Multi-layer Tablet: Current scenario and recent advances
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Abstract
The purpose of this article on tableting of multiple Active Pharmaceutical Ingredients(APIs) in the single oral solid dose in the form of Fixed Dose Combinations(FDCs), that focused on therapeutic justification, designing, its practical approach, summarize the problem encountered and parameters to be considered during development. This will help budding formulation development scientists working on generic development as such types of formulation is current need in various disease conditions. Looking to the necessity of medical practitioners, ultimately generic pharmaceutical companies taking interest in development of such formulation with correct medical justification due to various health problem not only in India but also globally. FDCs are highly popular in the Indian pharmaceutical market and also have been seen in the last few years. Presently very few generic companies are working on FDCs in the form of multilayer tablets resulting into small numbers of formulation in the market yearly.

Keywords: Multi-layer tablet, Bi-layer tablet, Fixed Dose Combinations, Tableting technology

Introduction
There are several reasons for development of combination of two or more drugs collectively in single dosage form in several diseases not only in case of emergency but also in common diseases like parkinsonism [1], allergic rhinitis [2] etc. The previous intention for development of such formulation is that when patient unable to take frequent dosing due to many reasons, The combination of different API in single dose was preferred, but these days if any patient suffering from one particular disease medical doctor primarily prescribe two or more medicine separately for the single illness. However, human beings thought is to get relief in single dose and to attain site therapeutic concentration immediately and maintain the same dose over 12 h or more in currently faster life and therefore development of FDCs gaining importance globally.[3]

Very few drugs and their formulations are available in the form FDCs which are therapeutically justified and are available in critical disease conditions. The global regulatory bodies like WHO are contributing for such development in untreatable diseases conditions for example in AIDS, cancer and pulmonary diseases.[4] Therefore, greater attention by various generic manufacturer due to FDCs gaining importance in recent years as Oral Solid Drug Delivery System(OSDDS) in pharmaceutical industries over traditional conventional or modified release single dose tableting due to its many advantages.[5]

FDCs in the form of powder mixture of two or more API’s or multilayer tablets being used in the treatment of a wide range of conditions and are particularly useful in the management of chronic conditions. They are applicable for broad range of compatible as well as incompatible drugs for both immediate as well as modified release dosage forms. It is also found that very few generic pharmaceutical companies having bilayer or tri-layer tablet compression machine and even of machines are there is lack of manpower having expertise in this technology.[6]

In India DCGI(Drug Controller General of India) published guidelines for FDCs in year 2010. FDCs use to prepare products containing two or more active ingredients for particular indication/s. Several fixed-dose single tablet combinations are now available in domestic market for the management of various diseases. The most common FDCs in the form of multi-layer dosage form available are bilayer tablets followed by the tri-layer and up to four layer tablets. There are many reasons for choosing multi-layer tableting technology due to its different therapeutic and technical advantages. FDCs are not restricted to layered tablets as powder mixture of two or three API along with excipients compressed in single tablets with justified therapeutic
Why Multilayer tableting?

Currently about two-third of all prescriptions are dispensed as solid dosage forms. Many combinations are available wherein DUREDAS (Dual Release Drug Absorption System), technology is being used which can provide immediate and modified release of two drugs or dual release rate of same drug in single dosage form by using hydrophilic and hydrophobic polymer matrices. It is therapeutically justified that combination of modified and immediate release matrix found to increase bioavailability. Compaction of different granules in the form of various layer in single tablets are called as multilayer tablets. It generally consists of parallel, clear, coloured, visual distinct layers two to three or more APIs or APIs along with functional or non-functional placebo layers, sometimes to avoid interaction between different incompatible layers. Many formulator utilised DUREDAS technological approach and its release rate is due to combination of diffusion or erosion or both through various matrices. Oral solid multiple drug delivery system in the form of FDCs are beneficial than the other oral formulation. Many of multiple API containing liquid formulations with preservative, alcohol etc. is difficult to dispense, formulate, transport and to administer accurate dose.

There are many problems encountered with formulation and development of conventional or modified release monolithic tablets. Combination of immediate release and sustained release profile increases bioavailability and patient compliance. Three layer tablets are formulated for controlled release, usually consists of drug core layer sandwiched by external layers, which may contains different amount of drug to form a concentration gradient matrix or just act as a barrier layer in order to restrict release or to minimize burst effect upon in-vivo placement. E.g. UROXATRAL® (alfuzosinHCl extended-release tablets) consists of a hydrophilic active matrix core enclosing alfuzosin hydrochloride in a single layer supported by two inert and non-functional layers (one swellable layer and one erodible layer) whose functions are to control the hydration and swelling rate of the core, and thereby slow down dissolution of the drug. When the tablet comes into contact with gastric juices, it increases considerably in volume and thus remains in the stomach for a longer time. There are many reasons for choosing multilayer tableting technology due to different therapeutic and technical advantages. Therapeutic advantages

Better execution of release profile

Layering on the tablet revealed better execution on release profile and it is one of the most important possible alternatives to conventional matrix tablets to avoid the initial burst release and to achieve zero-order release profile, which maintain availability of drug over 12 h or more. E.g. venlafaxine hydrochloride.

Decrease burst effect and fast initial release rate

Upon placement of controlled release formulation in release medium or in dissolution medium, there is an immediate release of an initial large bolus of drug, before the release rate reaches a stable profile (stable matrix formation). This phenomenon is typically referred to as ‘burst release’ which is controlled using multilayer tableting. E.g. terazosinHCl.

Multiple release profiles

Two or more layers in tablets are able to provide multiple release kinetics of same or different drugs of same or different physicochemical properties and it is possible to formulate each monolith in order to parcel out the delivery of drug dose by means of different release control mechanisms. E.g. Naproxen, loratadine and pseudoephedrine.

Synergistic effects

It is well known that presence of one drug enhances the effects of the second and formulation of two or more drugs together in single tablets offer therapeutic effect of these drugs is greater than the sum of the individual effects.

Reduction in dosing frequency

It is possible to formulate one layer in the form of immediate release disintegrating monolith that deliver the initial quick release required to achieve peak plasma concentration and then sustaining the same drug over the period of time more than 12 h so the multiple intake dosing frequency minimize and thus get programmable drug delivery system of same or different active in single dose and thus reduction in dosing frequency.

Delayed Release

Application of erodible monolith for immediate and delayed release pattern is possible, which deliver the second instalment of drugs in the latter part of GIT. E.g. naproxen and esomeprazole magnesium.

Controlled Release

Swelling monolith carry out by both swelling as well as eroding mechanism in which drug was continuously released throughout the GIT. E.g. Trimetazidinehydrochloride.

Patient compliance

Improved patient compliance by reducing tablet intake, “Layers” in tablets represented by two clearly different colours and produces a product that looked more attractive than a standard white “pill”.

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Some double-layer products are coated and appearing to be comprised of one uniform substance. This allows a decrease in the dosing frequency and a reduction in peak plasma concentrations, thereby improving patient compliance.

**Technical advantages**

**Dual release profile**

Multilayered tablets provide dual release repeat-action, in which one layer of tablet or outer compression coated layer provides the initial dose in the form of rapidly disintegrating matrix in the stomach and inner layer tablet is formulated with components that are insoluble in gastric media but release in the intestinal environment. [19]

**Release restriction**

Multilayer tablet give restriction to release surface of swellable matrix by barrier layers (two or three layer) and possible to create differential layer dissolution profile. [20]

**Flexibility**

Maximum suppleness in drug release patterns, ease of manufacturing, increase in safety boundary of high potency drug and reduction in health care cost etc.

**Manufacturing**

Two or more drugs are compressed in to single tablets by using modified multilayer tablet press. It is possible to avoid the incompatibility in between active-active, excipient-excipient and active-excipients by mean of physical separation in the form of multilayer and also Millard reactions occurring during tablet compression. [21]

**Multitalented**

It has higher drug loading capacity and ability to release multiple APIs with broad range of release profiles and ability to separate incompatible API’s. Cost saving can be achieved by reducing manufacturing activities, overall unique and cost effective dosage form.

**Regulatory advantages**

Expansion of patent life by preparing pharmaceutical alternative of same or different drugs or new therapeutically justified combination of drug product and possibility of patenting and registering the product in various markets worldwide.

**Disadvantages**

**Problems during In-process Quality Control(IPQC)**

In-process problems during bilayer compression such as layer-separation(delamination) occurs; sometimes not immediately but may be after compaction i.e. during storage, packaging, shipping. Problem such as insufficient hardness, inaccurate individual layer weight control, cross-contamination between the layers, insufficient binding between layers, reduction in practical yield of final compressed tablets, clear visual separation between the two layers are commonly observed. [5]

**Analytical Development and Pharmacopoeial Monograph**

It has been observed that very few FDCs monographs are available in various pharmacopoeias like USP, JP, IP, BP etc. Analytical developments of many FDCs are not included in pharmacopoeias.Preparations of finished product specification take long time for development of dissolution testing, assay, content uniformity and characterization of impurities. Moreover, issue related to development of cleaning validation, detection of residue after cleaning validation, determination of LOD, selection of primary packaging material for different types of physicochemical properties of individual active pharmaceutical ingredients in finished products are to be addressed.

**Regulatory**

It is true that development of FDCs should always be based on believable therapeutic and medical justification which is clinically relevant. Hence various pharmaceutical companies are demanding that individual compounds of same formulation available in market are safe and effective since long time and therefore FDCs of same are also safe but DCGI had restriction for development of FDCs. Unfortunately, many FDCs have been introduced in Indian market are usually irrational and therefore, many irrational combinations are banned by DCGI and guidelines were issued for getting marketing approval of FDCs. These guidelines concern to manufacture/ import and marketing approvals. [22]

**Machine setup**

Set up of bilayer or trilayer tablets is time consuming, take long time to initial setup, speed, requirement of skilled person and many times problem arise during tableting as compared to single layer conventional tablet press in machine setup, cost and production output.

**Ideal properties of multilayer tablets [23]**

1. Layer should not fuse into non-disintegrating matrix, should have clear, parallel, visual separation in final compressed tablets.
2. If it consists of disintegrating matrix, it should be disintegrated within GIT, modified release part should not be affected dissolution profile of IR part and slow and gradual erosion of second layer for slow release of drug.
3. Drug should not be affected by compaction of each layer and physically stable; and withstand the mechanical shock.
4. Separation of layers should not occur during various stages such as compression, coating, packing, shipping and storage.

**Objective of preparing multilayer tablets**

1. To treat critical disease condition when single active unable to produce complete therapeutic action and to maintain over a period 12 h or more. E.g. telmisartan/amlodipine tablet[24, 25]
2. To use combination having proven advantages over single compounds administered separately for therapeutic effect. [26, 27]
3. To combine different drugs for synergistic therapeutic effect or different drugs in order to achieve a specific release profile. E.g. efavirenz, emtricitabine, and tenofovirdisoproxilfumigate in multilayer tablet for the treatment anti HIV-1 infection. [28]
4. To overcome the limitations in case of a single drug which is unable to treat or avoid adverse drug effect, if any.
5. To establish a brand identity, as they are clearly different from other products from generic competitors and also from patient identity over routine white pills and when patient is unable to take frequent dosing of same drug.
6. To get dual release profile so as to reduce tablets intake and thereby increasing patient compliance.
7. To combine compatible or incompatible drugs with different release characteristic in same dosage form and enhancing the stability of dosage form as compared to its conventional monolith counterpart.

Steps involved in preparation of bilayer tablets

- Parameters to be considered during Multilayer tableting [5, 29]
- Following parameters primarily be considered during multilayer tableting. It's totally depending upon handling and experience of such multi-dosing tablet press.

**Dwell time**

It is the contact between punch head and compression roller. If shorter the first layer-dwell time, which results into pours, aeration, capping and hardness problems. It may be removed the mistakes by reducing the turret-rotation speed or by extending the dwell time.

**Risk of separation and capping**

It is necessary to avoid risk of separation and capping, by forming correct bonding which can be attained by the first layer formation at low compression force. Therefore this first layer can still interact with the second layer during final compression of the tablet.

**Cohesiveness**

When the first layer is compressed at a very high compression force, bonding between layers is severely controlled. Various bilayer formulations necessitate a first layer compression force NMT 3 Kp or 30 N to maintain the ability of first layer to bond with the second layer. Above 50 Nforces, this ability may be gone astray and thus bonding between layers may be insufficient, resulting in little hardness which leading to layer separation. Thus at elevated manufacturing speed, the jeopardy of separation and capping increases which can be minimised by adjusting adequate dwell time at all compression stages.

**Tamping force**

Tamping force applied on the first layer of bilayer tablet to circumvent capping and separation of the two individual layers. If dwell time is increased at pre-compression of both first and second layer, it provides sufficient hardness and also low pre-compression forces, which is required to secure interlayer bonding.

**Cross-contamination**

Multilayer tablet machines are equipped with suction nozzles or dust extractor to remove fine powder or granules to eliminate cross-contamination between the two layers and getting a clear visual separation between layers. It is very important to remove any powder residue from the die plate and for this purpose dedicated scraper plate are located before and after each die fill, to remove residual powder dust to the outside of the die table, where the high efficiency suction nozzles are located.

**Deaeration**

If dwell time increases, it increases the deaeration of the powder and the re-arrangement of the granules in the die. So, these two factors increase the hardness of the tablets significantly and avert potential capping problems. [30]

**Final compression force**

This force is applied on the final bilayer tablet is always more than the compression force on first layer, which results in suitable bonding of both the layers.

**Re-circulation**

Powder is always re-circulated over the turret whereas, other granules having powder outlet, in order to reduce mixing. Some modified release compression machine not recommended due to limitation of recirculation of powder as it can create more dust and risk of contamination.
Formation of multilayer tablets

Fig. 1. Steps involved in the preparation of bilayer tablets

1. Dosing of granules for bottom layer into die from first hopper
2. Precompression of first layer by first roller
3. Reduced first layer to smaller size in order to create the space required for the second hopper
4. Transfer of the prepared core to second hopper
5. Ejection of bilayer tablets
6. Final compression of two layer tablets into die with distinct layers
7. Transfer filled die to second roller for compression
8. Dosing of the top layer from second hopper into die
Table 1. Technology used for different layer tablets

<table>
<thead>
<tr>
<th>Company</th>
<th>Name of Technology</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skye pharma[31]</td>
<td>Geomatrix Technology</td>
<td>One or two impermeable polymeric coating applied on one or both bases of the core tablet.</td>
</tr>
<tr>
<td>Accu-Break pharmaceuticals, Inc[32]</td>
<td>Accu-Break Technology: Accu-B &amp; Accu-T bilayer or tri-layer tablet technology</td>
<td>Suitable for FDCs combination, easily divided, and ability to separate IR from CR and to take appropriate half tablets and the free layer drug dose not affect drug release.</td>
</tr>
<tr>
<td>Alza Corporation[33]</td>
<td>OROS push pull technology, Bilayer or trilayer core</td>
<td>Consists of one push layer and 1 or more drug layer, osmotic agent &amp; water swellable polymer.</td>
</tr>
<tr>
<td>Flamal Technologies[34]</td>
<td>FlamalMicropump technology</td>
<td>Permits DR and ER drug delivery system</td>
</tr>
</tbody>
</table>

Table 2. Different two drugs in individual layer of bilayer tablet

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Objective</th>
<th>Purpose</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Diclofenac sodium</td>
<td>Immediate release of paracetamol and tailored release of diclofenac sodium</td>
<td>Reduce dose frequency and decrease incidence of GI side effects</td>
<td>[36]</td>
</tr>
<tr>
<td>Metformin Hydrochloride</td>
<td>Pioglitazone</td>
<td>Metformin HCl in extended release matrix form and Pioglitazone HCl in immediate release for the treatment of diabetes mellitus</td>
<td>Decrease frequency of administration and improve patient compliance</td>
<td>[37]</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Acetaminophen</td>
<td>Prolonged release of tramadol and acetaminophen up to 12 h</td>
<td>Prolonged release up to 12 h and improve patient compliance</td>
<td>[38]</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Theophylline</td>
<td>Bilayer sustained release tablet of salbutamol and theophylline</td>
<td>Increase patient compliance and prolong bronchodilation</td>
<td>[39]</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>Amlodipinebesylate</td>
<td>Metoprolol succinate as sustained release and amlodipine besilate as immediate release</td>
<td>Lower doses of drug to reduce patient blood pressure, minimize dose dependent side effects and adverse reactions</td>
<td>[40]</td>
</tr>
<tr>
<td>Atorvastatin calcium</td>
<td>Nicotinic acid</td>
<td>Atorvastatin calcium as an immediate release layer and nicotinic acid as an extended release layer</td>
<td>Develop potential dosage form</td>
<td>[41]</td>
</tr>
<tr>
<td>Metoclopramide hydrochloride</td>
<td>Ibuprofen</td>
<td>Immediate release of metoclopramide hydrochloride and sustained release ibuprofen for the effective treatment of migraine</td>
<td>Effective treatment of migraine and avoid chemical incompatibility between drugs</td>
<td>[42]</td>
</tr>
</tbody>
</table>

Table 3: Commercially available bilayer tablets

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Chemical Name</th>
<th>Developer</th>
<th>Therapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprax Plus [43]</td>
<td>Sertraline, Alprazolam</td>
<td>Torrent Pharmaceuticals Ltd.</td>
<td>Anti-depressant</td>
</tr>
</tbody>
</table>
Weight variation

Weight variation occurs some time due to non-uniform flow of granules, incomplete die filling and lower punch jamming due to excessive fines in final blend and thus these parameters should be controlled carefully during tableting.

First layer weight layer measurement

When producing multilayer tablets, this stage is challenging for different reasons because sampling of first layer for weight check at the start and in-between compression cycle is difficult. For this reason, first weight layer is compressed at high hardness to make sampling and easy separation and weighing is possible because first layer hardness is generally low and difficult to handle. Once the target weight of first layer achieves, reduce pressure as much as 20 to 30 N. Many modified tablet press has push button which automatically separate layered tablet due to pressure difference.

Weight adjustment

First layer pressure is useful for weight adjustment of second layer. Many formulators use such technique to achieve desired weight instead of using weight adjustment knob that totally depends on handling experience of such double rotary press.

Layer weight ratio

Generally layer weight ratios 50:50, 60:40 and 25:75 are used for formulation of such tablets, provided that granules are having good binding property.

To get high yield

This is one of main consideration during the multilayer compression. It is different from the single layer compression machine in which manufacturing loss limits 2 to 3% in most cases, whereas, in multilayer tableting manufacturing losses can be very high such limits may increase up to 5 to 15%. It is because of loss of granules or blend during the compression, which is mainly due to dust suction nozzle for controlling dusting or excessive fines of granules on turret. It avoid cross contamination with other granules present on turret. Suction nozzles are situated on both sides of each feed frame. If the flow of granules not properly controlled during compression, excessive sucking of granules occurs and this loss may increase than standard limits. Chances of loss of granules from the entrance of feed frame are also possible if the feed frame is not properly adjusted. Incoming granules flow from turret to feed frame may sucked by nozzle before reaching in feed frame. The second parameters is out coming granules from first feed frame, which is again collected and reused but due to improper fitting of feed frame loss of granules is increased and thus affect the final yield.

Hardness and Thickness

This parameters need to be tightly controlled during final compression because it directly affect the release of active. Many times due to high hardness disintegrating matrix may take time more than limits.

Segregation

Sometimes segregation occurs in out coming granules in most machines and therefore it is better to blend granules before putting into hopper for reuse to minimize the content uniformity in finished products.

Multilayer tablet presses

Many companies having leadership in Pharma machinery supply machines from single layer to two to three layered tableting for lab scale such as Cadmach, Karnavati, Elizabeth-Hata, KG pharma, Fette, GEA Process Engineering, Korsch etc. It has D or B or both types of tooling with additional facility for manufacturing in various sizes and shape with maximum output with advanced facilities.

Examples of few Technologies with familiar marketed FDCs

Many patented technologies available for development of FDCs formulation and their marketed FDCs as shown in table 1.

Conclusion

Multilayer tablet can be considered as a promising delivery system for oral delivery of drugs useful in diseases and/or disorders such as hypertensive, HIV, tuberculosis, diabetic, bacterial infection etc. The multilayer tablet is used to provide sequential release of more than two incompatible drugs in combination and also for sustained release. In case of bilayer tablet, generally it was found that one layer is immediate release as initial dose and second layer is maintenance dose. Several pharmaceutical industries are presently developing multilayer tablets for a variety of reasons like patent extension and to reduce capital investment.

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