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AN INNOVATIVE APPROACH OF SPECIAL LAYERED TABLET TECHNOLOGY

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ABSTRACT

Aims: The aim of this research was to describe multiple layered tablet dosage form and their advantages, as well as recent developments in the field of layered tablets, as well as local & globally marketed layer tabled was discussed. **Place and Duration of Study:** The study was carried out in August 2017 in the Department of Pharmacy, Jagannath University, Dhaka, Bangladesh. **Materials & Methods:** lactose, Anhydrous Talc, sodium Carboxy methyl cellulose, Carboxy methyl cellulose, Aerosol-200, Mannitol, Sodium Benzoate, PPS, MPS, Polyvinylpyrrolidone K 30, and Maize Starch was used for the production of bi-layered by using of EN SO TROL & OROS Push Pulls Technology. **Results & Discussion:** Layered Tablet technology was created a new era for the pharmaceutical industry was known as successful drug delivery system which ensured better compliance & convenience. Pharmaceuticals products which given orally are currently available mostly in the immediate release pattern for rapid absorption into the body. Layer tablets were a well-developed product effectively address these issues by including appropriate control strategies and establishing the functional relationships of the material attributes and process parameters critical to the layer tablet quality. Layer matrix tablet was one of the methods which were used for controlled or sustained drug delivery system. Moreover, the ultimate goal was to design controlled or

sustained drug delivery system which can reduced the frequency of dosing and providing uniform drug delivery.**Conclusion:** A well-developed product will effectively address these issues by including appropriate control strategies and establishing the functional relationships of the material attributes and process parameters critical to the layer tablet quality. Hence, layered tablets may be considered as improved beneficial technology to overcome the shortcoming of other tablets.

KEYWORDS: Layered Tablet, OROS, Technology, Compaction, EN SO TROL, L-OROS, Angle of Repose.

1. INTRODUCTION

In the oral drug delivery system, the pharmaceutical products which administered orally are currently available mostly in the immediate-release pattern. For the drug delivery and rapid absorption into the body, tablets are formulated by immediate release pattern. To enhance the efficacy of drug controlled and sustained release formulations are being used more and more. The main objective of sustained release drug delivery system is to ensure the safety and efficacy of drugs as well as patient convenience and compliance. Several advantages over the conventional formulations are seen but still some problems have found for preparing this kind of dosage form such as physical incompatibility, chemical incompatibility etc. As a result, the bi-layer and multi-layer tablets are known as a novel drug delivery system. Bilayer tablet is a suitable option for sequential release of two drugs combined, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Multi-layered tablets possess various benefits, such as the ability to prevent incompatibility between drugs and excipients. In addition, by providing multiple releases kinetics profiles in single delivery system of either the same or different drugs, by means of different release control mechanisms. Different polymers are used in this sustained as well as controlled drug delivery system, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependent polymers. The ultimate goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery.

2. MATERIALS AND METHODS

Mateirials Used in Layered Tablets

Polymers	HPMC 5 cps, HPMC 15 cps, Eudragit S 100,HPMC E 5, HPMC K4M,Carbopol 934,, Xanthan gum, guar gum, locust bean gum, Propyl cellulose etc
Fillers	Lactose, Anhydrous Talc, sodium Carboxy methyl cellulose, Carboxy methyl cellulose, ,Aerosol-200, Mannitol etc
Gas generating agents	Citric acid, Sodium bicarbonateetc
Preservatives	Sodium Benzoate, PPS, MPS.
Glidant	Clloidal Anhydrous Silica, Magnesium Stearate, Talcum Powder
Binder	Polyvinylpyrrolidone K 30, Maize Starch.

Layer tablets are consisted of two or three layers of granulation compressed together. When the edges of each layer are exposed, they look like sandwich. This dosage form has the advantage of separating two incompatible substances by an inert barrier between them. It makes possible sustained-release preparations with the immediate-release quantity in one layer and the slow release portion in the second. A third layer with an intermediate release might be added.

Single- Layer Tablet Bi-Layer Tablet Multi- Layer Tablet

When two or more active pharmaceutical ingredients are required to be administered simultaneously where they are incompatible, the best option is to formulate multi-layered tablet. It consists of several different granulations that are compressed to form a single tablet having two or more layers where each layer is of different color to produce a distinctive looking tablet. Dust extraction is done during compression to avoid contamination. Consequently, each layer can possess light compression as each and every component is laid down which avoids granules intermixing if the machine vibrates.

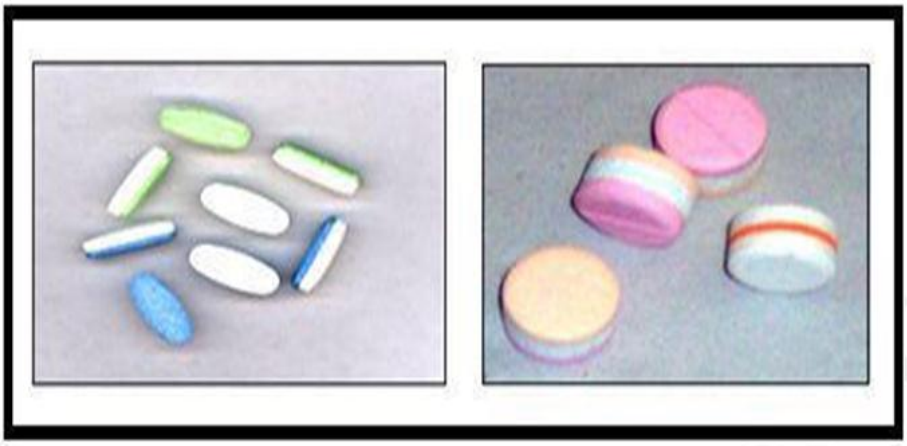


Figure. Bi & Tri-Layer Tablets.

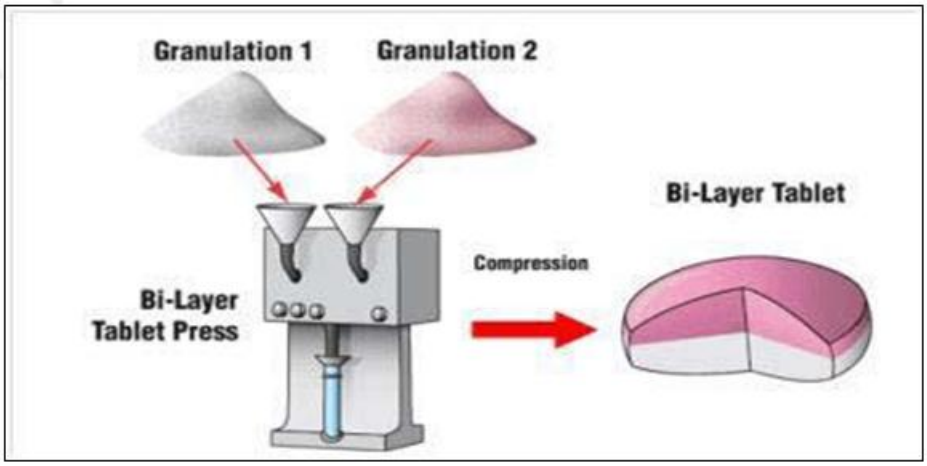
3. RESULTS

This kind of tablet has two parts, internal core and surrounding coat. The core is tiny porous tablet and prepared on one turret. For the preparation of final tablet, a larger die cavity in another turret is used in which first the coating material is filled to half and then core tablet is mechanically transferred, again the remaining space is filled with coating material and finally compression force is applied. This tablet readily lend itself into a repeat action tablet as the outer layer provides the initial dose while the inner core releases the drug later on. To avoid immediate-release of both the layers, the core tablet is coated with enteric polymer so that it will not release the drug in stomach while, the first dose is added in outer sugar coating. Even so, coating operation requires interpretation while manufacturing and dawdling the manufacturing process. Sometimes, inner core may be of liquid formulation to provide immediate-release of core after the coat gets dissolved.

A type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is completely exposed. Here only the bottom of the die cavity is filled with coating material and core is placed upon it while preparation. Some coating material is displaced to form the sides and compress the whole tablet when compression force is applied. To reduce capital investment quite often existing but modified tablet presses are used to develop and produce such tablets. The development and production of quality bi-layer tablets needs to be carried out on tablet presses to overcome common problems of bi-layer technology. Using a modified tablet press may therefore not be the best approach to producing a quality bi-layer tablet under GMP conditions. Especially when in addition high production output is required.

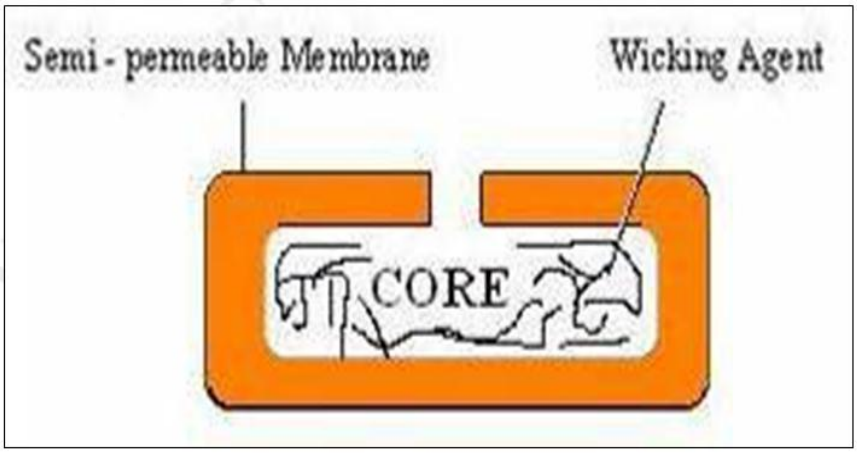
Production of Bi-Layer Tablets

Bi-layer tablets are prepared with one layer of drug for immediate-release with the second layer designed to release drug later, either as a second dose or in an extended-release form. The bi-layer tablets with two incompatible drugs can also be prepared by compressing separate layers of each drug so as to minimize area of contact between two layers. An additional intermediate layer of inert material may also be included.



EN SO TROL Technology

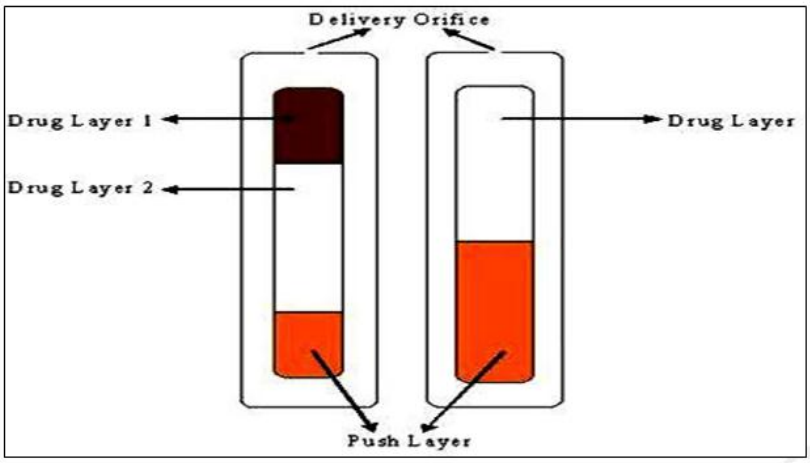
Solubility enhancement of an order of magnitude or to create optimized dosage form Shire laboratory use an integrated approach to drug delivery focusing on identification and incorporation of the identified enhancer into controlled-release technologies.



OROS Push Pulls Technology

This system consists of mainly two or three layers among which the one or more layers are essential of the drug and other layer are consisting of push layer. The drug layer mainly

consists of drug along with two or more different agents. Thus, this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi-permeable membrane surrounds the tablet core.



Recent Developments in the Field of Bi-Layer Tablets

The introduction of bi-layer tablets into the pharmaceutical industry has enabled the development of pre-determined release profiles of active ingredients and incorporation of incompatible active ingredients into the single unit dosage form. Large number of work has been done in this field.

Drugs	Dosage Form	Indication
Diclofenac, Cyclobenza-prine	Bi-layer tablets	Synergistic effect in pain
Atenolol, Lovastatin	Bi-layer floating tablets	Synergistic effect in hypertension and biphasic release profile
Atorvastatin, Calcium	Bi-layer buccal tablets	To overcome bioavailability problem, reducing side effects and frequency of administration
Ascorbic acid, Cyano-cobalamine	Double layer suppositories	To avoid interaction b/w incompatible vitamins
Rifampicin, Isoniazid	Capsule & tablet in capsule	To avoid interaction b/w incompatible vitamins
Metformin HCL, Glimipiride	Bi-layer tablets	Synergistic effect in diabetes

4. DISCUSSION

Bi-layer tablet is stated a new era for successful development of controlled-release formulation along with various features and advantages to provide successful drug delivery. It is suitable for sequential release of two drugs in combination and also for sustained-release of tablet in which one layer is for immediate-release as loading dose and second layer is maintenance dose. Thus, bi-layer tablet is widely used in different aspect for anti-

hypertensive, diabetic, anti-inflammatory and analgesic drugs as well as for combination therapy. Modify the total surface area available for API layer either by sandwiching with one or two in active layers in order to achieve swell-able / erodible barriers for modified release.

To separate incompatible Active pharmaceutical ingredient (APIs) from each other, to control the release of API from one layer by utilizing the functional property of the other layer such as, osmotic property . The displacement tablet weight control principle is fundamentally different from the principle based upon compression force. When measuring displacement, the control system sensitivity does not depend on the operation point but depends on the applied pre-compression force. Multi-layered systems which contains bi-layered, triple-layered, quadruple-layered, etc. are becoming increasingly recognized as controlled-release drug delivery systems. Multi-layered tablets possess various benefits, namely the ability to prevent incompatibility between drugs and excipients, such as: Multi-layered systems consist of a hydrophilic matrix layer containing either or only one active ingredient and one or more impermeable or semi-permeable layers with other drugs incorporation.

The presence of the barrier layers modifies hydration, swelling rate, lag time for diffusion, dissolution etc. By varying the number of layers and geometry of devices provide different drug release. These multi-layered formulations may swell gel or erode to modulate drug release.

Problems in Bi-Layer Tablet Production Process

Weight Variation

Cause	**Remedies**
Poor flow characteristics of material	➢ Wrong setting of hopper ➢ Material bridging in hopper ➢ Too much recirculation
Dies not filling	➢ Press running too fast ➢ Wrong feeder paddle speed or shape
Material loss or gains after proper die fill	➢ Recirculation band leaking ➢ Excessive vacuum or nozzle improperly located

Product yield

Cause	Remedies
Die table scraper action insufficient	➢ Scraper blade worn or binding ➢ Outboard edge permitting material to escape
Incorrect action on recirculation band	➢ Gap between bottom edge and die table ➢ Binding in mounting screw ➢ Too little hold down spring pressure
Incorrect feeder fit to die table	➢ Feeder bases incorrectly set (too high or not level)
Loss at compression point	➢ Compressing too high in the die ➢ Excessive or misdirected suction on exhaust nozzle

Low hardness

Cause	Remedies
Factors related to machine	➢ Tablet press having pre-compression and main compression facilities ➢ Press speed is reduced to increase total compression time
Lubricant level	➢ Over mixing can reduce tablet hardness
Non-optimized formulation	➢ Incorporate plastically deforming matrix
High compression force	➢ Reduced compression force ➢ Reduced press speed
Ratio of pre-compression to main compression is insufficient	➢ Pre-compression force high can be harmful ➢ Use large compression roller diameter
Curled or damaged punches	➢ Tools should be rewashed or replaced

Quality and GMP Requirements: To produce a quality bi-layer tablet, in a validated and GMP way, it is important that the selected press is capable of:

1. Preventing capping and separation two individual layers that constitute the bi-layer tablet.
2. Preventing cross-contamination between the two layers.
3. Producing a clear visual separation between the two layers.
4. Providing sufficient tablet hardness and high yield (Kumar *et al*., 2013).
5. Accurate and individual weight control of the two layers these requirements seem obvious but are not as easily accomplished as this article aims to demonstrate.
6. Very short first layer dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems. This may be corrected by reducing the turret rotation speed (to extend the dwell time) but with the consequence of lower tablet output.

5. CONCLUSION

Layered tablets provide an excellent opportunity for manufacturers to separate themselves from their competitors, improve their products efficacy, and protect against impersonator

products. The quality of layered tablets can be improved and GMP requirements greatly achieved by using recent sophisticated and up-to-date technologies.

Layered tablets are capable of providing abundant advantages like to get immediate-release as well as controlled-release in single dosage form to avoid incompatibility between two or more active pharmaceutical ingredient, cost reduction and stability enhancement.

The feature of multi-layered tablets provides unique product performance objectives which are otherwise not achievable by conventional tablets, but also brings a new set of challenges for formulation design, manufacturing process, controls and product life performance requirements. They are also required to add challenges in establishing relevant regulatory controls to meet the product performance requirements over the life of the drug product. To meet these requirements a higher level of understanding in the ingredients and manufacturing variables is critical to manage the risks associated with product acceptability over the life cycle to avoid batch failures and batch recall.

The development and production of quality bi-layer tablets require a comprehensive understanding of the product and process in order to address challenges in manufacturing such as accuracy in weight control of each individual layer, delamination / layer-separation during manufacturing and storage, insufficient tablet breaking force and cross-contamination between the layers (especially for incompatible APIs).

The objective of the dosage form is to ensure that the drugs available to the patient are not only safe and effective but are also properly manufactured and packaged to meet the established quality and target product profile over its shelf-life. A well-developed product will effectively address these issues by including appropriate control strategies and establishing the functional relationships of the material attributes and process parameters critical to the layer tablet quality.

Hence, layered tablets may be considered as improved beneficial technology to overcome the shortcoming of other tablets.

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