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Multi-Layered Matrix Tablets with Various Tablet Designs and Release Profiles

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ABSTRACT – Tablet dosage forms have been preferred over other formulations for the oral drug administration due to their low manufacturing costs and ease of administrations, especially controlled-release applications. Controlled-release tablets are oral dosage forms from which the active pharmaceutical ingredient (API) is released over an intended or extended period of time upon ingestion. This may allow a decrease in the dosing frequency and a reduction in peak plasma concentrations and hence improves patient compliance while reducing the risk of undesirable side effects. Conventional single-layered matrix tablets have been extensively utilized to deliver APIs into the body. However, these conventional single-layered matrix tablets present suboptimal delivery properties, such as non-linear drug delivery profiles which may cause higher side effects. Recently, a multi-layered technology has been developed to overcome or eliminate the limitations of the single-layered tablet with more flexibility. This technology can give a good opportunity in formulating new products and help pharmaceutical companies enhancing their life cycle management. In this review, a brief overview on the multi-layered tablets is given focusing on the various tablet designs, manufacturing issues and drug release profiles.

Key words – Multi-layered tablets, Drug release, Matrix, Tablet design, Manufacturing

Oral solid dosage forms have been regarded as the most convenient and commonly used method of drug administration due to their numerous advantages such as ease of drug administration, high patient compliance, least aseptic constraints, well-controlled scale up processes and flexibility for the design of the dosage forms (Krishnaiah et al., 2002).

Various types of the oral dosage forms have been developed for better efficacy, safety and patient compliance, such as capsules or tablets with immediate release, modified release, delayed release, extended release or sustained release forms. Immediate release dosage forms allow a drug to dissolve with the intention of fast dissolution and absorption of the drug. Modified release dosage forms can be both delayed and extended release drug products. Delayed release dosage forms can release the drug at a time later than that immediately following its administration. Extended release dosage forms can release the drug over an extended period of time after its administration. Various mechanisms have been used to modify the drug release profile from a modified release tablets or capsules, such as osmoticlally driven system, film coated pellets, systems controlled by ion exchange mechanism, systems of three dimensional printing technology, systems using electrostatic deposition, muco-adhesive systems, and microcapsules, which makes them a more sophisticated and complicated drug delivery systems. Though, various systems have been used in the modified release dosage drug products, the main purpose is the optimization of a therapeutic regimen by providing slow but continuous delivery of drug over the entire dosing interval. Moreover, they provide greater patient compliance and convenience (Chien, 1982; Buri et al., 1985; Wilding et al., 1991).

The typical modified release drug delivery system is of matrix type in which drugs are uniformly dissolved or dispersed throughout a polymer matrix. The matrix can be tablets or granules. Typical matrix-forming polymers are HPMC (hydroxypropyl methylcellulose), Na-CMC (sodium carboxymethyl cellulose), HPC (hydroxypropyl cellulose), MC (methylcellulose), Eudragit® and natural gums. Among the various polymers, hydrophilic polymers are preferred in the modified release matrix tablets (Abdul and Poddar, 2004). The matrix tablet or capsule formulation can prolong the drug release profile relatively over a long period of time effectively with low cost and ease of manufacturing (Lee, 1992; Peppas, 1988).

The drug release profile of a hydrophilic matrix formulation is typically a time dependent profile (Narasimhan and Langer, 1997; Conte and Maggi, 2000; Nelson et al., 1987; Peppas and Sahlin, 1989; Buri and Doelker, 1980; Lee, 1985). However, the drug release profile of an oral modified release matrix tablet (plain matrix tablet) containing hydrophilic polymer

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showed initial high release rate and followed by near first-order diffusion due to the dissolution of the drug present at the surface of the matrix (Figure 1). The initial high release rate observed in the beginning of the release process is known as burst effect, which is often undesirable as it may have negative therapeutic effects (Abdul and Poddar, 2004). After the burst effect hydration and consequent swelling and/or erosion of the polymer occur. This phenomena control the release process. However, the diffusion path length increases with time and a saturation effect is attained, resulting in a progressively slow release rate toward the end of dissolution period (Narasimhan and Langer, 1997; Conte and Maggi, 2000; Nelson et al., 1987; Peppas and Sahlin, 1989; Buri and Doelker, 1980; Lee, 1985).

A number of variables affect the release pattern of drug from polymeric matrix devices such as physiochemical properties of drug and excipients, content of drug and polymers, drug/polymer weight ratio, design of dosage forms and manufacturing process. Over the past decades, new drug delivery concepts to achieve zero-order or near zero-order release rate have been investigated extensively (Cobby et al., 1974 a, b; Hildgen and McMullen, 1995; Danckwerts, 1994; Kim, 1994; Benkorah and McMullen, 1994; Samuelov et al., 1979; Scott and Hollenbeck, 1991; Brooke and Walshkuhn, 1977; Hsiesh et al., 1983; Zin El-Din et al., 1989; Shah and Britten, 1990; Bodmeier and Paeratakul, 1990). Various matrix geometries have been used over the last two decades to achieve an almost constant release rate of the drug with time. One of these techniques relies on the use of multi-layered matrix tablets as drug delivery devices (Figure 1).

In multi-layered matrix tablets, one or two layers of controlled release polymers are used on one or both sides of the matrix tablet such that the swollen hydrophilic polymer control the drug release after its oral administration. In other words, the polymer coated layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent pen-

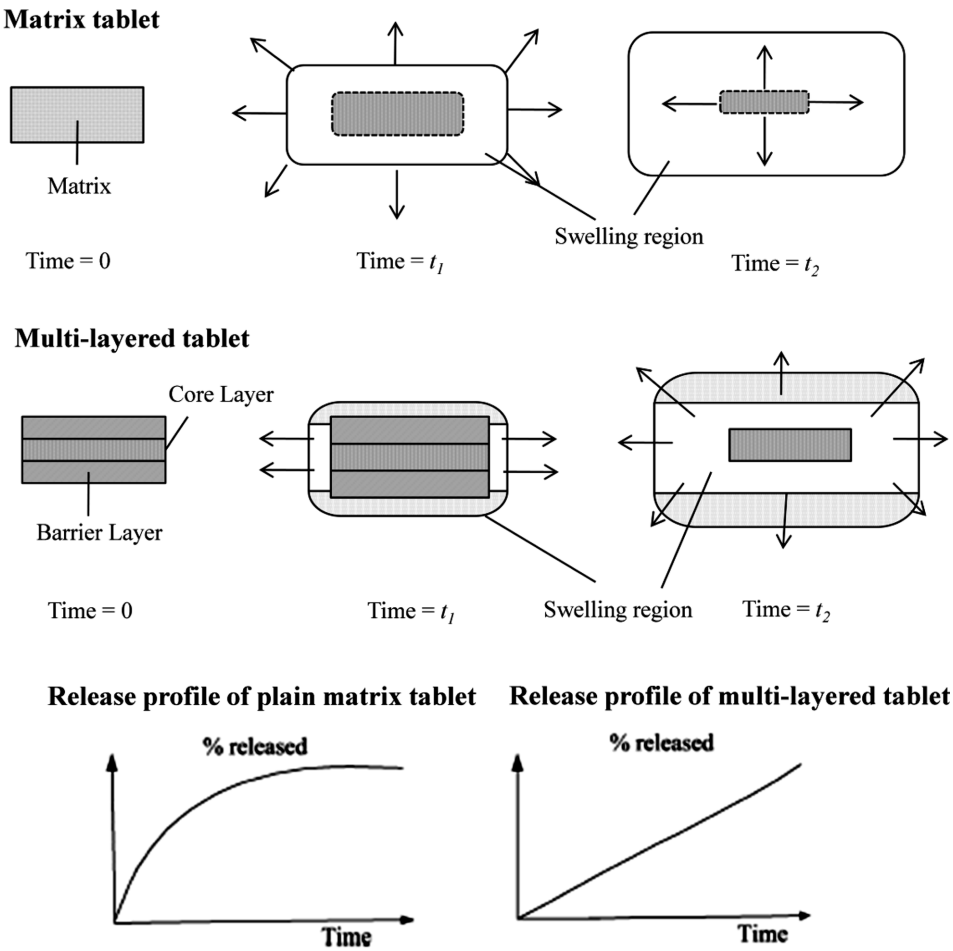

Figure 1. Effect of the application of polymeric layers (barriers) on the drug release from a matrix core in a multi-layered tablet compared to a matrix tablet (modified from Abdul and Poddar, 2004).

etration rate (Colombo et al., 1990; Conte et al., 1993; Conte and Maggi, 1998). Therefore, the drug release can be controlled at relatively constant level and the burst effect can be avoided. The multi-layered matrix tablet release the drug at a controlled and predetermined rate while maintaining their therapeutically effective concentrations in the systemic circulation for prolonged time.

Market trends of multi-layered tablets

Multi-layered matrix dosage forms recently have drawn a lot of attention from industry and even in academia due to the advantages of the dosage forms. They can control the delivery rate of either single (Bogan, 2008) or two different active pharmaceutical ingredients (APIs) (Kulkarni and Bhatia, 2009; Nirmal et al., 2008), separate incompatible APIs from each other, control the release of an API from one layer by utilizing the functional property of the other layer, and modify the total surface area available for API layer either by sandwiching with one or two inactive layers in order to achieve swellable/erodible barriers for modified release (Efentakis and Peponaki, 2008; Phaechamud, 2008). Because of these unique characteristics, multi-layered matrix tablets are often used to provide a combination of immediate release dose for fast acting relief and a dose of controlled release to maintain the therapeutic effect. Table I shows the multi-layered products in the market with active ingredients and applied diseases.

Current issues and challenges of multi-layered tablets

Even though many progresses have been achieved on the multi-layered matrix tablet formulations, several issues are still coming up including layer separation, insufficient hardness, inaccurate individual layer weight control, and cross-contamination between the layers. These problems might be critical for the product quality as well as safety. They occur mainly during the manufacturing process and sometimes in *in vitro* experiments. Pharmaceutical scientists and engineers have to evaluate the physicochemical characteristics of the APIs and excipients carefully to overcome or avoid the issues. Separation of the each individual layer in a multi-layered tablet is a common problem and significantly impacts the quality and efficacy of the product. It can occur during the compression and/or the dissolution process. The main cause of the separation can be insufficient bonding between the adjacent layers during the tablet compression. However, this issue can be relieved by assessing the force required to separate the layers of a multi-layered tablet. This might help to identify why each layer separates and to consequently take corrective action effectively.

When the two symmetrical moving swelling fronts meet in the multi-layered matrix tablet using a swellable hydrophilic polymer, the strong swelling pressure associated with the disappearance of the glassy core could be developed. It might result in the lamination of the tablet and the formation of "the butterfly-shaped" hydrated matrix. Under the influence of swelling pressure and the differential extent of hydration in the split region, the edges of the matrix would curl outwards leading to the formation of "the butterfly-shaped" matrix (Figure 2) (Cahyadi et al., 2011). This phenomenon might be affected by the compaction forces and the ratios of matrix components. The extent of the butterfly effect was relatively common to very thin tablets compressed by enough forces. This phenomenon may affect the undesirable release properties of the multi-layered matrix tablet.

Design factors to formulate multi-layered matrix tablets

There are various factors have to be considered while designing a multi-layered matrix tablets; matrix hydration and swelling rate, diffusion and release mechanism and modulation

Table I. *Multi-layered matrix tablet products in the market with product information*

Product Name	Active pharmaceutical ingredient	Applied disease	Company
Sular®	nisoldipine	calcium channel blocker	Shionogi Inc.
Zyflo CR®	zileuton	leukotriene synthesis inhibitor	Cornerstone Therapeutics Inc.
Coruno®	molsidomine	chronic angina pectoris	Therabel
Diclofenac-ratiopharm® uno	diclofenac Na	pain and inflammation in patients suffering from rheumatoid arthritis	Ratiopharm
Madopar DR®	levodopa and benserazide HCl	Parkinson disease	Roche
Paxil CR™	paroxetine	selective serotonin reuptake inhibitor	GlaxoSmithKline
Requip® XL™	ropinirole	Parkinson disease	GlaxoSmithKline
Dilacor XR	diltiazem HCl	calcium ion influx inhibitor	Watson Pharma, Inc.
Cordicant® Uno	nifedipine	hypertension and angina pectoris	Mundipharma GmbH

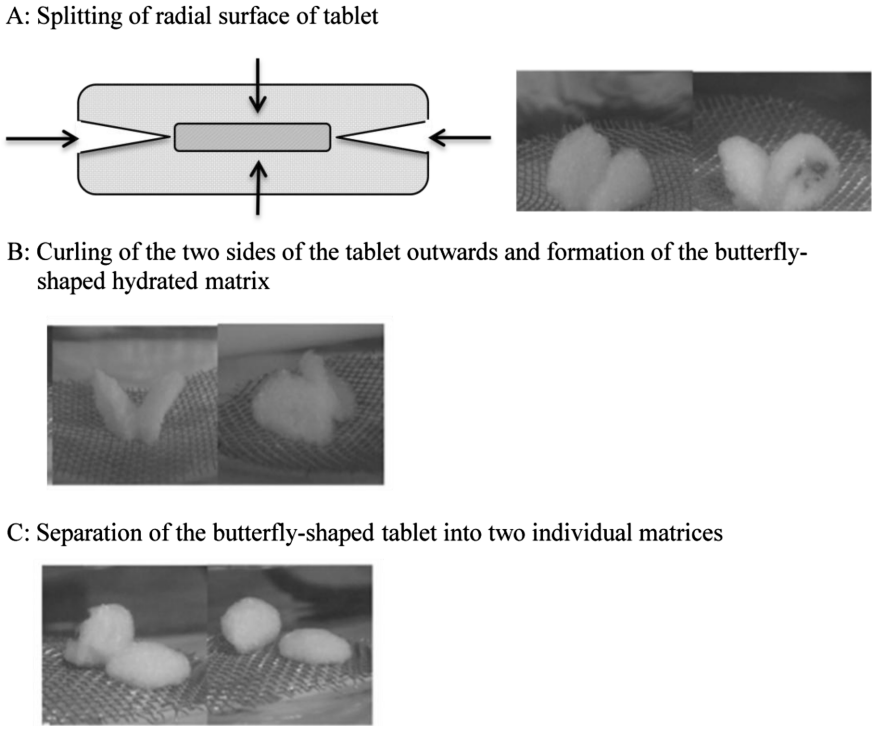

Figure 2. Progression of events during tablet dissolution with photographic pictures for the manifestation of butterfly effect (→ dissolution medium, ▭ glassy core): (A) splitting of radial surface of tablet, (B) curling of the two sides of the tablet outwards and formation of the butterfly-shaped hydrated matrix, (C) separation of the butterfly-shaped tablet into two individual matrices (modified from Cahyadi et al., 2011).

of the matrix surface. The drug release mechanism from each matrix layer of multi-layered tablet is affected mainly by polymer macromolecular relaxation and drug diffusion (Lee, 1985; Ritger and Peppas, 1987). The swellable polymer relaxation and drug diffusion depend initially on the rate at which water may enter the device. Therefore, design of multi-layered matrix tablets is based on a rate factor (matrix hydration rate and diffusion rate) and a modulation factor (modulation of the surface and inner of matrix through which the drug can be delivered) (Abdul and Poddar, 2004). With these considerations, multi-layered matrix tablets may result in a linearization of the release profiles, which can help to facilitate the development process.

Additionally, coating with an inert impermeable film has been applied selectively on the various sides of matrix layers (Colombo et al., 1987; La Manna et al., 1991). Figure 3 shows the typical examples of multi-layered matrix tablets with four partially coated designs. The coating was applied on the tablet faces and on the side wall. The resulting tablets showed significantly different release profiles (Figure 3). In general, the coating considerably reduces the drug releasing surface compared with the uncoated tablet and also able to modulate both release extent and kinetics.

Instead of the impermeable films, swellable polymers and erodible barrier layers can be utilized for the design of multi-layered dosage forms. The evaluation of the polymer barrier was carried out with different methods (Conte et al., 1993). The swellable barriers present a more all-in-one system in which both the core and the barrier may swell without any internal stress during the dissolution process (Conte et al., 1993). Based on the technology, Dilacor XR of Rhone Poulene-Rorer was launched in 1992 in the US market, which was a device for the 24-hour extended release of Diltiazem hydrochloride. Multi-layered matrices were used as modular units. Each unit was a three-layered tablet with two barrier coatings and a core containing 60 mg of API. Two, three, or four modular units can be placed into a hard gelatin capsule to obtain different dosage strengths (Figure 4). However, each maintains typical release properties of the geometry systems (Wilding et al., 1995). These various multi-layered design led to the production of variable tablet geometry with specific release properties.

Quick/slow drug delivery systems

During the early stage of pharmaceutical development, one of the major concerns was how to correlate *in vitro* drug

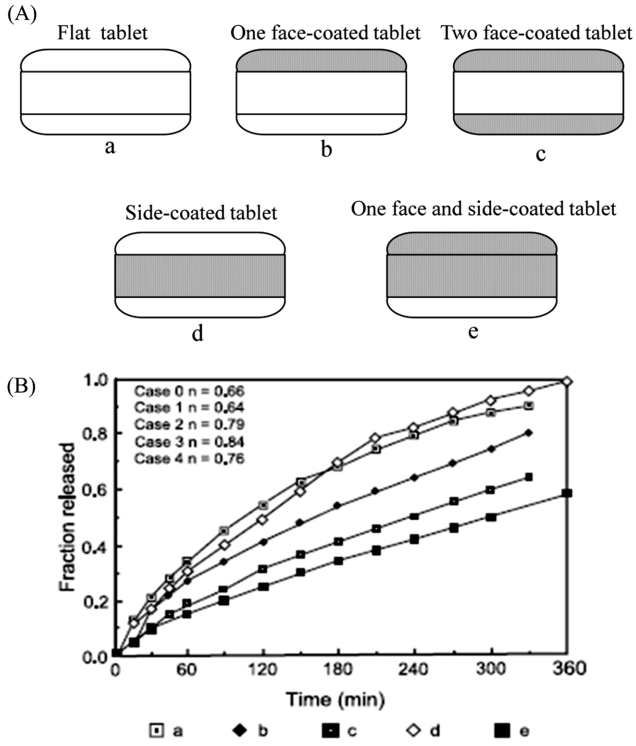

Figure 3. Schematic representation (A) and release profiles (B) of the matrix tablet (A-a) and of the four partially coated designs (A-b, A-c, A-d and A-e) (redrawn from Conte et al., 1993).

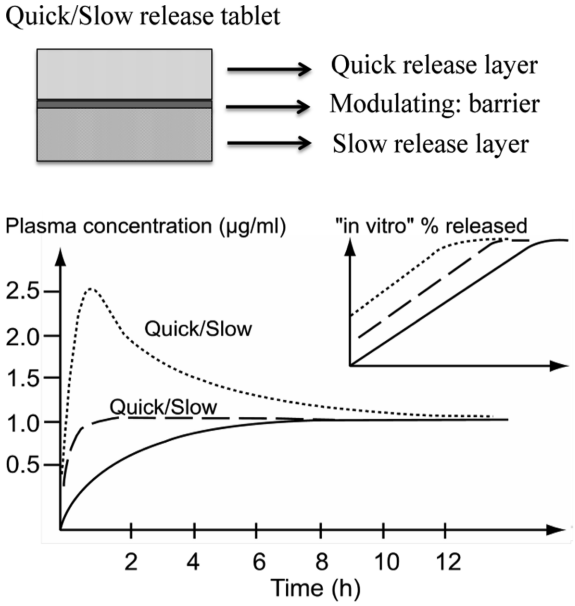

Figure 5. Simulated plasma levels for different dose fractions combinations for a quick/slow Geometric device. Simulated plasma levels for different formulations of a model drug: Quick/Slow dose combinations of 0/120 mg (——), 30/120 mg(---) and 90/120 mg (····) (modified from Conte and Maggi, 2000).

release characteristics with *in vivo* pharmacokinetic (PK) profiles in a short period of time. Efficacy of a drug product can be expected based on the *in vitro* release profiles with the help of a simple simulation approach using traditional PK models. Especially for the development of sustained release systems, the simulation can provide *in vitro* release targets or optimums to maximize efficiency of the drug product. Quick/slow delivery system was one of the approaching methods to obtain the efficiency of the product (Maggi et al., 1992; Maggi et al., 1997).

The quick/slow delivery system was composed of an immediate release layer and a conventional geomatrix system. It can provide the quick onset of drug plasma levels to obtain fast appearance of the therapeutic effect, followed by a period of constant release rate (Figure 5). As an example, the biphasic release of sodium diclofenac (Diclofenac-ratiopharm® Uno, Ratiopharm GmbH, Germany) and Naproxen quick/slow system was developed and launched in the market (Maggi et al., 1997). This system satisfied the ideal range of formulation properties, which was identified by the correlation of *in vitro* release and *in vivo* target (Maggi et al., 1992; Maggi et al., 1997; Conte et al., 1994).

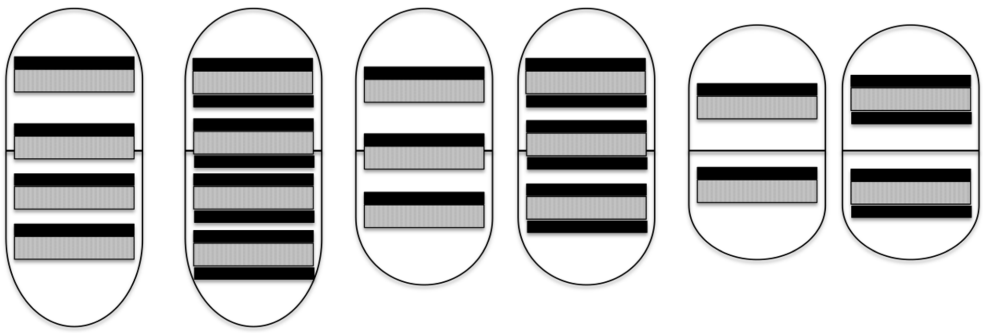

Figure 4. Various gelatin capsules containing geomatrix modular units to obtain different dosages or to combine different dissolution performance (modified from Conte and Maggi, 2000).

Sigmoidal release profiles of bimodal delivery system

In vitro zero order release rate has been regarded as an ideal pattern for maintaining constant drug levels in plasma. However, zero order release may not mean zero order drug absorption. Drug absorption rate is dependent on where the drug product is in the human body after the drug administration. Usually, drug absorption rate is slow in the stomach, rapid in the proximal intestine and decline significantly in the distal segment of the intestine (Abdul and Poddar, 2004). Therefore, in order to keep the zero order drug absorption, increasing or reducing the drug release rate in a timely manner is necessary to adjust constant drug levels in the plasma. A bimodal drug release system can provide such a variable release rate.

The bimodal release is characterized by sigmoid release profile, firstly rapid release, secondly slow but constant release and then followed by a rapid drug release again (Figure 6) (Junginger, 1993). This bimodal release system can provide many advantages. It offers fast drug release during the initial and later phase to compensate for the relatively slow absorption in the stomach and large intestine. As therapeutic agents can be provided more effectively at the site of action, the system can be used to design programmed release oral drug delivery systems. Many experiments have been conducted to obtain bimodal drug release patterns. Typical examples are HPMC-based matrix tablets (Shah, 1987; Shah et al., 1989), core-incup tablets (Sirkia et al., 1994; Sirkia et al., 1994; Halsas et al., 1998), three layer Geomatrix tablets (Conte and Maggi, 1987; Conte et al., 1997), and layered matrix tablets (Streubel et al., 2000). The four layered bimodal delivery system was shown in Figure 6, which is designed to have quick onset of dissolution, promoting greater concentration gradient to compensate for poor absorptivity in stomach. The sustained release portion is controlled by barrier layers to maintain constant release rate.

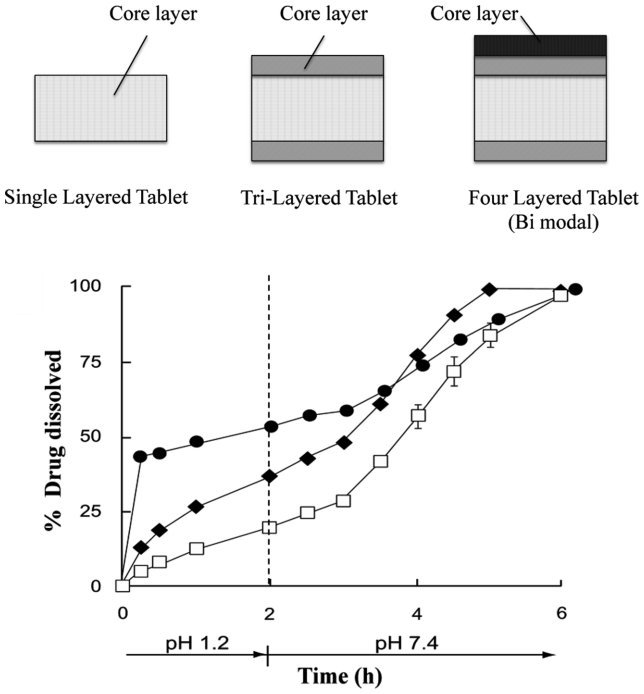

Figure 6. Release profiles of theophylline from investigated tablets (●) Bimodal; (◆) single layered tablets; (□) Tri-layered tablet (redrawn from Streubel et al., 2000).

Time-programmed delivery system based on geomatrix technology

Sometimes, optimal amounts of a drug need to be delivered when and/or where it is required. It can be called as "time-programmed delivery system" and different systems have been developed using various techniques and functional polymers or additives (Pozzi et al., 1994; Narisawa et al., 1994; Conte et al., 1992; Matsuo et al., 1995). Press coating system is one of the techniques controlling drug release rate and delivering the drug in the gut when it is needed. Special coating solvents or equipments are not necessary in this technique. This system is composed of a core (modified release formulation) and different polymeric barriers (press coated systems) (Figure 7) (Conte et al., 1993; Conte et al., 1995). The initial drug release from this system is delayed by the coating of polymeric barriers until the polymeric shell is completely swollen or eroded. The delayed drug release is dependent on the characteristics of the shell, but not influenced by the core composition (Otsuka and Matsuda, 1995; Takenchi et al., 2000; Ishino et al., 1992; Fukui et al., 2000). The coated polymeric barriers may prevent penetration of dissolution media so there is a long lag time of the initial drug release. However, once the media penetrates into the core, the core tablet will dissolve and/or swell to break the outer shell resulting in fast drug release (Fukui et al., 2000; Fukui et al., 2001; Lin et al., 2001). According to the dissolution profiles of core tablets and two types of press coated tablets, the press coated tablets showed the lag phase and the drug was released rapidly after the lag time (Fukui et al., 2000).

Preparation of multi-layered tablets

Weight control systems in the manufacturing

One of the issues during the manufacturing of the multi-layered tablets is how to control the weight in each layer in order to keep the total tablet weight consistent. For the practical manufacturing, a rotary tablet press needs to be utilized and a weight control device in the press should be manipulated carefully. Among the various types of the weight control, a closed-

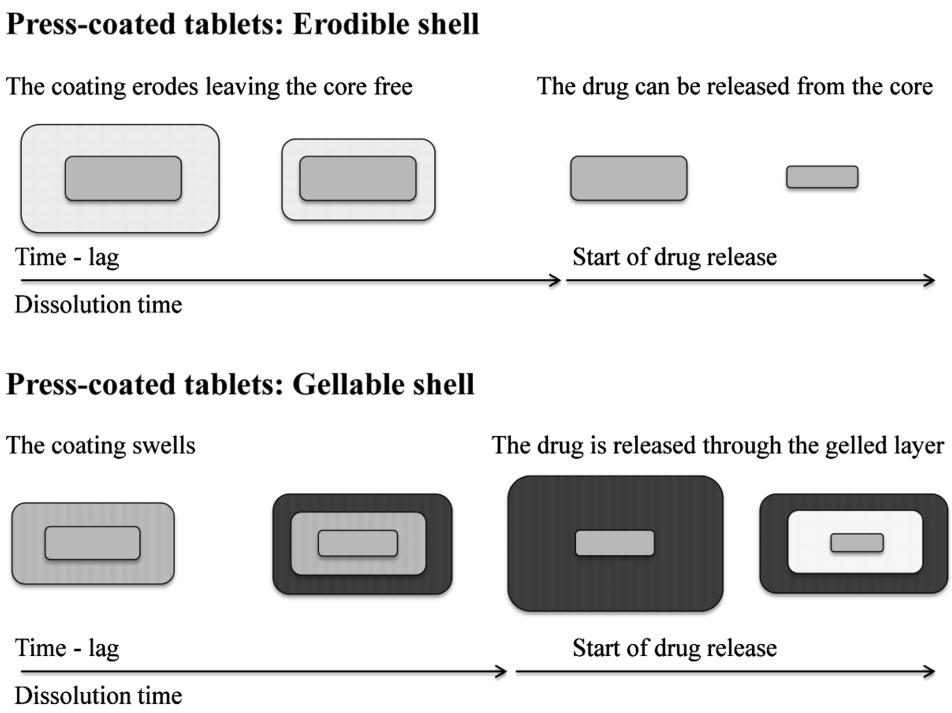

Figure 7. Geometric press-coated tablets with erodible and gellable shells for the delayed release of drugs (modified from Conte and Maggi, 2000).

loop control system might be the most common. In the system, the weight control involves two types of mechanisms; one is a force control and the other is a tablet thickness control. In case of the force control system, a fixed compression force is applied and simultaneously the actual exerted force is measured during the compression. The acceptable range of the compression force is determined based on the measured force of the individual layer. During the compression cycle, the weight control can be maintained as a feedback system to get the acceptable range of the measured force within the set points (Vaithiyalingam and Sayeed, 2010). The other one is to make use of the layer or tablet thickness. At the peak force applied during the compression, tablet thickness is measured and sent back to the weight control system as a feedback (Ebey, 1996). As the compression force can influence the adhesion of each layer, it should be considered carefully so that the optimum adhesiveness of each layer can be obtained.

Compression force and the delamination tendencies

When the multi-layered tablet is prepared, the materials are compressed more than twice. The compression force can affect the interfacial interaction and adhesion between the each layer and hence the delamination of layered tablets can be a great issue during the manufacturing process (Wu and Seville, 2009). It can be more obvious concern with the increase of compression speed on high-speed rotary machines (Podczeck, 2011).

The formulation of each individual layer for multi-layered tablet should be compressible and compactable on their own so that they can form mechanically strong and coherent solid dosage forms. When each layer is in contact, the interface between the layers should adhere together during compaction and strong interaction forces should be developed to hold the layers together. Moreover, the individual layers should be compressible and compactable so that they do not cause delamination. To prepare the first layer, the compaction pressure should be minimized to provide sufficient surface roughness for nesting and particle interlocking to take place between layers (Inman et al., 2007; Karehill et al., 1990). When the surface roughness is increased, there is a larger contact area between the layers, which enhances inter-layer adhesion. When the material making the lower layer of a bilayer tablet was more elastic, the tension introduced into the system weakened the strength of the layered compacts. (Inman et al., 2007, 2009; Anuar and Briscoe, 2009, 2010; Podczeck and Al-Muti, 2010)

Material properties

Materials properties and compaction parameters influence compressibility as well as breaking force of the tablets. The material properties may include brittleness, ductility, and elas-

ticity, which influence compressibility, tablet hardness, and porosity. Moreover, the material properties should be considered extensively for not to cause delamination during the compression process.

Brittle and plastic deformations of the excipients have significant effect on the compaction process. When predominantly ductile material was compacted, it caused plastic deformation. Moreover, the compression stress developed by the elastic recovery did not exceed the bond strength (Danielson et al., 1983). For the robust manufacturing process, the each layer may include a well-balanced ratio of both brittle and ductile materials (Yang et al., 1997). A typical ductile material is microcrystalline cellulose and brittle material is calcium phosphate and lactose. During compress process, brittle materials fracture and fill the empty space. However, ductile materials tend to undergo deformation. The brittle materials generally produce smooth surface and brittle compacts but the ductile materials provide rough surface and ductile compacts. Therefore, if the first layer is dominantly composed of brittle materials, the multi-layer tablets interfacial interaction and the tablet breaking force can be increased.

Conclusions

The technological needs of developing novel dosage forms and combination of different drug products over the last decade has made the multi-layered tablet technology very popular in pharmaceutical industry as well as in academia. There are many advantages of the technology. The technology made it possible to develop formulations containing incompatible drugs within their matrices as inert barriers can be inserted between the incompatible matrices to prevent an interaction. Multi-layered tablets can also decrease the dosing frequency as the multiple layers keep the modified release portion separate from the immediate release portion. The tablets can eliminate the need to take multiple tablets, which makes dosing more convenient. Moreover, the technology can help to extend a patent and/or fend off competition. However, manufacturing issues still have been faced. Optimum instrumentation may permit qualification and validation of the manufacturing process for the products.

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