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Bi-Layer Tablets for Controlled Release Drug Delivery

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Abstract:

Bilayer tablets has the potential for successful combination therapy as novel drug delivery system. Bilayer tablets are modified release system in which one layer serves as loading dose and the other layer serves as maintenance dose to enhance the bioavailability or to avoid the interaction between the incompatible substances by separating them physically. Several The development of bi-layer tablets for a variety of reasons like patent extension, therapeutic, and marketing purposes. Bilayer tablets are advancing helpful technologies to overcome the disadvantages of single-layered tablets. The goal of this review article is to discuss different approaches, criteria for immediate and sustained release dosage form, manufacturing techniques of bilayer tablet technology.

KEYWORDS: LOADING DOSE, INCOMPATIBLE, BILAYER TABLETS,THERAPEUTIC

INTRODUCTION

Oral Drug Delivery System

For many decades, we know oral delivery has been recognized as the mostly used route for administration of drug or dosage form among every approach investigated for successful systemic delivery of any drugs by different dosage forms. Drug products are meant to deliver systemically by oral route of administration, regardless of mode of delivery (may immediate, controlled or extended release) or dosage form design (solid, semisolid, or liquid), must be developed within the intrinsic characteristics of GI physiology.[1,2]

The most advanced delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, an elementary understanding of the following three areas makes up the scientific framework necessary for the effective creation of an oral drug delivery system:[3]

These are the anatomical and physiological characteristics of the gastrointestinal tract.

- Physiochemical, pharmacokinetic and pharmacodynamics characteristics of the drug.
- Physic mechanical characteristics and the drug delivery mode of the dosage form to be designed.

Histology (tissue and its Layers) of the Human Stomach[4]

The wall of stomach is basically composed of four basic layers. The outer most mucosa is a layer of simple columnar epithelium cells called mucous surface cells. Epithelial cells also extend down in to the lamina propria, forming many narrow channels called gastric pits and composed of columns of secretary cells called gastric glands.

Gastrointestinal tract is composed of these physiological and anatomical characters.

Table No: 1

Region	Surface Area (m^2)	pH of The Region	Transit Time	
			Fluid	Solid
GIT	200	1-8	-	-
Stomach	0.1-0.2	1-3	45-50 min.	8 hrs.
Small intestine	4500	6-7.5	2-6 hrs.	4-9 hrs.
Large intestine	0.1-0.5	5.5-6	2-8 hrs.	3 hrs. to 3 days

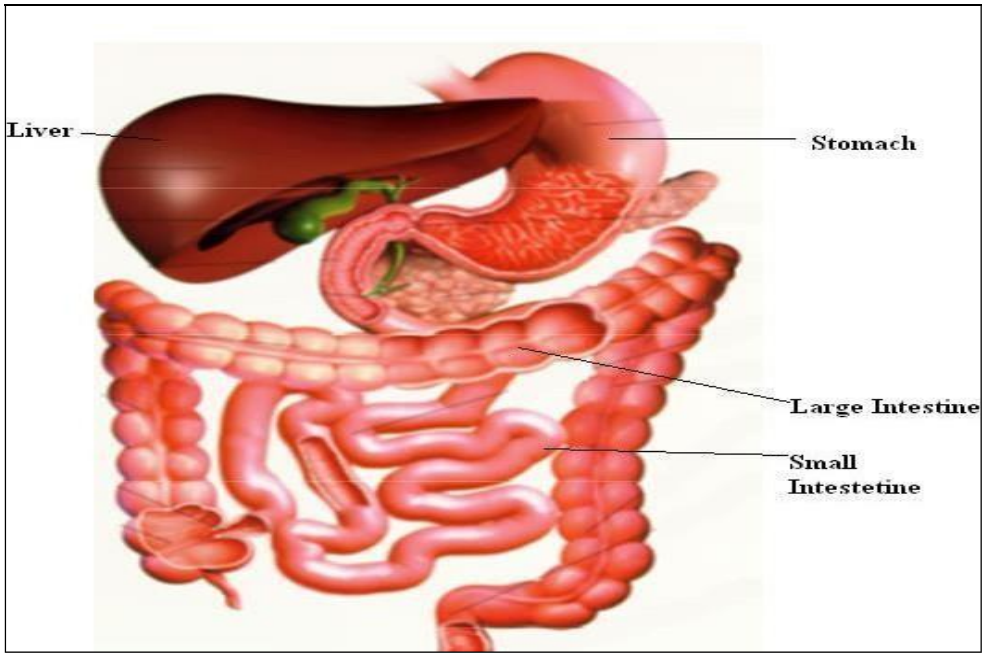

Figure 1: Gastrointestinal anatomy and dynamics

Stomach

The stomach is an organ with a function for digestion, storage and mixing. During fasting state the stomach is a collapsed bag with a residual volume of 50 mL and contains a small amount of gastric juice (pH 1-3) and air. The stomach consists of 4 parts, cardia, fundus, body, and pylorus. After 2-3 hours eating a meal goes to duodenum from stomach.

Intestine

The small intestine is a tubular viscous organ and has vast number of villi on its mucosal surface that covers a surface area (4500 m^2 compared to only 0.1-0.2 m^2 for the stomach). The surface of the small intestine(mm) contains about 5 million villi, each about 0.5-1 mm length. These villi are fingerlike projections of the mucosa and have a length of 0.5-1.5 mm, depending upon the degree of distension the intestinal wall and the state of contraction of smooth muscle fibers in their own interiors. Absorption of material occurs by3 main processes: 1. facilitate diffusion 2. osmosis 3.Active transport. The small intestine is the largest section of the digestive tube and it is divided in to three parts. Duodenum (20-35 cm), Jejunum (3-5 m) and the ileum (3-5 m). The duodenum has a pH of 5 to 6 and the lower ileum approaches a pH of 8.

Tablet

Tablets is a solid preparations each containing a single dose of one or more active ingredients and obtained by compressing with uniform volumes of particles. Tablets are intended for oral administration (some are swallowed whole, some after being chewed, some are dissolved or dispersed) in water before being administered and some are retained in the mouth where the active substance are released in control manner.The particles consist of one or more active substances with or without excipients (diluents, disintegrating agents, binder, glidants, lubricants etc.) substances capable of modifying the behavior of the preparation in the digestive tract, coloring agent and flavoring substances.[5,6]

Type and Classes of Tablets

A) Oral tablets taken as ingestion

- Compressed tablets
- Multiple compressed tablets
- Layered Tablet
- Compression-coated tablets
- Repeat-action tablets
- Delayed-action and enteric-coated tablets
- Sugar and chocolate –coated tablets
- Film coated tablets
- Chewable tablets

B) Tablets Used In the Oral Cavity

- Buccal tablets
- Sublingual tablets

- Troches and lozenges
- Dental cones

C) Tablets administered by other routes

- Implantation tablets
- Vaginal tablets

D) Tablets used to prepare solutions

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets
- Tablet triturates

Layer Tablet

In layer tablet mostly there are two parts i.e. immediately release and Extended release system.

Immediate Release Tablet

Pharmaceutical products designed for oral delivery and over-the-counter markets are mostly the immediate release type, which are designed for immediate release as it absorb rapidly in systemic circulation.

Disintegrating agents are substances routinely included in tablet formulations and in some hardshell capsule used to promote moisture penetration as its leads to dispersion of the matrix of the dosage form in dissolution fluids. Superdisintegrants improve disintegrant efficiency than traditional disintegrants.

Traditionally starch has been the choice for disintegrant sin tablet formulation, and it is still widely used. For instance, starch generally has to be used at levels greater than 5% to avoid adverse effect, especially in direct compression. addition of suitable disintegrants leads to effective drug release from the drug product .

Mechanism of Disintegrants

1) High swellability

2) Capillary action and high swellability

3) Chemical reaction

The most popular disintegrants are corn starch, soluble starch etc. which have been well dried and powdered. Starches have great affinity for water and swell when moistened thus facilitating the rupture of the tablet matrix, its disintegration action in tablets is due to capillary action. Spherical shape of starch increases the porosity of tablet thus promoting capillary action.

Classification of "Super disintegrants" may be organized into three classes based on their Chemical structure. As shown in below.

Table 2 :- Classification of "Super disintegrants".

Structure Type (NF Name)	Description	Trade Name
1. Modified starches (Sodium starch glycolate NF)	Sodium carboxy methyl starch, the carboxymethyl groups induced hydrophilicity and cross-linking reduces solubility.	Explotab Primojel
2. Modified cellulose (Croscarmallose NF)	Sodium carboxy methyl cellulose which has been cross-linked to render the material insoluble.	Ac-Di-Sol Nymcel Solutab
3.Cross-linked polyvinylpyrrolidone (Crospovidone. NF)	Cross-linked polyvenylpyrrolidone, the high molecular weight and cross-linking render the material insoluble in water.	Crospovidone Kollidon Polyplasdone

Extended-Release Tablet[7]

Extended release is defined as drug delivery systems that are designed to provide a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

Advantages

- The frequency of drug administration is drastically reduced.
- Compliance of patient can be improved, as well as drug administration can be made more convenient.
- Fluctuation of blood conc. characteristic of multiple dosing of conventional dosage forms is reduced, drug conc. In blood maintain a steady rate.
- A best advantage in the design of Extended-release forms, is that the total amount of drug administered can be reduced, thus maximizing availability with a minimum dose.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced by formulation in an extended action form.
- Increasing in safety margin of high-potency drugs, and the incidence of both local and systemic adverse side effects can be gradually decreased in sensitive patient.

Limitations

- Administration of Extended release medication does not permit the prompt termination of drug product in the body. Immediate changes in drug need during therapy, such as might be encountered if significant adverse effects are noted, can not be accommodated.
- The physician has less flexibility in adjusting dosage regimens. This is fixed by the dosage form design.
- Extended release forms are designed for the normal population i.e., on the basis of average drug biological half-life. Consequently, disease states that alter drug disposition, significant patient variation.
- Economic factors must be considered, as we follow costly processes and equipment in manufacturing of extended release forms.

Since it has lower chances of complication in manufacture of Extended release dosage forms involves the direct compression of blends of drug, retardant material, and additives to form a tablet in which drug is surrounded in a matrix core of the retardant. Alternately, retardant drug blends may be granulated to follow compression. Examples of three classes of retardant material used to formulate matrix tablets. Each class demonstrating a different approach to the matrix concept represents in Table 1.3.[8,9]

Table No 3:- Types of Matrix for Extended Release

Sr. No.	Matrix Characteristic	Material
1	Insoluble, inert	Polyethylene, Polyvinyl chloride Ethylcellulose
2	Insoluble, erodible	Carnauba wax, Castor wax
3	Hydrophilic	Methylcellulose, Hydroxypropylmethyl cellulose, Hydroxyethylcellulose
4	Hydrophobic	Ethyl cellulose, Glyceryl Behenate

Insoluble, inert material containing matrix are not suitable for high milligram potency formulations in which the polymer content would be sufficient to form a matrix, or for highly water-insoluble drugs in which dissolution in the matrix would become rate- limiting. Tablets may be directly compressed from mixtures of drug and ground polymer.

Hydrophilic matrix contains non-digestible materials that form gels in situ. Drug release is controlled by penetration of water through a gel layer produced by hydration of the polymer and diffusion of drug through the swollen, hydrated matrix, in addition to erosion of the gelled layer.[10]

a. Matrix systems offer several Advantages:

- Easy to prepare.
- Effective, good versatility ,low cost as well.
- Prepare to release high molecular weight compounds
- Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release.

b. Disadvantages of the matrix systems:

- The remaining matrix must be removed after the drug has been released.
- The drug release rate varies with the square root of time.

1.2 Mechanism of Extended Release:

a) Diffusion.

b) Dissolution.

c) Combination diffusion and dissolution systems

Diffusion

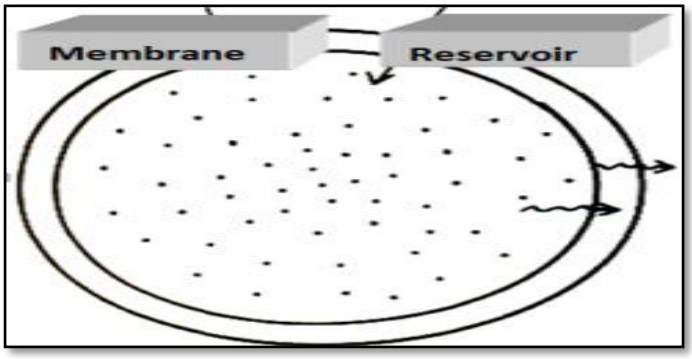

Figure No 2:- Diffusion control of drug release by water insoluble Polymer

Here, the polymer is water insoluble, so important factor is solubility of Drug in the membrane and so gives rise to the driving force for diffusion.

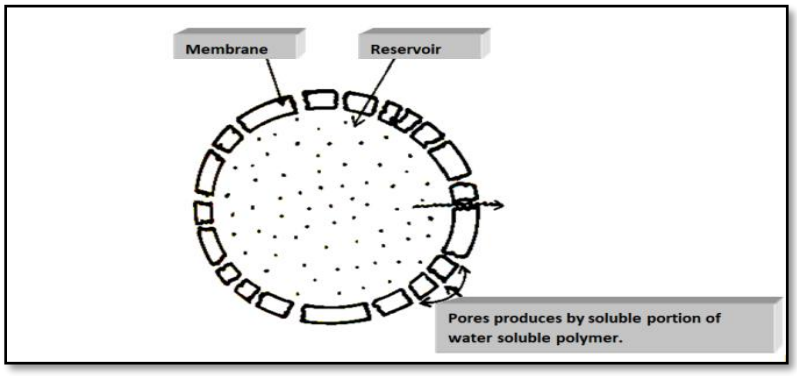

Figure No 3: Diffusion control of drug release by a partially water soluble polymer

Here, polymers are partially soluble in water or mixture of water soluble and Water insoluble polymer is used. The water soluble polymer then dissolves Out of the film/ layer, creates small channels/pores through which the drug can diffuse.

Matrix diffusion controlled drug delivery system [7,8,9]

In this type of controlled drug delivery system, the drug reservoir results from the homogeneous dispersion of the drug particles in either a lipophilic or a hydrophilic polymer matrix.

Gel layer thickness = Difference between erosion and swelling front position The rate of release of drug from the system is dependent on time and is given by,

$dQ/dt = (ACrDp/2t)^{1/2}$

Where, dQ /dt = rate of drug release,

A = loading dose

Cr = drug solubility in polymer

T = time

Dp = drug diffusivity in the polymer

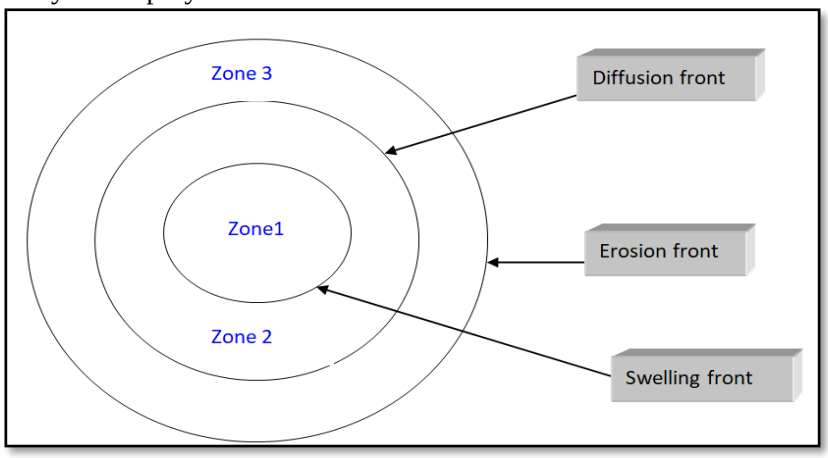

Figure 4: Matrix Diffusion Controlled Drug Delivery System

Zone 1: Undissolved drug, glassy polymer. Zone 2: Undissolved drug, gel layer.

Dissolution

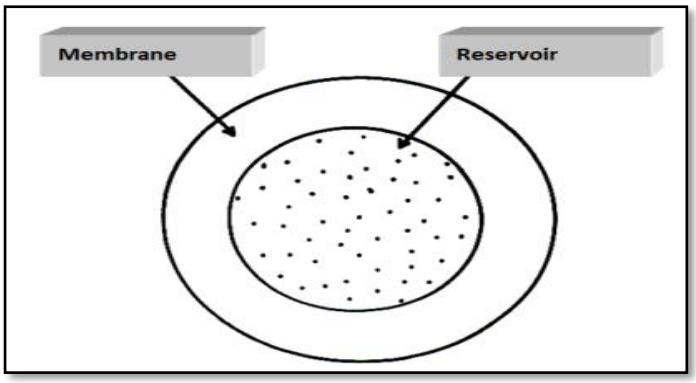

Figure 5: Dissolution control of drug release via thickness and Dissolution rate of the membrane barrier coat.

By varying the coating thickness/layering concentric sphere of coating material and Drug reservoir material, gives rise to different release times, Producing the repeat action dosage form.

Table No 4:- Types and mechanisms of Extended release system

Types	Mechanism
Matrix	**Diffusion through a matrix or membrane**
Reservior/Membrane	**Chemical reaction-erosion or cleavage**
Osmotic pumps	**Solvent activation**

Combination diffusion and dissolution systems[7,8]

The drug delivery systems will never be only depends up on dissolution or diffusion process. In practical the dominant mechanism for release of drug material will overshadow the other processes that classify as either dissolution rate-limited or diffusion-controlled release. We know the system is the combination of diffusion and dissolution of both the drug and the matrix material. Drugs not only can diffuse out of the dosage form, from specific matrix systems, but also the matrix itself undergoes a dissolution process. The complexity of the system arises from the fact that as the polymer dissolves the diffusional path length for the drug may change. This usually results in a moving boundary diffusion system. Zero-order release is possible only if surface erosion occurs and surface area does not change with time.Swelling-controlled matrices exhibit a combination of both diffusion and dissolution mechanisms. Here the drug is dispersed in the polymer, but instead of an insoluble or non-erodible polymer, swelling of the polymer occurs. which causes entrance of water, that leads to dissolution of the drug and fully diffusion of the swollen matrix. In these systems the release rate is directly proportional to the swelling rate of the polymer and drug solubility. This system usually minimizes burst effects, as rapid polymer swelling occurs before drug release.As we have to select swellable matrix systems, different models have been proposed to describe the diffusion, swelling and dissolution processes involved in the drug release mechanism. However the key element of the drug release mechanism is the forming of a gel layer around the matrix layer, capable of preventing matrix disintegration and also rapid penetration of water. When a matrix that contains a swellable glassy

polymer comes in contact with a body fluid/solvent and swelling agent ,which causes a drastic change from the glassy to the rubbery state, which is associated with the swelling process.

The individual polymer chains, originally in the uninterupted state absorb water so that their end-to-end distance and radius of gyration expand and maintain a solvated state. This is due to the lowering of the transition temperature of the polymer (Tg), which is controlled by the characteristic concentration of the swelling agent and depends on both temperature and thermodynamic interactions of the polymer– water system.A sharp distinction between the glassy and rubbery regions is observed and the matrix increases in volume because of swelling. On a molecular basis, this phenomenon can activate a convective drug transport, thus increasing the reproducibility of the drug release. The result is an anomalous non-Fickian transport of the drug causes due to the polymer-chain relaxation behind the swelling position. This, in turn, creates osmotic stresses and convective transport effects.

The gel strength is important in the matrix performance and is controlled by various factors the concentration, viscosity and chemical structure of the rubbery polymer. This restricts the suitability of the hydrophilic polymers for preparation of swellable matrices. Polymers such as carboxymethyl cellulose, hydroxypropyl cellulose or tragacanth gum, they do not form the gel layer quickly. Consequently, they are not recommended as excipients to be used alone in swellable matrices.

Bilayered Tablet[11,12,13]

Bilayer tablets these are composed of two or three layers of granulation compressed together. They have the appeared as a sandwich because the edges of each layer are exposed as shown in figure.

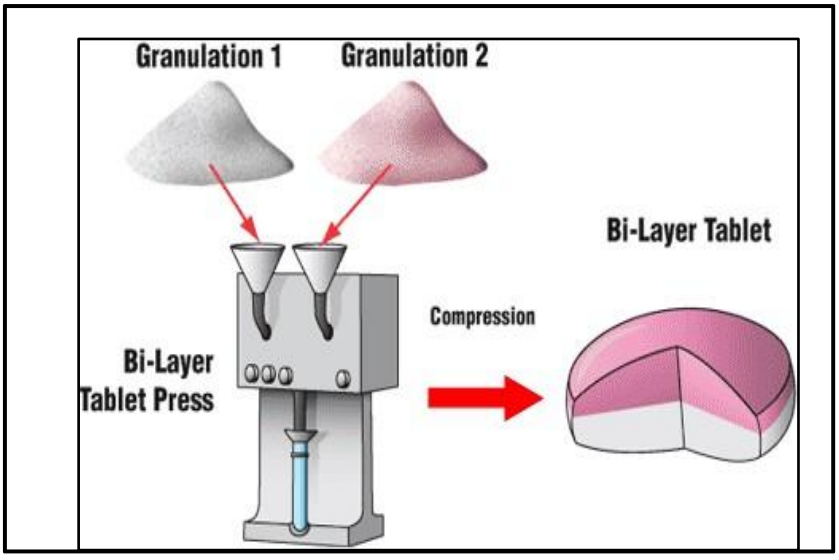

Figure 6:-General Concept of Bilayer Tablets

Advantages

- This special type dosage form has the advantage of separating two incompatible substances in a single preparation .
- It makes combination of Extended-release preparations with the immediate-release drug quantity in one layer and the slow-release portion in the second.
- The weight is accurately controlled in both the layers, in contrast to putting one drug of a combination product in a sugar coating.
- Require fewer materials to prepare two layered tablet than compression coated tablets, less weight, and may be thinner.
- Monograms and other distinctive markings may be impressed on the surfaces of the multi-layer tablets. Coloring may possibilities for unique tablet identity.
- Analytical work is becomes very simple by separating of the layers prior to assay.
- Since there is no transfer to second set of punches and dies, as with the dry-coating machines we can add different shapes (such as triangles, squares, and ovals) there is no operating problems except for those common tolling.

Bi-layer tablets are prepared with one layer of drug for immediate release with other layer design to release drug later, either as second dose or in an extended release manner.[14,15]

- Release Patten of Bilayer Tablets having Immediately Release part and Extended Release part

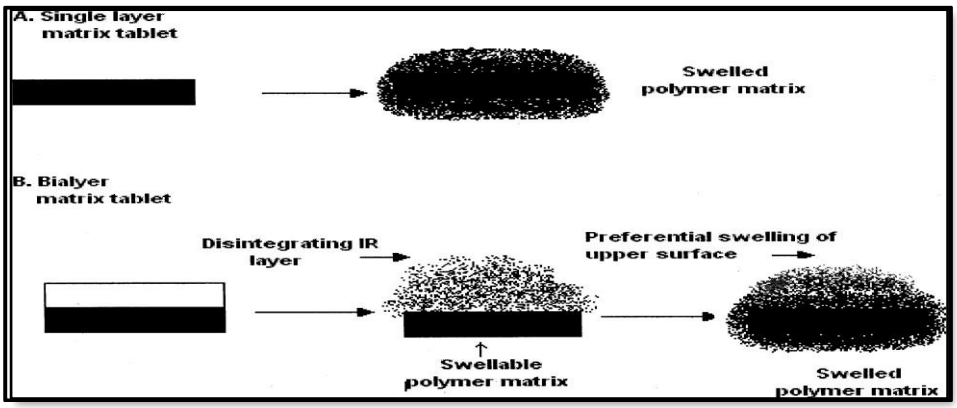

Figure 7:- Release pattern of Bilayer Tablets

Bi-layer tablets are made by compressing two different granulations given into a die compression in such a way that one on top of another, in layers. Both the layer comes from a separate feed frame with individual weight control and Rotary tablet press can be set up for two or three layers with many stations. More layers can be possible but the design becomes very complicated. **Figure 8** represents Cadpress, Bilayer Rotary Machine containing 45 stations.

Figure 8: Cadpress-Bilayer Rotary Machine

CONCLUSION

The bilayer tablet heralds a new chapter in the development of controlled-release formulations with a wide range of properties that result in an effective drug delivery technique. Controlled release dosage forms have been commonly used to increase the treatment of a variety of important drugs. Uses of bilayer tablets for anti-inflammatory and analgesic purposes are a unique feature. Bilayer tablets are useful for releasing two medications in sequence, separating two incompatible chemicals, and creating a sustained-release tablet with the first layer of immediate-release as the initial dose and the second layer as the maintenance dose. The bilayer tablet is a more modern technology that corrects the flaws of single-layer tablets.

REFERENCE

1.Jain NK, Pharmaceutical product development, 1st ed, Delhi: CBS Publication and Distribution, 2006, pp. 203-209

Gudsoorkar VR, Rambhau D. Sustained release of drugs. The Eastern Pharmacist, 1993, 36(429), pp.17-22.

2.Vyas SP and Khar RK, Controlled drug delivery: concepts and advances. 1st Ed, Vallabh prakashan, Delhi, 2002, pp. 103-110

3.Hoffman A. Pharmacodynamic aspects of sustained release preparations. Adv Drug Del Rev 1998, 33, pp.185-199.

Remington: The science and Practice of Pharmacy., 19th Ed., 1995, pp.1660-1676.

4.Jantzen GM, Robinson JR, Sustained- and controlled-release drug delivery systems In: Banker GS, Rhodes CT, editors. Modern pharmaceutics. 3rd Ed.; Marcel Dekker Inc; New York, 1996; 575-609.

5.Chein YW, Novel Drug Delivery Systems, 2nd ed. Vol 50. New York: Marcel Dekker. Inc, 1992, pp. 245-247

6.Brahmankar DM and Jaiswal SB, Biopharmaceutics and Pharmacokinetics a treatise, 1st ed, Delhi, Vallabh Prakashan, 2003, pp.198-208

7.Lachman L, Lieberman HA, Kanig JL,"The theory and practice of industrial pharmacy", 3rd Ed., Varghese Publishing House Bombay 1987, pp.293-345.

8.United States Pharmacopeia (**2005**). 28th ed., Rockville, MD, The United States Pharmacopoeial Convention Inc, pp.2749-2751.

9.Raymond CR, Paul JS, Weller PJ, Handbook of Pharmaceutical Excipients, 4th edition, London Pharmaceutical Press, 2003.

10.Sramek JJ, F.E., Cutler NR. " Review of the acetylcholinesterase inhibitor galantamine," Expert Opinion on Investigational Drugs 2000, 9, pp.2393–2402.

11.Durga Prasad Pattanayak and Subash C. Dinda, "Bilayer tablet formulation of metformin hydrochloride and glimepiride: A novel approach to improve therapeutic efficacy," IJDDHR 2011, 1(1), pp.1-4.

12.Mr. Ashish A Pahade, Dr. Mrs. V.M.Jadhav and Dr. Mr. V.J.Kadam, "Formulation And Development Of a Bilayer Sustained Released Tablets of Isosorbide Mononitrate," IJPBS 2010, 1(4), pp.305-314.

13.Patel M, Sockan GN, Kavitha, Mani T. "Challenges in the formulation of bilayered tablets: A Review," Int. J. of Pharm. Res. and dev.201, 2, pp-30-42.

14.Shobha R. Text Book of Pharmaceutics and Pharmacokinetics, 1st ed, Mumbai, India: Prism Book Pvt. Lmt. 2000, pp.176-185.