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Challenges in technology of bilayer and multi-layer tablets: a mini-review

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ABSTRACT

Bilayer and multi-layer tablets are enjoying growing popularity among original drug and generic product manufacturers. Multi-layer tablets have many key benefits compared to classic immediate-release tablets. The use of such solid oral dosage forms simplifies dosing regimens in combination therapy, and thus improves patient compliance. However, the technology of multilayer tablets is demanding and requires precise choice of excipients and production parameters with regard to each technological step. The main benefits of multi-layer tablets, certain aspects of their production and the challenges encountered during the compression process are reviewed in this paper.

INTRODUCTION

The aim of the review was to describe the modern technologies of bilayer and multilayered tablets. The difficulties in the production of multilayer tablets *i.e.* selection of the active substance possessing appropriate physicochemical properties, determination of the type, number and thickness of layers, determination of the optimal compression force, have been described.

Solid oral dosage forms are the most advantageous and habitually used route to deliver drugs due to ease of administration and flexibility of the design [1,2]. Compressed tablets are one of the most popular and acceptable dosage forms. Furthermore, controlled release oral dosage forms are increasingly popular. They contribute to a better patient compliance, maintaining uniform dose levels and reducing dose frequency, as well as side effects [3,4].

In some pathological conditions, immediate release of the dose must be achieved to provide a rapid onset of action, followed by extended drug release to maintain the therapeutic effect [5]. In order to execute the dual drug release concept, one solution is a multi-layer tablet preparation [6,7]. Over the past years, multi-layer tablets, whether as an oral immediate- or a controlled-release system, have, hence, become increasingly popular [2,8]. The multi-layer tablet is a delivery system that aims to deliver two or more drugs at different rates or simultaneously release two or more drugs with desired release rate [8,9]. What is more, two or more incompatible drugs may be formed into a multi-layer tablet.

Multi-layer tablets are favored due to the controlled release profiles of the active ingredients [10,11]. Modified/controlled release formulations offer more benefits than immediate release dosage forms with the same active substance [12]. Products with modified/controlled drug release are designed to optimize the treatment regimens and provide greater patient convenience and compliance [13]. The basic aim of controlled release systems is to maintain the drug delivery at a constant level.

Throughout the years of research aimed to develop new dosage form of zero order or nearly zero order kinetic [1,14-16], a variety of oral dosage forms have come about. These hold modified release properties, and include such forms as film coated capsules, pellets or tablets, compression-coated tablets, systems using electrostatic deposition, osmotic or ion controlled systems, technology three-dimensional (3D) printing dosage forms [1,17-23]. Miscellaneous release profiles e.g. delayed release, pulsatile or multimodal delivery profiles, may be attained using changes in the composition, combination of layers or the geometry of multi-layer tablets [1].

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Monolayer and multi-layer tablets are produced by compacting powder substances under compression force. The manufacture of a multi-layer tablet is a delicate process, yet it has many common technological features. Layered tablets are heterogeneous systems composed of two or more different layers that are separated by an interface within its final single body [10]. In these systems, control of the release kinetics is primarily achieved by the composition of each layer [24]. Properties of the finished layered tablets (such as hardness and the tendency to lamination) depend on the quantitative and qualitative composition, but also on the tendency to deformation during each layer of the tablet compression [8].

Although the manufacturing process of bilayer and multi-layer tablets has been refined for over 50 years, there is still a need for improvement in order to assure that the production meets both the technological and therapeutic expectations, as well as the regulatory requirements [1,25].

THE ADVANTAGES OF MULTI-LAYER TABLETS

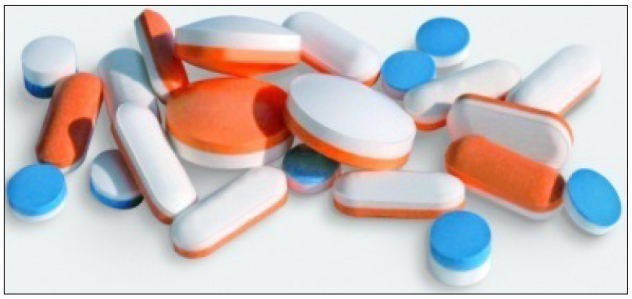
The main advantage of the multi-layer tablets is the ability to produce tablets with two or more incompatible active pharmaceutical ingredients (API) in a single tablet. Indeed, incompatible APIs can be formulated in two, three or more layers, etc. If the chemical stability of the APIs is still not acceptable, an alternative is to add a buffer layer between the two API-containing layers. The layer will block activity between the two APIs and thus hinder interaction at the layer interface [8,13,26-28]. This approach, often leads to much better overall chemical stabilization of the final drug product. In the multi-layer tablet, the API level in the individual layers may be the same or different.

Using the process of multi-layer compression, drugs with an extended release and immediate release profiles can be obtained [29,30]. Moreover, the same API or different APIs with different release profiles can be delivered as a single multi-layer dosage form [14,16,23]. The release profiles may be altered by including layers with various release patterns, or by combining slow-release with immediate-release layers [23]. Thus, the combination of several APIs in one multi-layer tablet simplifies the dosing regimen and contributes to a better adherence to the treatment recommendations [31-33]. Types of multi-layer tablets are shown in Figure 1 [5].

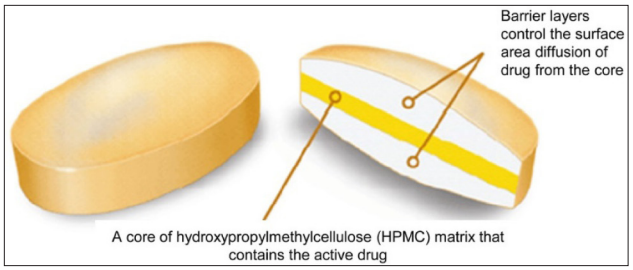
VARIOUS KINETIC MODELS IN DEVELOPMENT OF MULTI-LAYER TABLETS

By changing the geometry of the drug form or changing the composition of individual layers, tablets with a specific release profile can be obtained, such as: pulsed, bimodal, delayed and multimodal. The diverse forms of drugs include: zero order sustained release, quick/slow delivery system, time programmed delivery system, and bimodal release profile.

A zero order sustained release formulation contains in its composition a hydrophilic or hydrophobic polymer constituting a matrix or a protective layer. The release control is obtained by polymer coating the matrix on both sides, leaving the sides uncovered to dissolve the drug through the medium [34].



a. Bilayer tablets



b. Triple layer tablet

Figure 1. Types of multi-layer tablets

The quick/slow drug delivery system – type formulation is characterized by initially rapid and then prolonged release of the drug. In this way, immediate action of the drug is obtained and then constant drug release is maintained to ensure constant plasma concentration [35].

A time programmed delivery system provides immediate release of the drug and then controlled release over time, e.g. release in the intestines at the appropriate time. This system consists of a tablet core that is coated with different polymers. The release of the drug from the tablet core occurs after swelling/erosion of the hydrophobic or hydrophilic layer covering the core, then it is a pulsatile release [36].

A bimodal release profile/bimodal release system formulation is characterized by initially rapid release, then slow and quick again. This is a sigmoidal release profile (Fig 2). This system provides fast action to compensate for relatively slow absorption in the stomach and large intestine [5].

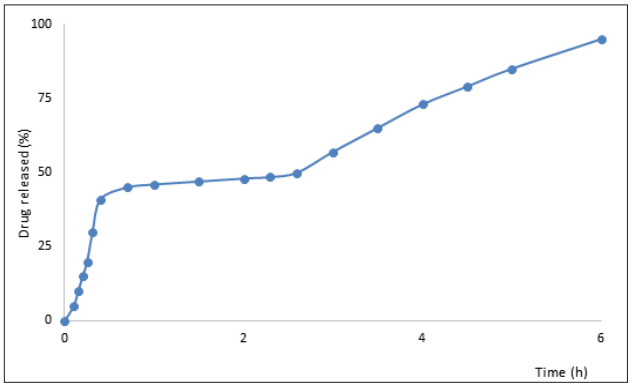


Figure 2. Bimodal release profile

DIFFICULTIES IN MANUFACTURING MULTI-LAYER TABLETS

In addition to the desired therapeutic properties, multi-layer tablets should also have adequate mechanical strength and hardness to endure the normal stresses of processing, handling, packaging and transporting [8,37]. Multi-layered

tablets might be composed of a core and one or more barrier layers and/or a core and outer shell in the case of press-coated tablet. As they are not easy to design and manufacture, several problems that affect the properties of the dosage form may emerge during production. Some of the principal difficulties include: inadequate hardness [1], imprecise regulation of layers and tablet weight [20], elastic mismatch between conterminous layers [38], and susceptibility to delaminate [1] during the various stages of manufacture.

Inadequate manufacturing process of multi-layer tablets may contribute to the delamination (distinct separation of layers along the interface). The delamination may occur directly after compression, at a subsequent step of technological process, or during storage [9,39] and could take place between adjacent layers (interlayer delamination) or within one of the layers (intralayer delamination) [13]. As a consequence, the patient cannot receive one of the intentional substances or receives an improper dosage. Therefore, to minimize the possibility of their occurrence, it is necessary to pay particular attention to the applied substances properties and formulation process parameters. These include the tools and materials which may be incorporated in the design of multi-layer tablets, the factors that cause delamination, the order and weight proportion of layers, the mechanical strength of tablet and each layer, and the interphase adhesion of the layers [8].

1. API and excipients

Physicochemical properties of API and excipients are crucial to the success of multi-layer tablets manufacturing [8,40]. The nature of materials plays a key role in the strength of multi-layer tablets and their manner of fracture [41,42]. In this regard, parameters including brittleness, viscoelasticity, plasticity and compaction properties, have a significant impact on the compression process [11]. Formulations for each layer of the multi-layer tablet should be chosen to demonstrate a sufficient volume reduction and create a mechanically strong and coherent solid form. Thus, they should be characterized by good compressibility (ability of a substance to reduce the volume under pressure) and compatibility (ability of powdered substances to transform into tablets) [8]. It is important to optimize the materials' particle size distribution, flow properties and compression ability when used in layered tablet manufacturing, so as to ensure accurate control of each layer weight. The latter is a decisive factor in ensuring acceptable uniformity of the APIs [13]. Moreover, to obtain satisfactory API content uniformity, it is recommended to set the compression of the layer of smaller drug dose or weight as the priority. Unfortunately, today's commercial presses are equipped with weight control mechanism that allows the monitoring of only the first layer and whole tablet mass. This greatly complicates the weight control of multi-layer tablets [8].

In order to address the challenges of the development of multi-layered tablet formulation, it is beneficial to maintain a certain level of similarity between the formulation layers. If it is impossible to keep a similar weight of each layer (e.g. the amount of drug is high in only one layer for clinical reasons or the weight of one layer is high for formulation reasons), the compositions of the layers should be created using the some common excipients. The similarity of the weight/formulation of the two layers subsequently leads to likeness of the physical properties of the materials used for the tablet preparation, such as particle size, density, and flow. Furthermore, this proceeding contributes to obtaining layers of similar compaction profiles and improves the physical integrity of the multi-layer tablet. When varied formulations must be used for each layer, it is frequently necessary to adjust the compression process in order to obtain acceptable physical properties [13].

2. Ratio and the sequence of the layers

Another aspect of the multi-layer tablet compression is the ratio of the layers and the sequence of their arrangement for the same purpose of reducing the potential of interlayer delamination or intralayer capping [8,13,37,43]. Most commonly, bilayer tablets are prepared so that the weight ratio of the layers is 1:1 or 1:2. Sometimes layer ratios of 1:3 or even 1:4 are used, and during developmental research, more disproportionately, layers up to 1:6 [8,13] have been formulated. In the case of using considerably more weight of the first layer over the weight of the second layer, second layer preservation of the integrity is more difficult. Therefore, it is preferable to firstly compress the layer of lower weight. Unfortunately, currently available presses do not allow the compression of a first layer of lower weight. Thus, there is no possibility to avoid problems associated with applying higher weight upon the first layer of tablet [8]. Still, Kottala *et al*. [43] has prepared bilayer tablets with methyl cellulose and lactose at ratios 1:1, 1:3, 3:1, and concluded that neither the ratio nor the used materials had any significant influence on the breaking force.

Akseli *et al*. [37] investigated the effect of the layers sequence on the mechanical strength of the bilayer tablets. When the first layer was made with methyl cellulose and the second with starch, a significant decreased surface roughness of the methyl cellulose layer was noticed, which resulted in a declined intramolecular attraction between two neighboring layers. After reversal of the layers sequence (starch in the first layer, methylcellulose in the second layer) the tablets were characterized by relatively high tensile strength compared to the previous. Thus, the sequence of layers with different compactability properties allows control of the interface roughness, and hence affects the interfacial strength [37]. Common practice in the manufacturing of multi-layer tablets is to use the materials with higher fragmentation tendency to form the first layer, and materials with a greater deformation capacity in successive layers. The compaction properties of each layer could be estimated on the basis of powder/granule ability to compaction (curve compact tensile strength versus solid fraction) [44].

3. Hardness of tablets

Tablet hardness is expressed as tensile strength and is calculated according to the Fell's and Newton's formula:

$$\sigma = 2P/\sigma\ Dt$$

σ – tensile strength [kg/cm^2]; D – tablet diameter [cm]; t – tablet thickness [cm]; P = force applied to fracture [kg] [45].

The tensile strength of bilayer tablets prepared with commonly used excipients can be precisely provided using a simple model compiled by Wu *et al*. [46] based on the Ryshkewitch-Dukworth equation. Examination of layered tablets properties in early formulation development can be carried out with various tools. Inter alia it is essential to determine the interfacial strength, perceive atypical extreme properties of compressed layers, assure consistency of the tablets obtained, elucidate the mechanisms of the material damage occurred during manufacture, understand the impact of the factors relevant to press equipment (e.g., the speed of punch, the compression forces, etc.), reduce energy consumption through minimizing manufacture defective tablets, and optimize environmental conditions [8]. Abebe *et al*. [8] pointed out that the most effective forms of testing are: horizontal or vertical axial strength test [37,39], three-point bending test [11], shear strength test for measuring the adhesion strength [47], acoustic measurements (in an ultrasonic bandwidth) [38], imaging with magnetic resonance [48], terahertz pulsed [49] and computed tomography (CT) [11,37].

4. Compression force

Compression force on the particular layer has a significant influence on the strength and interfacial adhesion between layers [1,8,28,37,39,41,47], thus contributing to the mechanical integrity of the subsequent multi-layer tablet [39]. Therefore, it is necessary to set an optimum compression force so as to form a finished product with the desired properties. During the compression process (especially ejection from the die and unloading), mechanical stress mismatches between the layers of plastic material may arise to the delamination of the tablet [10,50].

According to the research conducted by the Li *et al*. [27], the most crucial parameter in the production process of multi-layer tablet is the value of compression force used for the first layer, which affects the adherence of layers. The compression pressure and also punch speed greatly affect the compactibility and resistance to compressibility into the die [51]. The task of the first layer of compression forces (generally in the range of 2-18 kN) is to tamp the powder/granulated substances in order to diminish the volume, smooth the first layer surface of the first layer and create a space for depositing the second layer. In general, the application of greater compression force leads to increased tensile strength and decreased surface roughness. Smoothing the surface of the first layer may enhance the delamination by limiting the intermolecular adherence between adjacent layers [13].

The changes discussed above are generally independent of the formulation layers compositions. Karehill *et al*. [52] found that the increase in pressure force applied to the first layer of brittle material resulted in a reduction in surface adhesion and bonding between the layers, and consequently decreased the axial tensile strength of multi-layer tablets. Bilayer tablets based on brittle material show no delamination even at relatively higher compressive force applied to the first layer (e.g. 6 kN) [8]. Conversely, when polimeric material (e.g. methyl cellulose) was a component of both layers, an increase in the force applied to the compressed the first layer of tablet caused a decrease in the interfacial strength of bilayer tablets [42].

The level of the compressive force of the first layer is fundamental to determine the surface roughness of the first layer, which is crucial for the interfacial strength between layers [3]. Moreover, Kottala *et al*. [42] determined that the strength of the interfacial of bilayer tablets of the polimeric material also depends on the compression force applied to the second layer. Accordingly, the interface strength of bilayer tablets prepared of polimeric material is a function of both applied forces in the compression process [8]. Research conducted by Akseli *et al*. [37], Inman *et al*. [39], and Karehill *et al*. [52] demonstrated that force applied to the first layer should be minimal to ensure sufficient surface roughness for enhancing contact and adhesion between the adjacent layers. It is commonly advised to apply a low level of pressure for the pre-compression [13,53] or adjusting the compression zone in the die (especially for the second layer) to reduce the risk of delamination/capping. The phenomenon can be prevented by using one- or two-way die, which diminishes the air bubbles level during compression [13].

The turret speed has also significant impact on the strength of the multi-layer tablets. Tablet crushing strength is raised when the speed of the turret on the main compression force is enhanced. Importantly, these parameters when within a particular range do not affect content uniformity and performing release in the multi-layer and bimodal delivery systems [5,18,54]. However, the release rate of drug declines and the retardation time is augmented with the growing applied compression force. Upon reaching the critical point of the compression force, subsequent changes in these parameters are not noticed, which can be associated with no change in porosity of the tabletted material. To improve strength of adhesion, the run should experience low lubricant content, low compression force to create the core and high compression force for the outer tablet layer [1].

5. Interfacial strength

The main reasons for the capping, cracking, laminating and fracturing of multi-layer tablets are connected with interfacial cracks driven by residual stresses. It should be noted that these changes do not always become apparent immediately after the compacting process [1,8,39]. The presence of the above-mentioned changes in the interface reduce the overall stiffness and increase the tablet brittleness.

The difference in the Young's modulus between adjacent layers of the tablet contribute to an elastic mismatch which generates radial stress and consequently delamination of a multi-layer tablets [8,10,40,50,55,56]. Kottala *et al*. [41] indicated that layer tablets prepared with brittle material (e.g. lactose) in both layers manifested stronger interfacial strength compared to brittle/plastic or plastic/brittle or plastic/plastic compositions. This is because when a brittle material is applied in both layers, elastic mismatches between adjacent layers are minimized. The weakest interfacial strength, however, is obtained when plastic material is used in each layer. In addition, if the material forming the first layer is more elastic, the tension introduced into the system weakens the strength of the multi-layer tablets [55]. Such tablets may even delaminate upon coming off the die [41].

It has been demonstrated that the lack of flexibility of the brittle substance significantly reduces the deformation capacity of particles on the first layer of tablets and thus appropriate porosity of the layer is maintained. This provides nesting sites for mechanical interlocking [39]. It was also pointed out that for plastically deformable materials, the binding strength between conterminous layers diminishes with the reducing of interfacial roughness [52]. Too low porosity of individual layers contributes to the difficulty of the bonding with the next layer and thus the tablet properties are not satisfactory [37].

Furthermore, the amount of expansion of a tablet after ejection from a die varies for different excipients [57]. Since not all substances can be directly compressed, API granulation is performed. The amount of granulation liquid and drying temperature significantly affect the finished product properties [58]. These include the following physical characteristics of granulation – particle size distribution, flowability, bulk density, ability to settle, etc., extensometric responses – plasticity, elasticity, cohesion and lubrication index, ejection strength. Consequently, the physical characteristics of any tablet, e.g. weight variation, thickness, hardness, etc. are affected, as are certain analytical outcomes (such as content uniformity and dissolution profile) [1].

A factor that has a key impact on the value of the interfacial strength is the amount of added lubricious substance [41,44,47]. Tye *et al*. [44] noted that the influence of the quantity of lubricant on the strength of the multi-layer tablet is more pronounced for polymeric materials than for brittle materials. Indeed, the interfacial strength of the multi-layer tablet decreases with an increase in the concentration of lubricant (e.g. magnesium stearate) [41]. A study conducted by Sugisawa *et al*. [59] demonstrated that the increase in the quantity of lubricating agent deteriorated the roughness of the tablets, which entailed a decline of interfacial interactions between the layers. However, it is impossible to not apply lubricant in the manufacture of multi-layer tablets. No lubricant brings about picking and sticking of the first layer [8]. Perhaps the solution is to use an external lubrication (spraying onto the punches and die), as this approach has been shown to improve the production of monolayer tablets [60].

6. Adhesion strength

The adhesion strength is a factor that should be considered in the technological process of multi-layer tablets with layers that are formed singly (complex tablets). In the first step, the central layer of tablet (tablet core) is produced during pre-compression. In the second step, upper and lower layers are compressed onto the central layer [61,62]. Because the central-layer is already a compressed tablet and its rate of release is controlled by the outer layers [63], sufficient interlayer adhesion is difficult to achieve, but is necessary to maintain the physical integrity of a multi-layer tablet [13].

CONCLUSION

Multi-layer and monolayer tablet production share many common features of technology as both of these pharmaceutical forms are made by compacting powdered/granulated API with or without excipients. Multi-layer tablets have many key benefits compared to classic immediate-release monolayer tablets. Recently, substantial progress in the manufacturing of tablets has been made. This has contributed to the improvement of physicochemical properties of tablets, as well as the possibility of producing tablets with modified/controlled release. However, there are still a number of technological challenges that must be overcome in order to obtain a multilayer tablet with similar levels of reliability as found in monolayer tablets. A major source of challenges in the design and manufacturing of the multilayer tablets is heterogeneity of adjacent layers. Fluctuations of even one of compression parameters (e.g. the compression strength, ratio of the layers, arrangement of layers, the used excipients) can significantly affect the properties of each layer and the interfacial strength. However, considering the different parameters of the manufacturing process of multi-layer tablets, it is possible to achieve the desired release profile.

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