It produces prostanoids that mediate inflammation, pain and fever;
3. cyclooxygenase-3 (COX-3), recently discovered in the brain of the dog, it is a splice variant of COX-1.

The cyclooxygenase performs two activities: endoperoxide synthase, leading to the synthesis of prostaglandin G (PGG), and peroxidase, which converts PGG into prostaglandin H. All other prostaglandins derive (PGD, PGE, PGF, PGI belonging to the series 1,2 and 3) from prostaglandin H, chemically unstable. Thromboxanes and leukotrienes derived from the action of the thromboxane synthase and lipoxygenase, respectively, [6].

Inflammatory reactions are the basis for very common chronic diseases, such as rheumatoid arthritis, atherosclerosis, as well as life-threatening hypersensitivity reactions caused by insect stings, drugs and toxins. The arachidonic acid derivatives contribute significantly to the maintenance of the inflammatory process; for this reason, most of the anti-inflammatory drugs used act mainly as inhibitors of the biosynthesis of eicosanoids.

1.1.1 Therapeutic solutions

There are two classes of drugs, each one characterized by their mechanism of action [7]:

1. glucocorticoids: indirectly inhibit phospholipase A_2, inducing the synthesis of lipocortine protein that inhibits the enzyme. However, they have several side effects that limit their use, such as suppression of the immune response, osteoporosis, hypertension, hyperglycemia and growth retardation [8];
2. nonsteroidal anti-inflammatory drug (NSAIDs) inhibit cyclooxygenase enzymes by blocking the biosynthesis of prostaglandins and thromboxanes [9].

NSAIDs have three main effects:

1. anti-inflammatory: by blocking the synthesis of some important mediators of the inflammatory process (PGE2 and PGI2 in specific sites);
2. analgesic, by inhibiting the production of PGE2, a prostaglandin which helps the allogenic activity of bradykinin and other autacoids issued in the site of inflammation;
3. antipyretic, by suppressing the hypothalamic response by inhibiting the synthesis of PGE2.

It is believed that the therapeutic effects of NSAIDs are related to inhibition isoform COX-2, while the side effects would result from the simultaneous inhibition of both isoforms (COX-1 and COX-2) [6].

The most common side effects are gastric mucosal injury and inhibition of platelets aggregation, for which the isoform COX-1 plays a critical role. Taking advantage of the different structural characteristics of the active site of COX-1 and COX-2 isoforms, NSAIDs were synthesized for selectively inhibiting one isoform (COX-2, critical for the inflammatory process); these inhibitors have anti-inflammatory and analgesic effects but they have no anti-platelet aggregation activity.

The main therapeutic uses of NSAIDs include diseases such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, musculoskeletal pain, headache, post-operative pain, and primary dysmenorrhea.

From a chemical point of view, we can distinguish between the NSAIDs:

- derivatives of salicylic acid: salicylic acid, acetylsalicylic acid, salicylamide, diflunisal;
- aniline derivatives: acetaminophen;
- indoleacetic acid derivatives: indomethacin, sulindac;
- phenylacetic acid derivatives: diclofenac, ketorolac;
- anthranilic derivatives: mefenamic acid, flufenamic acid, niflumic acid;
- propionic acid derivatives: ibuprofen, naproxen, ketoprofen, flurbiprofen;
- enolic acid derivatives: piroxicam, tenoxicam, meloxicam,
- sulfonanilide derivative: nimesulide

From a pharmacological point of view, we can distinguish:

- NSAID with analgesic effect and poor anti-inflammatory action (paracetamol);
- NSAID with analgesic and anti-inflammatory moderate (propionic acid derivatives and anthranilic acid);
- NSAID with analgesic and anti-inflammatory action significant (salicylates).

1.1.1.1 Ibuprofen

Ibuprofen ((RS)-2-(4-(2-methylpropyl) phenyl) propanoic acid) is an active ingredient belonging to the family of NSAIDs (nonsteroidal anti-inflammatory drugs), propionic acid derivative (Figure 2). It is Insoluble in water, soluble in acetone, methanol and methylene chloride. Ibuprofen melts at a temperature between 75-78 °C [10].

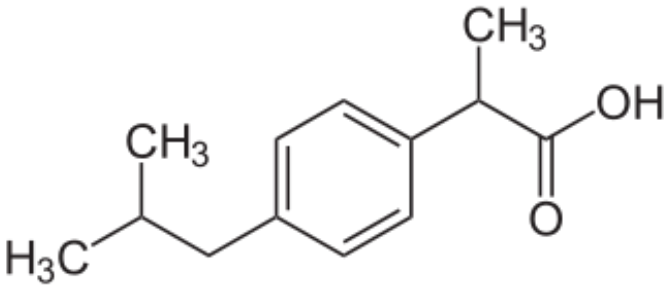

Figure 2: Chemical structure of ibuprofen

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Ibuprofen is marketed as a racemic mixture, although the pharmacological activity is due almost exclusively at the isomer (S) (+). It is used as such or as lysine, arginine or sodium salt. It is a drug having anti-inflammatory, analgesic and antipyretic activity, primarily indicated for the treatment of clinical signs and symptoms of rheumatoid arthritis and osteoarthritis, to relieve moderate and minor pain, to reduce fever and for the treatment of dysmenorrhea. Ibuprofen is rapidly absorbed after oral administration; in fact, the plasmatic concentration peak is reached in about 2 hours. It is characterized by a pk_a = 4.4, it extensively binds to plasma proteins (99%) and interacts with other acidic drugs, such as acetylsalicylic acid and methotrexate [11]. Ibuprofen is rapidly metabolized by CYP2C9 (90%) and CYP2C19 (10%) and almost completely excreted in the urine within 24 hours. The ibuprofen metabolism involves the formation of two catabolites: a hydroxylated-carboxylate and one where the ibuprofen is conjugated with glucuronic acid and excreted. Only a small fraction of the drug is excreted as unchanged; moreover, it was observed that does not concentrate in breast milk. Ibuprofen exerts its pharmacological

action through inhibition of the biosynthesis of prostaglandins for the isoenzymes of cyclooxygenase blockade (COX-1 and COX-2) and the inhibition is preferentially charged to the inducible COX-2. It directs the metabolism of arachidonic acid towards the way of 5-lipoxygenase resulting in increased production and release of leukotrienes. As an inhibitor of cyclooxygenase, Ibuprofen is less powerful than ketoprofen and naproxen but more active than propoxyphene, especially in the treatment of dental pain [12].

Ibuprofen, in the form of free acid, is characterized by a poor solubility that determines a slow onset of therapeutic effect. To obviate this drawback saline forms, such as ibuprofen lysine, which is more soluble and better absorbed from the gastrointestinal tract are used. Formulations containing ibuprofen in the salt form (lysine salt or arginine salt) show a faster absorption, a more effective reduction of pain and a more prolonged analgesic effect compared to a formulation containing Ibuprofen (Table I) [13].

Table I: Average values of T_{max}

Formulation	T_{max} (min)
Ibuprofen	90
Ibuprofen lysine salt	35
Ibuprofen arginine salt	29

1.1.1.2 Sucralfate

Sucralfate is a complex of aluminum hydroxide and sucrose octasolfate. His brute formula is the following:

$$C_{12}H_{30}Al_8O_{51}S_8[Al(OH)_3]_n[H_2O]_{n'}$$

where *n* can assume values between 8 and 10 while *n' can* assume values from 22 and 31 (Figure 3) [14].

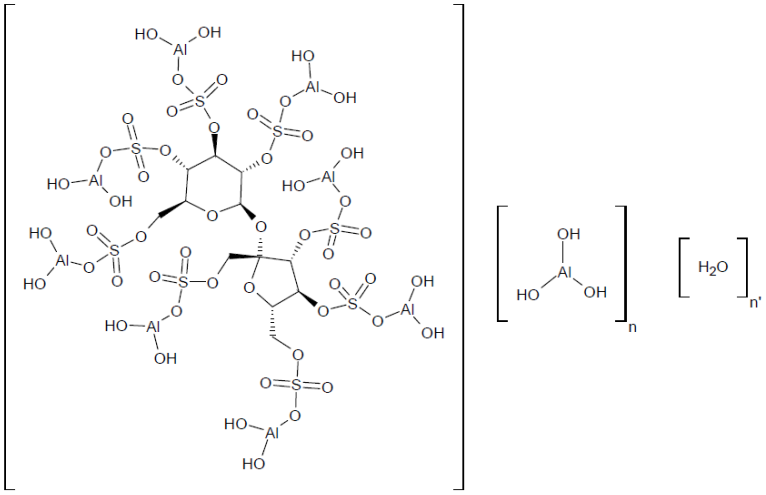

Figure 3: Structure of sucralfate.

Sucralfate is a powder with a color tending to white or in the form of gels, insoluble in water, in ethanol and methylene chloride. It is soluble in dilute solutions of mineral acids and alkali hydroxides. The sucralfate is classified as a cytoprotective agent with high affinity for the gastric mucosa. By binding to the gastric mucosa, the drug leads to the inhibition of pepsin and to the strengthening of prostaglandin. This also causes:

- increased gastroduodenal secretion of mucus and bicarbonate;
- increased cell proliferation of the gastric glands;
- stimulation of the renewal of the epithelial surface;
- increase in the resistance of the endothelium of blood vessels to various kinds of stimuli (alcohol, NSAIDs);
- promotion of regeneration of the damaged tissue by binding to certain growth factors, such as fibroblast growth factor (FGF or fibroblastic growth factor).

In an acidic environment (pH<4), the sucralfate reacts with hydrochloric acid in the stomach to form a cross-linking, viscous, paste-like compound capable to adhere to the surface of the gastric mucosa, protecting it thanks to the formation of a bio-adhesive barrier. The link with the gastric mucosa is based on an electrostatic/ionic interaction between negatively charged molecules and positively charged glycoproteins in the damaged mucosa. It is used for the treatment of various diseases of the gastrointestinal tract including stress induced ulcer, esophagitis, duodenal ulcers, secondary gastrointestinal ulcerations caused by NSAIDs and gastro-esophageal reflux. It is orally administered in different pharmaceutical forms (tablets, granules and suspensions); about 5% of the administered dose is systemically absorbed and excreted as unchanged in the urine. The remaining part reacts with hydrochloric acid present in the stomach; not being significantly absorbed, it is excreted in the feces. The dose is 2 g twice a day or 1 g for a maximum four times a day, preferably before meals. Sucralfate offers a protection of gastric mucosa for a period of about 6 hours through the formation of a paste which floats on the stomach contents. In fact, besides as protector of the gastric mucosa it is also used to prevent or reduce gastroesophageal reflux. It is not recommended its concomitant use with antacids or anti-secretory drugs that cause an increase in gastric pH limiting the activation of the molecule and the formation of the gel [15].

2 Aim of the research work

Multilayer tablets are proven to be an effective way of administering complex therapeutic solutions, allowing the manufacturing of single dosage forms with multiple APIs [16].

In this case, a therapeutic solution for chronic inflammation is proposed in the form of a multilayers tablet containing ibuprofen lysine and sucralfate.

The first part of this thesis was focused on the realization of a three-layers tablet containing one layer of ibuprofen lysine surrounded by two layer of sucralfate. The tablet was designed for the immediate release of the active substances into the stomach.

The second part was addressed to better comprehension of the challenges related to the manufacture of multilayers tablets, starting from basic excipients. Finally, a design of experiments on the formulation and process parameters was performed for the manufacturing of a bilayer tablet of ibuprofen lysine and sucralfate.

Chapter I

1 Introduction

1.1 Multilayer tablets

The tablet is one of the most popular dosage form in use today. In particular, therapeutic strategies based on oral delivery of bilayer (and multilayer) tablets are gaining more acceptance among brand and generic products due to a confluence of factors including advanced delivery strategies, patient compliance and combination therapy [16].

Recently, research has turned its attention on the development of these delivery systems for the treatment of complex diseases, such as type II diabetes, hypertension, malaria, pain treatment and AIDS.

Multilayer tablets are gaining popularity due to several factors:

1. Reduce the burden for patients by administering two or more active pharmaceutical ingredients (APIs) in a single dosage form.
2. Multilayer tablets can be designed to overcome chemical incompatibility between two active components.
3. Lastly, those tablets are also developed to control the delivery rate of one or more APIs, by interposing layers with different release profiles.

The manufacture of multilayer tablets is a delicate procedure: it needs to ensure both the physical and chemical stability (Critical Quality Attributes) of the tablet itself during the industrial processing procedures (manufacturing, handling, packaging and shipping) and to enable the activity of the drugs after the tablet administration, to reach the Target Product Profile. The construction of such complex oral dosage forms requires on one hand the complete control of any aspects of its formulation and compression processes, i.e. the critical material attributes and the Critical Process Parameters, and on the other hand the control of the release of, for example, each active substance with an individual and controlled manner.

Although the manufacture of multilayer tablets has been successful for over 50 years, there is still a need of an improvement, in order to ensure that the manufacturing process will make possible to satisfy both technological and therapeutic specifications as well as regulatory requirements.

Currently, in literature plenty of information can be found about the processes that intervene during the compaction of powders and the final tablet manufacturing. However, the current approach of analyzing the critical process parameters of compression is to use a model formulation made of excipients (and a proper lubricant) [17]. In particular, regarding the matter of tableting a multilayer tablet, a vast majority of the studies performed (and published) do not take into account the complexity added by working with active ingredients, to the final purpose of offering an innovative therapeutic solution.

Therefore, in this work of thesis, an investigation of the compression's critical parameters of a multilayer tablet, containing two drugs in combination, is proposed.

The multilayer system studied was a three-layer tablet, containing ibuprofen-lysine and sucralfate in combination (on different layers), with the aim of proposing a clinical viable way of treating inflammation, and expand the knowledge about the manufacturing of a multilayer release system.

1.2 Quality by Design approach

Quality by Design (QbD) is a systematic, scientific, risk-based, holistic and proactive approach to pharmaceutical development that begins with predefined objectives and emphases process understanding and control [18]. It means designing and developing formulations and manufacturing processes to ensure predefined product quality objectives [19]. QbD identifies characteristics that are critical to quality from the perspective of patients,

translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics [20]. The relationships between formulation and manufacturing process variables (including drug substance and excipient properties and process parameters) and product characteristics are established and the variables identified. This knowledge is then used to implement a flexible and robust manufacturing process that can allow the manufacturing of a consistent product over time. Thus, some of the QbD elements include [21]:

– Define target product quality profile

– Design and develop product and manufacturing processes

– Identify critical quality attributes, process parameters, and sources of variability

– Control manufacturing processes to produce consistent quality over time

Under the QbD methodology, pharmaceutical quality of the drug product is assured by understanding and controlling formulation and manufacturing variables. End product testing confirms the quality of the product and is not part of the manufacturing consistency or process control. A product specification is often set by observing data from a small number of batches, believed to be acceptable and then setting acceptance criteria that required future batches to be the same. The consistency comes from the design and control of the manufacturing process and the specification of drug product should be clinically relevant and generally determined by product performance. Under QbD, batches may not be actually tested, as the process understanding and process control provide sufficient evidences that the batches will meet the specification. Furthermore, the specification under the QbD is solely used for the confirmation of product quality, not manufacturing consistency and process control [22].

1.3 Manufacturing of a multilayer dosage form

Two drugs can be administered in a single dosage form, such as a multilayer system.

In general, a multilayer tablet is made of two or more drugs having identical and/or different release kinetics (Figure 4) [16]. Each layer constituting the tablet is obtained with a tableting machine. Each layer of powder, poured in the die, undergoes a precompression process. The force applied by the upper punch determines the compression of the various layers of material deposited on each other with the formation of the multilayer tablet.

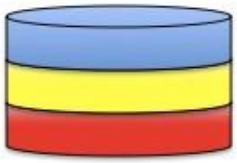

Figure 4: Graphic representation of a multilayer tablet

The manufacturing process presents several problems: the weight of the individual layers may be inaccurate, excessive compressive force may cause lamination of the tablets and eventual separation of the layers during the manufacturing or the storage. In addition, the mechanical properties and the compaction of the individual layers can differ substantially in relation to the compression process that is unique to each layer [23].

In the design and realization of multi-dose dosage form it must be taken into account different aspects, such as:

- elastic/plastic deformation of the active ingredients and the excipients used;
- cross-contamination between the adjacent layers;
- delamination of the layers;
- chemical and physical long term stability;
- sizes of the multilayer tablet;

- influence of temperature and ambient humidity on the adhesion of the layers.

These are just some of the problematics associated with the manufacture and storage of multilayer tablets. The most concerning one is surely the *delamination.* It consists in the separation of the layers, therefore mining the integrity of the tablet itself [24].

The layer separation of multilayer tablets is caused by various mechanical stresses that develop during the compression phase, and that are released during the relaxation and ejection phase. The mechanisms that underlie it involve both the cohesive / adhesive properties and plasticity/elasticity of the material, coupled with the parameters of compression (Figure 5).

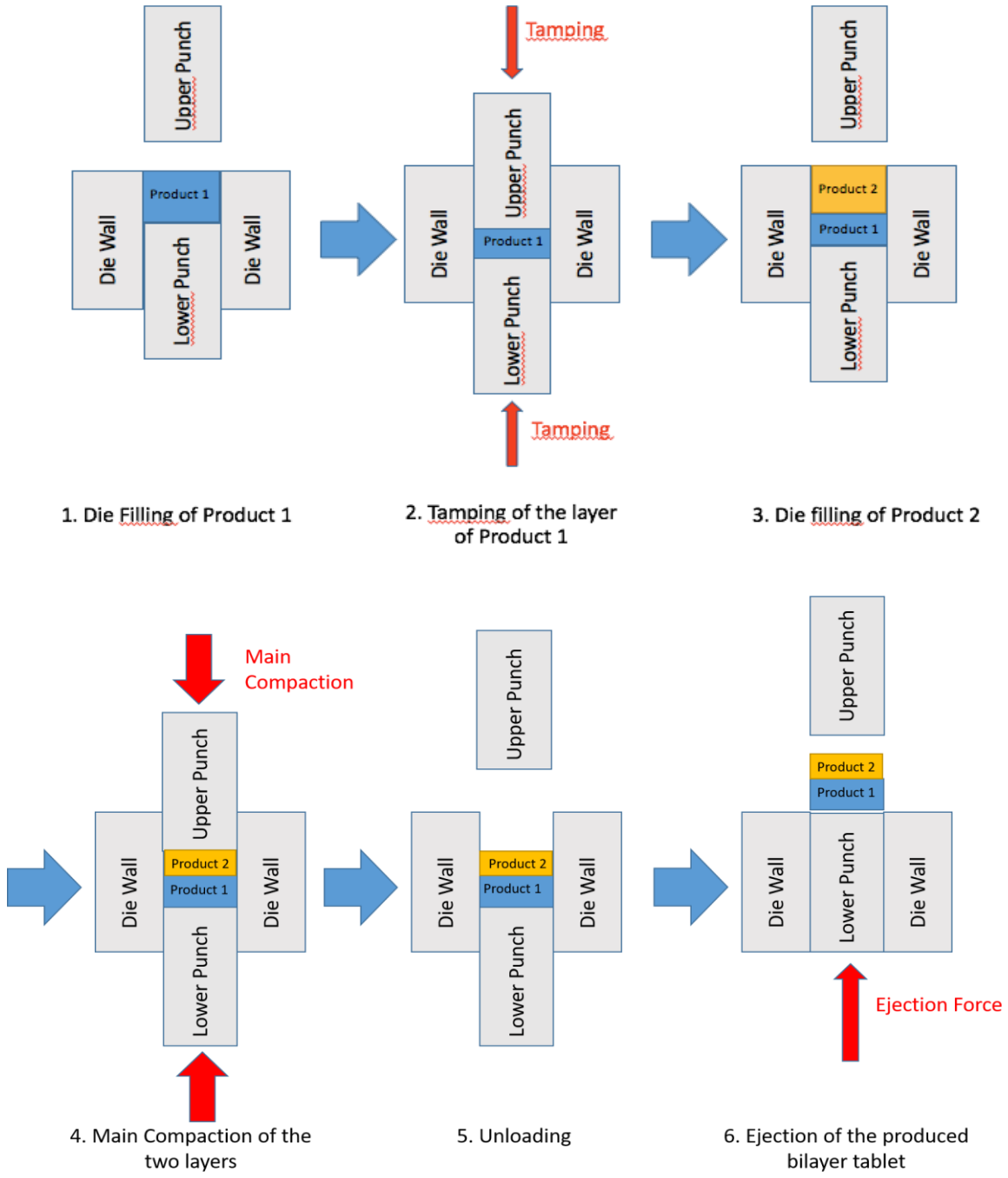

Figure 5: Cycle of compression for a multilayer tablet in an alternative tableting machine.

The manufacture of multilayer tablets consists, firstly, in the deposition of the first layer of powder in the die (Fig 5.1). Then a tamping force is applied to the first layer (Fig 5.2). This has a significant impact on the interfacial strength and adhesion between adjacent layers, also it contributes to the integrity of the final tablet. The precompression force, applied to the first layer, determines a reduction in the area of bonding surface, therefore the higher it is,

the lower is the contact area for the second layer, resulting in a weak adhesion between the layers. A certain degree of roughness must be maintained so that the adjacent layers adhere to the other. it has been observed that a high strength of precompression greatly reduces the contact surface on the first layer making labile the adhesion with the second layer. This might cause phenomena, such as capping/delamination at the interface of separation, both during and immediately after the compression process. Therefore, the compression force applied to the first layer is a critical factor that influences the adhesion between the layers [24].

After the deposition of the powder that constitute the second layer (Fig 5.3), the main compaction force is applied (Fig. 5.4). This force serves to form the physical bonds that compact the powder for each layer, but this applied force is also a critical factor for the strength of the interface between the layers. Then, the unloading phase (also known as the relaxation phase) takes place (Fig 5.5). During this time, the upper punch unloads the pressure it had on the powder. During this phase the elastic deformations occur, and, depending on the physical properties of the two different materials, they can result in an immediate delamination of the tablet [25]. Finally, the lower punch moves up for the ejection of the tablet (Fig. 5.6) and returns in position to start a new cycle.

The physical integrity of the tablets is expressed using the parameter of “tensile strength”. It expresses the breaking strength of the tablet, normalized by the surface. The tensile strength (MPa/cm^2) of the tablet decreases when the strength of the precompression (compression force applied to the first layer) increases. A high precompression force value produces a weak interaction between the layers, promoting the delamination (therefore the breaking of the tablet) when the tablet is subjected to various stress type. On the contrary, the application of a low precompression force does not reduce the contact area of the first layer enough, this can give rise to a phenomenon known as cross-contamination [26]. The powder of the first layer is mixed at the interface with that of the second layer, generating

not well defined layers, with mixing of the two products at the interface. This has strong repercussion on the final product quality.

The adhesion between the layers depends not only on the applied force but also by the physical-chemical nature of the excipients and of the active ingredients present in the formulation. The material properties have a significant impact on the process of compacting and adherence of the layers; some plastic materials possess properties (for example microcrystalline cellulose), other elastic properties (for example lactose), still others are fragile (for example lactose) [27]. During the compression, the brittle materials tend to fragmentize, giving rise to smaller particles that fill the voids between the larger particles (thus increasing the friction forces on the walls of the die and consequently increasing the ejection force). On the contrary, for plastic and elastic materials, plastic and elastic deformations occurs. During the decompression phase the materials relax in different way and rate, then the radial stress generated could determine the separation at the interface and cause delamination in the ejection phase. The plastic/elastic properties of a material are strongly related to its surface free energy (Young equation and equation of Wu) [28]. The tendency to delamination is significantly lower than in the case in which the layers are made of plastic materials or characterized by high surface free energy. Generally, a brittle material produces a smooth surface, while a plastic material produces a rough and irregular surface. As already underlined, the adhesion between the layers is strongly correlated to the latter aspect.

Other important aspects concern the characteristics of the powder bed to compress, as for example porosity, morphology, particle size and water content. Wet granulation is often used to standardize the properties of a powder blend (particle size) or to improve some aspects such as powder flowability.

Also important are the process parameters, such as the speed of the punches, the dwell time and the relaxation time. It has been shown that an increase of the speed of the punches

leads to a significant reduction of the porosity of each layer compressed, limiting the adhesion at the interface and promoting the delamination [24].

2 Aim of the research work

The purpose of the thesis work carried out at the University of Parma involved the construction of a three-layer tablet consisting of two different active principles, ibuprofen lysine and sucralfate, in combination.

The manufacture of three-layer tablets was performed using a compression simulator, which allows to study in detail the physics of the compaction process.

In a first instance, a model formulation was prepared, in order to fully understand the problematics involved in a preparation of a multilayer system. Thereafter, two different formulations of sucralfate, each containing a dose of 100 mg of the active were prepared. The formulations differ in the presence of two excipients, microcrystalline cellulose and lactose.

As regards the ibuprofen lysine salt, it was used a single formulation that contains a dose of active principle equal to 342 mg. This dosage is the currently used dosage in various commercial products already approved for market release (such as Rapid (Boots Pharmaceutical, London, UK), Nurofen (Reckitt Benckiser, Slough, U.K.)).

Both formulations were individually subjected to compaction, followed by the study of the critical factors that affect the compression process, in order to evaluate the impact of different excipients on the process.

The tablet manufacturing followed this order:

• cylindrical monolayer tablets of sucralfate

• cylindrical monolayer tablets of ibuprofen lysine

• cylindrical bilayer tablets (sucralfate and ibuprofen lysine)

• oblong bilayer tablets (sucralfate and ibuprofen lysine)

• oblong three-layer tablets (two layers of sucralfate and one of ibuprofen lysine)

3 Materials and methods

3.1 Materials

- Croscarmellose sodium (AcDiSol SD-711, FMC Philadelphia, United States)
- Hydrophilic fumed silica (Aerosil 200, Evonik Industries AG, Hanau, Germany)
- Microcrystalline cellulose (Avicel PH 101, ACEF, Fiorenzuola d'Arda, Piacenza, Italy)
- Lactose (FlowLac 100, MEGGLE, Wasserburg, Germany)
- Ibuprofen lysine (Lisapharma, Erba, Italy)
- Crospovidone (Kollidon CL/ Kollidon 30/ Kollidon VA, BASF, Ludwigshafen, Germany)
- Magnesium stearate (ACEF, Fiorenzuola d'Arda, Piancenza, Italy)
- Sodium bicarbonate (Sigma-Aldrich, Riedel-de Haen, Germany)
- Sucralfate gel (BK Giulini, Ludwigshafen am Rhein,Germany)
- Glycerol distearate (Precirol, Gattefossé, Lyon, France).

All materials and solvents used are of analytical grade according Ph. Eur last edition.

3.2 Methods

3.2.1 Preparation of sucralfate granulate

For the preparation of the granulate, sucralfate moist gel with a water content of 67.2% was used. Sucralfate gel was manually reduced in small pieces and dried in fluid bed dryer (Figure 6) “Mini Glatt” (Glatt GmbH, Binzen, Baden-Württemberg Germany).

Sucralfate gel was subjected to a 40-minute drying step (inlet air temperature 40 °C, air flow pressure 0.5 bar). Then, the drying process was stopped and the reduction of residual water

content (%) of the moist sucralfate gel was measured by using Karl Fisher Titration (Crison Titromatic, Barcelona, Spain) and compared with the weight of the moist sucralfate gel initially loaded. The drying process was continued till the water content of the sucralfate gel was between 50-52%. Those preemptive drying steps have the purpose of drying the sucralfate gel enough to be manipulated and stored. The sucralfate gel was then kneaded in a mortar with microcrystalline cellulose, lactose, or a mixture of microcrystalline cellulose and lactose. Granules were obtained by using an oscillating arm granulator (Figure 7, Erweka AR400, Düsseldorf, Germany), equipped with a 1.2 mm mesh.

Then, the granulate was subjected to a drying cycle in a fluidized bed (inlet air temperature 40 °C, air flow pressure 0.3 bar) for forty minutes to obtain a water content between 13 and 15%. The sucralfate granulate was then mixed with 0.5% of magnesium stearate in Turbula® (WAB, Basel, CH) for 5 minutes.

Figure 6: Mini Glatt Fluid bed.

Figure 7: Oscillating arm granulator

3.2.2 Preparation of the ibuprofen lysine granulate

The wet granulate of ibuprofen lysine was prepared by mixing (in presence of one steel ball) the drug and the excipients in Turbula® for 15 minutes. Afterwards, the blend was kneaded in a mortar with 35 ml of the binder solution of PVP K 30 (5% w/V) in ethanol. Granules were obtained by using an oscillating arm granulator (Erweka AR400, Düsseldorf, Germany), equipped with a 0.8 mm mesh. Granules were dried in an oven at 40 °C for about 2 hours. The granulate was then mixed in Turbula® for fifteen minutes with extra-granular excipients and further five minutes after the addition of magnesium stearate.

3.2.3 Particle size distribution analysis of the granulate

The particle size distribution analysis of the granulate was carried out by sieving method (Endecotts Limited, London, United Kingdom). The sieves were stacked on sieve shakers (Fritsch GmbH, Idar-Oberstein, Germany), according to the geometric progression of $\sqrt{2}$ order. The openings of the sieve mesh were the following: 1000, 710, 500, 355, 250, 180 and 125 μm.

Prior to analysis each sieve was accurately weighed. Then, the sieves were placed by putting the one with the largest opening on the top and the others in order of decreasing mesh opening up to finish with a round pan, called the receiver. Samples of granules (about 20 g) were poured into the top sieve and closed with a lid. Then, the stack of sieves was subjected to vibrations for 5 minutes at amplitude 4. The sieves were weighed and placed on the sieve shakers for additional 5 minutes at amplitude 4. The sieves were weighed again. Knowing the opening of each mesh sieve, the size class of the particles corresponding to the fraction collected on the sieve is equal to the arithmetic mean between the opening of the above sieve and that of the below one. The fractions collected on each sieve were weighed and the amount of granules for each size fraction was expressed as the percentage fraction of the weight of granulate analyzed.

3.2.4 Determination of water content of granulate by TGA

The determination of the residual water content in the sucralfate granulate was performed by means of the thermogravimetric analysis (TGA). The instrument used was the TG50 (METTLER Toledo, USA) equipped with STARe software. An amount of granulate was accurately weighed into an alumina crucible, positioned on the plate of the balance, and closed with a perforated alumina lid. Each sample was subjected to a heating program from 25 to 140 °C, at scan rate of 20 °C/min in a nitrogen atmosphere (flow of 100 ml/min), followed by an isotherm of 15 min at 140 °C. The analysis was conducted in triplicate.

3.2.5 Multilayer tablet manufacturing

The multilayer tablets were manufactured using the Styl’One Evolution Rotary Tablet Press Simulator (Medel'Pharm, Lyon, France). The apparatus, equipped with single location for die and punches (Figure 8), is able to simulate the industrial rotary tablet press using the

software Advanced ANALIS. The displacement of the upper and lower punches is controlled electronically and the force exerted by the punches on the powder bed is measured by the sensors.

Figure 8: Compression Simulator Styl'One Evolution

Two types of multilayer tablets were manufactured:

- flat cylindrical tablets, using EURO D punches of 11.28 mm diameter (HOLLAND Ltd, Nottingham, UK);
- oblong tablets, using EURO D punches (17.5 x 8.5 mm, HOLLAND Ltd, Nottingham, UK; Figure 9).

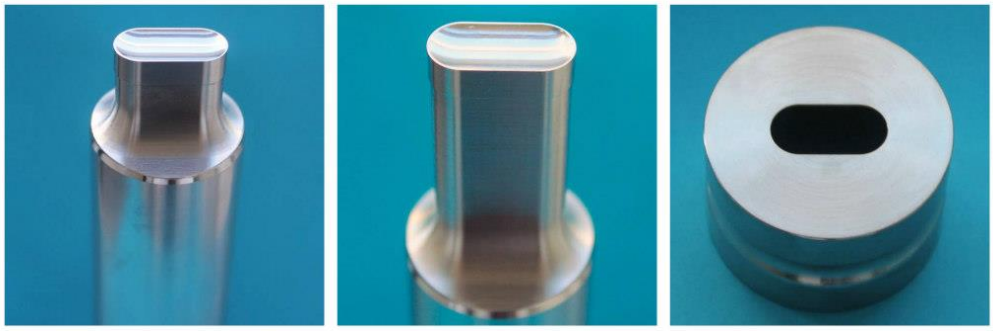

Figure 9: Oblong punches EURO D

The powder feed for the die filling during the manufacturing of ibuprofen and sucralfate layers was done by using a gravity-feed shoe for the sucralfate granulate and a force feeding shoe (Figure 10), for the ibuprofen granulate. This one is a particular shoe equipped with paddles. The rotation of the paddles inside the shoe facilitates the flowing of the powder and consequently the die filling.

Figure 10: An example of the shoe used during the manufacturing of the multilayer tablets.

Both monolayer tablets of sucralfate and ibuprofen lysine were obtained, using the cylindrical punches, at different compression force values (10, 20, 30 and 40 kN).

The bilayer tablets of sucralfate and ibuprofen lysine were prepared using EURO D cylindrical punches. Tablets were produced for each of the precompression (0, 1, 2, 4 kN) and compression force values (10, 20, 30 and 40 kN).

The bilayer oblong tablets of sucralfate and ibuprofen were produced using oblong punches EURO D. Tablets have been manufactured at each of the precompression (0, 1, 2, 4 kN) and compression force values (10, 20, 30 and 40 kN).

The bilayer tablets, cylindrical and oblong, were produced by placing as first layer the sucralfate granulate and as second layer the ibuprofen granulate.

Finally, the three-layers oblong tablets were manufactured, putting sucralfate granulate in the first and third layers and ibuprofen in the middle layer.

3.2.6 Tablets characterization

3.2.6.1 Dimensional measures

3.2.6.1.1 “In die” dimensions

The in-die dimensions of a tablets are the value of height and diameters that the tablet reaches during the compression phase. It is possible to measure this property using the Styl’One compaction simulator coupled with the software Advanced ANALIS (see 3.2.5).

3.2.6.1.2 “Out of die” dimensions

The measuring of the dimensions of a the single-layer and multilayer tablets (after the ejection from the tableting machine) was performed using a digital thickness gauge (Mitutoyo, Tokyo, Japan) on a sample of five tablets for each value of precompression/compression force applied.

3.2.6.2 Breaking strength test

The determination of the breaking strength of the tablets was carried out using a digital dynamometer (Acquati, mod. MC AG, Arese, Italy). The dynamometer is an instrument for the measurement of forces constituted by a transverse movable bar and two grippers that hold the tested tablet into position (Figure 11). To run the breaking test the dynamometer was equipped with a 50 daN cell. The analysis was conducted at a speed of advance of the cell of 50 mm/ min.

Figure 11: Dynamometer monocolumn Acquati

The monolayer and multilayer cylindrical tablets were subjected to an axial breaking strength, as shown in Figure 12; the same methodology was applied to multilayer oblong tablets.

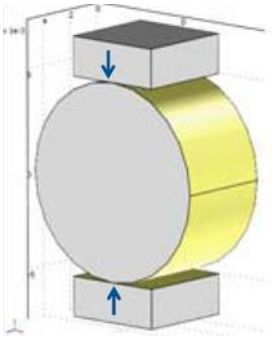

Figure 12: Rupture of the axial cylindrical compressed

3.2.7 Tablet disintegration test

The disintegration test was performed with a tester ZT 220 (ERWEKA FGS, Düsseldorf, Germany) with one motor driven USP/EP/JP compliant test station with basket rack assemblies. The unit incorporates an integrated flow-through heating system, a molded one-piece PET water bath and a water bath lid.

4 Results and discussion

An initial exploration of issues related to the manufacturing and the storing of a multilayer tablet was performed by producing a bilayer tablet of sucralfate (with a dosage of 100 mg) at the first layer and ibuprofen lysine (with a dosage of 342mg) as second layer.

The formulations of the sucralfate and ibuprofen lysine layers were developed starting from the manufacture of cylindrical monolayer tablets containing one of the two drugs. The critical parameters that influenced the manufacture of single-layer tablets, including tensile strength, elastic recovery and the energies involved in the compression process were studied. Furthermore, in the formation of the two-layer cylindrical and oblong tablets and of three-layer oblong tablets, in addition to the previously mentioned critical parameters, the attention was also focused on the influence of the precompression and compression forces on the layer separation.

The critical parameters studied were the following:

- sucralfate water content (%): the percentage of residual water content;
- breaking strength (N): the force, applied in the axial way, required to cause the break of the tablet;
- tensile strength (MPa);
- ejection energy (J) of the tablet from the die;
- plastic energy (J): the total energy during the compression process, equal to the sum of energy provided during the compression phase (compression energy) and the energy recovered from the tablet when the applied force decreases (elastic energy);
- elastic energy (J): energy recovered from the compressed powder when the compression force decreases.

4.1 Bilayer tablet of ibuprofen lysine/ sucralfate

In order to test the formulation and production conditions, a bilayer tablet was manufactured as show in Figure 13.

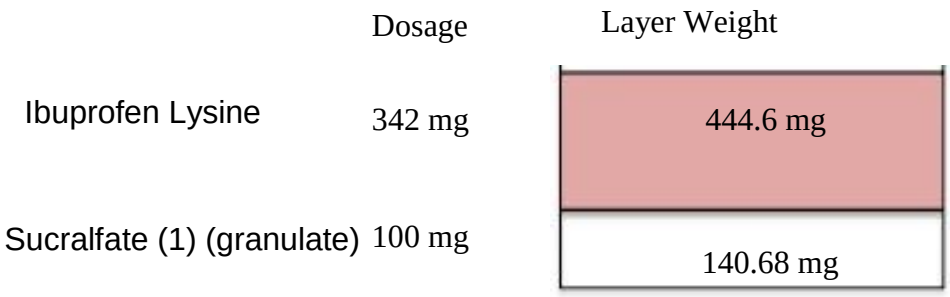

Figure 13: Composition of the bilayers tablet

Sucralfate granulate was obtained following the procedure described in paragraph 3.2.1, while ibuprofen lysine granulate was prepared as described in section 3.2.2 The final formulation is reported in Table II.

Table II: Components of the sucralfate and ibuprofen layers.

Sucralfate layer		
Components	mg	%
Dry sucralfate	100	71.08
Water	15.68	11.15
Microcrystalline cellulose	25	17.77
Total	140.68	100

Ibuprofen lysine layer		
Ibuprofen lysine	342	70
Kollidon VA	17.1	5
Sodium Bicarbonate	51.3	15
Precirol	17.1	5
Cornstarch	17.1	5
Total	444.6	100

The selected parameters used for the manufacturing of the bilayers tablets are summarized in Table III. In particular, the parameters are:

- dosage height: measured in mm, is the depth at which the lower punch goes during the filling phase. It determines the quantity of the powder inside the die.

- tamping force: is the force that the upper punch applies during the precompression phase. It determines the minimum distance between the punches, therefore the thickness of the first layer.
- main compression force: is the force that the upper punch produces during the main compression.

Table III: Compression parameters used to manufacture the bilayer tablet

	Sucralfate	Ibuprofen lysine
Dosage Height(mm)	2.609	10.319
Tamping Force (kN)	0.2	/
Main Compression Force (kN)	/	10, 20, 30, 40

Firstly, the powder of sucralfate is deposited by the shoe inside the die, for a dosage height of 2.61mm, that gives exactly a layer weighted 221 mg (which contains the desired dose of sucralfate (100 mg)).

Then a tamping force is applied to the layer of Sucralfate, of 0.2 kN (as reported in Table III). This was kept minimal to ensure that the layer was not excessively tamped, but high enough to ensure that there is enough space inside the die for the powder of ibuprofen lysine. Finally, the powder of ibuprofen lysine is deposited inside the die, and compressed with different compression forces.

As shown in Figure 14, the hardness of the bilayer tablets obtained (measured with the dynamometer as indicated in the section 3.2.6) linearly increases as the applied compression (Figure 14).

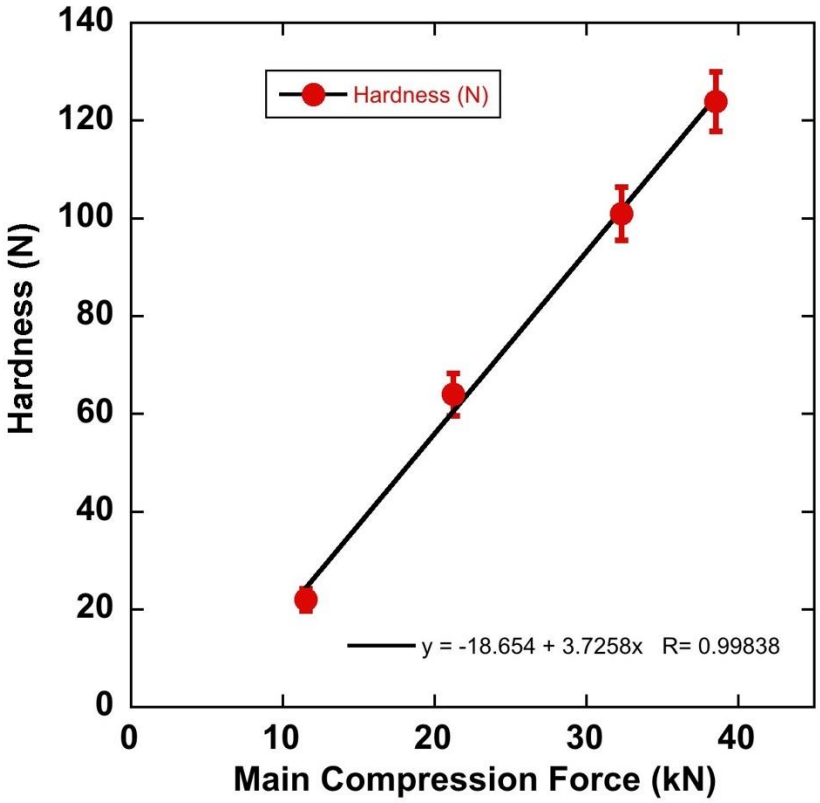

Figure 14: Main compression force versus tablet hardness (n=20)

The graph shows a linear relation between the hardness and the compression force, with an R^2 of 0.99838. This means that, even when a high compression force is applied, the bilayer tablet is still capable of converting that force into plastic deformation and reduction of porosity.

4.1.1 Stability test of bilayer tablets of sucralfate/ibuprofen lysine

The produced tablets were stored in sealed containers for 24h, at a measured humidity of 45%. The containers were made of plastic (PET), provided with pores to allow the flow of air. Those containers were then stored in glass chambers equipped with a saturated solution of potassium carbonate.

After this period of time, layer separation in the bilayer tablets was observed.

Then, a monolayer cylindrical tablet of sucralfate and a monolayer cylindrical tablet of ibuprofen lysine was produced, using the formulation reported in Table III. The tablets were manufactured at compression forces of 10, 20, 30 and 40 kN.

The tablets were tested measuring the dimensions in-die and out-of-die, as per section 3.2.6. The out-of-die volume was measured 24h after the tablet manufacturing, in order to include the influence of time into account.

Given that a changing in the dimensional properties of the tablet is correlated to the elastic energy of the tablet themselves, the difference in dimensions is named as “elastic recovery” and it is described by the equation of Picker [29]:

$$Ert = (Vout – Vi) / Vout * 100$$

where:

- Ert= elastic recovery
- Vout = volume of tablet out of die after 24h
- Vin = volume of tablet inside the die

For the layer of sucralfate and ibuprofen lysine, the calculated elastic recovery, plotted versus its compression force, is showed in Figure 15.

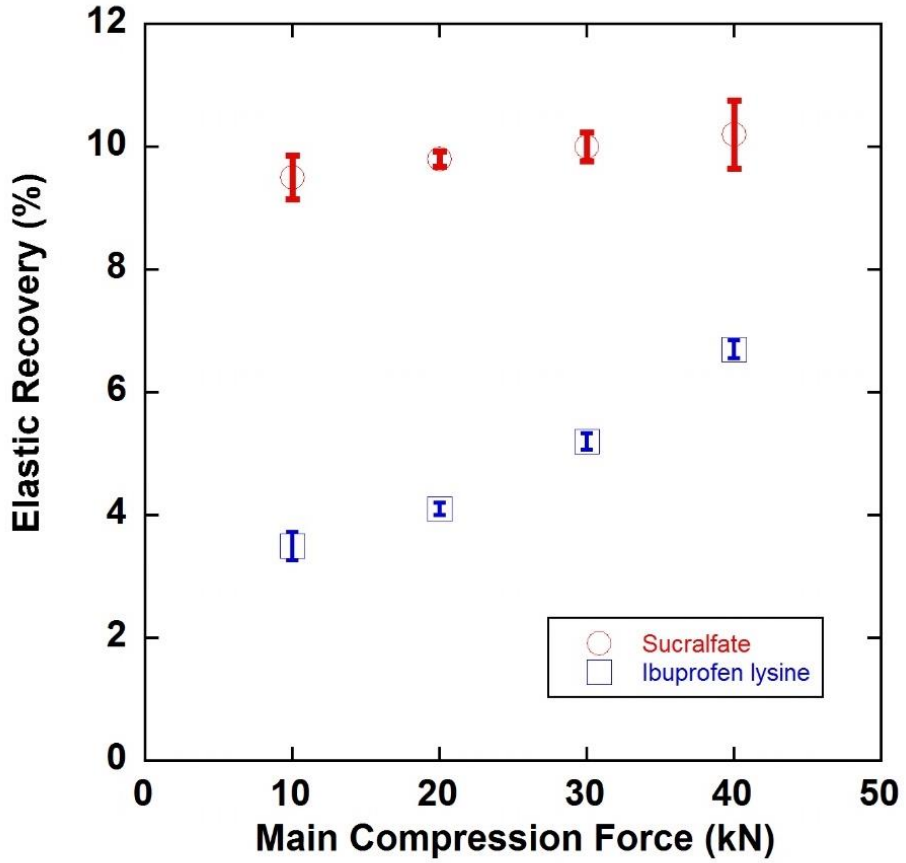

Figure 15: Elastic return of sucralfate and ibuprofen lysine layers versus the compression force applied (n=10).

The elastic recovery of sucralfate layer ranges from 9.5 to 10.3%, proving that the layer tends to have a meaningful elasticity. The same procedure was applied for the layer of Ibuprofen lysine. In this case the elastic recovery ranges from 3.5 to 6.4 %, in a seemingly force-dependent manner. This shows that there is a difference of elastic recovery between the two layers. In Table IV the difference in elastic recovery (ΔErt) between the cylindrical monolayer of sucralfate and ibuprofen lysine for each batches of tablet made at different compression force is reported.

Table IV: Difference of elastic recovery (ΔErt) between each batch of cylindrical monolayer of sucralfate and cylindrical monolayer of ibuprofen lysine.

Compression force	ΔErt
10	6.0 ± 1.5
20	5.7 ± 0.5
30	4.8 ± 1.4
40	3.5 ± 0.8

This elastic recovery stresses the interface between the layers, applying a tension force that leads to delamination. This does not happen during the compression phases or immediately after the ejection of the tablet from the die (as most of the reported cases in literature do [31]), but the delamination process takes places during the storage time.

This lead to the conclusion that one of the components of the bilayer tablet is subject to a changing of its volume over time.

It has been reported in the literature that sucralfate is a hygroscopic material [15, 30], but there is no link between the water content of the sucralfate, its ability to absorb water from the environment and the correlation between water intake / expansion of a sucralfate tablet (the elastic recovery). Therefore, further studies were performed to assess the influence of the water content of the sucralfate layer with its elastic recovery.

4.1.2 Sucralfate layer Water Content versus Elastic Recovery

Sucralfate at different water content was produced. Following the granulation step, the compacts were then dried in fluid bed for three different times (15, 30 and 45) obtaining three different level of water content.

A single layer tablet of Sucralfate was produced for each level of water content. Before its production, the water content of the powder was measured. Then, for each level of water content the elastic return was measured (Table V).

Table V: Drying time of the sucralfate granulate in fluid bed, water content (%) of the sucralfate granulate before compaction and the elastic return of the tablets

Batch #	Drying time (min)	Water content before compaction (%)	Elastic Return (%)
1	15	33.0 ± 4.2	14.2 ± 1.3
2	30	23.2 ± 3.5	9.5 ± 3.3
3	45	10.2 ± 1.6	4.6 ± 3.1

As shown in Table V the elastic recovery was reduced according to the water content of the powder. The chosen drying times gave rise to sucralfate with very different levels of moisture content and different elastic recovery. Even if the equilibrium moisture content was not reached, the results were sufficient to prove that water plays a pivotal role in increasing the elastic recovery, simply because water it is not in itself a compressible material.

In order to study the effect of different elastic recovery of the powder of sucralfate on the hardness of the bilayer tablets, four batches of bilayer tablets of ibuprofen lysine and sucralfate are produced, varying the sucralfate drying time (therefore its water content). The drying time in this study were much higher than the previous one, because it was necessary to obtain a sucralfate dry enough to obtain a bilayer tablet. Those tablets must have enough mechanical resistance to be safely stored and tested. The batches were differentiated by the sucralfate granulate drying time (Table VI).

Table VI: Batches produced by changing drying time of sucralfate.

Batch	Drying time (min)	Water content of the sucralfate powder (%)
#1	45	10.9
#2	60	8.8
#3	90	4.6
#4	120	2.5

The formulation of ibuprofen used for these bilayer tablets is described in paragraph 4.1 and kept constant for each batch.

In Figure 16, the adhesion force of the bilayer tablet (measured as described in par 3.2.6.2) and the difference in elastic recovery between the two layers are plotted versus the water content of the layer of sucralfate.

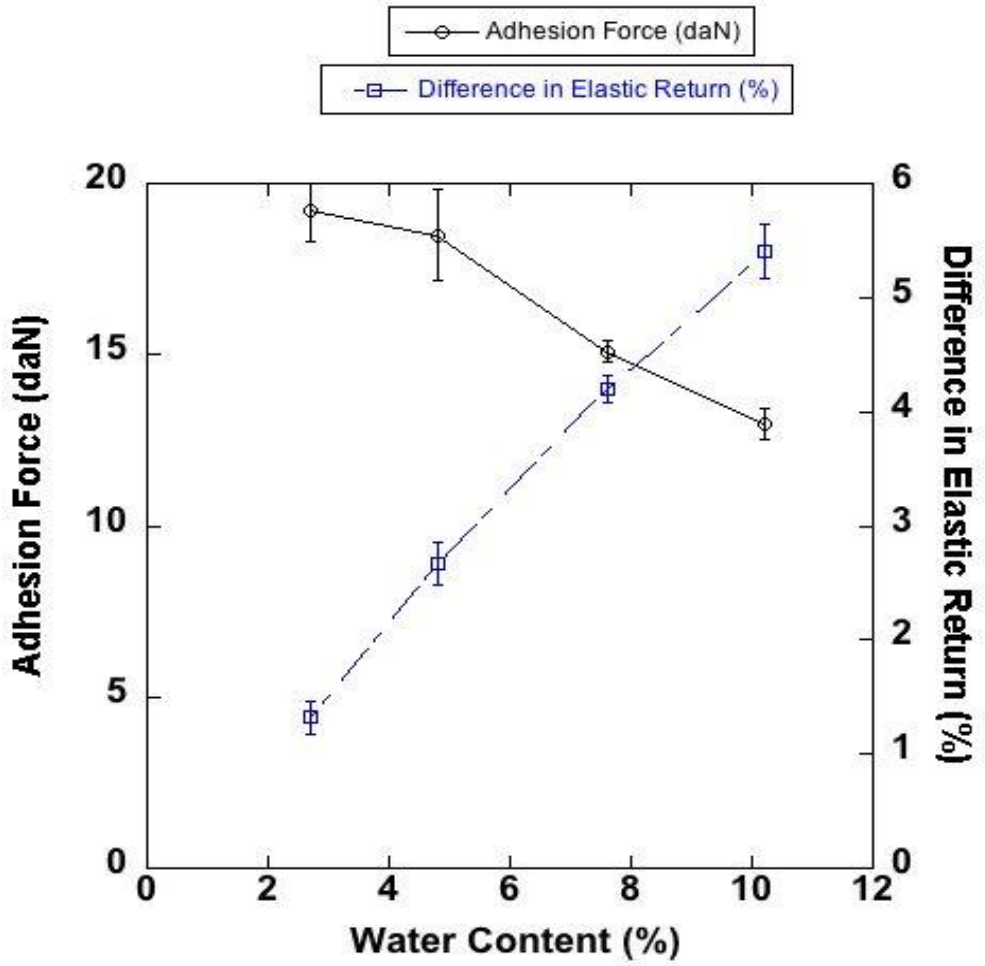

Figure 16: Adhesion Force of Bilayer Tablet and difference in elastic return between the layers versus the Water Content of the Layer of Sucralfate.

As can be observed from the graph reported in Figure 16, a linear relationship exists between the water content of the powder of sucralfate and the adhesion strength between the two layers of the bilayer tablet sucralfate / ibuprofen lysine.

The last one clearly decreases when increasing the water content of the layer of sucralfate. Moreover, the difference of elastic recovery between the layer of sucralfate and layer of ibuprofen lysine increases as the water content increases. This is interesting because it is possible to observe that, when the difference between the elastic recovery of the layer is small, then the adhesion force is at its maximum, and vice versa.

4.1.3 Single layer Water content vs Time

In order to investigate the effect of the water intake of the sucralfate granulate, different monolayer tablets of sucralfate were manufactured. Immediately after the production, the manufactured tablets were placed in closed polyethylene bottles. These bottles were placed in three different sealed humidity chambers (placed inside a room at controlled temperature of 25°C), each one containing a different saturated salt solution that creates a different relative humidity (R.H. %) inside the chamber. The humidity conditions of each chamber is reported in Table VII.

Table VII: Salt solutions used and their humidity

Humidity Chamber	Salt Solution	Relative Humidity (R.H., %)
1	Sodium chloride	75
2	Potassium carbonate	43.6
3	Lithium chloride	11.3

Water content of the monolayer tablet was measured at 1, 2, 3, 5, 7 and 14 days after the manufacturing, by grinding the sucralfate layer and analyzing by TGA at the heating program indicated in the section 3.2.4.

As shown in Figure 17 the water content of the single layer of sucralfate tends to reach a plateau for all three different environmental humidity levels. The plateau was reached at higher value of water content in the case of 25°C/75% RH (around 20%). In the case of 25°C/43.6% RH and 25°C/11.3% RH, the plateau is obtained at around 16% and 14%, respectively.

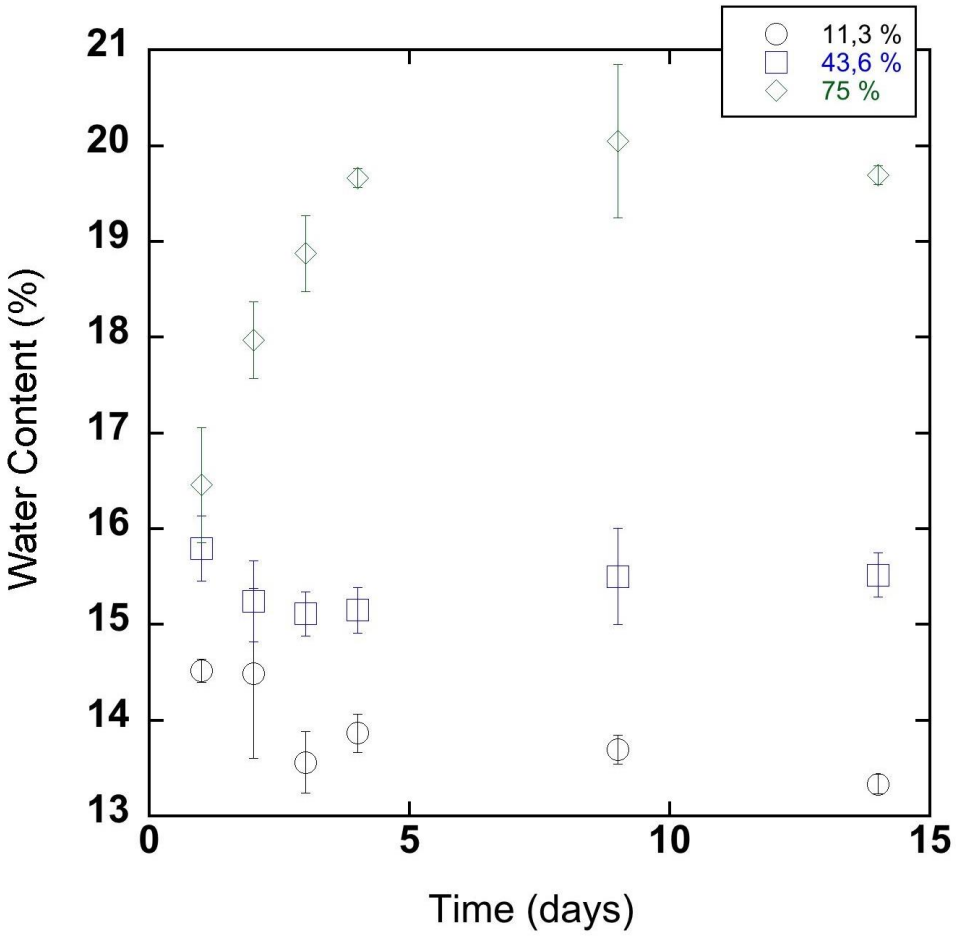

Figure 17: Water content (%) of the single layer of sucralfate versus time (n=10).

The impact of a high humidity storing condition on water uptake of the sucralfate tablets was relevant, as an increase of around 3 % after just 1 day and 5 % after 14 days was observed. Given that high water content is correlated with an increase of elastic recovery and that high difference in elastic recovery impacts negatively on the stability of a bilayer tablet, the fact that the sucralfate tends to absorb water from the environment is responsible for the layer separation of bilayer tablets stored at high humidity levels.

4.2 Cylindrical monolayer tablets

The manufacture of monolayer tablets was carried out using cylindrical punches EURO D from the diameter of 11.28 mm.

The tablets produced are divided into three different categories:

- cylindrical single-layer tablets of sucralfate (Sucr_1);
- cylindrical single-layer tablets of sucralfate (Sucr_2);
- cylindrical tablets monolayer of Ibuprofen lysine

4.2.1 Cylindrical tablets monolayer of Sucr_1

The composition of the formulation for the tablets monolayer Sucr_1 is reported in Table VIII.

Table VIII: Composition of the formulation Sucr_1

Components	mg	%
Sucralfate dry granulated	100	70.62
Water	20.2	14.27
Microcrystalline cellulose	20	14.12
Magnesium stearate	1.4	0.99
Total	141.6	100

To manufacture the cylindrical tablets of sucralfate, the gel was granulated by following the method previously described, with the sucralfate granulate produced using batch #1 according to Table VI.

The granulate of sucralfate was characterized in terms of size distribution (Figure 18).

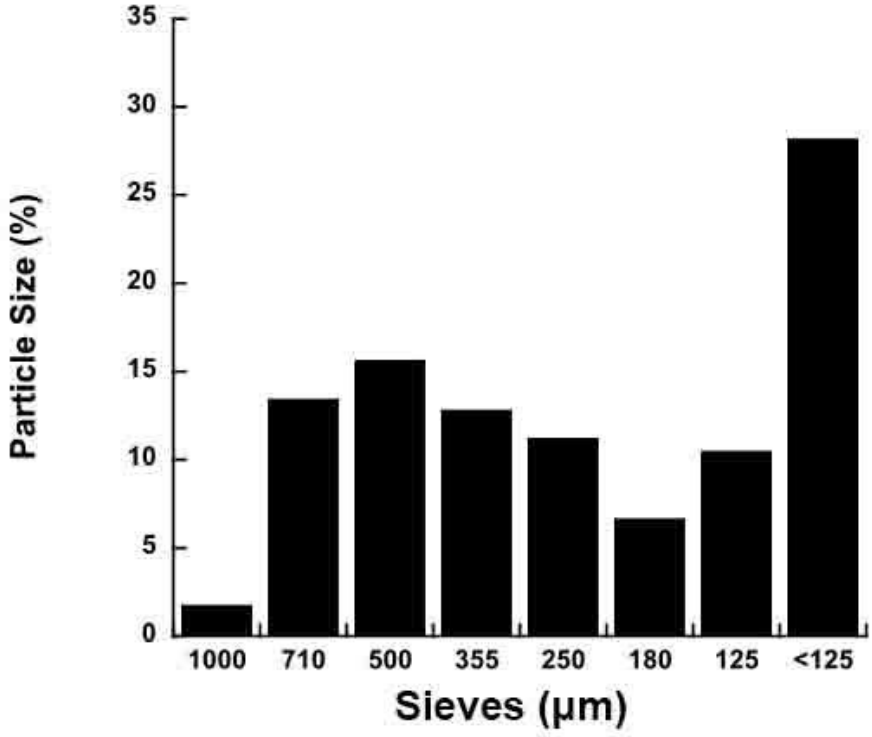

Figure 18: size distribution of the granulate of sucralfate Sucr_1

As can be noted from the histogram reported in Figure 18, the granules contain about 30% of fine particles (<125 μm).

After the addition of sucralfate to granulate the excipients reported in Table VIII, the mixture was mixed in a Turbula® and compressed by the compaction simulator Styl'One Evolution. The tablets of Sucr_1 were characterized in terms of change in weight, diameter and height (Table IX).

Table IX: Mean weight value, diameter, height of monolayers Sucr_1

(mean value ± standard deviation, n = 5)

	Sucr_1		Mean value ± st. dev.
	Weight (mg)		188.5 ± 1.5
Compression force (kN)	10	Height (mm)	1.46 ± 0.01
		Diameter (mm)	11.32 ± 0.01
	20	Height (mm)	1.25 ± 0.01
		Diameter (mm)	11.30 ± 0.01
	30	Height (mm)	1.15 ± 0.01
		Diameter (mm)	11.31 ± 0.01
	40	Height (mm)	1.13 ± 0.01
		Diameter (mm)	11.31 ± 0.01

The Sucr_1 formulation allowed the manufacture of cylindrical single-layer tablets at each selected force values. In addition, the powder blend showed good flowability and, consequently, the die filling from the shoe was constant.

The data reported in Table X showed that the increase of the compression force applied results in an increase of breaking strength, tensile strength and plastic energy of the tablets. The ejection energy was kept low at each compression force value, index of a good lubrication of the formulation despite the high component of fine particles of the sucralfate granulate.

Table X: compression parameters normalized by the weight of the tablets obtained with the Sucr_1 formulation (mean value ± standard deviation, n = 5)

Compression force measured (kN)	Breaking strength (N/g)	Tensile strength (MPa/g)	Ejection energy (J/g)	Plastic Energy (J/g)	Elastic energy (J/g)
10.30	242.6 ± 15.7	9.36 ± 0.6	3.01 ± 0.11	15.97 ± 0.22	0.566 ± 0.07
18.93	624.8 ± 43.6	28.14 ± 2.0	2.48 ± 0.03	29.16 ± 0.22	0.278 ± 0.02
27.96	744.5 ± 67.5	36.54 ± 3.2	2.08 ± 0.02	39.68 ± 0.43	0.345 ± 0.02
33.98	838.72 ± 134	41.89 ± 6.6	1.91 ± 0.04	44.67 ± 0.16	-0.55 ± 0.05

4.2.2 Cylindrical tablets monolayer of sucralfate Sucr_2

The composition of the formulation for the tablets monolayer Sucr_2 is reported in Table XI.

Table XI: Composition of the formulation Sucr_2

Components	mg	%
Sucralfate dry granulated	100	70.77
Water	20.3	14.37
Microcrystalline cellulose T2	10	7.08
Lactose	10	7.08
Magnesium stearate	1	0.71
Total	141.3	100.00

Before the addition of magnesium stearate, the sucralfate granulate was characterized in terms of size distribution. As can be noted from the histogram reported in Figure 19 the granules contain about 34 % of fine particles (<125 μm).

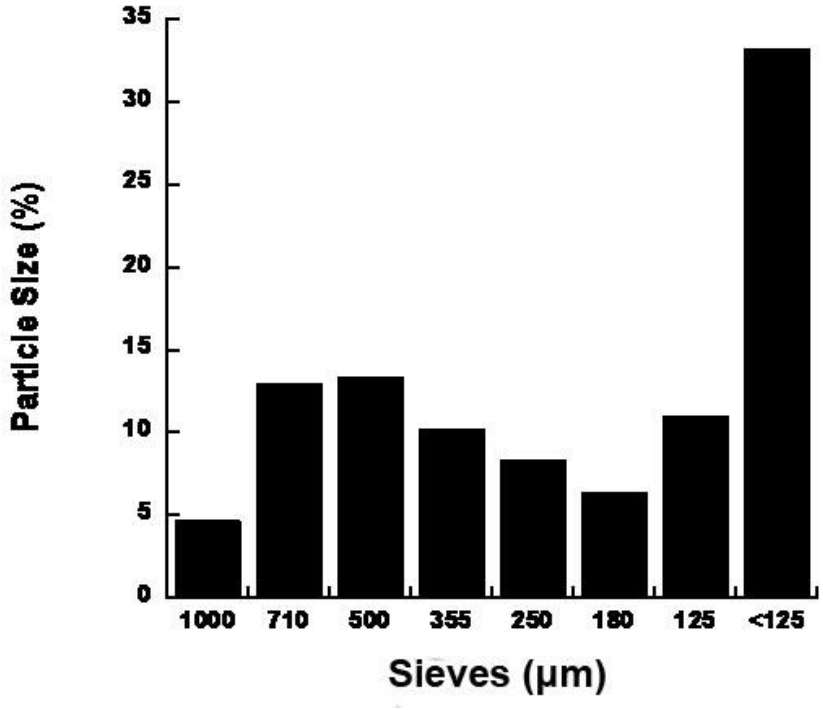

Figure 19: size distribution of the granulate of sucralfate Sucr_2

After the addition of sucralfate to granulate the excipients listed in Table VIII, the mixture was mixed in Turbula® and compressed by the compression simulator Styl'One Evolution. The tablets of Sucr_2 were characterized in terms of change in weight, diameter and height (Table XII).

Table XII: Average weight value, diameter and height of monolayers Sucr_2

(Mean ± st. dev., n = 5)

	Sucr_2		Mean value ± st. dev.
	Weight (mg)		187.2 ± 1.9
Compression force (kN)	10	Height (mm)	1.36 ± 0.02
		Diameter (mm)	11.32 ± 0.01
	20	Height (mm)	1.24 ± 0.01
		Diameter (mm)	11.31 ± 0.01
	30	Height (mm)	1 1.21 ± 0.01
		Diameter (mm)	11.30 ± 0.01
	40	Height (mm)	1.20 ± 0.02
		Diameter (mm)	11.30 ± 0.01

Table XIII: Compression parameters normalized by the weight of the tablets obtained with the Sucr_2 (mean value ± st. dev., n = 5).

Compression measured force (kN)	Breaking strength (N/g)	Tensile strength (MPa/g)	Ejection energy (J/g)	Plastic Energy (J/g)	Elastic energy (J/g)
10,54	343.66 ± 36.4	14.21 ± 1.3	2.32 ± 0.06	16.82 ± 0.12	-0373 ± 0.03
20,07	607.86 ± 61.1	27.72 ± 3.0	1.94 ± 0.05	26.44 ± 0.15	-0.689 ± 0.08
28,61	709.39 ± 38.1	33.18 ± 1.9	2.09 ± 0.04	29.70 ± 0.22	-1.101 ± 0.05
34,76	718.74 ± 53.5	33.80 ± 2.4	2.22 ± 0.07	30.71 ± 0.28	-1.443 ± 0.19

As noted in Sucr_1 formation, tensile strength, tensile strength and plastic energy of the tablets increases with the compression force applied.

From the comparison of the critical parameters of compression of monolayer tablets, obtained with the Sucr_1 and Sucr_2 formulations, it was observed a significant variation of the plastic energy values, normalized for the weight of the tablets (Figure 20).

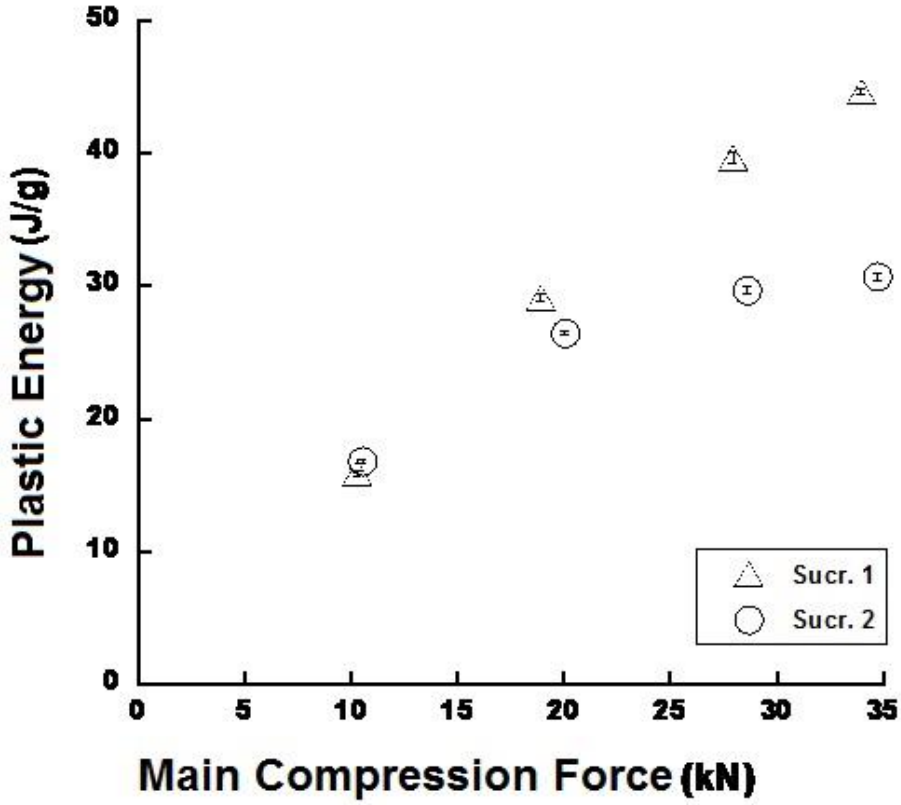

Figure 20: Plastic energy profile, normalized for the tablet weight, obtained for Sucr_1 and Sucr_2 formulations (mean ± standard deviation, n = 5)

This behavior can be attributed to the different plastic/elastic properties of the two formulations. In fact, microcrystalline cellulose (plastic material) present in the Sucr_1 formulation, and lactose (brittle material), mixed with microcrystalline cellulose in Sucr_2 formulation, show different behavior in the compression phase.

In the case of Sucr_1 tablets, the plastic energy linearly increased with the increase of the applied compression force, while in the case of Sucr_2 tablets the plastic energy reached a plateau at compression force value of 20 kN. This difference is also evidenced by the values of elastic energy, compared in Figure 21. Since the plastic energy given by the sum of energy applied to the tablet when the force increases (compression energy) and the energy recovered from the tablet when the force decreases (elastic energy), greater elastic energy

(in absolute terms) for Sucr_2 tablets, gives rise to a decrease of the plastic energy values for these tablets as the compression forces applied increases.

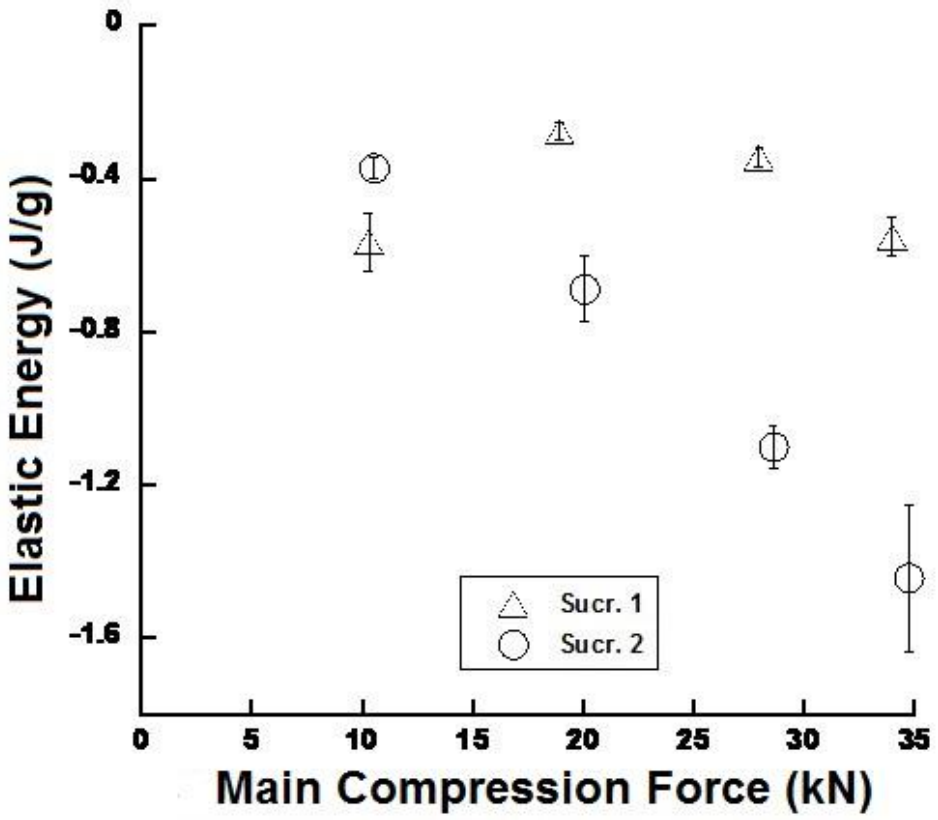

Figure 21: Elastic energy profile, normalized for the tablet weight, obtained for Sucr_1 and Sucr_2 formulations (mean ± standard deviation, n = 5).

4.2.2.1 Sucralfate monolayer disintegration test

In order to ensure that the layer of sucralfate complied with the specification of the Eur. Ph. regarding immediate release tablets, the disintegration test was performed on the cylindrical monolayer tablets of Sucr_1 and Sucr_2, manufactured at different compression forces.
In Table XIV the disintegration times (min) are summarised.

Table XIV: Disintegration times for each monolayer.

Compression Force (Kn)	Sucr_1 Disintegration Time (min)	Sucr_2 Disintegration Time (min)
10	1.10 ± 0.32	3.20 ± 0.21
20	1.03 ± 0.12	3.10 ± 0.27
30	1.10 ± 0.04	3.15 ± 0.12
40	1.20 ± 0.28	3.14 ± 0.32

The results show that clearly the formulation is suitable for an immediate release pharmaceutic dosage form. Each time is in fact inferior to the 5 minutes' limits that the Eu. Pharm. imposes.

It is also relevant to note how the compression forces do not play any role on the disintegration time. In fact, the driving force of the disintegration is the high hygroscopic tendencies of the Sucralfate itself.

4.2.3 Cylindrical monolayer tablets of ibuprofen lysine

The composition of the formulation for the tablets monolayer of ibuprofen lysine is reported in Table XV.

Table XV: Composition of the ibuprofen lysine formulation

Components	Mg
Ibuprofen lysine salt *	342
Kollidon CL	15
$NaHCO_3$	20
Microcrystalline cellulose	20
PVP K30	11.7
purple Lake	0.02
Aerosil 200	4
AcDiSol	16
Magnesium stearate	2
Total	431

* corresponding to 200 mg of ibuprofen lysine

Ibuprofen, because of unfavorable characteristics in compression (poor flowability and a tendency to packing) was wet granulated with PVP K30, microcrystalline cellulose (as diluent with good mechanical properties), $NaHCO_3$ and Kollidon CL (both with the purpose of enhancing the tablet disintegration). The ibuprofen lysine granulate was characterized in terms of size distribution. As can be noted from the histogram reported in Figure 22, the

granulate contains about 50% of particles having size in 355 and 250 μm range, while the fine fraction (<125 μm) was about 15 %.

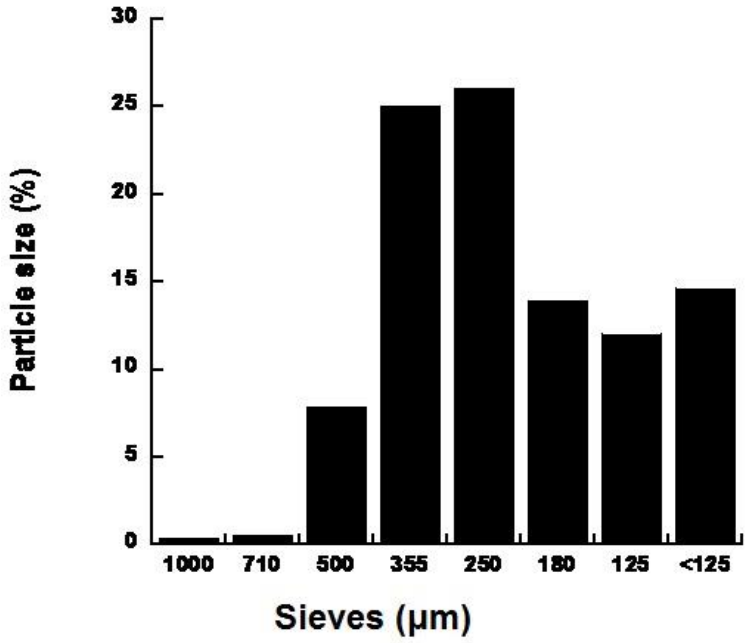

Figure 22: size distribution of the granules of ibuprofen lysine.

After the extra-granular addition of the other ingredients shown in Table XV, the mixture was compressed with the compression simulator Styl'One Evolution. The tablets of ibuprofen lysine were characterized in terms of change in weight, diameter and height (Table XVI).

Table XVI: Average weight value, diameter and height of ibuprofen monolayers (mean ± standard deviation, N = 5)

	Ibuprofen lysine monolayer		Mean value ± st. dev..
	Weight (mg)		432.3 ± 2.5
Compression force (kN)	10	Height (mm)	4.09 ± 0.03
		Diameter (mm)	11.33 ± 0.01
	20	Height (mm)	3.82 ± 0.02
		Diameter (mm)	11.32 ± 0.02
	30	Height (mm)	3.71 ± 0.02
		Diameter (mm)	11.31 ± 0.01
	40	Height (mm)	3.70 ± 0.02
		Diameter (mm)	11.32 ± 0.01

Table XVII: Compression parameters normalized by the weight of the tablets obtained with the ibuprofen lysine formulation (mean value ± standard deviation, n = 5)

Compression measured force (kN)	Breaking strength (N/g)	Tensile strength (MPa/g)	Ejection Energy (J/g)	Plastic Energy (J/g)	Elastic energy (J/g)
9.66	250.10 ± 9:53	3.44 ± 0.139	5.58 ± 0.107	14.97 ± 0.138	-0.436 ± 0.047
18.96	416.10 ± 27.90	6.14 ± 0.408	5.27 ± 0.05	23.22 ± 0.129	-1.140 ± 0.072
28.46	522.99 ± 19.47	7.93 ± 0.297	5.20 ± 0.01	28.34 ± 0.135	-2.310 ± 0.126
37.38	526.17 ± 32.27	8.00 ± 0.518	5.61 ± 0.140	31.48 ± 0.271	-4.062 ± 0.171

The tensile strength and tensile strength of tablets increased with increasing compression force applied. The tablets, manufactured at a compression force of about 20 kN, show a considerably higher resistance to rupture in those produced in about 10 kN; while in the compression strength values of 30 and 40 kN the difference in terms of resistance to breakage is reduced. This could be an indication of the attainment of the formulation of the compaction limit. The ejection energy is constant, regardless of the compression force value. It is noted, however, an increase, in absolute terms, of the elastic energy value with the increase of compression force, this suggests that the elastic deformation plays an important role in the ibuprofen formulation.

4.2.3.1 Ibuprofen lysine monolayer disintegration test

To ensure that the layer of Ibuprofen lysine will comply to the specification of the European Pharmacopoeia regarding the tablets for immediate release, the disintegration test was performed for each batch of cylindrical monolayer tablet of Ibuprofen lysine produced with different compression forces.

In Table XVIII the results, expressed in minutes, for the disintegration times.

Table XVIII: Disintegration times of the ibuprofen lysine monolayer.

Compression Force (kN)	Disintegration Time (min)
10	2.30 ± 0.21
20	3.40 ± 0.12
30	4.10 ± 0.50
40	4.14 ± 0.16

Even though the disintegration times are superior to the sucralfate layers, the results show that clearly the formulation is suitable for an immediate release pharmaceutic dosage form. There seems to be a correlation between the compression forces and the disintegration times. This is because the higher the compression force, the lower the tablet porosity is. Tablets of ibuprofen with a low porosity will not allow for an easy access of water inside the tablet itself, making the disintegration more difficult.

4.2.4 Cylindrical bilayer tablets of sucralfate/ibuprofen lysine

Two types of cylindrical tablets were manufactured bilayer:

- cylindrical bilayer tablets Sucr_1/Ibuprofen lysine
- cylindrical bilayer tablets Sucr_2/Ibuprofen lysine

4.2.4.1 Cylindrical bilayer tablets Sucr_1/Ibuprofen lysine

The cylindrical bilayer tablets were made of two different layers: the first layer was obtained with the Sucr_1 formulation, while the second layer contained ibuprofen lysine formulation. The characteristics of the bilayer tablets are reported in Table XIX.

Table XIX: Average weight value, diameter and height of Sucr_1/ibuprofen lysine bilayers tablets (mean value ± standard deviation, n = 5)

Mean compression force (kN)	Precompression (kN)	Weight (mg)	Height (mm)	Diameter (mm)	Bilayer obtained
9.5	0.06	514.2 ± 1.9	4.61	11.34	YES
	0.86	510.9 ± 2.3	4.57	11.34	YES
	1.92	512.1 ± 2.4	4.58	11.34	YES
	4.2	513 ± 1.4	4.60	11.34	YES
19.03	0.08	523 ± 1.7	4.21	11.32	YES
	1.13	517.8 ± 3.3	4,16	11.32	YES
	2.29	517.5 ± 1.8	4,16	11.32	YES
	4,19	-	-	-	Layer separation
28.4 9	0.07	520 ± 2.6	4.01	11.32	YES
	0.92	513.2 ± 2.2	3.95	11.32	YES
	1.82	510.3 ± 0.9	3.94	11.32	YES
	3.65	-	-	-	Layer separation
37.43	0.06	478.3 ± 2.5	3.59	11.31	YES
	0.84	509.4 ± 1.3	3.87	11.32	YES
	1.83	-	-	-	Layer separation
	3.98	-	-	-	Layer separation

At a compression force applied of 20 and 30 kN with a precompression of 4 kN the delamination of layers is observed, during the ejection phase of the bilayer tablet. In contrast, at 40 kN compression force the separation of the layers occurs even at the lowest value of precompression.

The separation of the bilayer tablets is probably due to the presence of microcrystalline cellulose (a plastic material). An increase of the force of precompression reduces the interfacial interactions between the adjacent layers. However, the bilayer tablets manufactured at low values of force of the precompression may give rise to cross-contamination between the layers.

4.2.4.2 Cylindrical bilayer tablets Sucr_2 / Ibuprofen lysine

As for the previous bilayer tablets, the cylindrical bilayer tablets were made of two different layers: the first layer was obtained with the Sucr_2 formulation, while the second layer contained ibuprofen lysine formulation. The characteristics of the bilayer tablets are reported in Table XX.

Table XX: Average weight value, diameter and height of Sucr_2/ibuprofen lysine bilayers tablets (mean value ± standard deviation, n = 5)

Compression force measured (kN)	Precompression force measured (kN)	Weight (mg)	Height (mm)	Diameter (mm)	Bilayer obtained
8.61	0.04	502.1 ± 8.2	4.50	11.35	YES
	0.89	513.7 ± 2.8	4.62	11.35	YES
	1.68	511.7 ± 4.0	4.62	11.36	YES
	3.04	502 ± 3.5	4.54	11.36	YES
17.99	0	508.9 ± 2.1	4.13	11.34	YES
	0.67	499.3 ± 4.2	4.05	11.33	YES
	1.53	497 ± 2.7	4.04	11.34	YES
	3.50	494.5 ± 2.9	4.01	11.33	YES
27.64	0	499.9 ± 1.2	3.93	11.32	YES
	0.80	492.7 ± 1.7	3.87	11.33	YES
	1.73	489.8 ± 3.2	3.85	11.33	YES
	3.63	485.4 ± 2.5	3.81	11.32	YES
36.52	0	492.3 ± 3.4	3.84	11.33	YES
	0.88	492.6 ± 0.93	3.84	11.31	YES
	1.59	491.1 ± 3.1	3.83	11.32	YES
	3.72	486.6 ± 1.1	3.80	11.30	YES

In the presence of lactose in the layer of sucralfate the phenomenon of separation of the layers has not been observed even with high values of precompression force. This is due to characteristics of the excipient (a brittle material), which tends to fragment into smaller particles creating a larger contact surface, it promotes adhesion between the adjacent layers.

The Sucr_2/ibuprofen lysine bilayer tablets have however shown a contamination between the two layers (being of a different color), also to high precompression forces, leading to an inaccurate weight control of the layers.

4.2.4.3 Comparison of the ejection energies of the sucralfate/ibuprofen lysine cylindrical bilayer tablets

As previously shown, the Sucr_1/Ibuprofen lysine cylindrical bilayer tablets exhibited lower layer adhesion at certain values of precompression and compression forces, but the ejection energy of these bilayer tablets didn't increase at greater applied compression force (Figure 23). The ejection energy value of Sucr_1 tablets remains constant (about 5 J/g). In the case of Sucr_2/Ibuprofen lysine cylindrical bilayer tablets the ejection energy linearly increased as the compression force applied was raised.

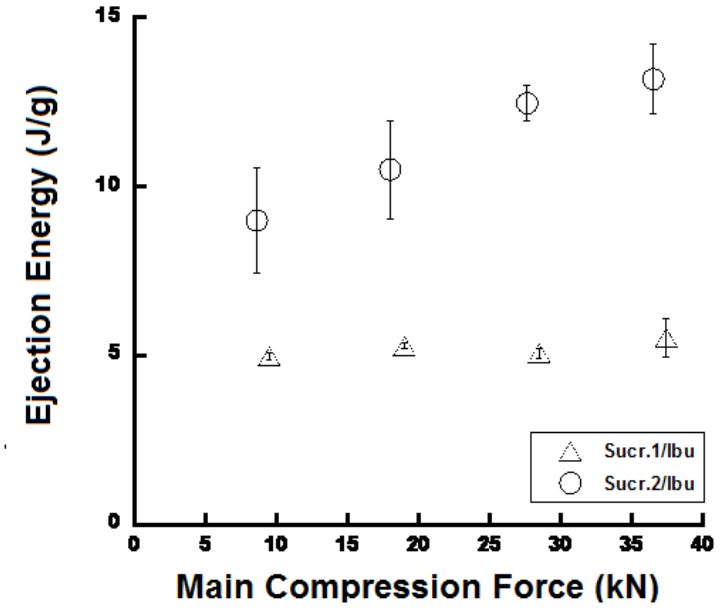

Figure 23: Ejection energy given to the bilayer tablets, normalized by the bilayer weight (△ Sucr_1, ○ Sucr_2; mean ± standard deviation, n = 5).

This behaviour was due to the fragmentation of lactose brittle material, present in the Sucr_2 formulation, which generated higher surface area free from lubricant increasing the friction coefficient.

4.2.4.3.1 Disintegration time the sucralfate/ibuprofen lysine cylindrical bilayer tablets

A disintegration test was performed on both bilayer tablets (Sucr_1/ibuprofen lysine and Sucr_2/ibuprofen lysine), to verify if the results are in agreement with those previously obtained for the monolayer. During the disintegration process, faster sucralfate layer disintegration was observed, followed by the disintegration of Ibuprofen lysine layer, although within the limit of 5 min.

4.2.5 Oblong bilayer

Because of the matrix dosage limit, it has not been possible to obtain tri tablets of sucralfate and ibuprofen lysine with the required dosages of APIs. For this reason, we used the oblong punches (17,50mmX8,50mm) and the relative matrix, to increase the volume of powder to compress.

Two types of bilayer tablets were manufactured:

- Oblong tablets bilayer Sucr_1/Ibuprofen lysine
- Oblong tablets bilayer Sucr_2/Ibuprofen lysine

4.2.5.1 Oblong bilayer tablets Sucr_1/Ibuprofen lysine

The oblong bilayer tablets were made of two different layers: the first layer was obtained with the Sucr_1 formulation, while the second layer contained ibuprofen lysine formulation. The characteristics of the bilayer tablets are reported in Table XXI.

Table XXI: Average weight value and height of Sucr_1/ibuprofen lysine oblong bilayers tablets (mean value ± standard deviation, n = 5)

* Not available

Compression force measured (kN)	Precompression force measured (kN)	Weight (mg)	Height (mm)	Bilayer obtained
10.22	0.02	658.06 ± 1.4	5.29	YES
	0.91	644.04 ± 1.3	5.20	YES
	1.92	642.5 ± 0.8	5.19	YES
	3.89	640.8 ± 3.1	5.17	YES
19.65	0.02	667.2 ± 1.2	5.00	YES
	0.95	652.1 ± 2.4	4.91	YES
	2.04	651.9 ± 2.1	4.90	Layer separation
	4,12	647.7 ± 2.2	4.87	Layer separation
28.97	0.03	672.6 ± 1.1	4.85	YES
	1.07	658.5 ± 1.7	4.75	YES
	2.07	651.9 ± 2.6	4.73	Layer separation
	4.22	648.5 ± 1.4	4.71	Layer separation
38.20	0.04	671.6 ± 1.2	4.73	YES
	1.13	657.8 ± 1.0	4.56	Layer separation
	n.a.*	650.3 ± 2.3	4.60	YES
	n.a.*	641.1 ± 0.9	4.56	Layer separation

As expected, the behavior of the Sucr_1 and ibuprofen lysine formulations during the compaction process of the oblong bilayer tablets was in agreement with that observed during the manufacturing of the cylindrical bilayer tablets.

4.2.5.2 Oblong bilayer Sucr_2/Ibuprofen lysine

The tablets are oblong bilayer consisting of two different layers; the first layer was obtained with the Sucr_2 formulation, and the second layer with the Ibuprofen lysine formulation. The characteristics of the bilayer tablets are reported in Table XXII.

Table XXII: Average weight value and height of Sucr_2/ibuprofen lysine oblong bilayers tablets (mean value ± standard deviation, n = 5))

Compression force measured (kN)	Precompression force measured (kN)	Weight (mg)	Height (mm)	Bilayer obtained
10.41	0.06	637.1 ± 3.4	5.13	YES
	0.89	620.8 ± 3.4	5.02	YES
	1.57	618.2 ± 3.2	4.99	YES
	2.89	613.3 ± 4.0	4.96	YES
19.68	0.03	640 ± 1.8	4.87	YES
	0.6	625.9 ± 3.2	4.77	YES
	1.17	622 ± 4.8	4.75	YES
	2.36	616.3 ± 2.5	4.71	YES
28.99	0.04	642.8 ± 3.6	4.72	YES
	0.52	627 ± 1.9	4.62	YES
	1.11	621 ± 2.8	4.60	YES
	2.24	612 ± 3.7	4.54	YES
38.10	0.03	639.6 ± 4.3	4.61	YES
	0.50	619.1 ± 4.9	4.50	YES
	0.94	609.4 ± 2.8	4.45	YES
	2.15	606.5 ± 2.4	4.43	YES

The change of punches had not effect on obtaining the bilayer tablets oblong, the behavior of the formulations and Sucr_2 Ibuprofen lysine during the compaction process, has not deviated from what was observed previously.

4.2.5.3 Comparison of the ejection energies of the sucralfate/ibuprofen lysine cylindrical bilayer tablets

As already observed for the cylindrical bilayer tablets, the Sucr_1/Ibuprofen lysine oblong bilayer tablets, unlike the Sucr_2/Ibuprofen lysine oblong bilayer tablets, showed lower layer adhesion at certain values of precompression and compression forces. The ejection energy of both Sucr_1/Ibuprofen lysine and Sucr_2/Ibuprofen lysine oblong bilayer tablets increases as the applied compression force was raised (Figure 24). As expected, the oblong bilayer tablets containing lactose in the sucralfate layer showed greater ejection energy values. However, in general the values of ejection energy for the oblong bilayer tablets remained lower than those observed for the cylindrical bilayer tablets. This was due to the fact that in the case of oblong tablets the precompression and compression forces were applied to a larger surface area and consequently the friction forces were more distributed reducing the ejection energy. This was object of further investigation in the research work carried out at the University of Bordeaux.

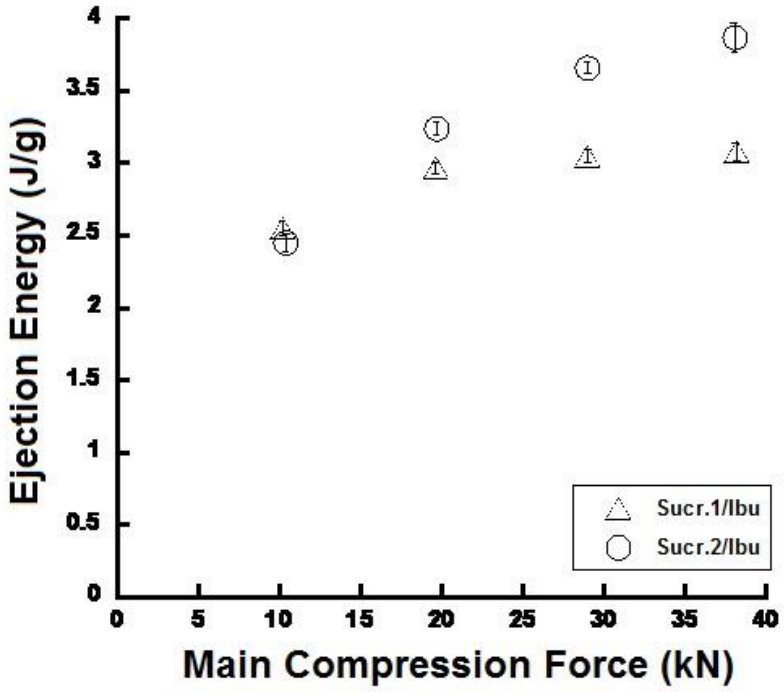

Figure 24: Ejection energy given to the oblong bilayer tablets, normalized by the bilayer weight (△ Sucr_1, ○ Sucr_2; mean ± standard deviation, n = 5).

4.2.6 Oblong three-layers tablets

Based on the results so far obtained with the manufacturing of bilayer tablets, the three layer oblong tablets were obtained starting from the Sucr_2 formulation for two sucralfate layers. produced. This choice has been motivated by the fact that all cylindrical and oblong bilayer tablets containing this sucralfate formulation did not exhibited layer separation phenomenon; moreover, for the oblong bilayer tablets layers the ejection energy values were not too high.

Then, the three-layer oblong tablets were manufactured by putting:

- first layer: Sucr_2 formulation
- second layer: Ibuprofen lysine formulation
- third layer: Sucr_2 formulation.

The characteristics of the three-layer tablets are summarised in Table XXV.

Table XXIII: Average weight value and height of Sucr_2/ibuprofen lysine/Sucr_2 oblong three-layers tablets (mean value ± standard deviation, n = 5)

Compression force measured (kN)	1st layer Precompression force measured (kN)	2nd layer Precompression force measured (kN)	Weight (mg)	Height (mm)	Three-layer obtained
9.58	0.02	0.02	845.6 ± 2.6	6:59	YES
	0.78	0.65	812.3 ± 4.1	6.35	YES
	1.63	1.40	801.0 ± 3.9	6:28	YES
	3.42	2.89	787.0 ± 4.2	6.22	YES
18.69	0.03	0.02	844.8 ± 4.7	6.08	YES
	0.67	0.62	803.6 ± 5.6	5.86	YES
	1.44	1.35	796.3 ± 5.6	5.82	YES
	3.32	2.80	780.0 ± 2.4	5.72	YES
27.78	0.02	0.02	838.2 ± 2.1	5.78	YES
	0.66	0.58	797.5 ± 3.2	5.55	YES
	1.49	1.27	790.2 ± 3.7	5.52	YES
	3.13	2.55	773.5 ± 3.5	5.42	YES
36.42	0.03	0.02	837.6 ± 1.5	5.58	YES
	0.62	0.83	827 ± 12.8	5.58	YES
	1.45	1.92	835.3 ± 5.6	5.65	YES
	2.95	3.98	826 ± 5.4	5.60	YES

The three-layer tablets produced using the formulation Sucr_2 did not give any separation of layers, confirming what has been observed for the tablets cylindrical and oblong bilayer.

Furthermore, a disintegration test has been performed on the three-layers tablets obtained. The test reported values coherent with the values previously obtained for each single layer, therefore we can state that the manufacturing of a multi-layer tablet does not affect the disintegration time of each single layer.

5 Conclusions

The three-layer tablets of sucralfate and ibuprofen lysine salt were produced using the compression simulator.

The formulations were first characterized by the manufacture of cylindrical tablets monolayer; followed by studying several reports about the compressibility of the formulations, defining some key parameters such as the breaking strength, the tensile strength and the energies involved in the compaction process. From the studies carried out it was observed that the addition of lactose in the formulation of sucralfate determines a reduction of the total plastic energy, due to an increase of elastic energy.

The next step involved the manufacture of cylindrical bilayer tablets, where it was evaluated the adhesion between the adjacent layers. The cylindrical bilayer tablets formed from the formulation Sucr_1 they encounter the phenomenon of separation of the layers during the step of expulsion of the compression process. This was not observed for cylindrical two-layer tablets comprise the Sucr_2 formulation containing lactose. It is therefore hypothesized that the presence of lactose in the formulation of sucralfate limits the separation of the layers, although causing a considerable increase in the energy of ejection.

For dosing issues, due to a limit imposed by the compression simulator, it has gone from EURO D cylindrical punches to oblong EURO D punches, which allow to load a matrix in the majority of powder volume. Bilayer tablets can be manufactured with the oblong tooling, and this confirms what has already been observed for cylindrical two-layer tablets.

The last part of the thesis project involved the manufacture of three-layer tablets, using the Sucr_2 formulation containing lactose. The three-layer tablets were made without following the separation of the layers.

Chapter II

1 Introduction

1.1 Problematics encountered during the production of multi-layer tablets of ibuprofen lysine and sucralfate

The development of the Ibuprofen-lysine/Sucralfate layered tablets is a complex procedure, which starts with the formulation of each single layers (that have to respect the desired drug release profiles) and end with the combination of the previously formulated layers in a single tablet. This final product must be prepared taking into account its physical and chemical stability, thus modifying certain procedure parameters that will exert a relevant effect on the multi-layer tablets critical mechanical properties, as shown in the first part of this thesis.

In fact, the currently used procedure to prepare multi-layer tablets is to subject the powder of the lower layer to a precompression (tamping) pressure and then, once the powder of the second layer is distributed above the precompressed first layer, to apply a main compression pressure [31]. The precompression step is critical: a high precompression force reduces the possibilities of cross-contamination between the layers, but also decreases the roughness of the interfacial surface, diminishing the contact surface between the layers, thus enhancing the probability of a delamination [32].

It is also critical to consider the difference in mechanical properties under compression between the different powders. Plasticity and brittleness, but also size and shape of the particles can interfere with the interfacial adhesion. This parameters are all studied extensively in the current pharmaceutical literature [23].

The main problem that occurs during the manufacturing of the bilayer tablet is delamination [24]. It corresponds to the splitting of the tablet at the interface between the layers. This

separation between the layers may take place just after compaction or later during the storage. Some explanation of the delamination phenomena can be found in the literature, and this phenomenon is related to different parameters such for example the elastic recovery of the two layers or the roughness of the interface. It was also shown that the process parameters can influence the interfacial strength. For example, to ensure a good cohesion, the pressure applied to the first layer should be kept to a minimum, and the pressure applied on the second layer should be high enough.

1.1.1 Testing the interfacial strength of a multi-layer tablet

During the first part of this thesis, a qualitative approach to the subject was taken, by simply registering whether or not the tablet was delaminated after the compression cycle. But no real information was given on the actual strength of the formed interface. This should be of interest, given the fact that several compression parameters where changed, along with excipients and shape of the punches, during the manufacturing of the different batches.

Due to the importance of the adhesion at the interface between layers, it is critical to perform a relevant and robust method to quantify its strength. This is also a matter that is becoming of more interest as with the development of Quality by Design (QbD) for the manufacturing of a bilayer tablet. Product and processing understanding is a key element to QbD. As such, it is clear that the control of each single step and the quantification of each single parameter should be as accurate as possible [20].

When applying the QbD methodology to the design of a bilayer tablet, the accurate quantification of the mechanical resistance of interface between the two layers is necessary to correctly assess the quality attributes of the final product.

Unfortunately, as currently stated by the European Pharmacopoeia (ver. 8), there is no standard methodology to measure the interfacial strength of bilayer tablet. The only

methodology that is described in the European pharmacopeia to test the strength of tablet is the diametral compression test but in the corresponding monograph, there is no reference of its use in the case of bilayer tablets. Nevertheless, several articles in literature can be found that perform the diametral compression test to characterize the interfacial strength of a bilayer tablet (and therefore the final robustness of the tablet itself).

On the other hand, other testing methodology are acknowledged, such as the relatively new indentation test [33]. This test proved, with a pharmaceutical quality by design approach, to be suitable for the measurement of the interfacial adhesion of bilayer tablets. Another test that is currently under investigation is the shear test [34]. This fixture is described carefully in the material and methods of this publication. Lastly, it is possible to measure the interfacial strength via traction testing [17]. This testing is operatively complicated to execute, because the examined bilayer tablets must be individually glued to two tablet holders using a fast-acting glue and left, for example, for an hour to ensure a good adhesion. It must be also ensured that no glue migrate through the pores up to the interface of the examined bilayer tablets.

1.1.2 Testing the influence of the shape of the interface on the strength of a multi-layer tablet

The study of the compaction of pharmaceutical powder in multi-layer tablets is often performed on flat faced tablets due to the difficulty in precisely measure the compression parameters (stresses applied and punch displacement) when using complex shaped punches. Unfortunately, the results obtained using flat punches cannot always be generalized to the cases of more complex punch shapes [35]. This is in contrast with the industrial tendency to use convex shaped punches when preparing both single layer and multi–layer tablets. This is not only because a convex shape is more commercially

appealing, but also because of technical reasons. For example, convex tablets tend to be less fragile and it is easier to perform a coating on a convex tablets, because this shape prevent the adhesion between tablets during the coating procedure [36].

Previous studies performed on tablets with convex shape for both experimental and showed that the results obtained for convex shape, i.e., the density and stress distributions, are different from the ones obtained on flat faced tablets [35]. A recent publication [37] underlined that, in the case of convex tablets, the density distribution was also influenced by the thickness of the compact. These results show that, even if they are obtained under the same compression load, tablets obtained using different punch curvatures are difficult to compare and may have different mechanical properties.

In the case of bi-layer tablets the shape could thus play an important role in the adhesion between the layers. Nevertheless there is, to our knowledge, only one study about the effect of the punch curvature on the interfacial strength of bilayer tablet [38]. In the cited study, the comparison was performed between bilayer tablets manufactured with two different sets of tooling: 12.77 mm diameter round flat faced B type tooling, and 20.47 mm 10.90 mm capsule shaped D type tooling. The authors compare the interfacial strength of bilayer tablets obtained with these two sets under the same compression force. Unfortunately, these two punch sets have a very different projected surface area. The tablets obtained can thus be hardly compared and the results showed in this paper should be taken with caution.

Considering the existing literature on convex tablets, two main differences are expected between bilayer tablets made with flat or concave punches. The first one is the possibility of having a curved interface, the curvature being linked with the respective values of the precompression and main compression pressure. The second one is the fact the concave punches give a more heterogeneous stress distribution at the interface. These two aspects could have an influence of the interfacial strength of the tablet, and this is the focus of the present study.

This work aims to compare the interfacial strength of convex and flat-faced bilayer tablets. For this purpose, several batches of tablets were produced, flat-faced, biconvex but also tablets obtained with one flat punch and one concave punch. The non-symmetric configuration was used to try to separate the effects due to the curvature of the interface and those due to the stress distribution. The interfacial strength was tested using a previously presented indentation test [39]. The obtained results were submitted to a statistical analysis.

2 Purpose

To try to clarify the testing conditions, we chose in this work to use three different tests to study the interfacial strength of a model formulation: diametral compression, shear test and indentation test. These three tests were chosen because they are easy to perform, applicable to various compacts shape and they don't necessitate specific sample preparation. As such, they could be chosen as a standard test at an industrial level. The aim was to study if these three tests were indeed able to discriminate tablets with different interfacial strength or if they should be avoided for the characterization of the interfacial strength of bilayer tablets, and this will be the focus of the first part of discussion of this work. Then, after resolving the necessity of validating a testing method, the matter of the influence of the shape on the strength of the tablet will be addressed. When considering the existing literature on convex tablets, two main differences are expected between bilayer tablets made with flat or concave punches. The first one is the possibility of having a curved interface, the curvature being linked with the respective values of the precompression and main compression pressure. The second one is the fact the concave punches give a more heterogeneous stress distribution at the interface. These two aspects could have an influence of the interfacial strength of the tablet, and this is the focus of the present study.
This work aims to compare the interfacial strength of convex and flat-faced bilayer tablets.

Finally, after assessing both the testing methodology and the shape of the influence, a final investigation on the strength of the bilayer tablet made of Ibuprofen Lysine/Sucralfate will be performed. This will lead to a Design of Experiment where the water content of the sucralfate, the bilayer production parameters and the storage conditions will be considered as factors. The expected responses include a quantitative measure of the interfacial strength.

3 Comparison of breaking tests

In this study, several tests were compared in order to understand if there is a proper way of testing a multilayer tablet.

3.1 Materials and Methods

3.1.1 List of excipients

- Microcrystalline cellulose (Vivapur 12, JRS PHARMA GmbH & Co, Rosemberg, Germany)
- Lactose (Flowlac 90, Meggle, Wasserburg, Germany)
- Magnesium Stearate (ACEF, Fiorenzuola d'Arda, Piacenza, Italy)

3.1.2 Manufacturing of tablets

As studied in previous works, and as explain above, the main process parameters that have an influence on the strength of a bilayer tablets are the applied force on the first layer and the main compaction force. Then, in order to compare the ability of each test to discriminate the robustness of a bilayer tablet, tablets with different mechanical strengths at their interface were produced by playing with these 2 process parameters.

The compaction experiments were performed using a Styl'One Evolution compaction simulator (Medelpharm, Lyon, France). This device is a single punch tableting press, monitored by Analis software. The displacement of the upper and lower punches is controlled electronically.

The pressure applied by the punches to the powder bed is measured with strain gauges. The machine can be also controlled with a given pressure to be reached. For all the

experiments, the tablets were produced using standard Euro D round and flat punches with a diameter of 11.28 mm.

Bilayer tablets were manufactured using a model formulation: microcrystalline cellulose for the first layer, and spray-dried lactose as second layer, adding 1% of magnesium stearate to both powders as a lubricant. The filling height for the layers was adjusted to obtain a total height of about 10 mm before compaction for the layer of microcrystalline cellulose, and 8 mm for the layer of lactose. The filling height will remain constant for every tablet produced. These filling highs were chosen to obtain bilayer tablet in which both layers have approximately the same thickness.

In order to have tablets with different interfacial strengths, tablets were produced in two different batches: varying the applied main compaction force but keeping the tamping force applied on the first layer constant (Batch 1), and keeping the main compaction force constant but modifying the tamping force (Batch 2) (Table XXIV).

Table XXIV: Parameters (Tamping and Main Compaction Pressures) of the batches of tablets produced

Batch 1	
Tamping pressure (MPa)	Main Compaction Pressure (MPa)
10	100
10	150
10	200
10	300
10	400

Batch 2	
Tamping pressure (MPa)	Main Compaction Pressure (MPa)
10	300
25	300
40	300

According to the literature, in the first batch, the adhesion between the layers should increase with the maximum compaction force. For the second batch, the adhesion should decrease with increasing tamping force.

3.1.3 Tablets testing

As already discussed, different tablet breaking tests and mechanisms were taken into account. Those are the Diametrical breaking test, the indentation test and the shear test (Fig. 26).

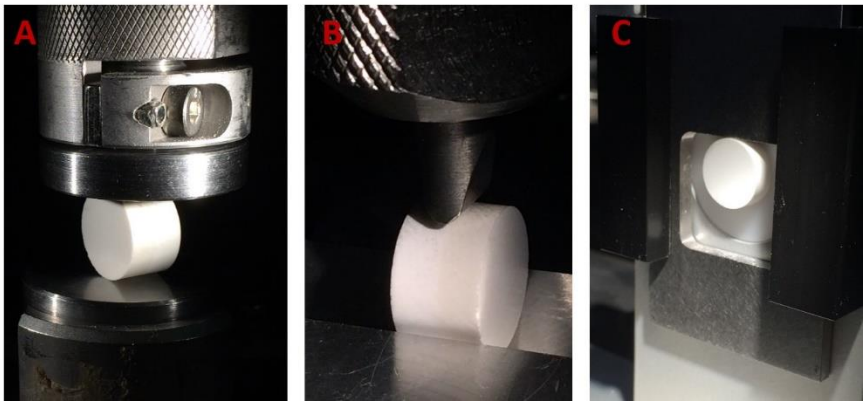

Figure 26: A, diametrical test; B, indentation test; C, shear test.

3.1.3.1 Diametrical Breaking Test applied to bilayer compacts:

For this test, a Micropress (Cegitab, Lyon, France) tester was used. The tablet is placed here vertically between two anvils (Fig. 26A). The instrument can apply a displacement of the upper anvil at a constant rate (0.05 mm/min) the upper punch, thus squeezing the tablet. The load is measured using a force transducer with a resolution of 0.01 N. The measured force for each value of displacement applied is recorded, with a frequency of 10 Hz. This apparatus allows to obtain a Force/Displacement curve.

3.1.3.2 Indentation Test

An adapted version of the previously illustrated Micropress (Cegitab, Lyon, France) was used. The bilayer tablets were put on a V-support with an opening angle of 90° and a depth of 6 mm (Fig. 26B). The samples were then stressed with a punch designed for the experiment. The punch tip is a half cylinder shape with a diameter of 2.80 mm and a width of 6 mm. The system is designed to apply a stress, through the very tip of the punch, exactly at the interface between the layers. The breaking force corresponds to the breaking force

needed to separate the two layers of the tablet. This force is determined at the maximum of the force-displacement curves obtained during the test.

3.1.3.3 Shear Test

For this test, a TA HD Plus apparatus (Stable Micro System, Surrey, UK) was used. The tablet is inserted into a fixture cavity so that the tablet layers lie in the plane of a “guillotine-like” blade (Fig. 26C). A layer of the bilayer tablets must fit perfectly inside the cavity, holding the tablet in position for the test, while the other layer is completely outside of the fixed cavity. The blade then applies an increasing stress on the layer of the tablet outside of the system until the two layers are sheared apart. This system allows to control of the speed of the blade. To be in a quasi-static condition, the minimum possible speed allowed by the machine is used, 0.01 mm/sec.

3.1.4 Numerical Simulation

Finite Element Method (FEM) simulation was performed using Abaqus 6.13 software (Dassault Systems). Linear elastic model was used to understand the mechanical behaviour of the tablets. The elastic properties of both microcrystalline cellulose and lactose were already characterised by using experimental test [30] and their respective values were used in this simulation. The metal tools (Avils, V-support and punch) were considered with the elastic properties of steel.

3.2 Results and Discussion

3.2.1 Observation of the fracture mechanisms during the different tests

3.2.1.1 Diametrical Breaking Test

When a tablet is broken via diametrical test, a curve displacement/force is obtained, as shown in Fig. 27.

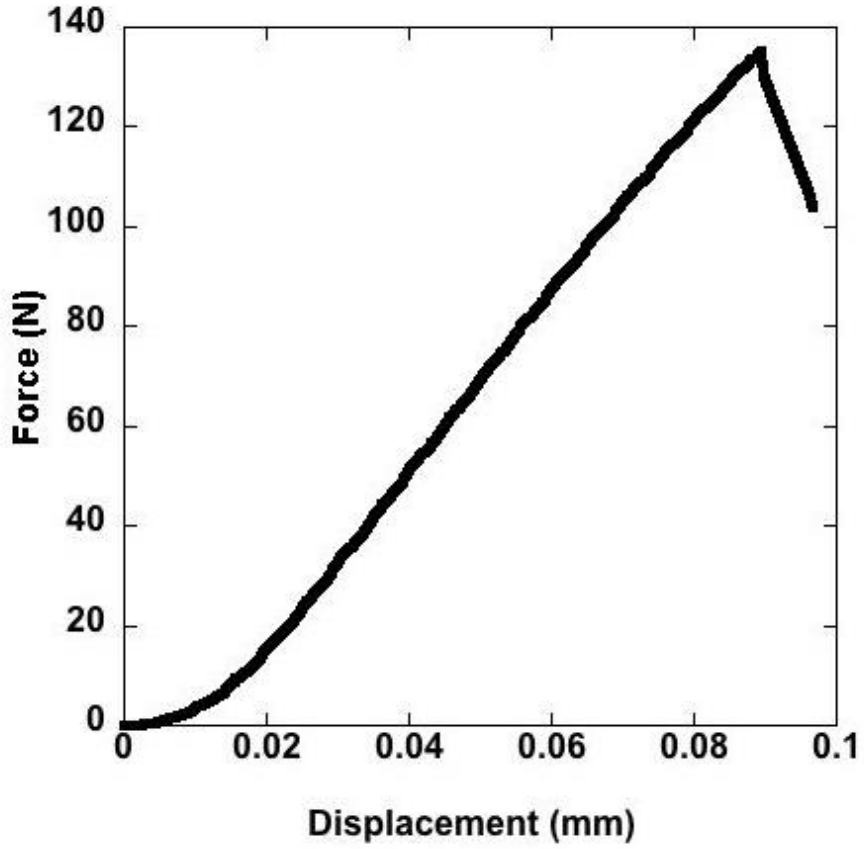

Figure 27*: Example of force recorded vs Displacement applied by the diametrical test*

As showed, the force increased with increasing displacement of the upper punch, until it reached the breaking point. After said breaking point, the value did not drop immediately to the zero value, because the tablet was not totally broken and still hold in place. At the end of the test, the tablet did not show any macroscopic sign of delamination.

To understand what phenomenon caused the force drop, a batch of tablets was produced with a tamping force of 10 MPa and a main compression force of 100 MPa. This time, the test was stopped immediately after the drop and the tablets were carefully examined. The first observation was that the interface was still cohesive, i.e. no delamination had taken place. After the MicroPress testing, a further exam of the tablets was conducted by Scanning Electron Microscopy. The results are shown in Figure 28. The tablets showed no clear difference at the interface between the 2 layers, before (Fig. 28A) and after (Fig. 28B) the tablet testing, with no sign of fracture or breaking. However, it is possible to see that a breaking occurred at the level of lactose layer (Fig. 28B), starting from the interface. In fact, when examining each layer via SEM, it was clear that the layer of lactose is clearly broken, with a fracture that propagates though this layer. At the same time, the layer of microcrystalline cellulose appeared almost unbroken. Fig. 28C and Fig. 28D point out the difference between the lactose layer before and after the test.

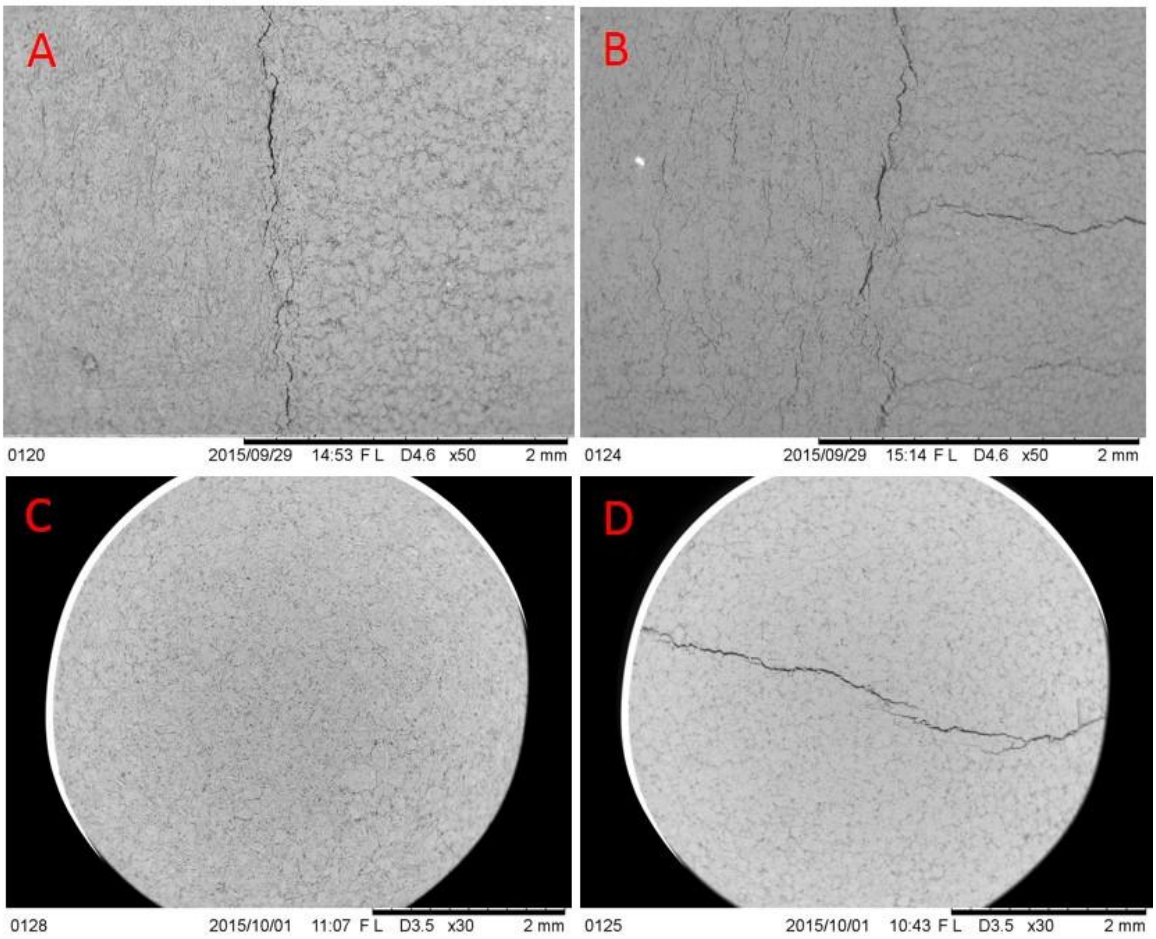

Figure 28: SEM images of bilayer tablets tested with the diametrical test. A: interface before testing; B: interface after testing, C: lactose layer before testing. D: lactose layer after testing

With this fundamental observation, it was clear that the force drop during this test was not due to the delamination of the tablet but to the failure of one of the layer.

To further understand what happened during this test, the numerical simulation of the test was performed. The material properties of both lactose and microcrystalline cellulose tablets (obtained with a compression pressure of 100MPa) were used. The results of the simulation are shown in Fig 29. The tablet at the left shows the stress distribution in lactose layer and at the right is shown the stress distribution in microcrystalline cellulose layer. Some areas of the tablet were in compression and in order to better represent the tensile stress (which causes the crack of one layer during this test) the scale was modified and plotted between

-5 and 6 MPa. The numerical results, reported in Fig. 29, showed that the stress was different in the two layers of the tablet. Mainly, the stress was higher in the lactose layer than in the microcrystalline cellulose layer which means that during this test we solicited more one layer rather than the other one, depending on their respective mechanical properties. This explains why only one layer failed during the test, while the other one stays intact.

Thus, all these results show that this test would not be well suited to test the interfacial strength of bilayer tablets.

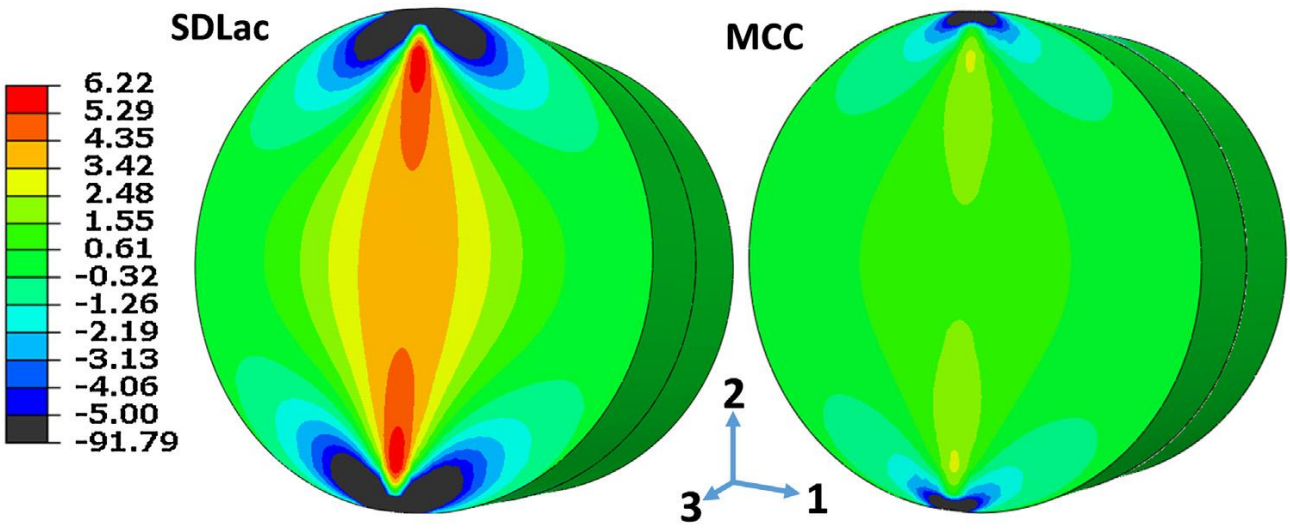

Figure 29: Stress (σ_{11}) distribution inside bilayer tablet.

3.2.1.2 Shear test

In this test one layer of the tablet is fixed inside an ad-hoc adjusted cavity, while the other layer is exposed to the blade. The blade then cuts through the bilayer tablet at the interface. Therefore, a curve force (registered on the blade) versus displacement (of the blade itself) is recorded (Figure 30). The maximum value of the curve corresponds to the breaking point:

at this value the layers are completely separated. Then, there is no more resistance applied by the tablet and the force recorded drops immediately to the zero value.

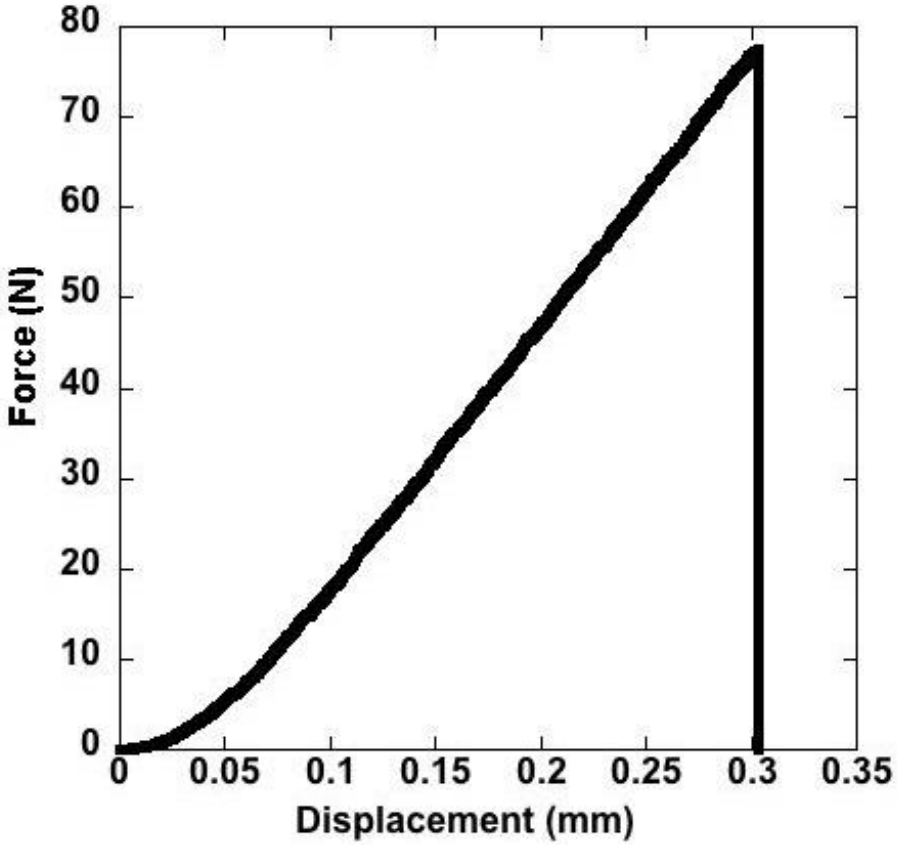

Figure 30: Force recorded vs Displacement applied by the shear test

3.2.1.3 Influence of the dimensional properties of the tablet

In order to ensure that the resulting shear force has no correlation with the thickness of the layers and is thus characteristic of the interfacial strength, specific batches of tablet were prepared. For these batches; the tamping force and the main compression force were kept constant (10 MPa of tamping pressure and 300 MPa of main compression); varying only the dosage height of the powder before the tableting cycle. In this way, it is expected that the final height of each layer will be different. The batches produced are shown in Table XXV.

Table XXV: Height of the layers for each tested batch

	Microcrystalline celliulose layer height (mm)	Lactose layer height (mm)
Batch A	4	3.8
Batch B	3.3	3
Batch C	2.5	2.3

The batches were then analyzed. The speed of the shear test was kept constant at 0.01 mm/sec. For each batch, 10 tablets are produced and tested. The results are shown in Table XVII.

Table XXVII: Shear “breaking” forces measured for the different batches tested (n=5)

	Shear Breaking Force (N)	
	Mean	St. Dev.
Batch A	109.38	6.31
Batch B	112.30	7.49
Batch C	111.79	7.92

A bilateral t-test was performed on the obtained results to confirm that there is no statistical difference. As expected, the test proved that there is no significant difference ($\sigma>95$) between the values of the measured shear forces. The shear test is then an accurate measure of the strength of the interface and it is not influenced by the dimensional (thickness) properties of the tablets.

3.2.2 Indentation test

As the indentor applies displacement right at the interface of the bilayer tablet, a curve force versus displacement is obtained (Fig 31). This curve, no matter the bilayer tablet tested, is characterized by three different parts:

1. Portion of the curve before the first relative maximum (1)
2. First relative maximum point (2)
3. Second relative maximum (3)

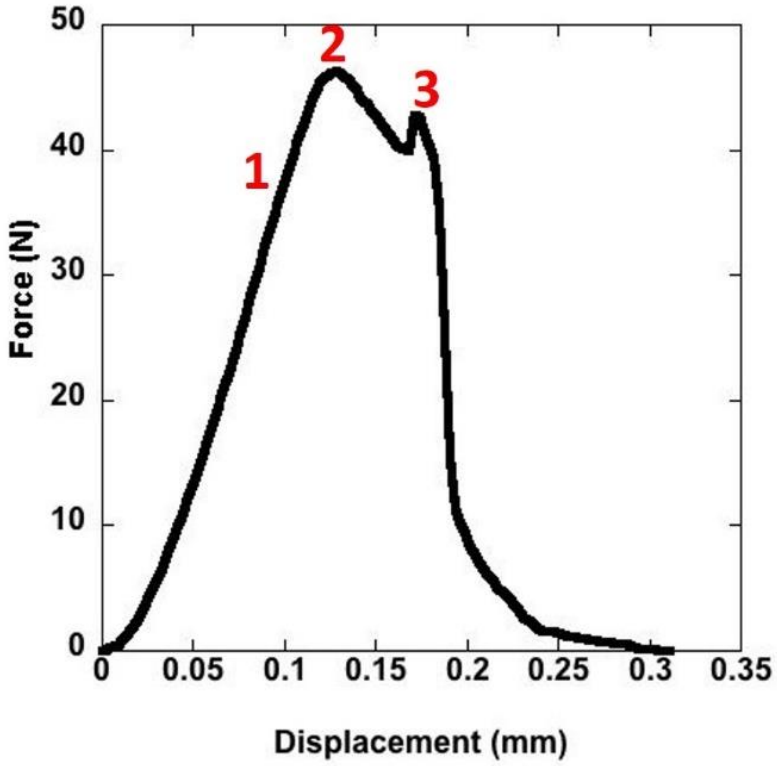

Figure 31: *Force recorded vs Displacement applied by the indentation test. 1: portion before the first relative maximum, 2: first relative maximum value; 3: second relative maximum value*

The curve exhibits two clear maximum points. To understand the difference on the structure of the tablet between these two points, three batches of tablets were analyzed via SEM. For

the first batch, the indentation test was stopped immediately before reaching the first maximum point (2). For the second batch the test was run immediately after the first maximum point and the third batch undergo until after the second maximum point (3). The SEM picture are shown in Figure 32. Pictures were taken along the crowned of the tablets, both at the indentation mark and at 90° respect of the indentation mark to evaluate the crack propagation.

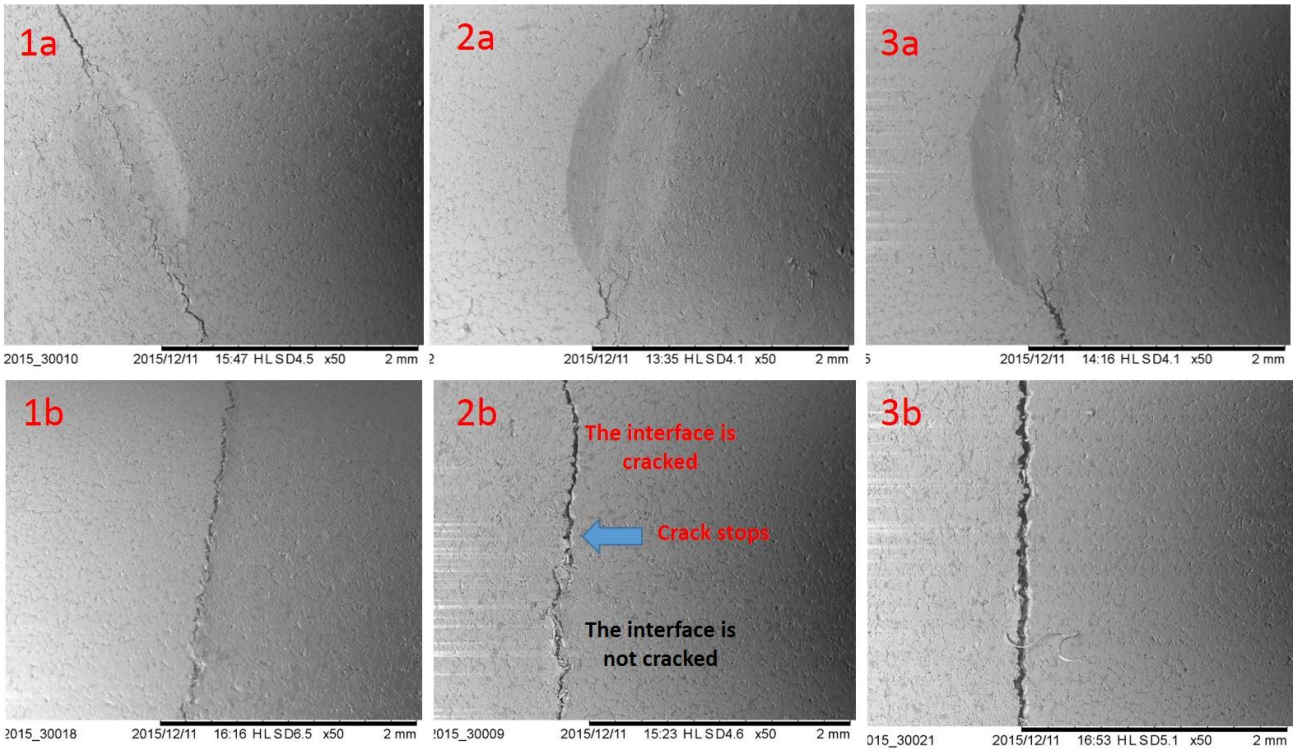

Figure 32*: SEM images of bilayer tablets tested with the indentation test. 1a: indentation mark before the first maximum point; 2a: indentation mark after the first maximum point; 3a: indentation mark at the second maximum point. 1b: interface before the first maximum point; 2b: interface cracked after the first maximum point; 3a: interface cracked after the second maximum point*

As it is possible to observe, before the first maximum point the interface appeared to be intact (1b), except for the mark that the indentor left on the surface corresponding to a local

plastic deformation (1a). After the first maximum point, it is possible to observe that there is a crack at the interface (2b), although it does not propagate on the whole surface. The mark left by the indentor is clear at this point (2a). After the second maximum point it is possible to observe both the propagation of the crack at the edges of the indentation mark (3a) and the complete breaking of the interface of the bilayer tablet (3b). Thus, the indentation test starts cracking the interface at the maximum point (2). The cracking thus propagates on the whole interface until point (3) were the tablet is finally delaminated. Therefore, the value of the first maximum is clearly characteristic of the crack formation at the interface and thus of the interfacial strength.

3.2.2.1 Numerical Simulation of indentation test

To illustrate this progress of the crack, the numerical simulation of indentation test was carried out by using Abaqus® software. The adhesion between the two layers was simulated by defining a surface-based cohesive behaviour implemented in Abaqus/Standard. This cohesive interaction between the layers was used in conjunction with a crack criterion to assess the start of the crack and its progress when the applied force increases. A variable which indicates the crack initiation was added. The possible values of this variable are between 0 and 1 and when the crack criteria are reached this variable takes the value 1. The results of the simulation are presented in Fig. 33. Fig. 33A and 33D show the beginning and the end of the test respectively and Fig. 33B and 33C the intermediate states of the test. It can be seen that at the beginning of the test, the interface remains intact. As the applied force increases, the crack starts near the applying point of the force and progresses toward the bottom of the tablet. These findings are coherent with the experimental results.

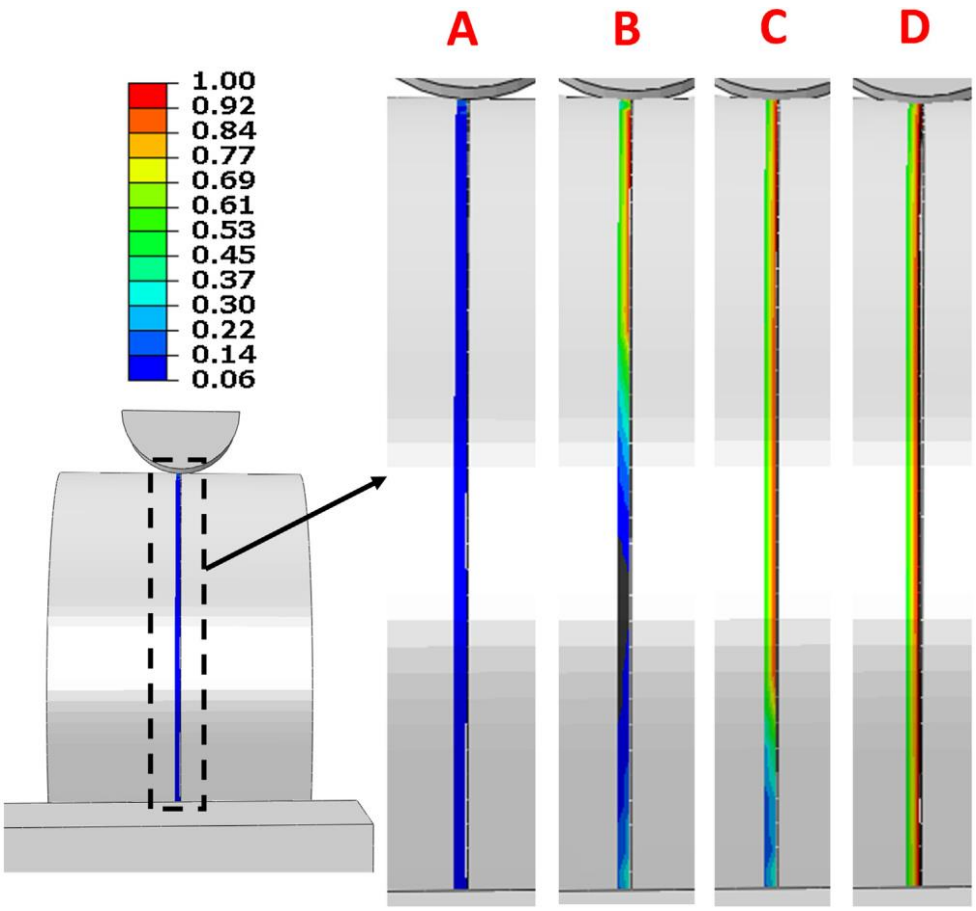

Figure. 33: *Crack start and its growth (A–D) at the interface of bilayer tablet during the indentation test*

3.2.3 Experimental results for batches 1 and 2.

As stated above, to check the ability of the different tests to characterize the interfacial strength of the tablets, two batches of tablets were produced. The results for batch 1 are presented in Fig. 34.

As stated in the literature, it is expected that the interfacial strength should increase with increasing compaction force. For each test an increase of the measured force was indeed observed. Nevertheless, for indentation and shear test, the force seemed to reach a plateau for main compression values higher than 20kN. This trend was not observed for the diametral compression.

The results for batch 2 are presented in Figure. 35. For this batch, the interfacial strength should decrease when increasing the tamping force on the first layer. The shear test and the indentation test measured, as expected, values of breaking force that decreased with increasing tamping force. On the contrary, the diametrical testing apparatus, did not show any significant differences when the different batches of tablets compressed with varying tamping are compared. For this latest test, the breaking force was clearly independent of the tamping force.

The two previous results can be easily explained by considering the fracture mechanisms described above. The diametral compression in fact measures, in this case, the cohesion of the lactose layer and not the interfacial strength. This cohesion, increases with increasing main compression and there is no reason to obtain a plateau in Fig. 34. Moreover, the tamping force has no influence on the cohesion of the lactose layer because the cohesion is driven by the main compaction force. As a consequence, for batch 2, as the main compression is kept constant, the measured failure force is also constant, whatever the applied tamping force might be. These results prove that, in this case, the diametral compression does not measure the interfacial strength of the bilayer compact. Thus, this test cannot be taken as a reference test for the measure of the interface hardness of bilayer tablets.

On the contrary, both indentation and shear tests gave results that were expected (Fig. 35), according to the literature. The measured value is a true characterization of the interfacial strength of the compact. In conclusion, both tests could be proposed as standard test for the characterization of the interfacial strength of bilayer tablets instead of using diametral compression test.

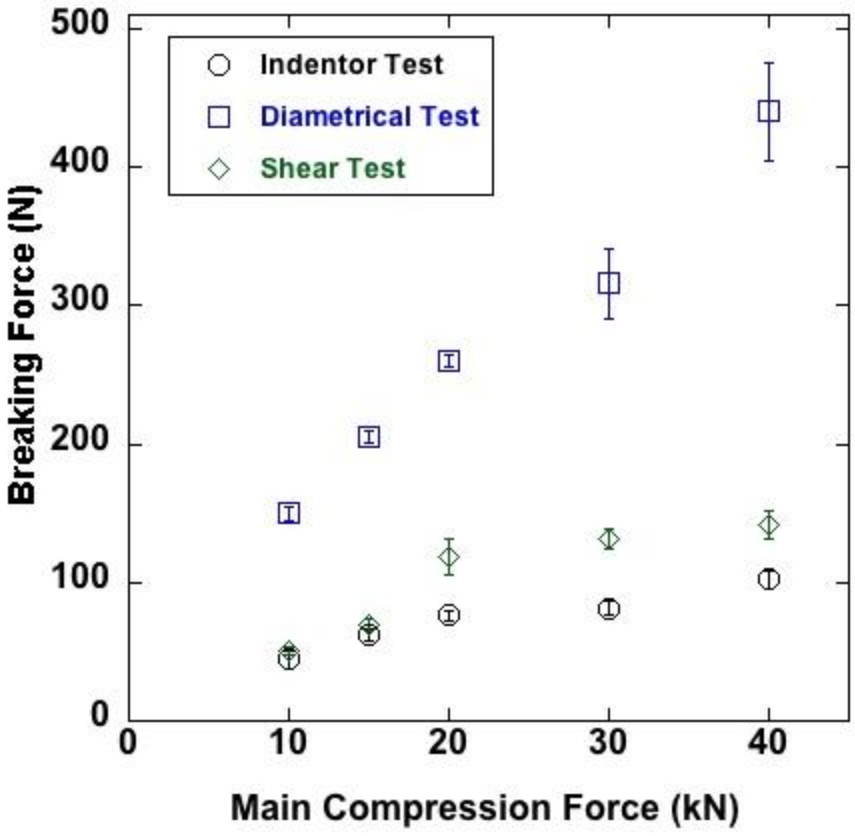

Figure.34: *Breaking Force for different tests (n=20) versus Main Compaction Force*

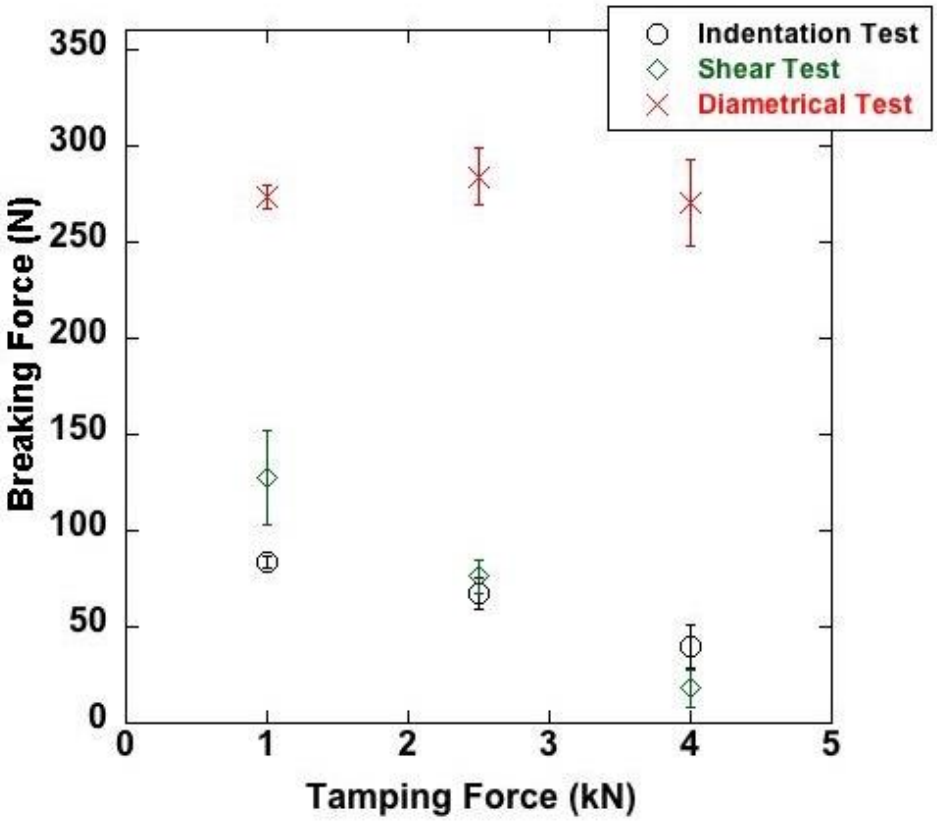

Figure.35: *Breaking Force for different tests (n=10) versus the tamping force.*

3.3 Conclusions

In this study, three different tests were used for the characterization of the interfacial strength of bilayer on a model formulation. The diametrical test proved to be not suitable for testing the robustness of the interface of bilayer tablets. This test is not able to discriminate between bilayer tablets with different interfacial strength because it just tested the cohesion of one of the layers. An implementation of a diametrical test in a design space that aims to obtain an optimized multilayer tablet will lead to an erroneous selection of further parameters in a QbD procedure. On the contrary, indentation and shear test were able to discriminate tablets with different interfacial strength. Such tests could be chosen as standard tests for the characterization of the interfacial strength of bilayer tablets.

4 Effect of the shape on the interfacial strength

As already described, in this session tablets with different interfacial shapes are produced and tested.

4.1.1 Materials and methods

4.1.1.1 List of excipients

- Calcium phosphate (DCP, ACEF, Fiorenzuola d'Arda, Piancenza, Italy)
- Microcrystalline cellulose (MCCVivapur 12, JRS PHARMA GmbH & Co, Rosemberg, Germany)
- Lactose (Lac, Flowlac 90, (Meggle, Wasserburg, Germany)
- Magnesium stearate (ACEF, Fiorenzuola d'Arda, Piancenza, Italy)

4.1.1.2 Tablet production

Three classical excipients were used: microcrystalline cellulose, calcium phosphate dihydrate and spray-dried lactose. Each powder was lubricated adding 1% of Magnesium stearate. The blending was performed at 50 rpm for 5 min using a Turbula mixer (Type T2C, Willy A Bachofen, Muttenz, Switzerland). Two different bilayer systems were produced: MCC/DCP (MCC first layer, DCP second layer) and MCC/Lac (MCC first layer and Lac second layer).

In order to produce tablets with different interfacial shapes, 4 different punches were used: flat-faced and concave faced with three radii of curvature (6, 8 and 11 mm). All the punches were round Euro B with a diameter of 8mm. Four different punch configurations were used: upper flat/bottom flat (UF/BF), upper flat/bottom curved (UF/BC), upper curved /bottom flat (UC/BF) and upper curved/bottom curved (UC/BC). For each configuration with curved punches, the three radius of curvature were used. For the UC/BC configuration, both

punches had the same curvature. Table XXVII summarizes the different punch configurations used.

Table XXVII: Punch configurations of bilayer tablets produced.

Configuration	radius of curvature	
	upper punch	lower punch
UF/BF	flat	flat
UC/BF	11	flat
	8	flat
	6	flat
UF/BC	flat	11
	flat	8
	flat	6
UC/BC	11	11
	8	8
	6	6

For each configuration, tablets where produced varying the tamping force :0.5kN, 1.5kN, 3.5kN and 5kN [40]. This forces correspond to applied pressure of 10 MPa, 30 MPa, 70 MPa and 100 MPa respectively. The main tableting force was set to 15kN (i.e. a compacting pressure of 300 MPa). This makes it possible, on one hand to produce tablets with different interfacial strength and on the other hand to vary the shape of the interface as it will be demonstrated below. The force values were chosen based on our experience on the studied products

The compaction experiments were performed using a Styl'One Evolution compaction simulator (Medelpharm, Lyon, France). This device is a single punch tableting press,

monitored by Analis software. The displacement of the upper and lower punches is controlled electronically, and the displacement of the punches and the pressures applied are measured with strain gauges.

4.1.2 Tablet testing

4.1.2.1 Indentation test

The test used was already described in details in session 3. The system is designed to apply a stress, through the tip of the punch, exactly at the interface between the layers (Fig. 36). The interface is clearly visible because of the different colors of the layers, despite the curved punches used.

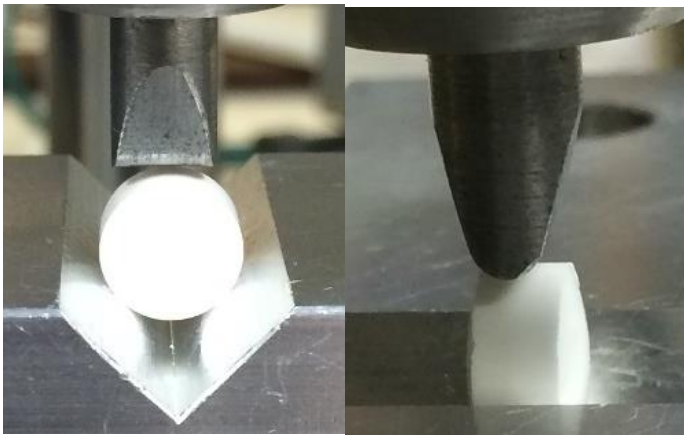

Figure 36: Frontal and side views of the indentation test

4.1.2.2 Dimension measuring

The shape of the interface was measured after the delamination using an optical binocular (Meiji Techno, Chikumazawa, Japan) equipped with a digital camera Invenio-3SII (Deltapix, Hassellunden, Denmark). The images were analyzed with DeltaPix image software (DeltaPix, Hassellunden, Denmark), able to convert the pixels in dimensional units (mm)

after the calibration though a specific calibration bar. The convex shape was evaluated as the radius of the circle that inscribed it.

4.1.3 Statistical Analysis

The analysis was performed using the software MODDE (Umetrics, Sweden). As it will be described below, the analysis was performed to study the influence of the curvature of the upper punch (Cup), the curvature of the lower punch (Cbot) and the tamping force (Tamp) on both the radius of curvature of the interface and the ratio between the breaking force of one configuration and the breaking force of the UF/BF configuration obtained under the same compression parameters. The curvature of the punch was quantified by the inverse of the radius of curvature of the punch. This made it possible to have a numerical value for flat punches (0) and to have a factor that increased when the curvature of the punch increased. The relation between the two factors and the response was obtained by fitting with MLR (multiple linear regressions) a quadratic model:

$$Res = b_0 + b_{Cup}Cup + b_{Tamp}Tamp + b_{Cbot}Cbot + b_{Cup\times Tamp}Cup \times Tamp + b_{Cup\times Cbot}Cup \times Cbot + b_{Tamp\times Cbot}Tamp \times Cbot$$

Were “Res” was the response variable and b_{cup}, b_{Tamp}, b_{Cbot}, $b_{CupxTamp}$, $b_{CupxCbot}$, and $b_{TampxCbot}$ were the model parameters.

The correlation between experimental factors and the response variable was evaluated with a summary of the fit method which included the goodness of fit (R^2) and the goodness of prediction (Q^2). The goodness of the quadratic model was also estimated with ANOVA. The model was considered good if the difference $R^2 - Q^2$ was lower than 0.2, Q^2 was higher than

0.5 and the p value obtained for the model was lower than 0.05 (which is significant at a confidence level of 95%).

4.2 Results and discussion

4.2.1 Shape of the interface

As explained above four different punch configurations were used some of them containing various punch curvatures. The tablets produced with these different configurations were then tested for interfacial strength. These results will be presented below. But first, to help to understand the rational of the four configurations chosen, it is necessary to present the measurement of the shape of the interface made on the delaminated tablets obtained after the test.

Obviously, the compacts obtained with the BF/UF configuration gave tablet with a flat interface. These tablets are commonly found in the literature. The results also shown that the configuration BC/UF gave tablets with a flat interface. The curved punch at the bottom did not influenced the shape of the interface in this case.

For the two other configurations, BF/UC and BC/UC, it was found the tablets had a curved interface. The measurement of the interface radius of curvature can be found in figure 37. It can be noted that the tablet obtained with a tamping pressure of 0.5 kN are not included in the graph. For these tablets it was difficult to obtain reliable results due to the roughness of the interface and the low curvature.

The statistical analysis of the results is reported in figure 38. The studied response was the radius of curvature of the interface. For the system MCC/DCP the statistical parameters were R^2=0.96, Q^2=0.90 and p=0.000 and for the system MCC/Lac they were R^2=0.96, Q^2=0.91 and p=0.000. Considering the criteria mentioned above the model was found suitable in both cases.

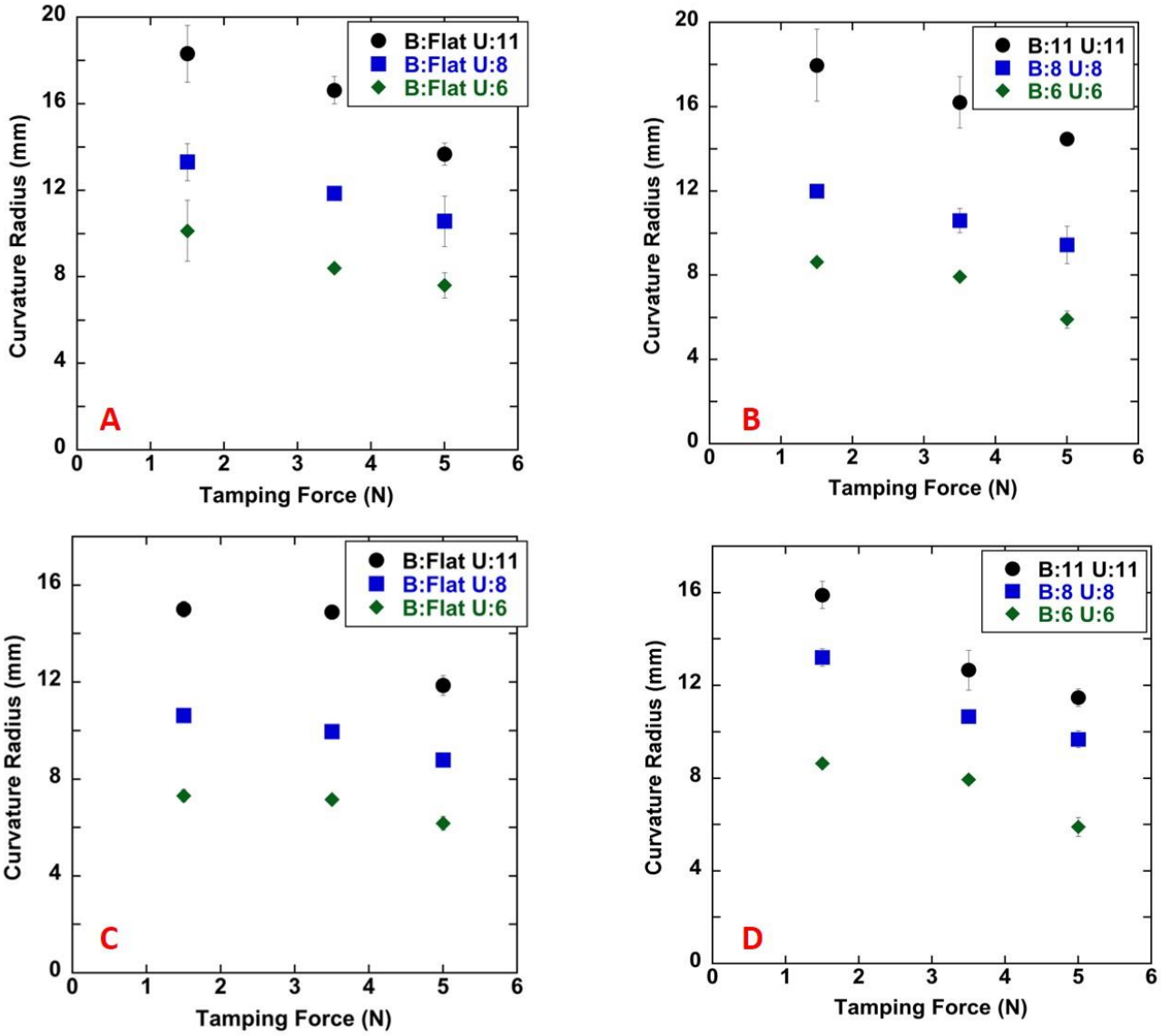

Figure. 37. Radius of curvature of the interface of the tablets as function of the tamping force. MCC/DCP: UC/BF(a) and UC/BC (b) ; MCC/Lac UC/BF(c) and UC/BC (d)

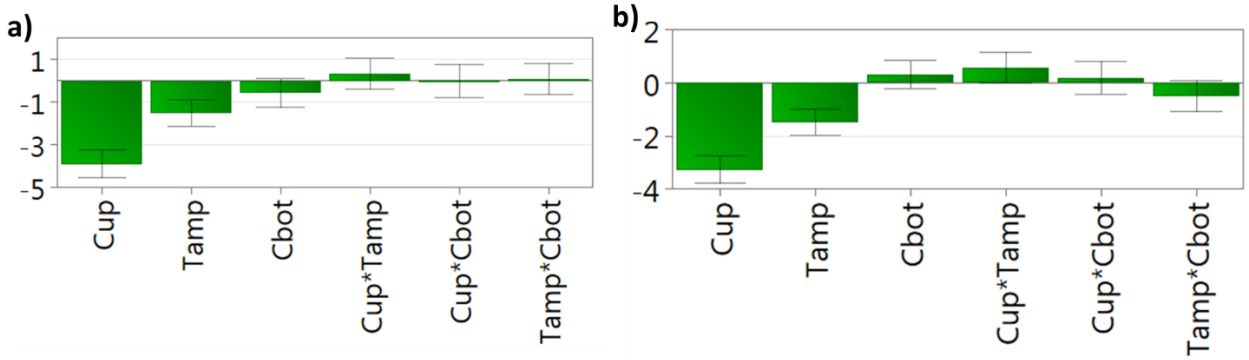

Fig. 38: Statistical analysis of the influence of the studied factors on the curvature of the interface (a) MCC/DCP and (b) MCC/Lac

The results in Figure 37 indicates that both systems behaved in the same manner. There were only two significant parameters that influenced the curvature of the interface. The first one was the curvature of the upper punch. The effect was negative, meaning that the curvature of the interface increased (i.e. the radius of curvature decreased) when the curvature of the punch (Cup) increased. This result was easy to foresee.

The other significant parameter was the tamping force. Again, the effect was negative which means that when the tamping force increased, the radius of curvature decreased, i.e. the curvature increased. To understand this fact, it is important to think back to process itself. The tamping force is applied to the first layer, then the second layer is poured into the die. This means that before the main compression, the shape of the interface is approximatively equal to the one of the upper punch, whatever the tamping force. But, by increasing the tamping force, the density of the first layer increases along with its mechanical resistance. The results shown in Fig. 38 indicate that the second compression tends to flatten the interface (the radius of curvature of the interface is always higher than the one of the upper punch). Nevertheless, this flattening is more efficient if the first layer is less densified. Tablets obtained with a low tamping force will thus have flatter interface than tablets obtained with high tamping force.

The last of the three parameters, the curvature of the bottom punch (Cbot), is found to be not significant. Again, as in the case of the configurations that gave flat interfaces, the curvature of the interface is not influence by the curvature of the lower punch.

Finally, the four punch configurations chosen can be divided into two groups: those that gave flat interfaces (BF/UF and BC/UF) and those who gave curved interfaces (BF/UC and BC/UC). Into each group, the two configurations gave the same shape of the interface but, as they have a different bottom punch, the stress distribution at the interface during the compression might be different for each configuration. This means that studying the difference in interfacial strength between the two configurations of a same group will make

it possible to study the influence of the stress distribution at the interface without the contribution of the curvature of the interface. After that, comparing the results between the two groups will make it possible two study the influence of the shape of the interface on the interfacial strength.

4.2.2 Study of the interfacial strength

Tablet were made for each punch configuration with the different punch curvatures. Due the amount of experiment performed, it was not possible to perform all in a single day with the same powder preparation. Each punch configuration (UC/BC, UF/BC, UC/ BF) was made on a single day with a fresh batch of powder. To avoid problem of reproducibility from one day to another, the configuration UF/BF was re-prepared each time to verify day to day reproducibility and to be sure to be able to compare one configuration to the other.

The results for MCC/DCP tablets are presented in Fig. 39, the results for MCC/Lac are in Fig. 40. The points that have a breaking force equal to zero on the graph correspond to tablets that delaminated spontaneously after the ejection. Finally, the statistical analysis of the results is presented in Fig. 41. As the aim of this study was to characterize the difference between tablets with flat or curved interface, the response chosen for this analysis was the ratio between the breaking force of the shaped tablet and the breaking force of the flat tablet produced under the same condition of tamping force and on the same day. This made it possible to study the effect of the parameters on the difference between the interfacial strength with curved interface and with flat interface. The use of the ratio avoids also to have problems due to the day to day reproducibility as the UF/BF configuration was remade each day in parallel with the studied configuration. The statistical parameters for each case were: R^2=0.856, Q^2=0.756 and p=0.000 for MCC/DCP and R^2=0.906, Q^2=0.869 and p=0.000 for

MCC/Lac. Considering the criteria mentioned above the model was found suitable in both cases.

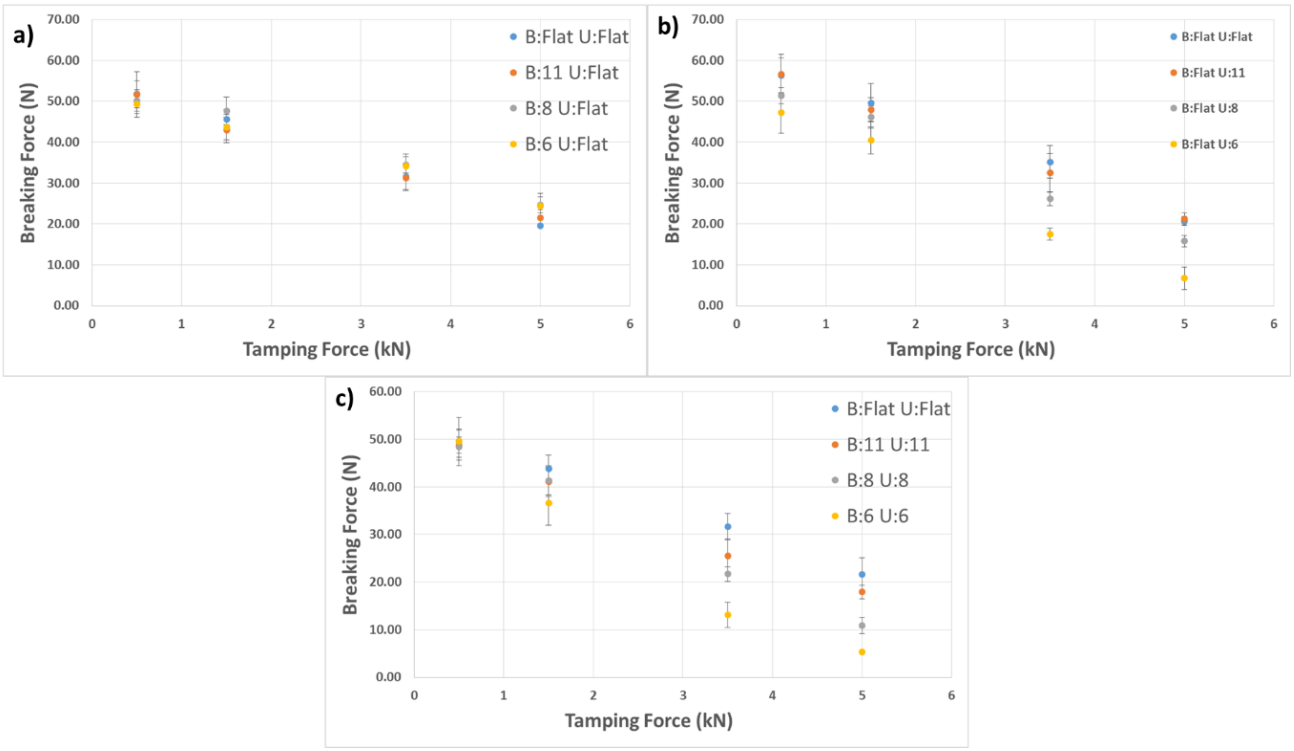

Figure 39: Interfacial strength of bilayer tablets MCC/DCP as a function of the tamping force: (a) BC/UF (b) BF/UC (c) BC/UC. The reference BF/UF configuration is represented on each graph.

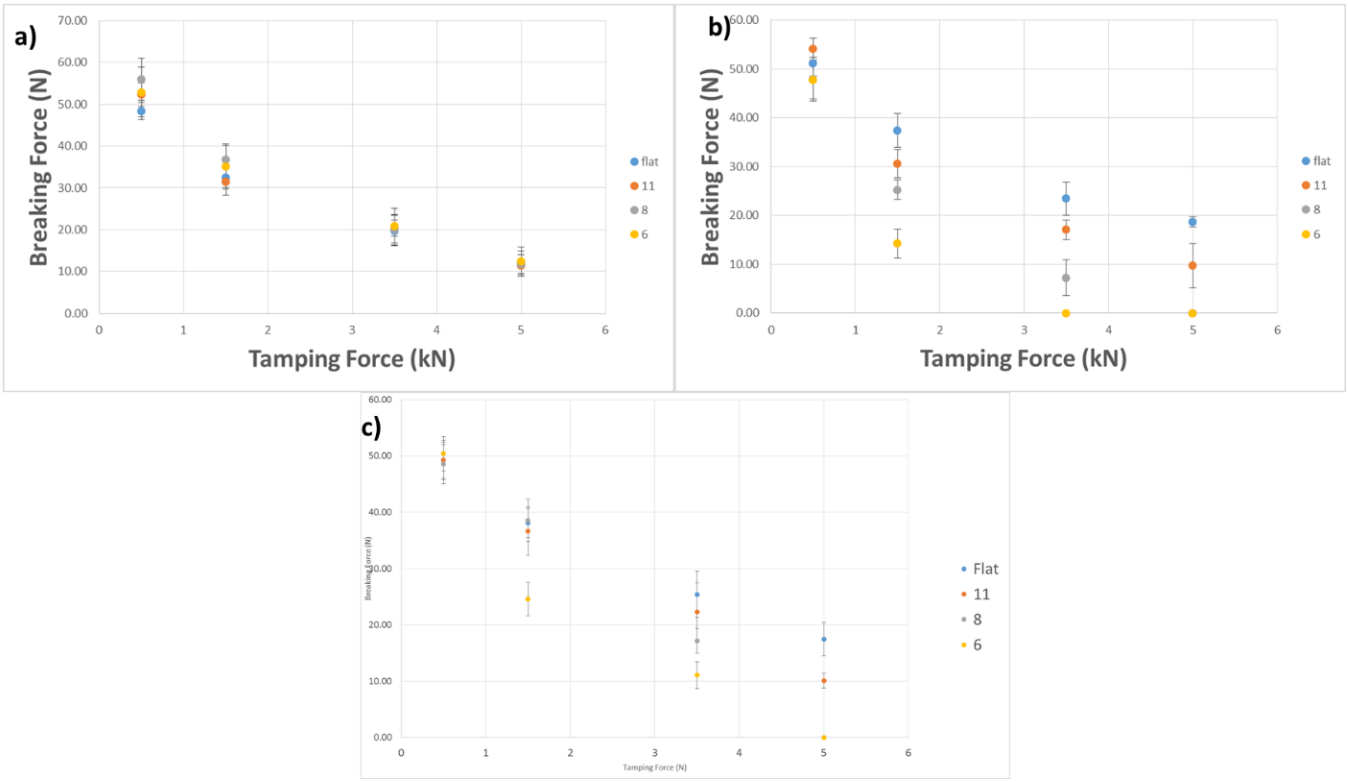

Figure 40: Interfacial strength of bilayer tablets MCC/Lac as a function of the tamping force: (a) BC/UF (b) BF/UC (c) BC/UC. The reference BF/UF configuration is represented on each graph.

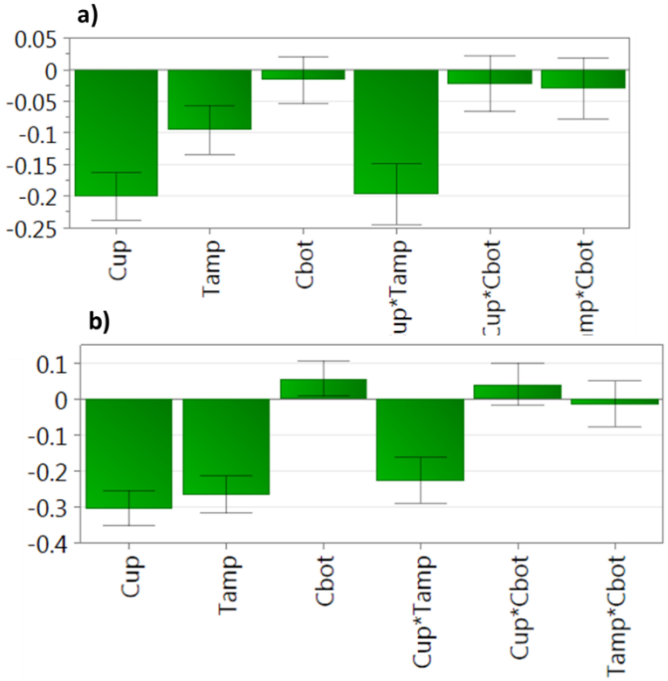

Figure 41: statistical analyses of the results, values of the coefficients of the model for (a) MCC/DCP and (b) MCC/Lac.

As explained above, in this analysis we wanted to try to separate the effect due to the curvature of the interface and the one due to the stress distribution at the interface during the compression. For this last point, we needed to compare UF/BF with UF/BC and UC/BF with UC/BC. This could be made by looking at the parameter Cbot. For the system MCC/DCP, the parameter was not significant, which means that the curvature of the lower punch had no influence on the interfacial strength. This can be visualized of fig.39a for the case of the flat interface: all the configurations gave the same breaking force value. The same comment can be made for the case of the curved interface by comparing fig.39b and 39c.

For the case of the system MCC/Lac, the coefficient Cbot had a small positive influence which is given significant by the model (p=0.03). This influence is due to the results of the tablets with a curved interface. In fact, when looking at figure 40a no difference can be made, for the tablet with a flat interface, between tablets obtained with flat lower punch and tablets obtained with curved lower punch. On the contrary for the tablets with a curved interface, the difference is visible for tamping force of 1.5kN and 3.5kN and punch curvature R6 and R8. In these case the value of the breaking force was lower when the lower punch is flat than when it is round. This explains the small positive coefficient found in fig. 40b.

The conclusion about this parameter and about the influence of the stress distribution at the interface is that, in most of the case, it has no influence on the breaking strength of the tablet, and in some particular configurations and operative conditions it can have a small influence. It can thus not be considered as the most influent parameter.

The two other parameters, Cup and Tamp, have a very significant negative impact on the ratio between the breaking force of the shaped tablet and the breaking force of the flat tablet. As explained in the first part of the results, increasing Cup and Tamp corresponds to an increase of the curvature of interface. Moreover, both effects are interdependent as it is shown by the significance of the parameter Cup*Tamp. This interaction can be seen using

the interaction plot presented in figure 42. The response decreases when Cup increases (i.e. the curvature increases) and this effect is more and more marked when Tamp increases. These results show that, increasing the curvature of the interface is unfavorable for the interfacial strength of the tablet.

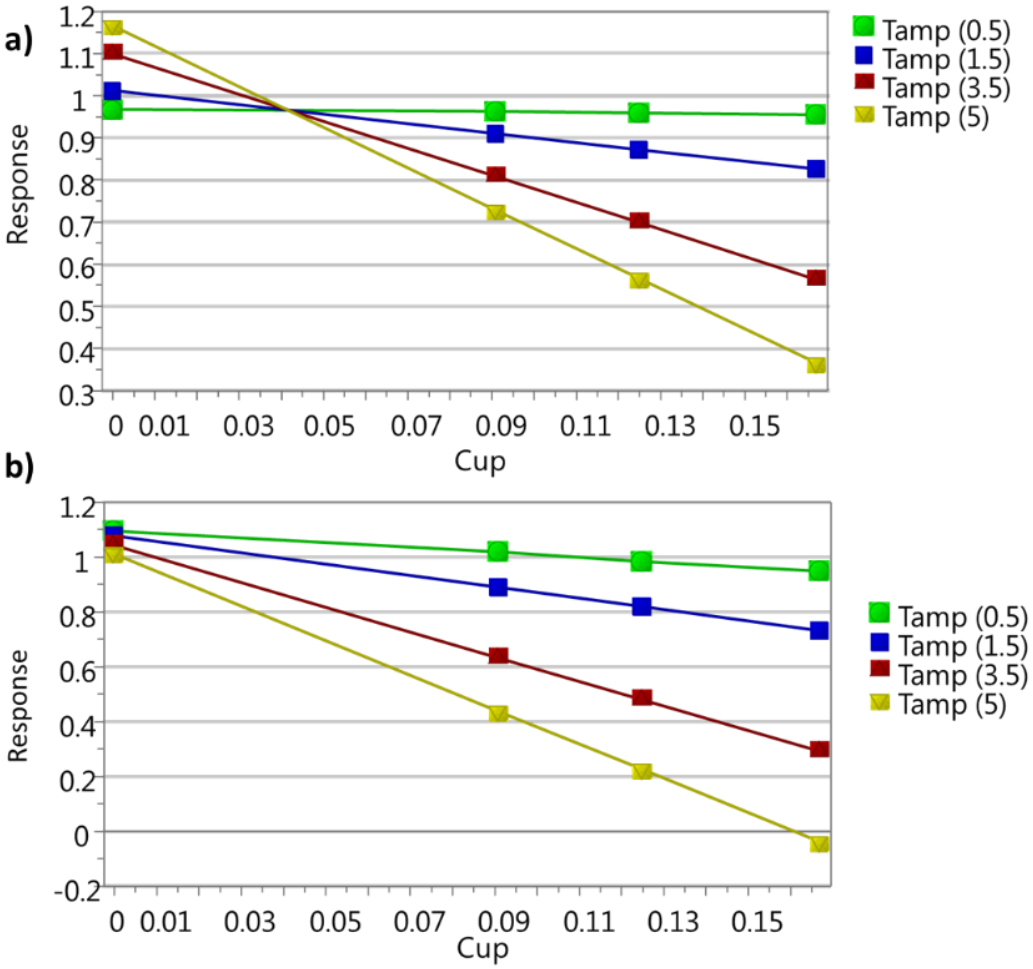

Figure 42: interaction plot between the parameters Cup and Tamp. (a) MCC/DCP. (b) MCC/Lac. On each graph, the Y-axis (response) represents the ratio between the breaking force of the shaped tablet and the breaking for of the flat tablet obtained the same day under the same conditions of compression.

An interesting point is that, for the system MCC/Lac, the curvature of the interface was so unfavorable that it promoted, in some cases, direct delamination of the tablets after ejection. This behavior makes it possible to affirm that the decrease of the breaking force measure during the test is not an artefact due to the test itself but a real effect of interfacial weakening. This validates, if necessary, the use of the indentation test for the study of bilayer tablet with a curved interface.

4.3 Conclusion

When producing a bilayer tablet, the shape of the interface is rarely taken into account as one of the parameters that can influence the adhesion of the two layers. In this work it is proved that this factor is able to influence bilayer tablets strength. Increasing the curvature of the interface by increasing the punch curvature and/or increasing the tamping pressure has a weakening effect of the interface. This can, in some cases, lead to direct delamination of the tablet under operating conditions that, for flat tablet gives a correct interfacial strength. When producing bilayer tablet with curved punch, the operating conditions might be set to obtained tablets with an interface as flat as possible. The easiest way of doing it is to use a tamping force as low as possible. In this case, the interfacial strength of tablets obtained using curved punches is comparable to the one of the tablets obtained with flat punches which is, moreover, higher when low tamping force is used.

5 Design of Experiment of a bilayer tablet of Ibuprofen Lysine/Sucralfate

5.1.1 Materials and Methods

5.1.1.1 Preparation of Ibuprofen Lysine formulation

In order to have a powder that is ideal for compression, a process of wet granulation of the Ibuprofen lysine and excipients is done.

The excipients showed in Tab XXVIII were mixed in a mortar. As a binder it is used an alcoholic solution of PVP K 30 (5% w/v). The powder was then granulated used a granulator with oscillator rotor, equipped with meshes sized 0.8 mm. The granulate was then heated in oven for 2 hours at 40 °C. Then, the extraganular excipients (Silica, AcDiSol) were added (highlighted in red in tab IV). Lastly, Magnesium stearate (1%) was added, and then the powder was mixed in Turbula for 5 min.

Table XXVIII: Formulation of ibuprofen lysine granulate.

Extragranular excipients are highlighted in red

Components	mg	%	g	%
Ibuprofen lysine	342	83.7	44.97	79.4
Kollidon CL	15	3.7	1.97	3.5
$NaHCO_3$	20	4.9	2.63	4.6
Lactose	20	4.9	2.63	4.6
PVP K30	11.7	2.9	1.53	2.7
SiO2	4	0.9	0.53	0.9
AcDiSOL	16	3.7	2.10	3.7
Magnesium stearate	2	0.5	0.26	0.5
Total	431	100	56.6	100

5.1.1.2 Preparation of Sucralfate formulation

The sucralfate gel (initial WC% 67.2%) was dried using the Fluid bed (40°C; 0.5 bar).

In order to have sucralfate with different water content, two different drying steps, at 15 minutes and at 45 minutes, were performed. Therefore, two batches of sucralfate were obtained, each one with different water content.

The water content was measured with a scale equipped with an internal heater. This scale works by heating a sample of the product to a pre-determined temperature (60°C) and measuring the weight every minute. The measure stops when the sample stops losing weight. The difference between the initial weight and the final one, in percentage, is the water content of the sample. Table shows the sucralfate batches prepared with different water contents.

Table XXIX: Prepared sucralfate batches.

Batch	Drying time (minutes)	Water Content (%)
Sucr_1	15	33.2
Suc_2	45	10.2

. The composition of the layer for each batch of Sucralfate is shown in Table XXX.

Table XXX: Composition of the layer of sucralfate for both batches. In red, the extragranular components. The percentages are related to the quantity of dried Sucralfate.

Batch 1		
Components	mg	Percentage
Sucralfate	150 mg	
Water	15.3 mg	10.2 %
Lactose	30 mg	20 %
Magnesium stearate	1.5 mg	1 %
Total	196.8	
Batch 2		
Components	mg	Percentage
Sucralfato gel	150 mg	
Water	45.75 mg	30.5 %
Lactose	30 mg	20 %
Magnesium stearate	1.5 mg	1 %
Total	225.75	

5.1.2 Tablet manufacturing

The compaction experiments were performed using a Styl'One Evolution compaction simulator (Medelpharm, Lyon, France). This device is a single punch tableting press, monitored by Analis software. The displacement of the upper and lower punches is controlled electronically.

The pressure applied by the punches to the powder bed is measured with strain gauges. The machine can be also controlled with a given pressure to be reached. For all the experiments, the tablets were produced using standard Euro D round and flat punches with a diameter of 11.28mm.

For all the experiments, a precompression pressure of 5 MPa was used. This pressure was kept to a minimum in order to have the maximum possible interfacial strength, as already studied in the literature.

5.1.3 Design of experiment

A half-factorial design with 5 factors was employed, allowing for the estimation of the main effects and two factors interactions. The number of experiments to perform for the half fractional factorial design was 2^{n-1}.

The included factors derive from the formulation aspects, the tableting processes and the storage conditions. From a formulation point of view, the water content of the Sucralfate layer was considered, with two different levels. The processes factor considered were the dwell time, the layer disposition and the main pressure force, each one with two levels. After the production, the tablets were stored in sealed humidity chambers, with three levels of storage conditions.

It must be noted that the precompression force was be kept constant. This is because the effect of this parameters is already well-known from the literature, and confirmed by the work of this thesis in previous paragraphs (3.2.3).

Table XXXI shows a comprehensive list of the factors and levels.

Table XXXI: list of the factors and their levels for the DoE.

Factors	Levels
Sucralfate Drying Time	15 min, 45 min
Main Compaction Pressure	100 MPa, 300 MPa
Dwell time	20 ms, 1000 ms
Layer Disposition	1*, 2*
Storage RH	5%, 45%, 75%

1*: the sucralfate layer is precompressed first, then the ibuprofen lysine layer is accommodated in the matrix.
2*: the ibuprofen lysine layer is precompressed first, then the sucralfate layer is accommodated in the matrix.

The design matrix, reported in Table VII included 20 experiments. The design space was constructed and analyzed with a DoE software, MODDE (MKS Data Analytics Solutions, Umeå, Sweden). The list of the experiments is shows in table XXXII.

Table XXXII: list of the experiment for the DoE.

Experiment	Sucralfate Drying Time (min)	Dwell time (ms)	Layer deposition	Main pressure (MPa)	Storage R.H. (%)
1	15	20	2	300	5
2	45	1000	1	300	75
3	15	1000	2	100	5
4	15	20	1	100	5
5	45	20	1	300	5
6	15	1000	1	300	5
7	15	1000	1	100	75
8	45	20	1	100	75
9	15	20	2	100	75
10	45	1000	1	100	5
11	45	1000	2	100	45
12	45	20	2	300	75
13	45	1000	2	100	75
14	15	20	1	300	75
15	45	1000	1	300	45
16	45	1000	2	300	5
17	15	1000	2	300	75
18	15	20	2	300	75
19	45	20	2	100	5
20	45	20	1	100	45

5.1.4 Tablet analysis

5.1.4.1 Breaking strength test

The previously described indentation test was used. This consist of a V-support with an opening angle of 90° and a depth of 6 mm, in which the tablet can be placed. The samples were then stressed with a punch designed for the experiment. The punch tip is a half cylinder shape with a diameter of 2.80 mm and a width of 6 mm. The system is designed to apply a

stress, through the very tip of the punch, exactly at the interface between the layers. The breaking force corresponds to the breaking force needed to separate the two layers of the tablet. This force is determined at the maximum of the force-displacement curves obtained during the test. This test proved to be suitable for testing the strength of a bilayer tablet (3.3)

5.1.5 Storage conditions

In order to store the manufactured batches of tablets in three different humidity conditions, three different humidity chambers were prepared, as per Table XXXIII. The chambers are kept at the desired humidity level by filling them with a saturated salt solution, and letting them equilibrate for 2 days. This bottles were placed inside humidity chambers pre-equilibrated at 25°C/11.3% RH; 25°C/43.6% RH and 25°C/75% RH respectively. At predetermined time points, a bottle was pulled from the oven and tested for hardness, dimensions and weight.

Table XXXIII: tablets storing conditions

Salt Solution	Final Humidity
Sodium Chloride	75%
Potassium Carbonate	45.5%
Silica Gel	5%

5.2 Results and discussion

5.2.1.1 Responses and statistical analysis

The studied responses are the breaking strength of the tablets

after 1 day of storage and after 7 days of storage. Then, in order to compare them, the fraction between the two was calculated (Delta Breaking Force). In Table XXXIV there are the obtained responses for each different run.

Table XXXIV: obtained responses for each run.

Run Order	Breaking Force 1 Day (kN)	Breaking Force 7 Days (kN)	Delta BF (kN)
1	23.92	13.46	0.437291
2	56.66	38.16	0.326509
3	13.76	2.5	0.818314
4	11.51	6.3	0.45265
5	53.81	60.72	-0.128415
6	17.92	12.25	0.316406
7	10.84	5.4	0.501845
8	21.05	14.03	0.333492
9	12.9	11.51	0.107752
10	36.6	36	0.0163934
11	23.54	19.32	0.179269
12	50.19	39.58	0.211397
13	24.1	7.85	0.674274
14	32.8	28.4	0.134146
15	62.04	56.9	0.0828498
16	52.93	68.54	-0.294918
17	21.2	18.2	0.141509
18	22.6	17.1	0.243363
19	22.9	21.85	0.0458515
20	27.87	17.58	0.369214

The model proved to be robust. as shown in Figure 43 there is a correlation between the measured points and the predicted ones. with a statistically significant r^2.

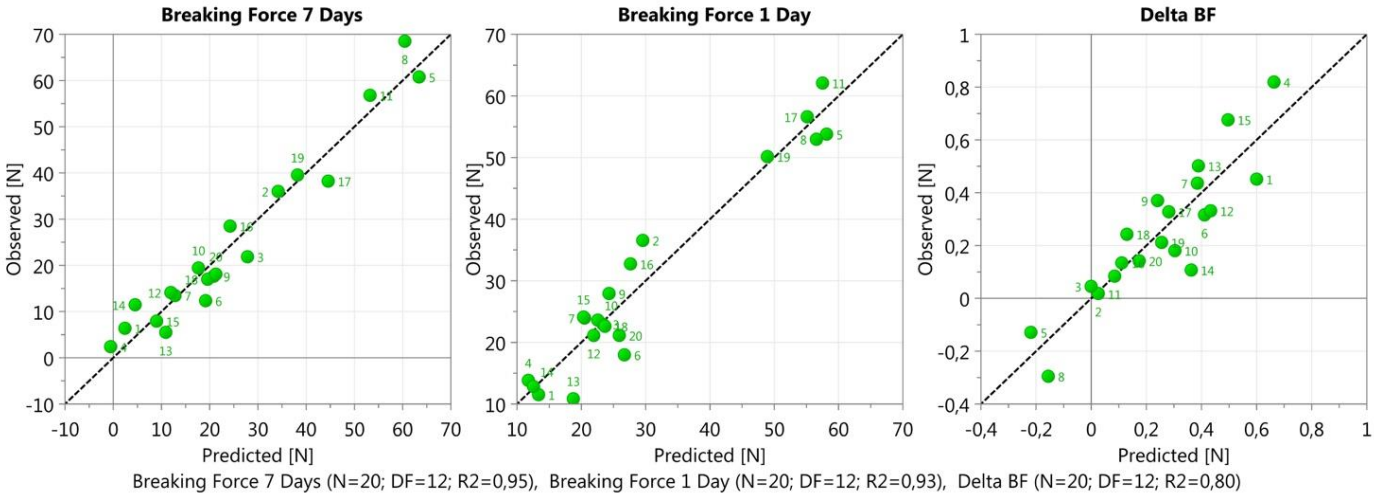

Figure 43: Observed vs Predicted Plot for the values of Breaking Forces.

In order to understand the interaction between the formulation and production factors and the breaking force of the tablets, the coefficients of the model were studied, and a coefficient plot was produced. In this plot, only the significant factors and interaction of factors (and their coefficients) are shown in Figure 44.

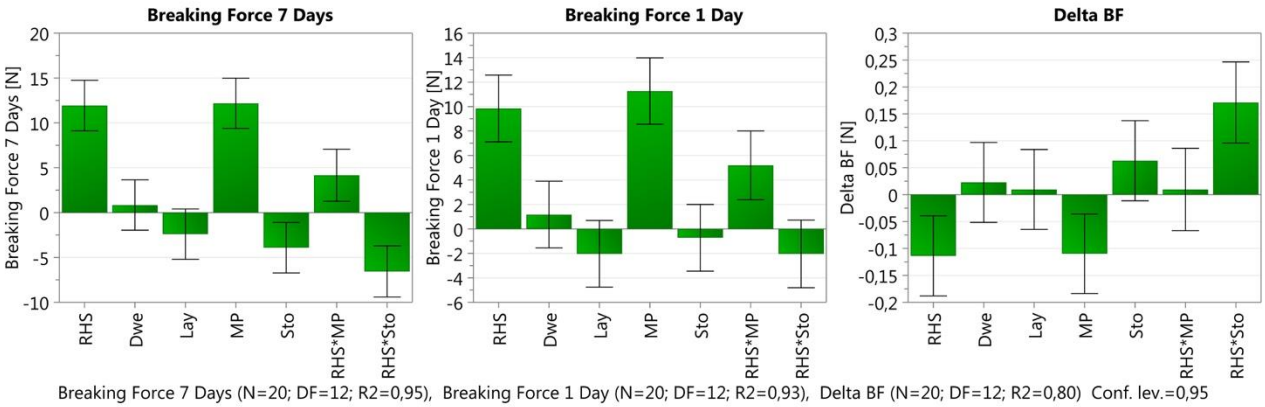

Figure 44: coefficient plot of factors and interactions between them

Both for the values of breaking force at day 1 and at day 7, the residual humidity of the Sucralfate layer is one of the most influential factor. As per manufacture parameters, the main pressure proved to be the most relevant factor. As shown in fig.44 in this design of experiment is not possible to see an effect of the dwell time and layer disposition.

Finally, the storage time is not relevant on the strength of the bilayer tablets when the tablets are tested after just 1 day, but its influence starts to increase at day 7.

Always at 7 days, it is possible to measure a cross-effect of the residual humidity of the layer of sucralfate with the storage conditions. This became of interest considering that this cross effect is the main effect on the DeltaBF. The interaction is shown in the interaction plot (Figure. 45)

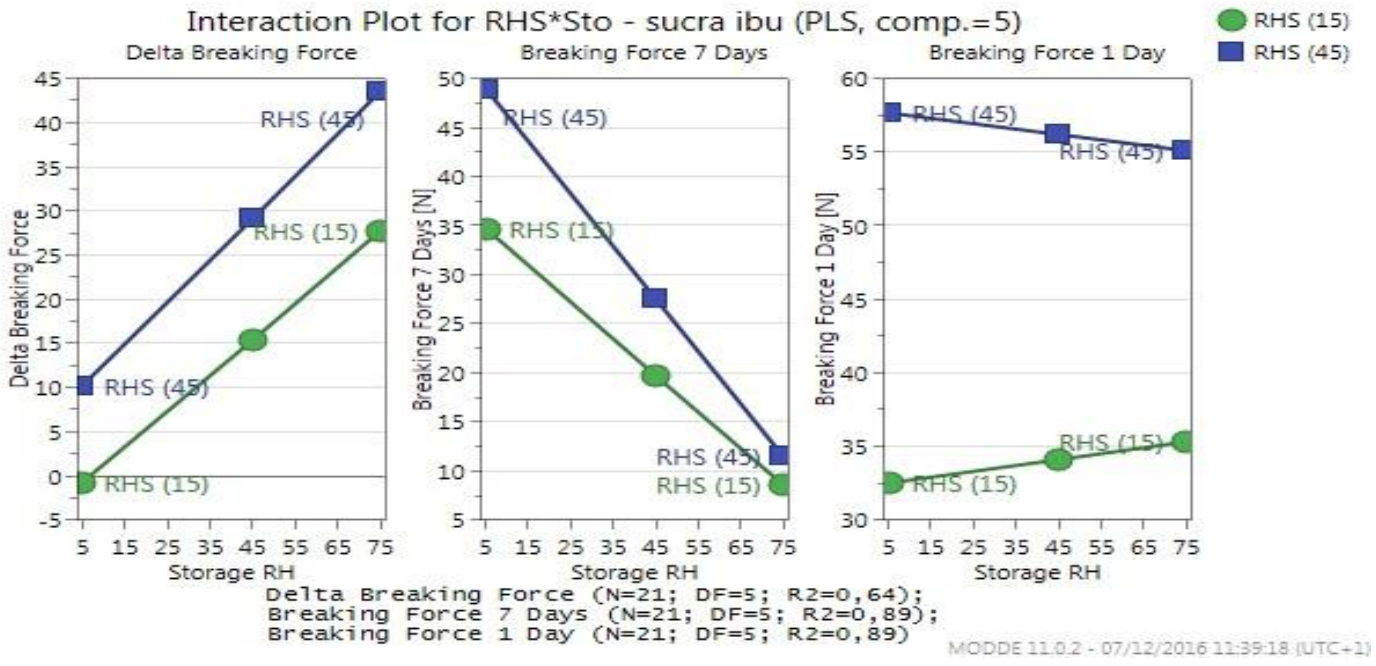

Figure 45: interaction plot of the Sucralfate humidity levels and the storage conditions.

As shown in Figure 45, the higher the storage RH is the lower is the final breaking force. In particular, after 7 days of storing the effect of the high storage humidity is extremely relevant, reducing the strength of the adhesion between the layers no matter what are the condition

of sucralfate production. indicating that high storage humidity is especially dangerous to the correct storing of bilayer tablets at long times. After 1 day, on the other hand, we have a slight increase in breaking force of the tablet produced with Sucr_1 (showed as RHS (15), dried 15 minutes, and with a final water content of 33.2%) stored at high RH. This indicates that for short periods of time, the tablets are more robust when the humidity of the environment is higher than the water content of the tablet itself. A possible explanation to this is that the sucralfate, when stored at low humidity conditions, tends to shrink by water loss, causing structural damages (caused by the changing in dimensions) to the interface in the process. Oh the other hand the sucralfate produced with a high drying time, Sucr_2 (showed as RHS (45), dried 45 minutes and with a water content of 10.2%) gave much higher breaking forces than the bilayer made with Sucr_1. In this case, the humidity of the storing environments has a negative effect on the strength of the tablet, probably because the sucralfate will retain water from the environment itself, changing his dimension, and leading to a weakening of the adhesion of the layers.

5.2.2 Optimization of the factor

A optimization process has been performed in order to establish the influence of each factor on the final breaking force of the bilayer tablet. To include the effect of storing time in the optimization process, the chosen parameter to optimize is the Breaking Force at 7 days.

The optimization process gave a list of factors, their ideal values, and their coefficient of influence on the final product. Those are reported in Table XXXV.

Tablet XXXV: Factors, ideal values and coefficients of influence

Factor	Role	Value	Factor contribution
RH sucralfate	Free	45	18.2067
Dwell time	Free	1000	12.4139
Layer disposition	Free	2	6.99254
Main Pressure	Free	300	20.9197
Storage RH	Free	5	41.4672

The role of each factor is set to “free”, meaning that it is possible to modify each factor independently from the other ones. The results show that, when aiming to the manufacture of a robust bilayer tablet of sucralfate / ibuprofen lysine, the most important factor to consider is the storing humidity (contribution of 41.4). In a second instance the effect of the main pressure of compression became relevant, together with the water content of the sucralfate (contribution of 20.9 and 18.2 respectively) ideally these parameters are set to the maximum compression pressure and the driest sucralfate. A minor importance is related to the dwell time, meaning that it is possible to produce strong tablets even with lower dwell times. This is important in case of an industrial scale-up, because a high production speed is preferable. Lastly, the layer disposition does not play an important role (contribution of 6.9), giving the option to produce bilayer tablets with comparable strength no matter the disposition of the layers themselves.

6 Conclusions

In this part of this work of research, two different aspects were taken in consideration: how to properly test the strength of a multilayer tablet and how the production parameters influence the shape of the interface of a multilayer tablet.

As regarding the first part of this work, the reached conclusion is clear: the commonly used (and approved by the Pharm: European, last version) test is not suitable for testing a multilayer tablet. In this work, other suitable tests are proposed.

In the second part of the work, different multilayer tablets with different interfaces were produced. By testing the strength of the interface of each batch of multilayer tablet produced, it is possible to say that a flat interface gives a more cohesive multilayer tablet.

Lastly, given the conclusion reached, a Design of Experiment for a bilayer tablet of ibuprofen lysine and sucralfate was conducted. The bilayer tablets were all produced with a flat interface (to maximize their strengths) and tested with a suitable test. This DoE led to the conclusion then the characteristic of the product used (such as relative humidity) and storage conditions are fundamental to determine the robustness of a multilayer tablets.

Thesis Conclusions

Conclusions

Multilayer tablet technology is a viable way of administering multiple drugs in one single dosage form. This technology is based on the compression of different layers of powder in different steps. The research project was devoted to the studying and the application of the multilayer tableting technology for the preparation of an immediate release dosage form of ibuprofen lysine and sucralfate. According to the co-tutorship agreement, the research was carried out both at University of Parma, Italy, and University of Bordeaux, France.

During the first part of the project, carried out at University of Parma, Department of Pharmacy, several multilayers tablets made of ibuprofen lysine and sucralfate were studied, in order to test the influence of several parameters of production on the final tablet quality.

During the second part of the project, carried out at the Department of Mechanics and Engineering of the University of Bordeaux, testing conditions and production parameters of excipient-made multilayers tablets were studied. This led to defining the best production parameters (in order to have a robust tablet) and the most suitable way of testing it. Finally, a design of experiment was performed on the ibuprofen lysine – sucralfate bilayer tablet to check for the best formulation parameters, production and storage conditions.

The project will continue with a novel Design of Experiment focused of manufacturing the three-layer tablets (a middle layer of ibuprofen lysine with the first and third layer of sucralfate). The formulation of the layer of Ibuprofen Lysine will be kept constant (the same already discussed in this thesis), while different formulations of sucralfate will be studied according to the DoE.

In particular, this formulation will include different diluents (MCC, Lactose and Starch) with different quantities and three-layer tablets will be produced and studied.

This DoE will allow us to understand the influence of the different properties of each excipient in the formulation of a three-layer system.

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LIST OF PUBLICATIONS

POSTER

- Comparison of breaking tests for the characterization of the interfacial strength of bilayer tablets; Luca Castrati, Vincent Mazel, Virginie Busignies, Harona Diarra, Alessandra Rossi, Paolo Colombo, Pierre Tchoreloff. APV 10th Word Meeting, April 2016, Glasgow (UK).
- Influence of layer composition and compaction parameters on the manufacturing of sucralfate / ibuprofen lysine bi-layer tablets. A. Rossi, L. Castrati, M. Molinari, G. Colombo, D. M. Rekkas, S. Politis, R. Bettini, P. Colombo. APV 10th Word Meeting, April 2016, Glasgow (UK).

PUBLICATIONS

- Luca Castrati, Vincent Mazel, Virginie Busignies, Harona Diarra, Alessandra Rossi, Paolo Colombo, Pierre Tchoreloff. Comparison of breaking tests for the characterization of the interfacial strength of bilayer tablets. Int. J. Pharm. 513 (1-2), 709-716 (2016).
- Luca Castrati, Vincent Mazel, Harona Diarra, Virginie Busignies, Pierre Tchoreloff. Effect of the curvature of the punches on the shape of the interface and the delamination tendency of bilayer tablets. Submitted to J. Pharm. Sci.

Comparison of breaking tests for the characterization of the interfacial strength of bilayer tablets

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Introduction

BILAYER TABLETS

Advantageous oral solid dosage form
- Administering two or more APIs in a single dosage form.
- Overcome chemical incompatibility between two active components.
- Control the delivery rate of one or more APIs

Critical quality attribute: delamination (separation of the layers), due to:
- Difference in elastic recovery of the two layers
- Roughness of the interface
- Tableting parameters (tamping and main compression pressures) [1]

Hardness tests for a bilayer tablet should provide a quantification of the mechanical resistance of the interface between the two layers

Aim of the Work

➡ **Comparison on three different tests to study the interfacial strength of a model formulation: Diametrical breaking test, Shear test, Indentation test.**

➡ **Study the ability of this test to discriminate tablets with different interfacial strengths**

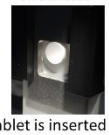
Materials and Methods

TABLET MANUFACTURING

A model formulation was used:
Layer 1: Vivapur 12(microcristalline cellulose (MCC)) + 1% Magnesium stearate
Layer 2: Flowlac 90 (SD Lactose) + 1% Magnesium stearate
Therefore, in order to obtain tablets with different interfacial strength, tablets were manufactured in two different batches:
Batch 1: varying the applied main compaction pressure (from 100 MPa to 400 MPa) but keeping the tamping force applied on the first layer constant (at 10 MPa),
Batch 2: keeping the main compaction pressure constant (at 300 MPa) but modifying the tamping pressure (10 MPa, 25 Mpa and 40 MPa).

The tableting was performed using a **Styl'One Evolution** (Medelpharm, Lyon, France), equipped with Euro D flat punches with a diameter of 11.28 mm.
FEM Simulation was performed using Abaqus.

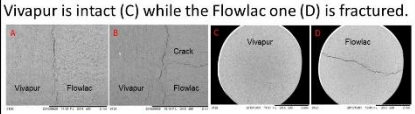
TABLET HARDNESS TESTING

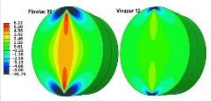
Diametrical Test	Shear test	Indentation test
		
The tablet is placed vertically between two anvils. The instruments applies a displacement squeezing diametrically the tablet	The tablet is inserted into a fixture. The blade applies an increasing displacement (rate: 0.01 mm/sec) on the outer layer until the two layers delaminate.	The tablet is on a V shaped support. The tip of the Ad Hoc punch applies a stress directly at the interface between the layers. [2]

Results and Discussion

DIAMETRICAL TEST

SEM images: no clear difference at the interface between the layers before (A) and after (B) the test. The layer of Vivapur is intact (C) while the Flowlac one (D) is fractured.





FEM simulation confirms that stress is higher in the Flowlac layer than in the vivapur one, due to differences in the mechanical properties.

Diametral test measures the hardness of one layer

SHEAR TEST

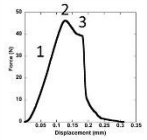
Correlation of the breaking force with tablet thickness:

Layer 1 (mm)	Layer 2 (mm)	Breaking Force (N)	St. Dev.
4	3.8	109.38	6.31
3.3	3	112.30	7.49
2.5	2.3	111.79	7.92

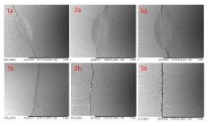
A bilateral t-test proved that there is no meaningful statistical difference. Therefore, the **shear test is not affected by the tablets dimensional properties.**

The tested tablets always break at the interface.

INDENTATION TEST



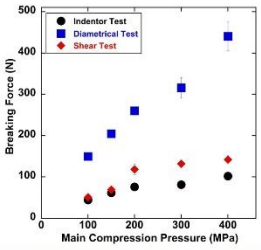
Force – Displacement curve shows three different parts. For each, SEM images at the indentation mark (a) and at 90° of the indentation mark (b) were taken.



1a, 1b: intact interface, only plastic deformation
2a, 2b: interface crack
3a, 3b: crack propagation
Point 2 is characteristic of the breaking force.

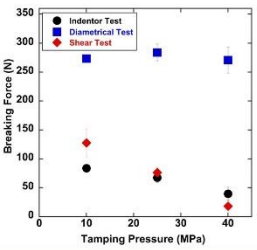
COMPARISON BETWEEN THE TESTS

BATCH 1



The interfacial strength should increase with the increasing main compression pressure. The results shows that:
- Diametrical test values increase linearly with the main compression pressures
- Shear and indentation tests reach a plateau.

The diametrical test detects the strength of the Flowlac layer, which is heavily affected by the main compression pressure.



BATCH 2

The interfacial strenght should decrease with the increasing of the tamping pressure.
- Diametrical test does not show any significant difference between the batches of tablets
- Shear and indentation tests values decreases with the increasing of the tamping force.

The diametrical test does not detect the interfacial strength.

Conclusions

The diametrical breaking test is a measure of the strength of one layer and it is unable to discriminate between bilayer tablets with different interfacial cohesion. Otherwise, the shear and indentation tests could be used when testing the interfacial strength of a bilayer tablet.

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Influence of layer composition and compaction parameters on the manufacturing of sucralfate/ibuprofen lysine bi-layer tablets

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Introduction

Multi-layer tablets (MLT) are designed for the manufacturing of fixed-dose combination products that simplify the medication regimen and potentially increase the patient's compliance. MLT are heterogeneous systems in which two or more layers of compacted powders are separated between them by a discrete interface. The hardness and the delamination tendency of MLT depend not only on the layer composition but also on the deformation property of each layer during tableting.

Aim

Study of the influence of layer composition and compaction parameters on the delamination propensity of bi-layer tablets for the immediate release of two drugs in combination.

The first layer was made of sucralfate, a gastric mucosa protector, while the second layer consisted of ibuprofen lysine, an anti-inflammatory drug.

Figure 1. Styl'One Evolution Rotary Tablet Press Simulator

Methods

Layer composition

Sucralfate layer (dose 150 mg). Sucralfate gel was granulated with microcrystalline cellulose (SUCR_1) or a mixture of lactose and microcrystalline cellulose (SUCR_2) and dried in Mini Glatt until the residual water was about 15%. Magnesium stearate was added to granulate and mixed in Turbula® for 5 min.

Ibuprofen lysine layer (dose 342 mg). Ibuprofen lysine was granulated with sodium bicarbonate and lactose using a alcoholic solution of polyvinylpyrrolidone (5% w/v) and dried for 2 h in oven at 40°C. Colloidal silica and croscarmellose sodium were added to granulate and mixed in Turbula® for 15 min. Then, magnesium stearate was added to the blend and mixed for 5 additional minutes.

Tablet manufacturing

The bi-layer tablets were manufactured using a Styl'One Evolution Rotary Tablet Press Simulator (Medelpharm, France (Figure 1)). This apparatus is a single punch tableting press, in which the displacements of the lower and upper punches are electronically control. The tablets were produced using standard EURO D punches of 11.28 mm diameter, at different pre-compression force (0, 1, 2 and 4 kN) and compression forces (10, 20, 30 and 40 kN). The compaction process was performed using Advanced Analysis Software.

Results and Discussion

Two types of bi-layer tablets, differing on sucralfate layer composition, were manufactured. In the case of bi-layer tablet SUCR_1, as the pre-compression and compression forces applied increased the bi-layer tablets delaminated during the ejection from the press die (Table I and Figure 2).

The layer separation was due to the presence of microcrystalline cellulose, which behaves as plastic material.

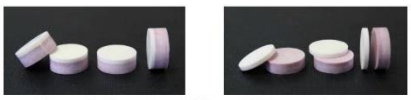

Figure 2. Examples of bi-layer tablets manufactured

Table I. Pre-compression and compression forces applied for Sucralfate/Ibuprofen lysine bi-layer tablets

SUCR_1/Ibuprofen lysine			SUCR_2/Ibuprofen lysine		
Compression force (kN)	Pre-compression force (kN)	Bi-layer tablet manufacturing	Compression force (kN)	Pre-compression force (kN)	Bi-layer tablet manufacturing
10	0	YES	10	0	YES
	1	YES		1	YES
	2	YES		2	YES
	4	YES		4	YES
20	0	YES	20	0	YES
	1	YES		1	YES
	2	YES		2	YES
	4	LAYER SEPARATION		4	YES
30	0	YES	30	0	YES
	1	YES		1	YES
	2	YES		2	YES
	4	LAYER SEPARATION		4	YES
40	0	YES	40	0	YES
	1	YES		1	YES
	2	LAYER SEPARATION		2	YES
	4	LAYER SEPARATION		4	YES

The surface roughness of microcrystalline cellulose in the first layer was reduced as the pre-compression force increased, decreasing the mechanical interlocking between the two adjacent layers. Brittle material, as lactose, was introduced in the granulation in order to increase the interfacial strength.

In the case of bi-layer tablet SUCR_2, in which lactose and microcrystalline cellulose were both present in the sucralfate granulation, no delamination was observed, independently from the pre-compression and compression forces applied (Table I). The presence of lactose, which tends to fracture creating new surfaces, helps the adhesion of the layers.

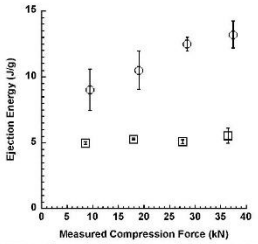

Figure 3. Ejection energy given to the bi-layer tablets, normalized by the bi-layer weight (□ SUCR_1, ○ SUCR_2; mean ± standard deviation, n = 5).

Moreover, being lactose fracturing compared to plastic material, it retained more surface roughness for mechanical interlocking of adjacent layers.

Nevertheless, the bi-layer tablets SUCR_2 exhibited higher ejection energy compared to the bi-layer tablets SUCR_1, containing only microcrystalline cellulose in the sucralfate layer (Figure 3). The ejection energy for the bi-layer tablets SUCR_1 was about 5 J/g, almost constant at increasing compression forces. On the contrary, the ejection force was significantly greater for the bi-layer tablets SUCR_2 and proportionally increased as the compression force was raised. This behaviour was due to the fragmentation of lactose brittle material which generated an higher surfaces area free from lubricant increasing the friction coefficient.

Conclusion

The presence of a brittle material in the formulation was beneficial for the layer adhesion during the manufacturing of bi-layer tablets. However, its fracture in smallest particles caused an increase of the radial frictions between the tablet and the die wall, negatively affecting the tablet production.

This problem could be overcome by manufacturing bi-layers tablets of SUCR_1/ibuprofen lysine at pre-compression forces below 2 kN to avoid the layer separation.

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Comparison of breaking tests for the characterization of the interfacial strength of bilayer tablets

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ABSTRACT

The bilayer tableting technology is gaining more acceptance in the drug industry, due to its ability to improve the drug delivery strategies. It is currently assessed by the European Pharmacopoeia, that the mechanical strength of tablets can be evaluated using a diametral breaking tester. This device applies a force diametrically, and records the tablet breaking point. This approach has been used to measure the structural integrity of single layer tablets as well as bilayer (and multi-layer) tablets. The latter ones, however, have a much complex structure. Therefore, testing a bilayer tablet with the currently used breaking test methodology might not be appropriate.

The aim of this work was to compare results from several tests that have been proposed to quantify the interfacial strength of bilayer tablets. The obtained results would provide an indication on which tests are appropriate to evaluate the robustness of a bilayer tablet.

Bilayer tablets were fabricated using a model formulation: Microcrystalline Cellulose (MCC) for the first layer, and spray dried lactose (SDLac) as second layer.

Each set of tablets were tested using the following tests: Diametral Test, Shear Test and Indentation Test.

The tablets were examined before and after the breaking test using Scanning Electron Microscopy (SEM). When a bilayer tablet was subjected to shearing or indentation, it showed signs of clear delamination. Differently, using the diametral test system, the tablets showed no clear difference, before and after the testing. However, when examining each layer via SEM, it was clear that a fracture occurred in the layer made of SDLac. Thus, the diametral test is a measure of the strength of one of the two layers and therefore it is not suited to test the mechanical strength of bilayer tablets.

1. Introduction

The compressed tablet is one of the most popular dosage form in use today. Moreover, the association of drugs in a single tablet is a therapeutic strategy that is gaining more acceptance. Therefore, bilayer (or multilayer) tablets are gaining popularity due to a confluence of factors. It can reduce the burden for patients by administering two or more active pharmaceutical ingredients (APIs) in a single dosage form. The bilayer tablets can be designed to overcome chemical incompatibility between two active components. Lastly, those tablets are also developed to control the delivery rate of one or more APIs, by interposing layers with different releasing properties (Abebe et al., 2014; Kottala et al., 2014).

The manufacture of a bilayer tablet is a delicate procedure: it needs to ensure both the physical and chemical endurance (the Critical Quality Attributes) of the tablet itself during the industrial processing procedures (manufacturing, handling, packaging and shipping) and to enable the activity of the drugs after the tablet administration, to reach the Target Product Profile (Kottala et al., 2014). The construction of such complex oral dosage forms requires on one hand the complete control of any aspects of its formulation and compression processes, i.e. the Critical Material Attributes and the Critical Process Parameters, and on the other hand the control of the release of each active substance with an individual and controlled manner.

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Although the manufacture of bilayer tablets has been successful for over 50 years, there is still a need for improvement, in order to ensure that the manufacturing process will make possible to satisfy both technological and therapeutic specifications as well as regulatory requirements (Abdul and Poddar, 2004).

In fact, the main problem that occurs during the manufacturing of bilayer is delamination (Podczeck, 2011; Vaithiyalingam and Sayeed, 2010). It corresponds to the splitting of the tablet at the interface between the layers. This separation between the layers may take place just after compaction or later during the storage (Kottala et al., 2012b). Some explanation of the delamination phenomenon can be found in the literature, and it is related to different parameters such as the elastic recovery of the two layers (Anuar and Briscoe, 2010; Busignies et al., 2013; Podczeck and Al-Muti, 2010; Podczeck et al., 2006) or the roughness of the interface (Kottala et al., 2012a). It was also shown that the process parameters can influence the interfacial strength. For example to ensure a good cohesion, the pressure applied on the first layer should be kept to a minimum, and the pressure applied on the second layer should be high enough (Dietrich et al., 2000; Inman et al., 2007, 2009; Vaithiyalingam and Sayeed, 2010).

Due to the importance of the adhesion at the interface between layers, it is critical to have a relevant and robust method to quantify its strength. This is a matter that is becoming more interesting with the development of Quality by Design (QbD) for the manufacturing of a bilayer tablet. Product and processing understanding is a key element to QbD (Yu, 2008). As such, it is clear that the control of each single step and the quantification of each single parameter should be as accurate as possible.

When applying the QbD methodology to the design of a bilayer tablet, the accurate quantification of the mechanical resistance of interface between the two layers is necessary to correctly assess the quality attributes of the final product.

Unfortunately, as currently stated by the European Pharmacopoeia (ver. 8), there is no standard methodology to measure the interfacial strength of bilayer tablet. The only methodology that is described in the European Pharmacopoeia to test the strength of tablet is the diametral compression test but in the corresponding monograph, there is no reference of its use in the case of bilayer tablets. Nevertheless, several articles in the literature can be found that perform the diametral compression test to characterize the interfacial strength of a bilayer tablet (and therefore the final robustness of the tablet itself) (Wu and Seville, 2009; Papós et al., 2015).

On the other hand, other testing methodology are acknowledged, such as the relatively new indentation test (Busignies et al., 2014). This test proved, with a pharmaceutical Quality by Design approach, to be suitable for the measurement of the interfacial adhesion of bilayer tablets. Another test that is currently under investigation is the shear test (Dietrich et al., 2000; Klinzing and Zavaliangos, 2013). This device is described carefully in the materials and methods part of this publication. Lastly, it is possible to measure the interfacial strength via traction testing (Akseli et al., 2013). This testing is operatively complicated to execute, because the examined bilayer tablets must be individually glued to two tablet holders using a cyanoacrylate-based fast-acting glue and left for an hour to ensure a good adhesion. It must be also ensured that no glue migrates through the pores up to the interface of the examined bilayer tablets.

To try to clarify the testing conditions, we chose in this work to use three different tests to study the interfacial strength of a model formulation: diametral compression test, shear test and indentation test. These three tests were chosen because they are easy to perform, applicable to various compacts shape and they do not necessitate specific sample preparation. As such, they could be chosen as a standard test at an industrial level. The aim was to study if these three tests were indeed able to discriminate tablets with different interfacial strength or if they should be avoided for the characterisation of the interfacial strength of bilayer tablets.

2. Materials and methods

2.1. Manufacturing of tablets

As studied in previous works, and as explain above, the main process parameters that have an influence on the strength of bilayer tablets are the applied pressure on the first layer and the main compaction pressure. Then, in order to compare the ability of each test to discriminate the robustness of a bilayer tablet, tablets with different mechanical strength at the interface were produced by varying these two process parameters.

The compaction experiments were performed using a Styl'One Evolution compaction simulator (Medelpharm, Lyon, France). This device is a single punch tableting press, monitored by the Analis software. The displacement of the upper and lower punches is controlled electronically.

The pressure applied by the punches to the powder bed is measured with strain gauges. The machine can be also controlled to reach a given pressure. For all the experiments, the tablets were produced using standard Euro D round and flat punches with a diameter of 11.28 mm.

Bilayer tablets were manufactured using a model formulation: Microcrystalline cellulose, MCC (Vivapur 12, JRS PHARMA GmbH & Co, Rosemberg, Germany) for the first layer, and spray-dried lactose, SDLac (Flowlac 90, Meggle, Wasserburg, Germany) as second layer, adding 1% of Magnesium Stearate to both powders as a lubricant (Wang et al., 2010). The filling height for the layers was adjusted to obtain a total height of about 10 mm before compaction

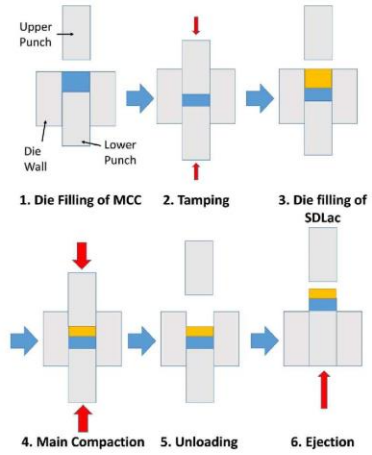

Fig. 1. Bilayer compression cycle used in this work.