

**ORAL CONTROLLED RELEASE DRUG DELIVERY SYSTEM: AN OVERVIEW**Modi Kushal^{1*}, Modi Monali², Mishra Durgavati², Panchal Mittal², Sorathiya Umesh³, Shelat Pragna¹¹Department of Pharmaceutics and Pharmaceutical Technology, K. B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwavidyalaya, Gandhinagar, Gujarat, India²Department of Pharmaceutical Technology, L. J. Institute of Pharmacy, Ahmedabad, Gujarat, India³Department of Pharmaceutics, Indukata Ipcowala College of Pharmacy, Vitthal Udyog nagar, Gujarat, India

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ABSTRACT

Oral drug delivery is the most preferred and convenient option as the oral route provides maximum active surface area among all drug delivery system for administration of various drugs. The attractiveness of these dosage forms is due to awareness to toxicity and ineffectiveness of drugs when administered by oral conventional method in the form of tablets and capsules. Usually conventional dosage form produces wide range of fluctuation in drug concentration in the bloodstream and tissues with consequent undesirable toxicity and poor efficiency. The maintenance of concentration of drug in plasma within therapeutic index is very critical for effective treatment. These factors as well as factors such as repetitive dosing and unpredictable absorption lead to the concept of oral controlled release drug delivery systems. Controlled release drug delivery system works on many different mechanisms to control the release rate of drugs. Various mechanisms like osmotic pressure, matrix system, reservoir system, altered density system etc. have been utilized as formulation approaches. The present article contains brief review on various formulation approaches for controlled release drug delivery system.

Keywords: Controlled release drug delivery system, matrix type system, reservoir system.

INTRODUCTION

Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention is being paid on development of oral controlled release drug delivery systems. The goal in designing controlled release drug delivery system is to reduce the frequency of the dosing, reducing the dose and providing uniform drug delivery. So, controlled release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ¹⁻³. Controlled release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. The modified release oral delivery system classification is shown in figure 1^{3,4}.

Controlled Release Drug Delivery System

Controlled release system means any drug delivery system that maintains adequate and desired release of drug over an extended period of time. Hydrophilic polymer matrix is widely used for formulating an controlled dosage form^{2,4}. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval and at right site of action to maintain therapeutic range of drug in blood plasma. The IR drug delivery system lacks some features like dose maintenance, controlled release rate and site targeting. The oral controlled drug delivery has some potential advantage like controlled release rate and dose maintenance in plasma. The CR formulations have some swelling polymer or waxes or both which controls the release rate. The use of reservoir system is also well known for controlling release rate. Figure 2 shows the relation between plasma concentration verses time.

Advantages of controlled release drug delivery system over the conventional dosage form⁴

- Reduced dosing frequency.
- Dose reduction.
- Improved patient compliance.
- Constant level of drug concentration in blood plasma.
- Reduced toxicity due to overdose.
- Reduces the fluctuation of peak valley concentration.
- Night time dosing can be avoided.

Limitation of Oral Conventional Dosage Form^{2,3}

1. Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication in narrow therapeutic index drug.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition impossible.

Factors affecting the Formulation of Oral controlled release Drug delivery system**Physicochemical factors****Aqueous Solubility**

Most of the drugs are weak acids or weak bases. Drugs with low water solubility will be difficult to incorporate into sustained release mechanism^{2,3}. For a drug with high solubility and rapid dissolution rate, it is often quite difficult to retard its dissolution rate. A drug of high water solubility can dissolve in water or gastrointestinal fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to less soluble drug. It is often difficult to incorporate a highly water soluble drug in the

dosage form and retard the drug release especially when the dose is high. The pH dependent solubility particularly in the physiological pH range would be another problem for controlled release formulation because of the variation in the pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system (BCS) allows estimation of likely contribution of three major factors solubility, dissolution and intestinal permeability which affect the oral absorption.

Class III (High solubility- Low permeability) and Class IV (Low solubility- Low permeability) drugs are poor candidates for controlled release dosage form compound with solubility < 0.1 mg/ml face significant solubilisation obstacles and often compounds with solubility 10 mg/ml present difficulties to solubilisation dosing formulation. In general, highly soluble drugs are undesirable for formulation in to a controlled release product.

Partition coefficient (P (o/w))

Partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Drugs that passes through biological membrane, if partition co-efficient of drug influences shows very much bioavailability because lipophilic nature of biological membrane. Drugs that have lower partition coefficient are not suitable for oral CR drug delivery system and drugs that have higher partition co-efficient are also not suitable for oral CR drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane⁵.

Drug pKa and ionization at physiological pH

Drugs existing largely in ionized form are poor candidates for oral controlled release drug delivery system. Absorption of the unionized drugs are well whereas permeation of ionized drug is negligible because the absorption rate of ionized drug is 3-4 times less than that of the unionized drug. The pKa range for acidic drug whose ionization is pH sensitive is around 3.0-7.5 and pKa range for basic drug whose ionization is pH sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0%².

Drug stability

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. If the drug in the solid state the degradation will occur in reduced rate, for the drugs that are unstable in stomach that prolong delivery to the entire GI tract are beneficial. If drug is administered in extended release dosage form that are unstable in small intestine may demonstrate decreased bioavailability. This occurs due to the fact that a greater quantity of drug is delivered in small intestine and is being subjected to more degradation⁸⁻¹⁰.

Molecular size and diffusivity

Diffusivity depends on size and shape of the cavities of the membrane¹. The diffusion co-efficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10^{-6} - 10^{-4} cm²/sec. For drugs having molecular weight > 500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10^{-12} cm²/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.

Biological Factor

The absorption behaviour of a drug can affect its suitability as an extended release product. The aim of formulating controlled release product is to place a control on the delivery system². It is essential that the rate of release is much slower than the rate of absorption. If we assume the transit time of dosage forms in the absorptive areas of GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours. Otherwise the dosage form will pass out of absorptive regions before drug release is complete. Therefore, the compounds with lower absorption rate constants are poor candidates. Some possible reasons for low extent of absorption are poor water solubility, small partition co-efficient, acid hydrolysis and metabolism or its site of absorption. The distribution of drugs in tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug are poor candidate for oral CR drug delivery system. For design of sustained release products, formulation scientist must have information on disposition of the drug.

A drug which extensively metabolizes is not suitable for CR drug delivery system. A drug capable of inducing metabolism, inhibiting metabolism, metabolized at the site of absorption or first-pass effect is poor candidate for CR delivery, as it could be difficult to maintain constant blood level. Drugs that are metabolized before absorption, either in lumen or the tissues of the intestine, can show decreased bioavailability from the controlled releasing systems. Most intestinal walls are saturated with enzymes. As drug is released at a slow rate to these regions, lesser drug is available in the enzyme system. Hence, the systems should be devised so that the drug remains in that environment to allow more complete conversion of the drug to its metabolite.

Half-life

The half-life of a drug is an index of its residence time in the body. If the drug has short half life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of 8 hours or more are sufficiently controlled in the body, when administered in conventional dosage form and controlled release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of 3-4 hours for formulation of drug delivery system^{2,5}.

Therapeutic index

Drugs with low therapeutic index are unsuitable for incorporation in controlled release formulations. If the system fails in the body, dose dumping may occur, which leads to toxicity¹.

Size of dose

If the dose of a drug in the conventional dosage form is high, then it is less suitable candidates for CRDDS. This is because the size of a unit dose controlled release oral formulation would become too big to administer without difficulty⁶.

Absorption window

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is

referred to as the 'absorption window'. These candidates are also not suitable for CRDDS⁷.

Plasma concentration response relationship

Generally, plasma drug concentration is more responsible for pharmacological activity rather than dose. But the drug having pharmacological activity independent of plasma concentrations, are poor candidate for oral CR drug delivery system⁶.

Concentration dependency on transfer of drug

Transfer of drug from one compartment to other, if follows zero order kinetic process then such drugs are poor candidate for oral CR delivery system. It should be of first order kinetics⁷. The figure 3 represents various formulation strategies for oral controlled release drug delivery system.

Diffusion Sustained System

Diffusion process shows the movement of drug molecules from a region of a higher concentration to one of lower concentration.

Diffusion reservoir system

In this system, a water insoluble polymeric material covers a core of drug. Drug will partition into the membrane and exchange with the fluid surrounding the particle or tablet. Additional drug will enter the polymer, diffuse to the periphery and exchange with the surrounding media. The drug release takes place by diffusion mechanism. The diffusion type reservoir system is shown in figure 4.

Advantages

- Zero order delivery is possible.
- Release rates can be modified with polymer type and concentration.

Disadvantages

- Difficult to deliver high molecular weight compound.
- Generally increased cost per dosage unit.
- Potential toxicity if dose dumping occurs.

Diffusion matrix system

The matrix system is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Matrix systems are widely used for sustaining the release rate. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed^{7, 18}. A solid drug is dispersed in an insoluble matrix and the rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid dissolution. The diffusion type matrix system is shown in figure 5.

Advantages

- Easier to produce than reservoir or encapsulated devices.
- Versatile, effective and low cost.
- Possible to formulate high molecular weight compounds.
- Increased the stability by protecting the drug from hydrolysis or other derivative changes in gastrointestinal tract.

Disadvantages

- The ghost matrix must be removed after the drug has been released.
- The release rates are affected by various factors such as, food and the rate transit through the gut.
- Cannot provide pure zero order release.

Types of diffusion matrix system

The matrix system can be divided into two categories depending on the types of retarding agents or polymeric materials¹¹.

- Hydrophobic matrix system
- Hydrophilic matrix system
- Fat-wax matrix system

Hydrophobic matrix system

This is the only system where the use of polymer is not essential to provide controlled drug release, although insoluble polymers can be used. As the term suggests, the primary rate controlling components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes glycerides fatty acids, and polymeric materials such as ethyl cellulose, methyl cellulose and acrylate copolymer. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulations helps to maintain the physical dimension of hydrophobic matrix during drug release. Diffusion of active ingredient from the system is the release mechanism and the corresponding release characteristic can be described by Higuchi equation also known as square root of time release kinetic¹¹.

Hydrophilic matrix system

The primary rate limiting ingredients of hydrophilic matrix are polymers that would swell when in contact with aqueous solution and form a gel layer on the surface of the system¹⁸⁻²⁰. When the release medium is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allows the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since matrix swelling lengthens the diffusion path. It has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug delivery rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanisms. The presence of water decreases the glass transition temperature (T_g) (for HPMC from 184°C to below 37°C), giving rise to transformation of glassy polymer to rubbery phase (gel layer). The enhanced motility of the polymeric chain favors the transport of dissolved drug. Polymer relaxation phenomena determine the swelling or volume increase of the matrix. The main polymers used in hydrophilic matrices are hydroxy propyl methyl cellulose (HPMC) and Hydroxy propyl cellulose (HPC), Xanthan gum, Carbopol and Alginates.

Fat-Wax matrix tablet

The drug can be incorporated into fat wax granulations by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray-drying techniques^{12, 13}. In the bulk congealing method, a suspension of drug and melted fat-wax is allowed to solidify and is then comminuted for sustained release granulations. The mixture of active ingredients, waxy materials and fillers also can be converted into granules by compacting with roller compactor, heating in a suitable mixture such as fluidized-bed and steam

jacketed blender or granulating with a solution of waxy material or other binders. The drug embedded into a melt of fats and waxes is released by leaching and/ or hydrolysis as well as dissolution of fats under the influence of enzymes and pH change in the gastrointestinal tract. The addition of surfactants to the formulation can also influence both the drug release rate and the proportion of total drug that can be incorporated into a matrix.

Dissolution Controlled Systems

A drug with a slow dissolution rate is inherently sustained and for those drugs with high water solubility, one can decrease dissolution through appropriate salt or derivative formation^{13, 14}. These systems are most commonly employed in the production of enteric coated dosage forms. To protect the stomach from the effects of drugs such as Aspirin, a coating that dissolves in natural or alkaline media is used. This inhibits release of drug from the dosage form until it reaches the higher pH of the intestine. In most cases, enteric coated dosage forms are not truly sustaining in nature, but serve as a useful function in directing release of the drug to a special site. The same approach can be employed for compounds that are degraded by the harsh conditions found in the gastric region.

Soluble reservoir system

In this system drug is coated with a given thickness coating, which is slowly dissolved in the contents of gastrointestinal tract by alternating layers of drug with the rate controlling coats as shown in figure 6. A pulsed delivery can be achieved, if the outer layer is quickly releasing bolus dose of the drug, initial levels of the drug in the body can be quickly established with pulsed intervals. This is not a true sustained release system; the biological effects can be similar. An alternative method is to administer the drug as group of beads that have coating of different thickness.

Since the beads have different coating thickness, their release occurs in a progressive manner. Those with the thinnest layers will provide the initial dose. The maintenance dose of drug can be achieved by applying thicker coating. This is the principle of the sparsule capsule. Cellulose nitrate phthalate was synthesized and used as an enteric coating agent for acetyl salicylic acid tablets.

Soluble matrix system

It can be either a drug impregnated sphere or a drug impregnated tablet, which will be subjected to slow erosion^{14, 15}. The more common type of dissolution sustained dosage form is shown in figure 7.

Dissolution- sustained pulsed delivery systems

Amongst controlled release formulations hydrophilic matrix technology is the most widely used due to its following advantages^{16, 17}.

- Provide desired release profile for a wide therapeutic drug category, drug and solubility.
- Simple and cost effective manufacturing and robust.
- Patient acceptance.
- Ease of drug modulation through level, choice of polymeric systems and function coating.

A hydrophilic matrix tablet consists of mixture of drug, polymer and excipients (filler/diluents as well as other excipients) prepared by hydrophilic polymer in the matrix. Formulators often choose from a range of hydrophilic

polymer as stand alone or in combination with different polymers for release rate control.

Ion Exchange Resins Controlled Release

Ion exchange resins are cross-linked water-insoluble polymers carrying ionisable functional groups²⁷. The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrant, because of their swelling ability. It forms irreversible complex with ionisable drugs upon prolonged exposure of the drug to the resin. A resin bound drug is removed when appropriate ions are in contact with ion-exchanged groups. The area and length of diffusion pathway and the amount of cross-linked polymer in the resin moiety governs the rate of drug release. Sriwongjanya et al. has found the effect of ion exchange resin with drug containing opposite charge in matrix system. After this investigation they concluded that the release of drug containing opposite charge retarded by the addition of ion exchange resin to HPMC-matrices due to formation of complex between drug and resin.

Methods using Osmotic Pressure

In this method, the release controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment^{28, 29}. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. This technology provides zero order release used for hydrophilic drugs. Drug may be osmotically active or combine with osmotically active salt eg. NaCl. Osmotic pressure is the hydrostatic pressure produced by a solution in a space divided by a semi permeable membrane due to difference in concentration of solutes. Osmosis is the diffusion of fluid through a semi permeable membrane from a solution with a low solute concentration to a solution with a higher solute concentration until there is an equal concentration of fluid on both sides of the membrane. A semi permeable membrane is placed around a tablet, particle or drug solution that allows transport of water into the tablet with eventual pumping of drug solution out of the tablet through a small delivery aperture in tablet coating. The osmotic systems are classified in major two types, i.e. type-A and type-B. In type-A system, the core contains both, the drug and electrolytes. The electrolytes provide osmotic pressure and maintain the rate of drug release. In type-B system, the drug solution is present in a semi permeable membrane surrounded by the electrolytes. Both the systems are shown in figure 8 and 9 respectively.

The OCODDS can be conveniently classified in to following types:²²⁻²⁴

Single chamber osmotic pump

- Elementary osmotic pump (EOP)

Multi chamber osmotic pump

- Push pull osmotic pump.
- Osmotic pump with non expanding second chamber.

Specific types

- Controlled porosity osmotic pump.
- Monolithic osmotic systems.
- Osmotic bursting osmotic pump.

- OROS – CT
- Multi particulate delayed release systems (MPDRS)
- Liquid Oral Osmotic System (L-OROS)

pH Independent Formulations

Most drugs are either weak acids or weak bases. The release from controlled release formulations is pH dependent. However, buffers such as salts of amino acids, citric acid, phthalic acid phosphoric acid or tartaric acid can be added to

the formulation to help to maintain a constant pH thereby rendering pH independent drug release^{25, 26}. A buffered formulation is prepared by mixing a basic or acidic drug with one or more buffering agent, granulating with appropriate pharmaceutical excipients and coating with gastrointestinal fluid permeable film forming polymer. When gastrointestinal fluid permeates through the membrane, the buffering agents adjust the fluid inside to suitable constant pH thereby rendering a constant rate of drug release.

Table 1: Marketed drug products with their mechanism based classification

SN	Technology	Brand name	Drug	Manufacturer
1.	Diffusion controlled release	Wellbutrin XL	Bupropion	GlaxoSmithKline
2.	Matrix system tablet	Ambien CR	Zolpidem Tartrate	Sanofi-Aventis
3.	Method using ion Exchange	Tussionex Penkinetic ER suspension	Hydrocodone Polistirex and Chlorpheniramine Polistirex	UCB Inc.
4.	Methods using Osmotic pressure	Elementary Osmotic Pump Push-Pull Osmotic Systems	Efidac 24® Glucotrol XL®	Novartis Pfizer Inc.
5.	pH independent formulation	Inderal® LA	Propranolol HCl	Wyeth Inc.
6.	Altered density formulation	Modapar	Levodopa and Benserazide	Roche Products, USA



Figure 1: Classification of modified release drug delivery system

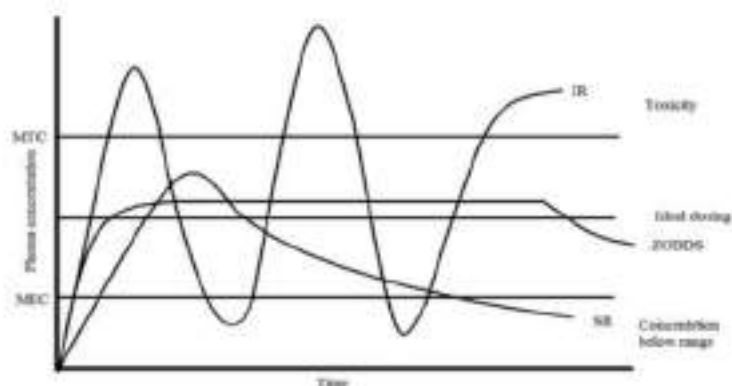


Figure 2: Ideal plasma concentration curves for immediate release, Zero order release, sustained release drug delivery system

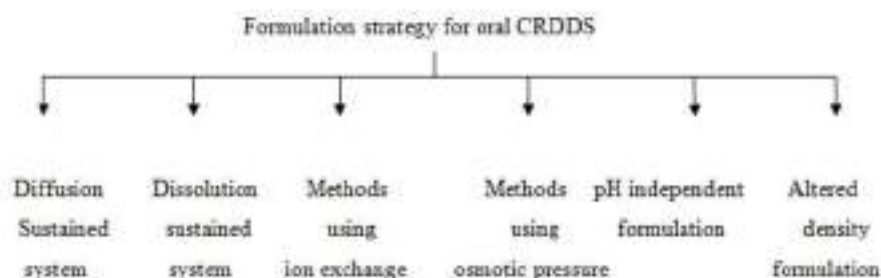


Figure 3: formulation strategy for oral controlled release drug delivery system

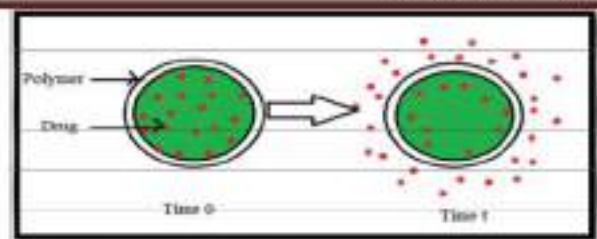


Figure 4: Schematic representation of diffusion type reservoir system

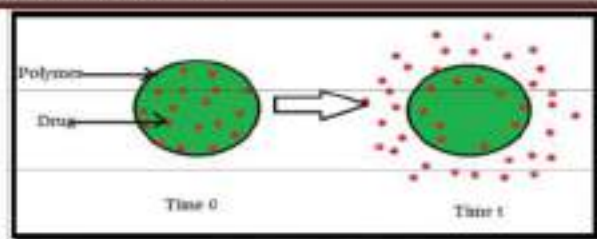


Figure 5: Schematic representation of diffusion type matrix system

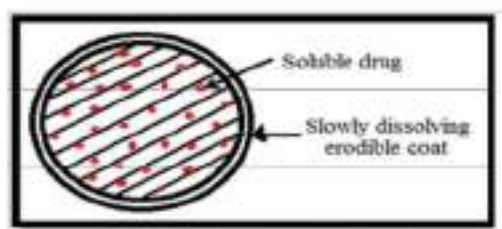


Figure 6: Schematic representation of dissolution of reservoir system

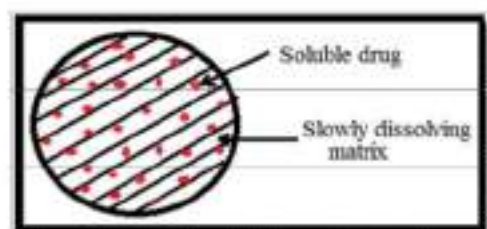


Figure 7: Schematic representation of dissolution matrix system



Figure 8: Type-A osmotic system

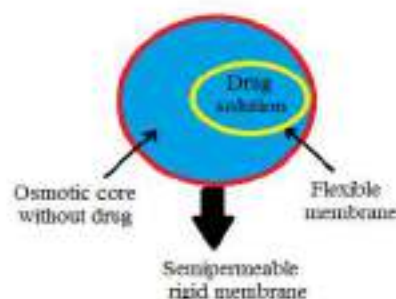


Figure 9: Type-B osmotic system

Altered Density Formulations

Several approaches have been developed to prolong the residence time of drug delivery system in the gastrointestinal tract^{21, 22}. The delivery system remains in the vicinity of the absorption site until most, if not all of its drug contents is released. In high density approach, the density of the pellets must exceed that of normal stomach content and should therefore be at least 1.4g/cm³. In low density approach, the globular shells which have an apparent density lower than that of gastric fluid can be used as a carrier of drug for sustained release purpose. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product. This system is generally used when, the single dose for the duration of treatment whether for days or weeks as with infection, diabetes or hypertension is required.

CONCLUSION

The controlled release drug delivery system aims to release the drug at the desired rate over extended period of time to maintain the therapeutic level in blood. Nowadays, the oral route of administration for controlled release drug delivery system has received more attention due to its more flexibility, reduced dosing frequency and better patient compliance. The design of oral controlled release drug delivery system depends on various factors like, physico-chemical properties of drug, type of delivery system, disease being treated, patient condition, treatment duration, presence of food, gastrointestinal motility and co-administration of other drugs.

From the above discussion, we can conclude that the controlled release drug delivery system is very helpful in increasing the efficiency of the dose as well as the patient compliance. Moreover, the reasonable cost of oral controlled release drug delivery system has lead ease of market penetration as replacement of oral conventional drug delivery system.

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