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Process Optimization and Scale-Up of Anti-Hypertensive Bi-Layer Tablet Formulation-A Quick Review

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ABSTRACT:

In a pharmaceutical industry, preparation of a dosage form need process scale- up in several stages. Pharmaceutical scale-up involves manufacturing drug product with increasing batch sizes on larger equipment. Production scale is typically differ-ent from R&D scale in terms of batch size. The processing conditions during R&D scale and commercialize scale are quite different from each other. The successful established conditions for a product at R&D scale would not be same at production scale. Therefore, each and every unit operation in the production of tablet formulation at production scale is optimized for successful scale-up. Therefore, scientific optimization techniques are used to provide effective, accurate, and less time consuming way to scaling up the production profile from laboratory to commercialize plant so as to have higher output without any objection on quality matters. In the present work, an attempt has been made to implement the quality by design (QbD) principles for successful process scale-up. The design of experiment (DoE) strategy was applied during the process scale-up of any product to reduce the risk of batch failure on quality attributes. Quality by design approach using design of experimentation can be implemented successfully to provide fully robust and reproducible process that will develop an assured quality product.

Keywords: Immediate Release Tablet, Immediate Release Bilayer Tablet, Anti-Hypertensive Bi-Layer, Optimization, Scale-Up

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INTRODUCTION:

Quality is a very crucial parameter in the manufacturing and packaging process. Without a justified quality a product seems to be useless one. In the pharmaceuticals and medical products, quality control has historically taken a backseat to innovate science and compelling market, the standard drivers of the industry's profitability. Recently companies have no choice but to improve their quality accordingly because companies have cost millions of dollars fine and also lost high revenue due to inappropriate or poor quality and related compliance issues. The pharmaceutical industry is transforming the mass production of drugs. Therefore, quality at an industrial scale remains variable for many of the world's top drug-makers although after investing a handsome capital in improving the quality. Early reports from the field of improvement suggest that progress will require massive change across organisations beyond the factory floor.

For a start, Pharma is one of the most heavily regulated industries. In the United States, the world's largest pharmaceutical market by far, the Food and Drug Administration (FDA) is in the midst of changing how it intends to approve pharmaceutical manufacturing applications by emphasizing a "quality by design"

model of regulatory approval compared with a "quality by testing" orientation that it used until recently. In 1980s, for instance, the primary focus of the FDA was to prevent fraudulent drugs from reaching to consumer. By the late 1990s it focused more on the "drugmakers" processes. Today FDA has taken much more on evaluating the quality of pharmaceutical manufacturing plant and networks.

In 2002, U S Food and Drug Administration (FDA) published a concept paper on current good manufacturing practice for the 21st century. This document expressed a desire that companies build quality, safety and efficacy into their new pharmaceutical and biopharmaceutical product. This concept became known as "Quality by design or QbD".

Advantages of bi-layer tablets

1. Bilayer execution with optional single layer conversion kit.1
2. Cost is lower when compared to other oral dosage forms.
3. Greatest chemical and microbial stability.
4. Objectionable odour and bitter taste can be masked by coating technique.
5. Flexible concept.
6. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
7. Easy to swallowing with least tendency for hang-up.

Disadvantages of bilayer tablets

1. Some drugs do not resist compression into dense compacts, owing to amorphous nature, low density character.2
2. Bitter drugs, unpleasant odour drugs, oxygen sensitive drugs may require encapsulation or coating.
3. Drugs with poor wetting, slow dissolution properties may be difficult to formulate or manufacture as a bilayer tablet.

VARIOUS TECHNIQUES FOR BILAYER TABLET 3, 4

A) OROS® push pulls Technology[6]

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So 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 (Figure 1).

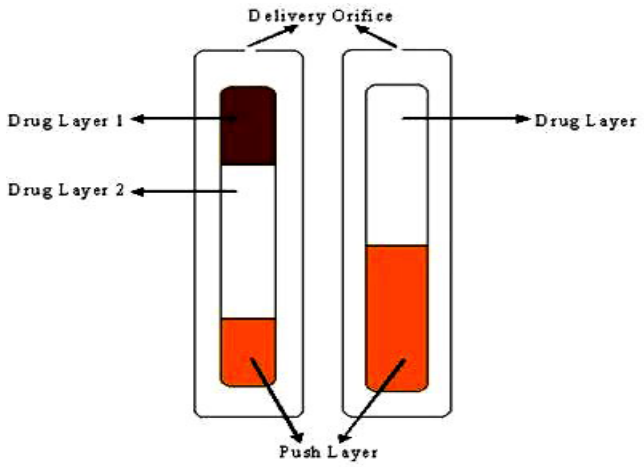

Figure. 1: Bilayer and tri layer OROS push pull technology

B) L-OROSTM Technology

This system used for the solubility issue Alza developed the L-OROS system where a lipid soft gel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, than osmotic push layer and then a semi permeable membrane, drilled with an exit orifice(Figure 2).

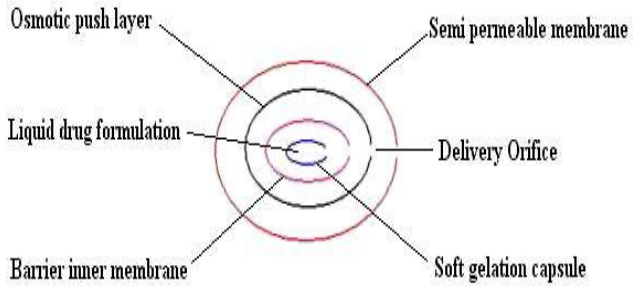

Figure 2: L–OROSTM Technology

C) ENSOTROL 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 (Figure3).

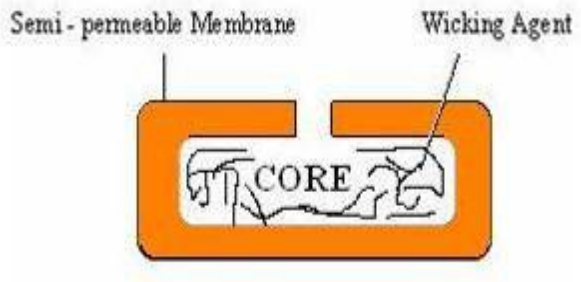

Figure: 3: EN SO TROL Technology

D) DUREDAS™ Technology

This system is also known as Elan drug technologies' Dual release drug delivery system. DUREDAS™ Technology is a bilayer tablet which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form. The tableting process can provide an immediate release granulate and a modified release hydrophilic matrix complex as separate layers within the one tablet. The modified-release properties of the dosage form are provided by a combination of hydrophilic polymers.

E) DUROS Technology[7]

The system consists from outer cylindrical titanium alloy reservoir. This reservoir has high impact strength and protects the drug molecules from enzymes. The DUROS technology is the miniature drug dispensing system that opposes like a miniature syringe and release minute quantity of concentrated form in continues and consistent from over months or year(Figure 4).

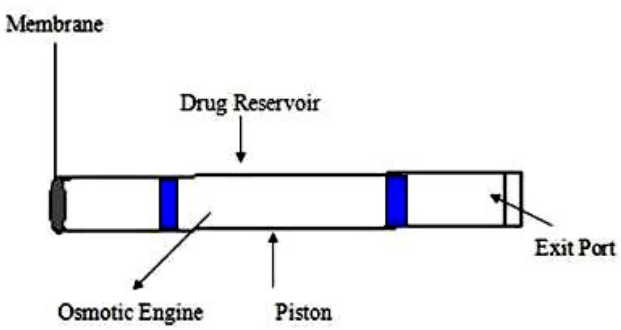

Figure 4: DUROS Technology

VARIOUS APPROACHES USED IN THE BILAYER TABLET4,5

a) Floating Drug Delivery System

From the formulation and technological point of view, the floating drug delivery systems are considerably easy and logical approach in the development of Gastro retentive dosage fo rms (GRDFs).

Approaches to design Floating Drug Delivery System

The following approaches have been used for the design of floating dosage forms of single and multiple-unit systems.

Intra gastric bilayered floating tablets

These are also compressed tablet as shown in figure and contain two layers i.e. Immediate and sustained release

Multiple unit type floating pills

These systems consist of sustained release pills as 'seeds' surrounded by double layers. The inner layer consists of effervescent agents while the outer layer is of swellable membrane layer. When the system is immersed in dissolution medium at body temperature, it sinks at once and then forms swollen pills like balloons, which float as they have lower density. (Figure 5)

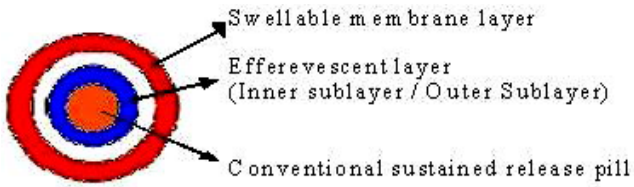

Figure 5: Multiple units of oral FDDS

b) Polymeric Bio adhesive System

These are designed to imbibe fluid following administration such that the outer layer becomes a viscous, tacky material that adheres to the gastric mucosa/mucus layer. This should encourage gastric retention until the adhesive forces are weakened.

These are prepared as one layer with immediate dosing and other layer with bio adhesive property.

Disadvantages*:* The success is seen in animal models with such system has not been translated to human subjects due to differences in mucous amounts, consistency between animals and humans. The system adheres to mucous not mucosa. The mucous layer in humans would appear to slough off readily, carrying any dosage form with it. Therefore, bio adhesive dosage form would not appear to offer a solution for extended delivery of drug over a period of more than a few hours.

c) Swelling System

These are designed to be sufficiently small on administration so as not to make ingestion of the dosage form difficult (e.g., less than approximately 23 mm long and less than 11 mm wide for an oval or capsule –shaped tablet whereas 10- 12mm in diameter for round tablets). On ingestion they rapidly swell or disintegrate or unfold to a size that precludes passage through the pylorus until after drug release has progressed to a required degree. Gradual erosion of the system or its breakdown into smaller particles

enables it to leave stomach. The simple bilayer tablet may contain an immediate release layer with the other layer as extended release or conventional release.

DEVELOPMENT OF THE FORMULATION AND OPTIMIZATION OF PROCESSING CONDITIONS FOR PROCESS SCALE-UP

A. Development of the formulation

The formulation trial range was developed by formulation and development (F&D) department at R&D centers, The formulation had already been established at the laboratory scale.

B. Development of pilot batch

Firstly, trials were done before starting manufacturing of commercial batches to have optimized conditions for the manufacturing. Although, the formulation process is optimized at R&D department but on scaling-up various parameters would change due to bulk or equipment design or processing variables etc.

C. Brief manufacturing procedure

- **Dispensing**

All the raw materials (Active and excipients) were dispensed from warehouse under the supervision of warehouse manager to dispensing booth.

- **Sifting**

In sifting, excipients were sifted in a vibro sifter through a 40 mesh size, materials like (Microcrystalline cellulose and Povidone K30) were sifted through 30 mesh size and collected in a separate double poly bags, and the drug was sifted through multimill having 2 mm mesh size, and collected in a separate double poly bag.

- **Binder preparation**

Weighed amount of binder powder was soaked in water in a steam jacketed pan. Then the temperature of water was increased (upto 80^0C) through steam and stirrer was started for mixing for half an hour. After that solution was cooled to 50^0C.

- **Addition of binder**

The prepared binder was added to the dry mixed powder in rapid mixer granulator (RMG) by the peristaltic pump with a constant addition rate.

- **Granulation**

Rapid mixer granulator was operated according to the prescribed standard operating procedure (SOP. The wet granulated mass was checked for optimum consistency time to time for effective granulation. The additional amount of water (if required) was added at first slow and then fast speed of impeller and slow speed of chopper for better granulation (if required).

- **Drying**

The wet granules were dried in fluidized bed dryer to obtain coarse milled dried granules. The inlet temperature, exhaust temperature, % LOD to be achieved. The coarser dried granules were milled through 2.5 mm mill screen and again drying was done. The samples were collected and were sent to QC for testing of % w/w LOD and assay of granules.

- **Milling**

The coarser dried granules were milled through 14 mesh size from vibro sifter and retained granules were passed through 2.0 mm mill screen with knives in forward direction and at medium speed.

- **Blending & lubrication**

The obtained milled granules were mixed with extra-granular material and loaded in octagonal blender, which were blended at 14 rpm speed and were evaluated for the lubrication time. The sample of lubricated blend was forwarded to QC for testing of blend uniformity.

- **Compression**

After lubrication, compression of granules was carried out. Compression was done on 27 station rotary tablet machine. In compression, hardness of tablet and speed of machine were optimized.

D. Evaluation of granules (for both layers blend)

- **Bulk density**

Bulk density (BD) was measured by slowly pouring a powder sample into a 100 ml graduated cylinder at a 45 degree angle. Care was taken not to shake the sample. BD of each sample is calculated as follows

$$\text{Bulk density (BD)} = \frac{\textit{Weight of the powder sample}}{\textit{volume of the powder sample}}$$

- **Tapped density**

To measure tapped density (TD), a powder sample was poured into a 100 ml graduate cylinder at a 45 degree angle. The sample was mechanically tapped 100 times. TD was calculated by dividing the sample weight by its final volume.

$$\text{Tapped density} = \frac{\textit{Weight of the powder sample}}{\textit{volume of the tapped powder sample}}$$

- **Compressibility index**

The values of bulk density (BD) and tapped density (TD) of the compression mixture (also called the final blend) were used to calculate their compressibility index, (CI).

$$\text{Compressibility Index, (CI)} = 100 \text{ X} \left(1 - \frac{\textbf{Bulk density}}{\textbf{Tapped density}}\right)$$

E. Evaluation parameters of the tablet formulation

a. **Hardness:** This test was performed on 5 tablets from a batch on Erweka hardness tester at an interval of 2 hours as per the prescribed SOP.

b. **Thickness:** 5 tablets of each batch were tested for their thickness using digital Vernier Calipers at an interval of 2 hours and the mean thickness was noted.

c. **Average weight:** It was checked in weighing balance (Metler Telledo). Twenty tablets were selected at random and weighed individually. The average weight of 20 tablets was calculated. Individual weights of the tablets were compared with the average weight.

Weight variation = (Mavg – M) / Mavg × 100

where, Mavg = Average weight of tablet

M = Weight of individual tablet

d. **Friability test:** Roche friabilator was used for evaluation of friability of compressed tablets. 10 pre-weighted tablets were taken and were placed into friabilator and rotated at 25 rpm speed for 4 minutes. After 100 revolutions in 4 minutes tablets were taken off from it and then weighed again and % friability was calculated by given formula:

$$\%\ \text{Friability} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{initial weight}} * 100$$

e. **Dissolution:** It was performed on 6 tablets in USP Dissolution apparatus (Basket type) in 6.8 pH Phosphate buffer at 37.0 ± 0.5 0C and at 100rpm. Samplings were done at 15, 30 and 60 min. appropriate dilutions were prepared.

F. Optimization of process scale up using design of experiments (DoE)

a. Selection of Experimental Design
b. Selection of Variables
c. Selection of Levels
d. Execution of Design
e. Analysis of Design
f. Optimization

CONCLUSION:

On the basis of literature it was found that granulation process and compression process affects the tablet dosage form mostly The R&D report suggested that binder solution level, kneading time and total drying time were having more impact on scale up rather than other factors. Similarly compression process contributed both conditions i.e. compression force and compression speed that impart some effect on scale up studies.

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