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## A Review On Mucoadhesive Bilayer Buccal Tablets

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### ABSTRACT

Mucoadhesive drug delivery systems interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules increase the residence time of the dosage form at the site of absorption. Bioadhesion may be defined as the state in which two materials, at least one of which is of a biological nature, are held together for extended periods of time by interfacial forces. Mucosal layer represents potential sites for the attachment of any bioadhesive systems because mucosal layer lines number of the body including the gastro intestinal tract, the urogenital tract, vaginal tract, the eye, ear, and nose. The mucoadhesive Bilayer tablets consisting of two various types of drug molecules and they show on set of actions at their particular sites. This review describes the structure of mucosal layer, mechanism of action of mucoadhesion, and preparation techniques of Bilayer tablets and evaluation parameters of tablets.

**Keywords:** Mucoadhesive drug delivery, Bilayer tablets, polymers, bioadhesive.

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## INTRODUCTION

Adhesion as a process, simply defined as the “fixing” of two surfaces to one another. There are many different terminological subsets of adhesion depending upon the environment in which the process occurs. When adhesion occurs in a biological setting it is often termed “bioadhesion”. Bioadhesion may be defined as the state in which two materials, at least one of which is of a biological nature, are held together for extend periods of time by interfacial forces (1). For drug delivery purposes, bioadhesion term implies the attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue or the mucous coat on the surface of a tissue. If the adhesive attachment is to a mucous coat, then the phenomenon is known as mucoadhesion. Mucosal layer represents potential sites for the attachment of any bioadhesive systems because mucosal layer lines number of the body including the gastro intestinal tract, the urogenital tract, vaginal tract, the eye, ear, and nose. The advance in the various mucoadhesive drug delivery system is oral transmucosal drug delivery gaining important than other mucoadhesive delivery systems like vaginal delivery, rectal delivery, nasal delivery, ocular delivery. However, the potential irritation and the irreversible damage to the ciliary of the nasal cavity was found by continuous application of nasal dosages form, as well as the large intra and inter subject variability in mucous secretion in the nasal mucosa, could significantly affect drug absorption from this site (2). Even though the rectal, vaginal and ocular mucosa all offer poor patients acceptability associated with these sites renders them reserved for local applications rather than systemic drug administration. On other hand oral cavity are highly acceptable because the mucosa is relatively permeable with a reach blood supply. Furthermore it’s also bypasses first pass effect and avoids pre systemic elimination in the GI tract.

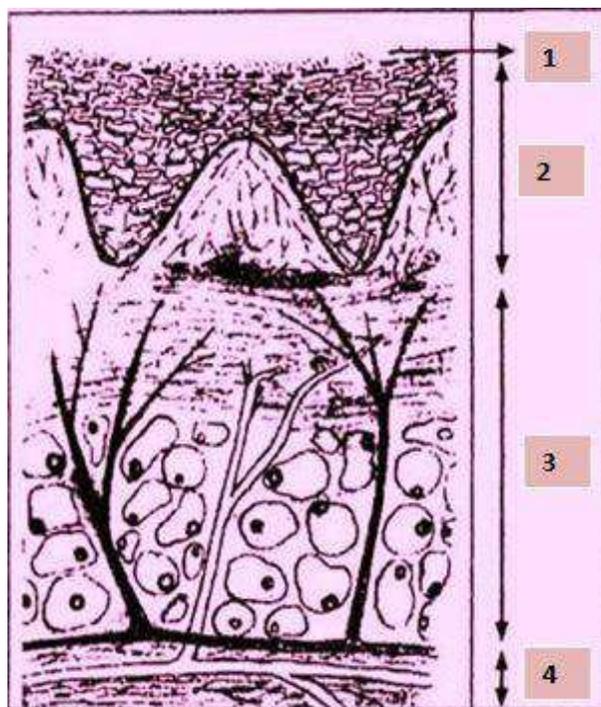
The delivery of drug into oral mucosal cavity is classified into three categories:-

1. Sublingual delivery- which is systemic delivery of drug through the mucosal membranes lining the floor of the mouth.
2. Buccal delivery- which is drug administration through the mucosal membranes lining the cheeks.
3. Local delivery- which is drug delivery into the oral cavity (1,2).

### **Structure and function of oral mucosal membrane:-**

The oral mucosa is composed of an outermost layer called stratified squamous epithelium (fig 1) and below a basement membrane; a lamina propria followed by the submucosa as the inner most layer. It also contains many sensory receptors including the taste receptors of the tongue (1,2). The

blood epithelium is classified as non-keratinized tissues. It is penetrated by tall and conical shaped connective tissues. These tissues which are referred to as lamina propria, consist of collagen fibers, a supporting layer of connective tissues, blood vessel and smooth muscles. The epithelium may consist of a single layer (stomach, small and large intestine, bronchi) or multiple layers (esophagus, vagina). The upper layer contains goblet cells, which secrete mucus components directly onto the epithelial surface. Specialized glands producing components of the mucous layer may also be located beneath the epithelium. The moist surface of the tissue results from the mucus – a viscous, gelatinous secretion whose composition includes glycoproteins, lipids, inorganic salts, and up to 95% water. Mucus may be secreted either constantly or intermittently. The volume of secretion changes under the influence of external and internal factors. Mucin (Glycoproteins) are the most important components of mucus and it is also very responsible for gelatinous structure, cohesion, and antiadhesive properties (2). Mucin consists of a three-dimensional network with a large number of loops. The main functions of the mucus are to protect and lubricate the supporting epithelial layer. In the gastrointestinal tract, the mucus facilitates the movement of food boluses along the digestive canal and protects the epithelium from harmful influences due to intrinsic peristaltic movements and proteolytic enzymes. The components of the mucus secreted onto the surface of the eye by goblet cells adhere tightly to the glycocalyx of corneal-conjunctival epithelial cells, protecting the epithelium from damage and facilitating the movement of the eyelids (1,2).



**Figure 1: Structure of the mucosa of the Oral Cavity**

(1) Mucus layer; (2) Epithelium; (3) Connective tissue (lamina propria); (4) Smooth muscles

### **Permeability:-**

It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than the skin. There are considerable differences in permeability between different regions of the oral cavity because of diverse structures and functions of the different oral mucosae. In general, the permeability of the oral mucosae decreases in the order of sublingual greater than buccal, and buccal greater than palatal. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized (1). The permeability barrier property of the oral mucosa is predominantly due to intracellular materials derived from the so-called – “membrane coating granules” (MCGS). Recent evidence has shown that passive diffusion is the primary mechanism for the transport of drugs across the buccal mucosa, carrier-mediated transport has been reported to have a small role. In buccal mucosa two routes of passive transport are found: one involves the transport of compounds through the intercellular space between the cells (paracellular) and the other involves passage into and across the cells (transcellular). Another barrier to drug permeability across buccal epithelium is enzymatic degradation. Some proteolytic enzyme has been found in the buccal epithelium.

### **Environment:**

The oral cavity is marked by the presence of saliva produced by the salivary glands and mucus which is secreted by the major and minor salivary glands as part of saliva. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water-rich environment of the oral cavity (3).

### **Role of Saliva**

1. Protective fluid for all tissues of the oral cavity.
2. Continuous mineralization / demineralization of the tooth enamel.
3. To hydrate oral mucosal dosage forms.

### **Role of Mucus**

1. Made up of proteins and carbohydrates.
2. Cell-cell adhesion
3. Lubrication

#### 4. Bioadhesion of mucoadhesive drug delivery systems

##### **Buccal Drug Delivery and Mucoadhesivity**

For the development of these Buccal drug delivery systems, mucoadhesion of the device is a key element. For proper and good mucoadhesion mucoadhesive polymer have been utilized in many different dosages form such as tablets, patches, tapes, films, semisolids and powders. Many studies showed that addition of various polymers to drug delivery systems such as gums, increased the duration of attachment of the formulations to the mucous surface and also increased the efficacy. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as –

1. Predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups.
2. Polymer and its degradation products should be non-toxic, non-irritant and free from leachable impurities.
3. Should have good spreadability, wetting, swelling and solubility and biodegradability properties.
4. P<sup>H</sup> should be biocompatible and should possess good viscoelastic properties.
5. Should possess peel, tensile and shear strengths at the bioadhesive range (1,2,3,4).

##### **Classification of mucoadhesive polymers**

**Table 1: Mucoadhesive polymers classification**

| <b>Types</b>                          | <b>Examples</b>  |
|---------------------------------------|--|
| Natural and modified natural polymers | Agarose, Chitosan, Gelatin, Pectin, Sodium alginate, CMC, Na CMC, HPC, HPMC, Methyl cellulose. |
| Synthetic                             | Carbopol, Polycarbophil, Polyacrylic acid, Polyacrylates                                       |
| Cationic and anionic                  | Aminodextran, Chitosan, Chitosan –EDTA, Dimethylaminoethyl dextran                             |

##### **Methods to increase drug delivery through buccal route:**

###### **Absorption enhancer:**

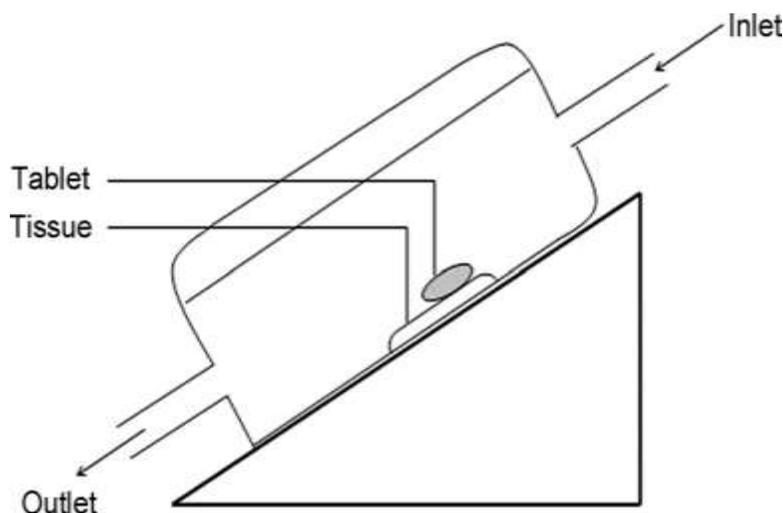
The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Sub-stances that facilitate the permeation through buccal mucosa are referred as absorption enhancers. As most of the absorption enhancers were originally designed for increase the absorption of drug and improved efficacy and reduced toxicity. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers (5). The efficacy of enhancer in one site is

not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of chitosan were also found to promote the transport of mannitol and fluorescent-labelled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism (1,5).

### **Mechanism:**

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows.

Changing mucus rheology: Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers' act by reducing the viscosity of the mucus and saliva overcomes this barrier.



**Figure 2: Schematic drawing of the dissolution apparatus used by Mumtaz and Ch'ng (1995) for studying the dissolution of buccal tablets.**

- Increasing the fluidity of lipid bilayer membrane: The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid or protein components.
- Acting on the components at tight junctions: Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.

- By overcoming the enzymatic barrier: These act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.
- Increasing the thermodynamic activity of drugs: Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to in-creased thermodynamic activity resulting better absorption (1,6,7).

Surfactants such as anionic, cationic, nonionic and bile salts increases permeability of drugs by perturbation of intercellular lipids whereas chelators act by interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface. Chitosan exhibits several favorable properties such as biodegradability, bioavailability, antifungal/antimicrobial properties in addition to its potential bioadhesion and absorption enhancer (5,6,7,8).

**Table 1: List of some permeation enhancers**

| S.No | Permeation Enhancers      |
|------|---------------------------|
| 1.   | Cyclodextrin              |
| 2.   | Glycol                    |
| 3.   | Lauric acid               |
| 4.   | Polyoxyethylene           |
| 5.   | Polysorbate 80            |
| 6.   | Sodium lauryl sulphate    |
| 7.   | Sodium salicylate         |
| 8.   | Sodium EDTA               |
| 9.   | Sodium taurochlorate      |
| 10.  | Sodium glycodeoxychlorate |

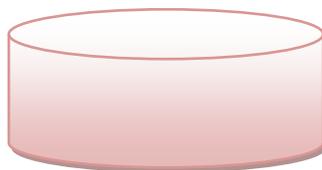
**Advantages of tablets:**

- Ease of accurate dosing and low content variability
- Good physical and chemical stability
- Competitive unit production costs
- High level of patient acceptability
- High convenience
- Easy to package and ship
- Simple to identify
- Convenience of self administration (9).

**Disadvantages of tablets:**

- Irritant effects on the gastro intestinal mucosa by some solids (e.g. aspirin)
- Possibility of bioavailability problems resulting from slow disintegration and dissolution

- Difficulty in swallowing in some patients; pediatrics and geriatrics
- Some drugs resist compression into tablets
- In emergency cases, intravenous or intramuscular injections are more effective (9).



**Figure 3: Structures of Bilayer tablets**

### **Bilayered tablets:**

Bilayer tablets are composed of two layers of granulation compressed together. Two-layer tablets require fewer materials than compression coated tablets weigh less and may be thinner. Monograms and other distinctive markings may be impressed in the surfaces of the multilayer tablets. Coloring the separate layers provides many possibilities for unique tablet identity. Separation of the layers prior to assay may simplify the analytical work. Since there is no transfer to a second set of punches and dies, as with the dry-coating machine, odd shapes (such as triangles, squares, and ovals) present no operating problems except for those common to keyed tooling. Several pharmaceutical companies are currently developing bilayered tablets, for a variety of reasons viz. patent extension, therapeutic, marketing to name a few. Various problems are associated with the formulation of bilayered tablets, such as layer-separation, insufficient hardness, inaccurate individual layer weight control, cross contamination between the layers, reduced yield etc. To overcome these problems, development and production of quality bilayered tablets need to be carried out on purpose built tablet presses (11).

### **Challenges in bilayered tablets manufacturing:**

Conceptually, bilayer tablets can be seen as two single-layer tablets compressed into one. In practice, there are some manufacturing challenges.

- **Delamination:** Tablet falls apart when the two halves of the tablet do not bond completely. The two granulations should adhere when compressed.
- **Cross-contamination:** When the granulation of the first layer intermingles with the granulation of the second layer or vice versa, cross-contamination occurs. It may conquer the very purpose of the bilayer tablet. Proper dust collection goes a long way toward preventing cross contamination.

- **Production yields:** To prevent cross contamination, dust collection is required which leads to losses. Thus, bilayer tablets have lower yields than single-layer tablets (11).
- **Cost:** Bilayer tableting is more expensive than single-layer tableting for several reasons. First, the tablet press costs more. Second, the press generally runs more slowly in bilayer mode. Third, development of two compatible granulations is must, which means more time spent on formulation development, analysis and validation.

These factors, if not well controlled/optimized, in one way or another will impact the bilayer compression per se and the quality attributes of the bilayer tablets (sufficient mechanical strength to maintain its integrity and individual layer weight control). Therefore, it is critical to obtain an insight into the root causes to enable design of a robust product and process (12).

### **Various Techniques involved in bilayer tablet formulation:**

#### **OROS® push pull technology:**

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.

#### **L-OROS® 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 than a semi permeable membrane, drilled with an exit orifice.

#### **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

#### **Duros Technology:**

The system consists from an 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 reglious minute quantity of concentrated form in continues and consistent from over months or year.

#### **DUREDAS™ technology:**

DUREDAS or Dual Release Drug Absorption System (Elan Corporation) utilizes bilayer tableting technology, which has been specifically developed to provide two different release rates or dual release of a drug from a single dosage form. The tablets are prepared by two separate direct compression steps that combine an immediate release granulate (for rapid onset of action) and a controlled release hydrophilic matrix complex within one tablet. The controlled release matrix remains intact and slowly absorbs fluid from the GI tract, which causes the matrix. To expand and transforms the hydrophilic polymers into a porous, viscous gel that serves as a barrier between the drug and the surrounding fluid. As the gel continues to expand, fluid penetrates further into the dosage form, dissolving the drug and allowing the resulting solution to diffuse out in a controlled manner. A further extension of the Duredas technology is the production of controlled release combination dosage forms whereby two different drugs are incorporated into the different layers, and the drug release of each layer is controlled to maximize therapeutic effect of the combination. Again both immediate release and controlled release combinations of the two drugs are feasible (13).

**Benefits offered by the DUREDAS™ technology include:**

- Bilayer tableting technology.
- Tailored release rate of two drug components.
- Capability of two different formulations combined.
- Capability for immediate release and modified release components in one tablet
- Unit dose tablet presentation

**Bilayer tablets: Quality and GMP requirements:**

To produce a quality bilayer tablet, in a validated and GMP-way, it is important that the selected press is capable of

- Preventing capping and separation of the two individual layers that constitute the bilayer tablets.
- Providing sufficient tablet hardness.
- Preventing cross-contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield, accurate and individual weight control of the two layers (12).

**Types of Bilayer tablet press:**

A. Single sided tablet press

B. Double sided tablet press

C. Bilayer tablet press with displacement monitoring.

**A. Single-sided press:**

- The simplest design is a single-sided press with both chambers of the double feeder separated from each other.
- Each chamber is gravity- or forced-fed with a different powder, thus producing the two individual layers of the tablet.
- When the die passes under the feeder, it is at first loaded with the first-layer powder followed by the second-layer powder.
- Then the entire tablet is compressed in one or two (pre and main-compression) steps.
- The two layers in the die mix slightly at their interface and in most cases bond sufficiently so that no layer separation occurs when the tablet is produced.

**Limitations of single – sided press:**

- No weight monitoring/control of the individual layers.
- No distinct visual separation between the two layers.
- Very short first layer-dwell time due to the small compression roller, possibly resulting in poor de-aeration, capping and hardness problems.
- Very difficult first-layer tablet sampling and sample transport to a test unit for in-line quality control and weight recalibration.

**Dwell time:**

Dwell time is defined as the time during which compression force is above 90% of its peak value. Longer dwell times are a major factor in producing a quality tablet, especially when compressing a difficult formulation.

**Double Sided press:**

- A double-sided press offers an individual fill station, pre-compression and main compression for each layer.
- Most double-sided tablet presses with automated production control use compression force to monitor and control tablet weight.
- The effective peak compression force exerted on each individual tablet or layer is measured by the control system at main-compression of that layer.
- Measured peak compression force (under constant thickness) is the signal used by the control system to reject out-of-tolerance tablets and correct the die fills depth when required.

**Limitations of compression force controlled system:**

- A compression force-controlled system requires a minimal compression force of several hundreds of daN.
- However, many bilayer formulations require less than 100 daN to compress first layer in order to retain the ability to bond with the second layer.
- Above 100 daN, this ability may be lost, bonding between both layers may not be sufficient, resulting in low hardness of the bilayer tablet and separation of the two layers.
- At higher production speed, the risk of separation and capping increases but can be reduced by sufficient dwell time at compression stages (11,12).

### **Bilayer tablet press with displacement monitoring:**

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 tablet weight but depends on the applied pre compression force. This double-sided tablet press has been specifically designed and developed for the production of quality bilayer tablets and provides:

- ‘Displacement’ weight monitoring/control for accurate and independent weight control of the individual layers.
- Low compression force exerted on the first layer to avoid capping and separation of the two individual layers.
- Increased dwell time at pre-compression of both first and second layer to provide sufficient hardness at maximum turret speed.
- Maximum prevention of cross-contamination between the two layers - a clear visual separation between the two layers – maximized yield (11,12,13).

## **CHARACTERIZATION OF BILAYER TABLET**

### **Particle Size Distribution**

The particle size distribution can be measured by sieving method.

### **Angle of Repose**

Angle of repose can be measured by fixed funnel method. It determines flow property of the powder. It is defined as maximum angle formed between the surface of the pile of powder and the horizontal plane.

The powder was allowed to flow through the funnel fixed to a stand at definite height (h). By measuring the height and radius of the heap of powder formed (r), angle of repose can be calculated by using formula,

$\tan \theta = h/r$  where h and r are the height and radius of the powder cone.

### **Moisture Sorption Capacity**

All disintegrates have capacity to absorb moisture from atmosphere which affects moisture sensitive drugs. Moisture sorption capacity can be performed by taking 1 g of disintegrate uniformly distributed in Petri-dish and kept in stability chamber at  $37\pm 1^\circ\text{C}$  and 100% relative humidity for 2 days and investigated for the amount of moisture uptake by difference between weights.

### **Density**

Bulk density can be determined by tapping method. It is determined by pouring the weighed powder (sieve #20) into a measuring cylinder and initial weight was noted and the initial volume of powder is called bulk volume. The bulk density is expressed in terms of g/mL and calculated by formula,

$$D_B = W / V_B$$

Where, W is the weight of the powder

$V_B$  is the bulk volume of the powder

## **EVALUATION OF BILAYER TABLET**

### **Tablet Thickness and Size**

Thickness and diameter of tablets are important for uniformity of tablet size. Thickness and diameter can be measured by venire caliper.

### **Tablet Hardness**

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness can be measured as  $\text{kg/cm}^2$ .

### **Friability**

Friability can be measured as tablet strength. Friability of tablet can be determined by using friabilator (Aarson). It is expressed in percentage (%). The tablets are subjected into a plastic chamber revolving at 25 rpm for 4 minutes or run upto 100 revolutions by dropping a tablet at height of 6 inches in each revolution. Pre weighed tablets were placed in friabilator and subjected for 100 revolutions. It is measured by  $\% \text{ loss} = [( \text{Initial weight of tablets} - \text{Final weight of tablets}) / \text{Initial weight of tablets}] \times 100$ .

### **Uniformity of Weight**

The weight of the tablet being made can be routinely determined to ensure that a tablet contains the proper amount of drug. Twenty tablets selected randomly were weighed individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP

specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

### **Dissolution Studies**

Dissolution rate of the tablets can be studied using dissolution test apparatus USP II employing a paddle stirrer at 50 rpm & at  $37^{\circ} \pm 1^{\circ} \text{C}$ . Phosphate buffer of pH 6.8 (500ml) was used as a dissolution fluid. Samples of 5 ml each, were withdrawn at 0, 0.25, 0.5, 1, 2, 4, 6, 8 hrs and the samples were assayed. And the cumulative amount of drug release is calculated using standard calibration curve. Each sample withdrawn was replaced with an equal amount of drug free dissolution fluid (14,15).

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