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A Review on Multilayer Tablets

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ABSTRACT
Oral drug delivery has been known for decades as the most widely utilized route of administration among all routes that have been explored for the systemic delivery of drugs in case of different dosage forms. Multilayer tablets are tablets made by compressing several different granulations fed in to a die in succession, one on top of another, in layer. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for 2 or 3 layers. More are possible but the design becomes very special. Ideally a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

Key words: Oral drug delivery, Multilayer tablet.

INTRODUCTION
Oral ingestion is the most convenient and commonly used method of drug delivery. These systems have the obvious advantages of ease of administration and patient acceptance. One would always like to have an ideal drug delivery system that will possess two main properties:

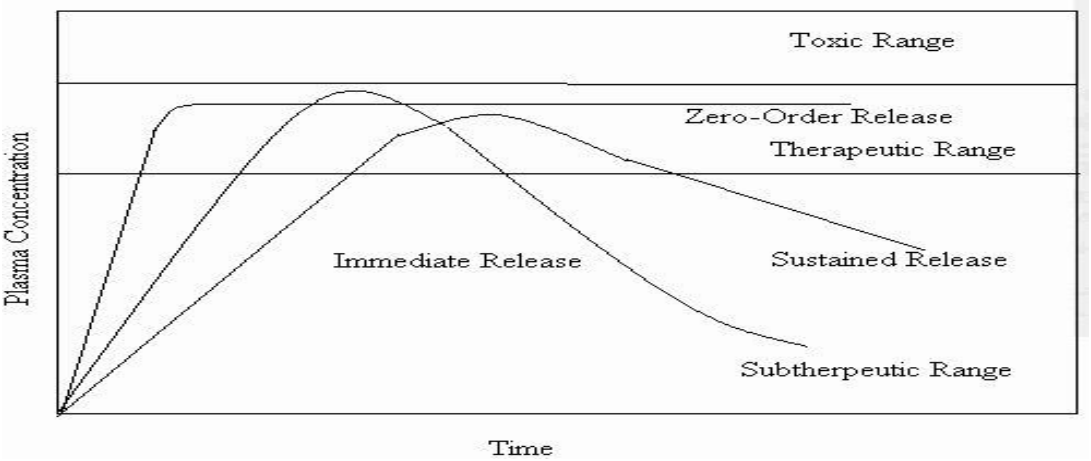
(a) It will be a single dose for the whole duration of treatment.

(b) It will deliver the active drug directly at the site of action. Unfortunately, such ideal systems are not available. Thus scientists try to develop systems that can be as close to an ideal system as possible.

ORAL DRUG DELIVERY SYSTEMS[1, 2]

Oral drug delivery has been known for decades as the most widely utilized route of administration among all routes that have been explored for the systemic delivery of drugs in case of different dosage forms. The scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of following aspects:

1. Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
2. The anatomic and physiologic characteristics of the gastrointestinal tract.
3. Physico mechanical characteristics and the drug delivery mode of the dosage form to be designed



COMPRESSED TABLETS

Are defined as solid dosage forms made by compaction of the formulation containing the drug and certain fillers or excipients selected to aid in the processing and properties of the drug product

ADVANTAGES OF TABLETS [3]

The primary potential advantages of tablets are,

- They are the unit dosage forms, which offer the great capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- The cost is lower of all oral dosage forms.
- They are the lightest and most compact of all.
- They are in general the easiest and cheapest to packaging and shipment.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They may provide the greatest case of swallowing with the least tendency for hang up above the stomach, especially when coated, provided the tablet disintegration is not excessively rapid.
- They lend themselves to certain special profile products, such as enteric or delayed release products.
- They are better suited to large scale production than with other unit oral dosage forms.
- They have the best combined properties of chemical, mechanical and microbiological stability of all the oral forms.

DISADVANTAGES

In spite of all these advantages, tablet also possesses some disadvantages. The disadvantages of tablets include the following

- Some drugs resist compression in to dense compacts, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting properties, slow dissolution properties, intermediate to large dosages, optimum absorption high in the GIT or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter tasting drugs, drug with obnoxious odour or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation / entrapment prior to compression / coating.

MULTILAYER TABLETS[5]

Multilayer tablets are tablets made by compressing several different granulations fed in to a die in succession, one on top of another, in layer. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for 2 or 3 layers. More are possible but the design becomes very special. Ideally a slight compression of each layer and individual layer ejection permits weight checking for control purposes.

ADVANTAGES OF MULTILAYER TABLETS

1. Incompatible substances can be separated by formulating them in separate layers as a two-layer tablet or separating the two layers by a third layer of an inert substance as a barrier between the two

2. Two layer tablets may be designed for sustained release –one layer for immediate release of the drug and the second layer for extended release, thus maintaining a prolonged blood level.
3. Layers may be colored differently to identify the product.

LAYER THICKNESS

Layer thickness can be varied within reasonable proportions with in the limitations of the tablet press. Thickness is dependent on the fineness of the granulation.

SIZES AND SHAPES

Size is limited by the capacity of the machine with the total thickness being the same as for a single layer tablet. Many shapes other than spherical are possible and are limited only by the ingenuity of the die maker. However, deep concavities can cause distortion of the layers. Therefore standard concave and flat face beveled edge tooling make for the best appearance, especially when layers are of different colors.

GRANULATIONS

For good quality tablets with sharp definition between the layers, special care must be taken as follows,

1. Dust fines must be limited. Fines smaller than 100 meshes should be kept as a minimum.
2. Maximum granule size should be less than 16 meshes for a smooth, uniform scrap off at the die.
3. Materials that smear, chalk or coat on the die table must be avoided to obtain clean scrape off and uncontaminated layers.
4. Low moisture is essential if incompatibilities are used.
5. Weak granules that break down easily must be avoided. Excessive amounts of lubrication, especially metallic stearates, should be avoided for better adhesion of the layers.
6. Formulation of the multilayer tablets is more demanding than that of single layer tablets for this reason, selection of additives is critical.

TABLET LAYER PRESS

A tablet multilayer press is simply a tablet press that has been modified so that it has two die filling and compression cycles for each revolution of the press. In short, each punch compresses twice, once for the first layer of a two layer tablet and a second time for the second layer. Three layer presses are equipped with three such compression cycles. here are two types of layer presses presently in the use- one in which each layer can be ejected from the press separately for the purpose of weight checking and the second in which the first layer is compressed so hard that the second layer will not bond to it or will bond so poorly that upon ejection the layers are easily separated for weighing. Once the proper adjustments have been made by adjusting the die fill, the pressure is adjusted to the proper tablet hardness and bonding of the layers. One hazard of layer tablet production is the lack of proper bonding of the layers. This can result in a lot of 100,000 tablets ending up as 200,000 layers after several days if the layers are not sufficient bonded. In a two layer tablet press, two hoppers above the rotary die table feed granulated material to two separate feed frames without intermixing. Continuous, gently circulation of the materials through the hoppers and that would otherwise carry over to the second layer and affect layer weight, appearance of the tablet. The same procedure is followed in the three layer press with three hoppers for the three granulations instead of two. Certain single layer or unit tablet presses are equipped with two pre-compression stations prior to the final compaction. This provides high speed production by increasing dwell time of the material under pressure making for harder, denser tablets. E.g. Prolonged and immediate release tablet containing penta errythritol tetra nitrate two layer tablets

SUSTAINED DRUG RELEASE[7]

The goal of sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form. Zero order release constituents drug release from the dosage form that is independent of the amount of drug in the delivery system (a constant release rate). Sustained release system generally do not attain this type of release and usually try to mimic Zero order release by providing drug in a slow first order fashion (concentration dependent).Systems that are designated as prolonged release can also be considered as attempts at achieving sustained release delivery. Repeat – action tablets are an alternative method of sustained release in which multiple doses of the drug are contained within a dosage form, and each dose is released at a periodic interval. Delayed release system in contrast, may not be sustaining, since often the function of these dosage

forms is to maintain the drug within the dosage form for some time before release. Commonly, the release rate of drug is not altered and does not result in sustained delivery once drug release has begun**.**

ADVANTAGES OF SUSTAINED RELEASE PRODUCTS[8]

- Decreased local and systemic side effects
- Reduced gastro intestinal irritation.
- Better drug utilization
- Reduction in the total amount of drug used.
- Minimum drug accumulation on chronic dosing.
- Optimized therapy.
- Reduction in fluctuation in drug level and hence more uniform pharmacological response.
- More uniform blood concentration.
- For drugs with very short elimination half –lives, sustained release products maintain the efficacy over a long duration.
- Improved patient compliance
- Less frequent dosing.
- Reduced night time dosing.
- Reduced patient care time.
- Economy result from a decrease in nursing time and hospitalization.

DISADVANTAGES OF SUSTAINED RELEASE PRODUCTS[9]

1. Dose dumping may occur either as a release of more than the usual fraction of drug or as the release of drug at a greater rate.
2. Removal of drug from the system is difficult in case of any toxicity, adverse drug reaction are accidentally becomes intoxicated.
3. Orally administered sustained release products may yield erratic or variable drug absorption as a result of various drug interactions with the content of GI tract and changes in GI motility.
4. Sustained release may not be practicable for drugs that are usually given in large doses in conventional dosage forms.
5. Higher cost of medication has compared to conventional drug products.

IMMEDIATE RELEASE DRUG DELIVERY SYSTEM

Immediate release drug delivery system is a conventional type of drug delivery. It is designed to disintegrate and release their medicaments with no special rate controlling features. These are the dosage forms in which ≥ 85% of labeled amount dissolves within 30 min (Patel HP et al., 2011)[1]. However for immediate release tablets, tablet disintegrates play an important role in ensuring that the tablet matrix break up on contact with fluid in the stomach to allow the release the active drug which then become available in whole or in part, for absorption from gastrointestinal tract.

MECHANISM OF DRUG RELEASE

On exposure to aqueous fluids, hydrophilic matrices take up water and the polymer starts hydrating to form a gel layer. Drug release is controlled by diffusion barriers/by surface erosions. An initial burst of soluble drug may occur due to surface leaching. When matrix containing a swellable glassy polymer comes into contact with an aqueous medium, there is an abrupt change from a glassy to rubbery state associate with swelling process with time, water infiltration deep into a case increasing the thickness of the gel layer. The outer layer becomes fully hydrated and starts dissolving or eroding. When water reaches the center of the system and the concentration of drug falls below the solubility value, the release rate of the drug begins to reduce. At the same time an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release.

ADVANTAGES OF IMMEDIATE RELEASE DRUG DELIVERY SYSTEM

- Release the drug immediately.
- More flexibility in adjusting the dose.
- It can be prepared with minimum dose of drug.
- There is no dose dumping problem
- Immediate release drug delivery systems can be used in both initial stage and final stage of disease.

The conventional dosage forms like solutions, suspensions, capsules, tablets and suppository etc. have some limitations such as Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range. The fluctuating drug levels may lead

to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.

"CHARACTERIZTION OF MULTILAYER TABLETS"

Twenty tablets from each batch were weighed and the average weights were calculated.

Average Weight = Total weight (mg)/20

THICKNESS

The thickness of the tablets was determined by Vernier caliper.Three tablets from each batch were used and the average values were calculated.

HARDNESS TEST

The hardness of the tablet was measured using hardness tester.

UNIFORMITY OF WEIGHT (WEIGHT VARIATION TEST)

This is an important in-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight. 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±5%). The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

FRIABILITY TEST

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula.

$$\text{Friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where,

W_1 = weight of the tablet before test

W_2 = weight of the tablets after test

The disintegration for immediate release layer was determined using the disintegration apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000 ml of purified water maintained at 37 ± 2^0 C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

***In vitro* DISSOLUTION STUDIES**

In vitro drug release studies for sustained release layer were carried out using USP XXIV dissolution apparatus type II, with 900ml of dissolution medium maintained at 37±1°C for 12 hr, first 2 hours at 50 rpm, in 0.1 N HCl (pH 1.2) and next 10 hours in 6.8phosphate buffer was used as a dissolution medium and 5ml of sample was withdrawn at predetermined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and drug content in each sample was analyzed after suitable dilution by UV/Vis Spectrophotometer. In vitro drug release for ritonavir immediate release layer was conducted in 0.1N HCL for 30minutes in paddle apparatus similar above mentioned conditions for temperature and rpm.

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