ISSN: 0975-766X
CODEN: IJPTFI
Available through Online *Review Article*
www.ijptonline.com

BIPHASIC DRUG DELIVERY IN CONTROLLED RELEASE FORMULATIONS – A REVIEW

P.Preetha*; A.Srinivasa Rao; P.Pushpalatha
Department of Pharmaceutics, Bhaskar Pharmacy College, Hyderabad.
Email: angelpreetha@rediffmail.com

Received on 02-03-2015 *Accepted on 28-03-2015*

Abstract:

Biphasic drug delivery system is an innovative drug delivery system for oral administration which is composed of one fast release layer and one sustain release layer. Layered tablet concept is utilized to develop controlled and sustained release formulations. This type of system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensive, antihistaminic, and anti-allergic agents, anti psychotics, hypnotics.

Keywords: Biphasic, Immediate release, extended release, Layered tablet

Introduction:

Oral route is the most commonly employed route of drug administration. Although different route of administration are used for delivery of drugs, oral route remain the preferred mode. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing and generally improved shelf life of the product. Even for sustained release system the oral route of administration has been investigated the most, because of flexibility in dosage forms design that the oral route offers.

Solid dosage forms can be divided into two main categories: immediate release dosage forms, where disintegration and subsequent drug release and dissolution occurs in stomach, and the (non-immediate) modified-release technologies, which utilize polymers to alter the site or time of drug release within gastrointestinal tract.

In recent years, a growing interest has developed in designing drug delivery systems that include an immediate release (IR) component to extended release (ER) dosages. The addition of an IR component allows one to design delivery systems having optimal pharmacokinetic profiles and enables the combination of different drugs thereby

improving patient compliance. In certain conditions (migraine and sleeping disorders), drug treatment may be advantageous to be delivered in a biphasic manner rather than a single phase extended release preparation. In the first phase of drug release, the immediate release dose fraction (also called "loading-dose") reaches a therapeutic drug level in the blood plasma quickly after administration, while the second extended release phase (called the "maintenance-dose) provides the dose fraction, required to maintain an effective therapeutic level for a prolonged period. Examples of such systems can be found as bilayer tablets, drug layered matrices, or combinations of immediate, and extended release multiparticulates.

Biphasic drug delivery system is an innovative drug delivery system for oral administration which is composed of one fast release layer and one sustain release layer. Layered tablet concept is utilized to develop controlled and sustained release formulations. This is designed to release the drug at two different rates and is usually composed of a fast release layer and sustain release layer. Conventional sustain release dosage form delay the release of drugs and do not provide the rapid onset of action after oral administration. Hence this layer tablet offer a pharmacokinetic advantage over conventional dosage forms as the drug is released quickly from the fast layer leading to the rapid raise in drug plasma concentration followed by continuation of drug release from the sustain-release layer.

Biphasic system contains two different release phases as immediate releasing phase and extended releasing phase. Biphasic delivery systems are designed to release a drug at two different rates or in two different periods of time: they are either quick/slow or slow/quick. A quick/slow release system provides an initial burst of drug release followed by a constant rate (ideally) of release over a defined period of time and in slow/quick release system provides an initial constant rate of release followed by a quick burst release at a predetermined time. It also includes bimodal drug delivery profile (fast release / slow release / fast release).

This type of system is used primarily when maximum relief needs to be achieved quickly, and it is followed by a sustained release phase to avoid repeated administration. Suitable candidate drugs for this type of administration include nonsteroidal anti-inflammatory drugs (NSAIDs) and antihypertensive, antihistaminic, and anti-allergic agents, anti psychotics, hypnotics. Generally conventional extended dosage forms delay the release of therapeutic systemic levels and do not provide a rapid onset of action. Immediate release DDS are intended to disintegrate rapidly, and exhibit instant drug release. They are associated with a fast increase and decrease, and hence fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increased incidence of side effects. Administration of the DDS several times per day is therefore necessary to compensate the decrease in drug plasma

concentration due to metabolism and excretion. In many therapies, extended-release preparations are considered desirable but, for many drugs, significant daily variations in pharmacokinetics and/or drug effects have been demonstrated on human beings. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract. A constant plasma concentration may not be obtainable even though a dosage form with a zero-order in vitro release is administered. It is conceivable that a delivery system that can provide a release profile with an initial burst of release followed by a relatively steady release or an accelerated release at a late stage may offer a better solution. Such a release profile, namely pseudo zero-order release with initial burst or bimodal release, may compensate for the lower absorption rate in the stomach and the large intestine. Moreover, for some drugs (such as NSAJDs, antihypertensive, antihistaminic, anti-allergic agents) a prompt disposition of a fraction of the dose should be reached in the shortest time possible to relieve the symptoms of the disease and then the continuation of the drug effect should be prolonged for some hours to optimize the therapy. For these types of drugs, extended release formulations generally lead to a delayed appearance of effective plasma levels and they cannot provide a prompt disposition of the dose immediately after administration. To fulfill the specific therapeutic needs of the different diseases, new drug delivery devices are required for a more accurate time-programmed administration of the active ingredients.

On the basis of these considerations, we have proposed a new oral delivery device, in the form of a double-component tablet, in which the one portion is formulated to obtain a prompt release of the drug, with the aim of reaching a high serum concentration in a short period of time. The second portion is a prolonged-release hydrophilic matrix, which is designed to maintain an effective plasma level for a prolonged period of time.

The pharmacokinetic advantage relies on the fact that drug release from fast releasing component leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining granules. There are several approaches to produce biphasic release system: they are bilayer tablets, multilayer tablets, compression coated tablets, aqueous coating, compressed mini tablets, single layer monolithic matrix tablets etc.

Advantages of biphasic release system:-

- Provide initial prompt drug release to provide rapid onset of action and to compensate for the relatively slow absorption in the stomach and large intestine followed by a period of sustain release in quick / slow system.

- Provide initial slow release followed by prompt drug release at later stage in slow / quick system which may prevent the exacerbation of symptoms caused by circadian rhythms. This is to compensate slower drug release in a region within the gastrointestinal tract (GIT) where absorption is good (e.g. the small intestine) and increased lower down the GIT (e.g. the colon) where drug absorption may be poor.
- Reduce dosage frequency.
- Allow high drug loading.
- Co-administration of two different active pharmaceutical ingredient (s) (API)
- Co-administration of incompatible APIs can possible.
- Improved patient compliance.

Disadvantages of biphasic release system:-

- Manufacturing is complicated
- Cost1y.

Different Methods for Manufacturing of Biphasic Release Systems[:-]

A. Liquid-filled hard gelatin capsules:

B. Multi-layer matrix tablets.

a. Bilayer tablet.

b. floating bilayer tablet.

C. Compression coated tablets.

D. Mini-tablets as a biphasic delivery system.

a. Compressed mini-tablets.

b. Encapsulated mini-tablets.

E. Single layer tablet with biphasic release.

A. Liquid-filled hard gelatin capsules:

The delivery system consists of a biphasic rapid and sustained release formulation containing lipophilic drug dissolved in oleic acid. The sustained release component is a solid erodible matrix of low HLB and melting point above 37˚c while the rapid release phase is a liquid. To maintain the performance of the biphasic delivery system in vitro and in vivo n it is necessary to use an enteric-coated dosage form.

Method:

The delivery system contain matrix forming polymers like Gelucire, Cremophore RH4O or Aerosil 200, oleic acid, drug base etc. The sustained release phase is prepared by mixing the sustained release formulation components at temperature above their melting point, until homogeneous, clear solution is formed. This mixture will be then filled in capsule. The rapid release component of formulation is manufacture by mixing drug base with oleic acid until drug completely dissolve to form clear solution and stored at room temperature until required for capsule fi1ling. Filling of rapid release phase is carried out immediately after solidification of the sustained release component by liquid capsule filling equipment.

B. Multi-layer matrix tablets:

The multilayered tablet concept has been long utilized to develop sustained release formulations. Such a tablet has a fast releasing layer and may contain bi- or triple layers to sustain the drug release. The pharmacokinetic advantage relies on the fact that drug release from fast releasing granules leads to a sudden rise in the blood concentration. However, the blood level is maintained at steady state as the drug is released from the sustaining granules.

a. Bilayer tablets:

The bilayer tablets can be prepared by the direct compression or wet granulation method. The drug and polymers for both fast release and slow release layers are passed through a 180-µm sieve before their use in the formulation.

b. Floating bilayer tablet:

Bilayer floating tablets comprised two layers, i.e. immediate release and controlled release layers. The immediate release layer comprised super disintegrant and the sustained release layer comprised rate retarding polymers. Sodium bicarbonate can be used as a gas generating agent. Direct compression or wet granulation method can be used for formulation of the bilayer tablets. Gas generating agent can be added in either controlled release layer or in both layers. On contact with 0.1 N HCI medium, the hydrochloric acid in medium react with the sodium bicarbonate in layer of the bilayer tablet, inducing carbondioxide formation. The generated gas bubbles can be trapped in the polymer matrix and can be well protected by the gel formed by hydration of the rate retarding polymers. Swelling of the polymers gives floating ability to the formulation.

Compression of bilayer tablet:

The quaintly of powder or granules for the sustained release layer is compressed lightly using a single punch-tabletting machine equipped with round, flat and plain punches. Over this compressed layer, the required quantity of

the fast release layer was placed and compressed to obtain hardness in the range of 5—7 kg cm2 to form a bilayer matrix tablet.

C. Compression coated tablets:

Compression-coating of dosage forms has a long history. The first patent for a press coating machine was granted in at the end of the 19th century. Between 1950 and 1960, interest in press-coated tablets became widespread. Press coated formulations can be used to protect hygroscopic, light-sensitive, oxygen labile or acid-labile drugs, to separate incompatible drugs from each other, or to achieve sustained release. Intermittent release can also be achieved by incorporating one portion of a drug in the core and the other in the coat. Press-coating is relatively simple and cheap. Compression coating can involve direct compression of both the core and the coat, obviating needs for separate coating process and use of coating solutions. Materials such as hydrophilic cellulose derivates can be used. Compression is easy on laboratory scale. On the other hand, for large-scale manufacture special equipment is needed. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly.

An approach to achieve quick / slow d rug release involves the use of a compressed core (Figure. 1 and 2). The core consists of a sustained release tablet, which is coated by compression over the whole surface with a fast-disintegrating formulation. Both the core tablet and the outer powder layer contain a drug. From the viewpoint of manufacturing this technology is an attractive alternative to the production of multilayer dosage forms, because getting additional layers to adhere to the pre compressed layers during the double-layer or multilayer tabletting process can be difficult. Furthermore, because this system uses conventional manufacturing methods, it is more acceptable to the industry.

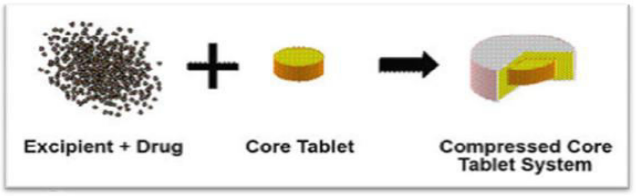

Fig 1.1: Compressed core tablet system as biphasic delivery system

Fig 1.2: Equatorial fracture showing the surfaces of the compressed ethyl cellulose core tablet system

Preparation of compressed coated tablet:

For the preparation of the quick/slow delivery system, the die of the tabletting machine is filled manually with the weighed amounts of the fast release component and the core tablet prior to compression. Half of the fast releasing powder was put into the die to make a powder bed, on the centre of which a core tablet is placed. Then the other half of the powder was added to cover the core tablet. Compressed core tablet systems are prepared by direct compression, with flat-tip punches and dies.

D. Mini-tablets as a biphasic delivery system:

Mini-tablets (micro tablets) are tablets with a diameter equal to smaller than 2—3 mm. These mini-tablets can be filled into hard gelatin capsules for the production of a sustained release multiple unit dosage form which has definite advantages over single unit dosage forms. These advantages are: less risk of dose dumping, less inter- and intra-subject variability, high degree of dispersion in the digestive tract thus minimizing the risks of high local drug concentrations.

a. Compressed mini-tablets:-

Compressed mini-tablets systems are presented as a biphasic delivery system designed for zero-order sustained drug release. The outer layer that fills the void spaces between the mini-tablets was formulated to release the drug in a very short time (fast release), while the mini-tablets provided a prolonged release. Different composition and number of mini-tablets were used to obtain different drug release rates. The in vitro performance of this system shows the desired biphasic behavior: the drug contained in the fast releasing phase (powder enrobing the mini- tablets) dissolved within the first 2 min, whereas the drug contained in the mini- tablets was released at different rates, depending up on formulation.

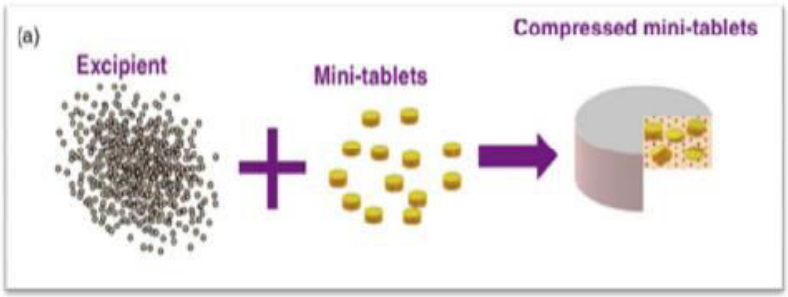

Fig 1.3: Mini-tablets delivered as a tablet.

Fig 1.4: Fracture equatorial showing surfaces of the compressed mini-tablets system

b. Encapsulated mini-tablets:-

In this method extended release mini-tablets according to dose of particular drug are filled in hard gelatin capsule shell. Remaining void volume of capsule shell is filled with fast releasing powder or granules (Figure1.5).

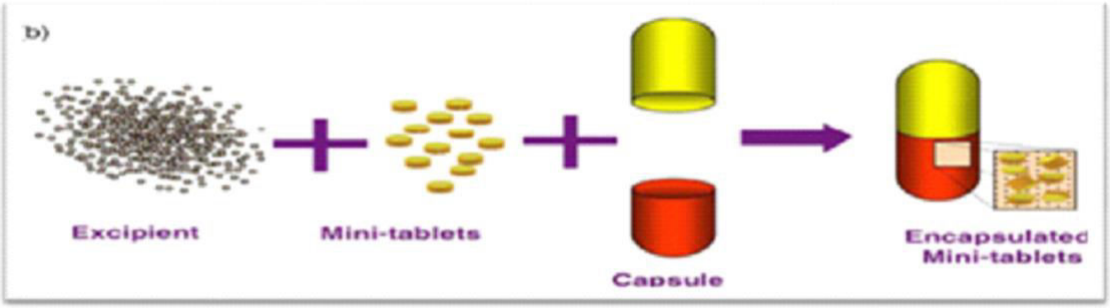

Fig 1.5: Mini-tablets delivered as a capsule.

ii. In this type of encapsulated mini tablets, immediate-release mini-tablets (IRMT) instead of fast releasing powder or granules sustained-release mini-tablets (SRMT) can be incorporated in a hydroxypropylmethyl cellulose (HPMC) or gelatin capsule shell according to requirement of release patterns. (Figure 1.6)

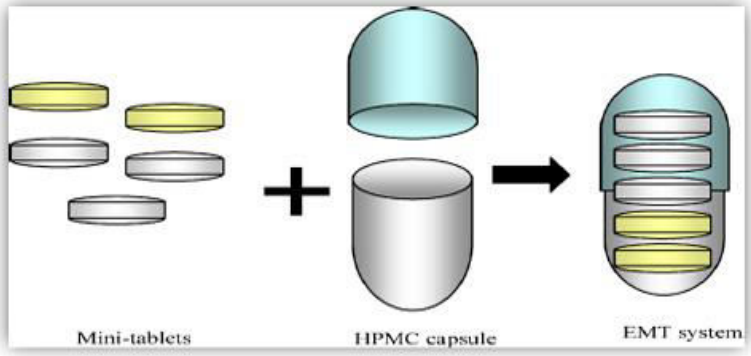

Fig 1.6: Capsule contains both immediate release mini-tablet (IRMT) yellow colours, and sustain release mini-tablets (SRMT) blue colour.

E. Single layer tablets with biphasic re1ease:-

This new approach is simple, cost effective and yields robust, stable tablets. Immediate release and sustained release granulations can be blended together and compressed into simple monolithic matrix tablets having a similar biphasic release pattern demonstrated by commercia1 extended release bilayer tablets.

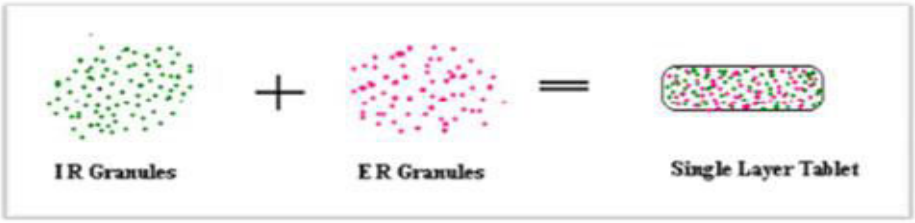

Fig 1.7: Schematic representation of Single Layer Tablet Containing Both the Immediate release and Extended release Granules.

Drug Delivery Systems:

a) **Diffusion-controlled DDS**: Oral matrix-type systems, hydrophobic matrix systems, Hydrophilic Matrix systems, Reservoir-type systems, Transdermal, Drug in Adhesive systems, Monolithic adhesive systems, Multilaminate Adhesive systems, inert matrix systems, Semisolid matrix systems Reservoir matrix systems, other diffusion controlled systems, Intrauterine devices and intra vaginal rings, Intraocular inserts Subcutaneous implants.

b) **Dissolution-controlled DDS**: Based on dissolution-controlled release of solid particles. Based on dissolution-controlled release coated technologies, Based on dissolution-controlled release matrix technology.

c) **Osmotic controlled DDS**: Osmotic delivery systems for solids and liquids.

d) **Biodegradable polymeric DDS**: Micro particules, Nanoparticules, Implants.

e) **Programmable DDS**: Palatial systems, Feedback-controlled systems.

f) **Stimulus responsive**: Physically modulated.

g) **Chemically modulated**: pH dependent.

Among various approaches to oral controlled drug release, matrix system of dosage form proves to be of great potential because of their simplicity, ease of manufacturing, low cost, high level of reproducibility, stability, ease of scale up, and process validation.

Matrix Systems

Matrix forming material can be of hydrophilic, lipid, inert and biodegradable type. In a matrix system the drug is dispersed as particles within a porous matrix. The release of the drug is by dissolution controlled as well as diffusion controlled mechanisms. In this system the drug reservoir is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer.

Advantages:

1. Can be made to release high molecular weight compounds.
2. Suitable for both non degradable and degradable systems.
3. No danger of dose dumping in case of rupture.

Limitation:

1. Zero order release cannot be achieved
2. The drug release rates vary with the square root of times.
3. Not all drugs can be blended with the given matrix.

Mechanism of Drug Release:

The diffusion – controlled release are split into two types: reservoir system and matrix or monolithic system. In the matrix or monolithic system, drug is distributed through a polymer that serves as the diffusion barrier. Though diffusion release is the major mechanism of drug release for inert matrices, matrix swelling and erosion can also have significant impact on release rate for other matrix material.

Types of Matrix Delivery Systems:

On the basis of polymer used the matrix drug delivery system can be classified into the following types:

(a) Hydrophilic matrix:

A hydrophilic matrix is a homogeneous dispersion of the drug molecules within a skeleton in which one or several of the excipient incorporated are a hydrophilic polymer, such as cellulose derivatives, sodium alginate, Xanthan gum, polyethylene oxide, or Carbopol among others, that swells upon contact with water. Thus, various hydrophilic polymers used in preparation of matrix system are of natural origin, such as agar –agar, alginates or Carrageenans and polymers of semi synthetic origin, such as modified starches, cellulose derivatives (methylcellulose (MC), hydroxypropyl cellulose (HPC), Hydroxypropyl methylcellulose (HPMC, Hypromellose), sodium carboxymethylcellulose (CMC Na)), or derivatives of acrylic and methacrylic acid. Of these the hydroxypropyl

methylcellulose (HPMC) a semi synthetic cellulose derivative is widely used as controlled release matrix former. Phenomena that govern gel layer formation and consequent drug release rate are water penetration, polymer swelling, drug dissolution, diffusion and matrix erosion. This gel layer formation is controlled by the concentration, viscosity and chemical structure of the polymer(s). Polymers of natural origin widely used in the food and cosmetics industry are now coming to the fore of pharmaceutical research.

(b) Lipid Matrix:

Lipophilic products such as waxes and lipids can be very attractive as formulation ingredients due to their low cytotoxicity and their ability to provide both sustained release and protection of the drug against chemical degradation. Lipids have received considerable attention in the development of drug delivery systems due to the advantages, which lipids offer. Examples of this class of materials include glyceryl monostearate (GMS), cetylester wax, cetylalcohol, yellow beeswax, glycerol, glyceryl palmitostearate and stearic acid. However, these products often present low flowability, limiting their application in industrial pharmaceutical processes. Drug release from lipid matrices occurs through both pore diffusion and erosion. Glycerol monooleate (GMO) matrix was found to be a gastro-retentive carrier system suitable for both polar and as well as non-polar drugs. In practice for the controlling and programming of drug release from matrix devices, different types of modified cellulose polymers are usually employed, either alone or in mixtures with other swellable polymers or with hydrophobic polymers which may alter the release mechanism and rate. Barakat et.al, have studied the combined effect of hydrophilic polymer (HPMC) and waxy polymer glyceryl behanate (Compritol®888 ATO) on release kinetics of Carbamezipine.

(c) Hydrophobic Matrix / Plastic Matrix:

For drugs with high water solubility, hydrophobic polymers are suitable, along with a hydrophilic matrix for developing sustained-release dosage forms. In a study, once daily sustained matrix tablet of nicorandil were prepared using ethyl cellulose, Eudragit RL-100, Eudragit R S-100, and polyvinyl pyrrolidone. The result indicated that use of hydrophilic polymer alone is not able to sustained the release of tablets for 24 hrs and use of hydrophilic polymer along with hydrophobic polymer is s a better system for once-daily sustained release of a highly water-soluble drug like nicorandil. Starch is a hydrophilic polymer; the introduction of acetylic functional groups changes the nature of starch (acetate) from hydrophilic to more hydrophobic. When the hydrophobic excipient is percolating, tablets maintained their shape and only crack during dissolution tests. This results in a slow release of the drug. The

existence of different matrices, as well as different pore networks, determined the physical changes of the tablets and the release mechanism of caffeine during dissolution tests.

d) Biodegradable Matrix:

The most important biomedical applications of biodegradable polymers are in the areas of controlled drug delivery systems, in the form of implants and devices for bone and dental repairs. Micro particles fabricated from poly (d, l-lactic-co-glycolic acid) (PLGA) are attractive for application due to many favorable characteristics such as good biocompatibility, their ability to degrade into natural metabolites and their safety profile for human use. The polysaccharide-based graft copolymers for controlled dug delivery is gaining tremendous importance because of their improved properties with all the usefulness of the biomaterial .In a study, polyacrylamide grafted pectin was cross-linked with varying amount of Glutaraldehyde and it was noticed that the cross-linked product showed better film forming property and gelling property than pectin . Naturally occurring Xanthan and Karaya gums are useful hydrogels for producing a constant release of drugs in vitro. Both Xantham and Karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role, especially in Karaya gum matrices. In order to prepare an oral dosage form specific for the release in the intestine and capable to protect drugs in the gastric environment, new semi-inter penetrating networks (IPNs) based on alginate (Alg) and scelroglucan (Sclg)/borax. These IPNs exhibited a strong pH dependent release of model protein Myoglobin.

Classification of Matrix Systems

Table 1: Classification of matrix systems.

Type of the Matrix System	Mechanism
Hydrophilic	- Unlimited swelling by diffusion - Limited swelling controlled delivery Eg: HEC,HPMC
Inert	- Inert in nature - Controlled delivery by diffusion Eg: EC
Lipophilic	- Delivery by diffusion and erosion Eg: Carnauba wax
Biodegradable	- Non lipidic nature - Controlled delivery by surface erosion
Resin Matrices	- Drug release from drug-resin complex Eg: Ion exchange resigns

TECHNOLOGIES USED FOR CRDD

Table 2: Technologies used for CRDD.

S. No.	Design or type of the System	Release Mechanism
1	Dissolution Controlled CR systems • Encapsulation - Barrier coating - Embedment into a matrix of fatty materials - Coated plastic materials or hydrophilic materials • Matrix dissolution control	The dissolution of drug from system
2	Diffusion controlled CR systems • Reservoir Devices • Matrix Devices	Diffusion of the drug solution through a water-insoluble, permeable polymeric film
3	Dissolution and Diffusion Controlled CR systems • Non disintegrating polymer • Hydrophilic matrices	Diffusion of a drug solution through a porous matrix
4	Ion-Exchange Resign CR systems	Ion-Exchange between the resign-drug complex and ions in the GI tract
5	pH-Independent formulation	Influence by change in pH and ionic permeability of the membrane coating
6	Osmotically Controlled CR systems	They contain the buffering agents in a system which maintains constant pH throughout the GIT, so the drug release from the device is not affected by variable

		pH of GIT. Water entering by Osmosis dissolves the drug, and the drug solution is forced out through a laser drilled orifice
7	Altered-Density systems	Diffusion from high-density pellets or from floating

Conclusion:

Biphasic drug delivery systems include an immediate release (IR) component and extended release (ER) component. The addition of an IR component allows one to design delivery systems having optimal pharmacokinetic profiles and enables the combination of different drugs thereby improving patient compliance. It provides an initial prompt drug release to provide rapid onset of action and to compensate for the relatively slow absorption in the stomach and large intestine followed by a period of sustain release in quick / slow system.

References:

1. Patel M, Sockan GN, Kavitha, Tamizh M. Challenges in the formulation of bilayer tablets: A Review International Journal of Pharma Research and Development.2010;2(10):30-42.
2. Songa Ambedkar Sunil*, Meka Venkata Srikanth, Nali Sreenivasa Rao, Ch. Manasa, Kolapalli Venkata, A Biphasic Release System of Lornoxicam Based on "Tablets in Capsule" Device, *Jordan Journal of Pharmaceutical Sciences, Volume 6, No. 1, 2013*
3. L. Lachman, HA Lieberman, Joseph L Kanig. The theory and practice of Industrial pharmacy, Verghesh publishing house, 3rd edition, 1990; 346.
4. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963; 52:1145-9.
5. Higuchi T.Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices.*J. Pharm. Sci*. 1963; 52: 1145-1149.
6. Nagori SA, Gohel MC, Parikh RK. Fabrication and evaluation of bi layer tablet containing onventional paracetmol and modified release diclofenac sodium. Indian J Pharm Sci. 2010; 72(2):191-6.
7. Tiwari A.K., Shah H., Rajpoot A., Songara R., Singhal M. Formulation development and valuation of extended release bilayer tablet of aceclofenac sodium. Int J Drug Form Res. 2011; 2(4):358-78.

8. S.M. Ashraful Islam, Hosna Banu and Mostafa Reaj Sahariar. Bilayer tablets of paracetamol and aceclofenac: formulation and evaluation. Int J PharmTech. 2011; 3 (4): 3668-81.
9. Chitra Kartikini. S, Jayaprakash. S, Abirami. A, Mohamad Halite S. Design and formulation of Aceclofenac Sodium bi-layer sustain release tablets. Int J Chem Tech Res. 2009; 1(4):1381-5.
10. Shiyani B, Surendra B, Sanjay S. Formulation and evaluation of bilayer tablet of metoclopramide hydrochloride and ibuprofen. AAPS Pharm Sci Tech. 2008; 9(3):818-27.
11. Chinam NP, Arethi BK, Hemant KP, Prakash S, Vimala DM. Design and evaluation of sustained release bilayer tablets of propranolol hydrochloride**.** Acta Pharm. 2007; 57:479–89.
12. N.N.Rajendran, R.natarajan R. Subashini, Hitesh Patel. Formulation and evaluation of sustained release bilayer tablets of metformin HCL and pioglitazone HCL. Int J Curr Pharm Res. 2011; 3(3): 118-22.
13. Prasanthi. N.L, Manikiran SS, Rama Rao N. Formulation and evaluation of bi-layered tablets of propranolol HCL by using natural gums. Asian J Pharm Cl Res. 2010; 3(4):104-5.

Corresponding Author:
P.Preetha*,
Email: *angelpreetha@rediffmail.com*