IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
January 2015 Vol.:2, Issue:2

A Brief Review on Modified Release Solid Dosage Form with Special Reference to Design

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

SUSANTA KUMAR ROUT[a], DURGA MADHAB KAR[b]

[a]Micro Advanced Research Centre, Bangalore, Karnataka.
[b] Siksha O Anusandhan deemed to be University, School of Pharmaceutical Sciences

Submission: 23 December 2014
Accepted: 11 January 2015
Published: 25 January 2015

Keywords: Controlled release, Sustained release, pharmacodynamics, bio-pharmaceutics, pharmacokinetic

ABSTRACT

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. Oral sustained release (S.R) / controlled release (C.R) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamics properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance. This review describes the basic information regarding modified release dosage form like designed to release their medication in controlled manner, criteria for selecting modified release dosage form and factors influencing the dosage and release pattern.

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 has been focused on development of sustained or controlled-release drug delivery systems. Oral route is considered to be convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process. However, this route has several physiological problems, including an unpredictable gastric emptying rate, a brief gastrointestinal transit time (8–12 h), and the existence of an absorption window in the upper small intestine for several drugs [1]. Usually conventional dosage form produces wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption [2, 3]. These difficulties have prompted researchers to design gastro retentive drug delivery systems [4, 5]. An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target site. The development of oral controlled release system has been a challenge to formulation scientist due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. Matrix type drug delivery system is an interesting and promising option when developing an oral controlled release system. Availability of wide variety of polymers and frequent dosing intervals help the formulation scientist to develop sustained/controlled release products. Oral sustained release (S.R) / controlled release (C.R) products provide an advantage over conventional dosage forms by optimizing bio-pharmaceutics, pharmacokinetic and pharmacodynamics properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possible time by smallest quantity of drug to assure greater patient compliance. The development of oral MR dosage forms has attracted much attention in the recent years and hydrophilic matrix tablets are among the commercially successful controlled release dosage forms [6]. The most important

variable in hydrophilic matrix systems is the rate at which the drug substance is released and the release of drug is controlled by the formation of a hydro-gel layer around the matrix following exposure to aqueous fluid [7]. The basic goal of the controlled release therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non toxic for an extended period of time [8]. This review describes the design how a modified release dosage form has prepared along with various factors influencing the design and performance of modified (sustained/controlled) release products.

CONTENTS

Oral solid dosage forms are the most stable and commonly administered dosage forms. Since the later part of nineteen-century, tablets have been widespread and their popularity continues. Tablets remain popular as dosage form because of the advantages afforded both to the pharmaceutical manufacturers and patients. These includes: simplicity and economy of preparation, stable and convenient in packing, ease of transporting and dispensing, accuracy of single dosage regimen, compactness and portability, and blandness of taste and ease of administration. Modified release dosage forms are formulations where the rate and/or site of release of the active ingredient(s) are different from that of the immediate release dosage form administered by the same route. This deliberate modification is achieved by special formulation design and/or manufacturing methods. Modified release dosage forms covered by this guideline include orally, intramuscularly, subcutaneously administered modified release and transdermal dosage forms [9]. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of modified release drug delivery systems. The modified-release delivery systems may be divided conveniently into different categories:

1. Prolonged release dosage forms: Prolonged release dosage forms are modified release dosage forms showing a sustained release compared to that of an immediate release dosage form administered by the same route.

2. Delayed release dosage form: The release of the active substance from such modified release dosage forms is delayed for a certain period after administration or application of the dosage. The subsequent release is similar to that of an immediate release dosage form. Examples of

delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating. Examples of delayed-release systems include repeat-action tablets and capsules, and enteric-coated tablets where timed release is achieved by a barrier coating.

3. Multiphasic release dosage forms:

a) Biphasic Release: The first phase of drug release is determined by a fast release dose fraction providing a therapeutic drug level shortly after administration. The second extended release phase provides the dose fraction required to maintain an effective therapeutic level for a prolonged period.

b) Pulsatile Release: Pulsatile drug release is intended to deliver a burst of drug release at specific time intervals.

4. Multiple-unit: A multiple unit dosage form contains a plurality of units e.g. pellets or beads each containing release controlling excipients, e.g. in a gelatin capsule or compressed in a tablet.

5. Single-unit: The single-unit dosage forms consist of only one unit, e.g. osmotic tablet.

Rationale for Development: During the past few years, conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics. The basic rationale for modified release drug delivery is to alter the pharmacokinetics and pharmacodynamics of drugs by using novel drug delivery systems or by modifying the molecular structure or physiological parameters inherent in a selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecule's inherent kinetic properties. Thus, optimal design of a sustained/ controlled release system necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug.

Marketing Authorization:

The dossier submitted in support of an application for a marketing authorization must provide a Complete justification of: [9]

- The physical form of the modified release device and the mechanism of the release form.
- The choice of the dosage form, defining the in vitro and in vivo performance of the product.
- The choice of active substance contents per unit of the dosage form.
- The clinical rationale for the new dosage form, particularly in relation to the proposed indications and posology.
- A prolonged release dosage form may be acceptable if the active substance can produce the desirable clinical effect with a different PK profile than that resulting from an immediate-release form.
- A biphasic modified release form may be considered if a rapid onset of action is required in addition to subsequent prolonged release characteristics.
- A delayed release dosage form may be considered to protect the active substance from the acid environment of the stomach, to protect the stomach from the active substance, or when the active substance is intended to be released in a defined segment of the intestine. Delayed release forms are generally not adequate for conditions requiring a rapid onset of action.
- Pulsatile release dosage form may be considered when treatment needs to be adjusted to a circadian rhythm of the underlying condition or when lower frequency of dosing is desirable, but the fluctuating plasma concentration profile of the immediate-release formulation is necessary for efficacy.

Advantages of modified release dosage form: [10]

- Decreased local and systemic side effects.
- Better drug utilization reduction in total amount of drug used.
- Improved efficiency in treatment, optimized therapy, more uniform blood concentration.
- Reduction in fluctuation in drug level and hence more uniform pharmacological response, cure of control of condition more promptly, less reduction in drug activity with chronic use.
- Achieved the bioavailability of some drugs e.g. drugs susceptible to enzymatic inactivation can be protected by encapsulation in polymer systems suitable for sustained release.

- Improved patient compliance, less frequent dosing, reduced night-time dosing, reduced patient care time. The importance of patient compliance in successful drug therapy is well recognized. It has been found that there is an inverse relationship between the number of dosages per day and the compliance rate.
- The initial unit cost is usually greater than that of conventional dosage forms because of the special nature of these products, the average cost of treatment over an extended time period may be less. Economy may also result from a decrease in nursing time and hospitalization time.

Disadvantages of modified release drug delivery:

- Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time complete release, site specific absorption, pH dependent stability, etc.
- Poor *in vitro – in vivo* correlation.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dose adjustment of drugs normally administered in varying strengths.

Guidelines:

A new chemical entity is developed first as a modified release formulation; the submitted dossier should contain the appropriate pharmaceutical and chemical data, necessary preclinical studies and a complete clinical data package as for any full application. Characteristics of modified release drug delivery systems in humans and to set out general principles for designing, conducting and evaluating respective studies. However, the precise types and number of studies to be performed have to be defined on a case-by-case basis taking into consideration the intrinsic properties of the active substance, the route of administration, the type of the delivery system and the intended therapeutic indication(s).

Separate guidance and standards are required for each of the circumstances in which a modified release (MR) formulation might be developed. These circumstances fall into three groups:

- Applications for modified release forms of new chemical entities (NCE).

- Application for a modified release formulation of a drug that is authorized in a formulation with a different release rate (e.g. immediate release formulation).
- Abridged applications for modified release forms referring to a marketed modified release form, e.g. applications according to Article 10(1) or 10(3).

For NCE (New Chemical Entity): [9]

Pharmacokinetic studies required for oral MR formulation of a new chemical entity

Food effect studies with oral modified release forms: Food effect studies for new MR formulations are recommended to be conducted early during drug development so that appropriate recommendations regarding intake in relation to food can be included in clinical efficacy and safety studies.

The rate and extent of absorption: Rate and extent of absorption from a modified release formulation should be evaluated by comparison with an immediate release formulation following single dosing and if there is accumulation also following repeated dosing.

Fluctuations in drug concentrations at steady state: If the active substance and the MR formulation exhibit linear pharmacokinetic properties it may be sufficient to compare the modified release formulation and the immediate release formulation after single and, in case of drug accumulation, after multiple dose administration at one dose level

Inter-subject variability in pharmacokinetics arising from the drug formulation: The inter-individual variability of the pharmacokinetic parameters of interest should be determined in the single dose or multiple dose studies.

Dose proportionality: Several strengths or when several single units can be taken simultaneously to achieve the desired dose, dose proportionality for different strengths / doses of the modified release formulations should be adequately addressed. Dose proportionality should be evaluated by means of a single dose and, in case of drug accumulation, a multiple dose study, where the PK parameters of interest of all the strengths/doses are compared after dose adjustment.

Factors affecting the performance of the modified release formulation [9]

Food: The influence of food on the bioavailability of oral modified release formulations must be investigated in a single dose study.

Gastro-intestinal function: Oral modified release formulation is to be usually co-administered with active substances affecting gastrointestinal physiology (e.g. opioids) it is necessary to investigate the performance of the oral modified release formulation under these conditions.

Unexpected release characteristics (e.g. dose dumping):

The active substance is not released unexpectedly from the test formulation. Unintended, rapid drug release of the entire amount or a significant fraction of the active substance contained in a modified release dosage form is often referred to as "dose dumping". Depending on the therapeutic indication and the therapeutic index of an active substance, dose-dumping can pose a significant risk to patients, either due to safety issues or diminished efficacy or both. For modified release formulations the risk for unexpected release resulting in unforeseen exposure should be excluded.

Effects of alcohol:

Some modified-release oral dosage forms contain active substances and/or excipients that exhibit higher solubility in ethanolic solutions compared to water. Concomitant consumption of alcoholic beverages with such products may induce dose dumping.

Other factors:

Different physiological conditions (e.g. transit times, pH, food intake and type of food) in vegetarian, paediatric and elderly patients or in patients routinely taking antacids should be taken into consideration especially when designing oral once daily MR formulations.

There are modified release preparations that have been developed solely in order to mimic a TID or QID dosage schedule. In these cases the plasma concentration - time profile of the modified release preparation should be equivalent with the immediate release formulation given in the dose schedule that is imitated unless compareable efficacy and/or safety is supported by additional clinical data.

Design for clinical studies:

Comparative studies should be adequately designed and conducted to assess the intensity and duration of the therapeutic effect and undesirable effects of the modified release formulation in comparison with the authorised immediate release formulation.

In the assessment of the efficacy and safety of certain therapeutic classes it is necessary to measure the effects of the formulation throughout a 24-hour period and particularly at the end of dosage interval.

Clinical trials which compare the modified release form and the immediate release formulation on the basis of equal exposure may be planned to demonstrate non-inferiority of therapeutic efficacy or equivalence.

Pharmacodynamic /clinical studies should show equivalence or non- inferiority as compared to the standard formulation depends on the direction of the effect or safety issue at stake. In case efficacy and safety are closely related equivalence studies are needed for showing that the effect studied remains within the equivalence margins.

A generic MR formulation should be compared with the MR formulation that is either the originator or the line extension of an IR originator formulation, with which bioequivalence is claimed. The general recommendations regarding study design, conduct, evaluation and reporting of bioequivalence studies detailed in the Guideline on Bioequivalence (CPMP/EWP/QWP1401/98) are applicable also for bioequivalence studies for modified release products.

The pharmacokinetics of the originator modified release product are linear, single and multiple dose studies should be conducted at the highest strength. If the pharmacokinetic of the originator modified release product are nonlinear the studies must be conducted with the most sensitive strength. The choice of a lower dose has to be based on safety considerations.

DRUG SELECTION FOR MODIFIED RELEASE DOSAGE FORMS [11]

The biopharmaceutical evaluation of a drug for potential use in controlled release drug delivery system requires knowledge on the absorption mechanism of the drug form the G. I. tract, the

general absorbability, the drug's molecular weight, pKa, solubility at different pH and apparent partition coefficient.

A] Physicochemical properties:

1] Aqueous solubility and pKa:

Absorption of poorly soluble drugs is often dissolution rate-limited. Such drugs do not require any further control over their dissolution rate and thus may not seem to be good candidates for oral controlled release formulations. Controlled release formulations of such drugs may be aimed at making their dissolution more uniform rather than reducing it.

2] Partition coefficient:

Drugs that are very lipid soluble or very water-soluble i.e., extremes in partition coefficient, will demonstrate either low flux into the tissues or rapid flux followed by accumulation in tissues. Both cases are undesirable for sustained release system.

3] Stability of the drug:

Since most oral controlled release systems are designed to release their contents over much of the length of GI tract, drugs that are unstable in the environment of the intestine might be difficult to formulate into prolonged release system.

4] Size of the dose:

For drugs with an elimination half-life of less than **2 hours** as well as those administered in large dosages, a controlled release dosage form may need to carry a prohibitively large quantity of drug.

5] Molecular size and diffusivity:

In addition to diffusion through a variety of biological membranes, drugs in many sustained release systems must diffuse through a rate controlling membrane or matrix. The ability of drug to pass through membranes, its so called diffusivity, is a function of its molecular size (or molecular weight). An important influence upon the value of diffusivity, D, in polymers is the molecular size of the diffusing species. The value of D thus is related to the size and shape of the cavities as well as size and shape of the drugs.

B] Biological properties:

1] Absorption:

Slowly absorbed drugs or the drugs absorbed with a variable absorption rate are **poor** candidates for a controlled release system. Water-soluble but poorly absorbed potent drugs and those absorbed by carrier mediated transport processes or absorbed through window are poor candidates for controlled release system.

2] Metabolism:

Drug metabolism can result in either inactivation of an active drug or conversion of an inactive drug to an active metabolite. The process of metabolism can take place in variety of tissues but the organ mainly responsible for metabolism is liver as it contains variety of enzyme systems and thus greatest metabolic alteration of a drug takes place after its absorption into the systemic circulation. Thus the metabolic pattern of a drug may influence the choice of the route of administration. There are two factors associated with metabolism that significantly limit controlled release product design. First, if a drug is capable of either inducing or inhibiting enzyme synthesis it will be difficult to maintain uniform blood levels of drug upon chronic administration. Second, if the drug undergoes intestinal (or other tissue) metabolism or hepatic first pass metabolism, this also will result in fluctuating drug blood levels. Examples of drugs that undergo intestinal metabolism upon oral administration are hydralazine, salicylamide, nitroglycerin, isoproterenol, chlorpromazine, and levodopa. Examples of drugs that undergo hepatic first pass metabolism are; propoxyphene, nortriptyline, phenacetin, propranolol and lidocaine. Successful controlled release products for drugs that are extensively metabolized can be generated as long as the location, rate and extent and metabolism are known and the rate constant(s) are not too large. It can be assumed that a controlled release product can be developed as long as the metabolism remains predictable.

3] Elimination or Biological half-life:

The rate of elimination of drug is described quantitatively by its biological half- life. The biological half-life and hence the duration of action of a drug plays a major role in considering a drug for controlled release systems. Drugs with short half-life and high dose impose a constraint because of the dose size needed and those with long half-lives are inherently controlled.

4] Safety considerations and Side effects:

For certain drugs the incidence of side effects is believed to be a function of plasma concentration. A controlled release system can, at times, minimize side effects for a particular drug by controlling its plasma concentration and using less total drug over the time course of therapy. The most widely used measure of the margin of safety of a drug is its therapeutic index (TI), Where TD50 is median toxic dose ED50 is median effective dose In general, larger the value of TI, safer is the drug. Drugs with very small values of TI usually are poor candidates for formulation into CR products primarily because of technological limitations of precise control over release rates. A drug is considered to be relatively safe if its TI value exceeds.

5] Protein binding:

The characteristics of protein binding by a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug, and such drugs generally do not require a sustained release dosage form.

6] Disease state:

Disease state is an important factor in considering a drug for controlled release system. In some instances better management of the disease can be achieved by formulating the drug as controlled release system. For example, in case of rheumatoid arthritis, sustained release form of aspirin would provide desired drug blood levels, particularly throughout the night, thus relieving morning stiffness. Other examples include nitroglycerin in the management of angina pectoris and belladonna alkaloids and synthetic anti-cholinergics in the treatment of peptic ulcers.

7] Circadian rhythm:

Many biological parameters like liver enzyme activity, blood pressure, intraocular pressure and some disease states like asthma, acute myocardial insufficiency, and epileptic seizures have been shown to be influenced by circadian rhythm. Hence the response to certain drugs like digitalis glycosides, diuretics, amphetamines, barbiturates, carbamazepine, ethyl alcohol, and chlordiazepoxide display time dependent nature.

Drug-candidates suitable for modified release products [12]

For a successful modified-release product, the drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time, and be absorbed at a rate that will replace the amount of drug being metabolized and excreted. Zero order oral drug release can be achieved, in principle, by surrounding a core tablet with a membrane that is permeable to both drug and water. After swallowing, the core becomes hydrated, and drug dissolves until it reaches its saturation concentration or solubility. The core serves as a saturated reservoir of drug. Drug release proceeds by partitioning from the reservoir into the membrane, followed by diffusion across the membrane into the gastrointestinal fluid. So long as saturation is maintained in the core, there will be a stationary concentration gradient across the membrane, and release will proceed at constant rate. Eventually, the dissolved drug's concentration in the core falls below saturation, reducing the concentration gradient and hence the release rate, which decays to zero. If the membrane consists of a water-soluble polymer of high molecular weight, then it will initially swell into a gel, through which drug diffuses. The thickness of the gel layer initially increases with time due to swelling, but ultimately it decreases due to disentanglement and dissolution of polymer chains. At intermediate times, the gel layer may be of approximately constant thickness, and release occurs at a relatively constant rate.

As an alternative to dissolution/partition/diffusion based devices, osmotic pumps have been developed to provide zero order release. A small hole is drilled into the membrane. Upon ingestion, water is osmotically imbibed into the core through the semi permeable membrane, dissolving the drug. A constant osmotic pressure gradient is established between core and the external medium, setting the stage for water influx, which displaces drug through the hole at a constant rate. Eventually, drug concentration falls below its solubility, and the rate of osmotic pumping decays. The efficiency of osmotic devices can be improved by enriching the core with excipients such as water soluble polymers. The drug formulation is layered between the water soluble polymer and the exit orifice. As water crosses the semi permeable membrane, drug is dissolved. Meanwhile, swelling of the polymer excipients, which is also caused by osmosis, pushes drug through the orifice surrounded by a semipermeable membrane, with a small, drilled orifice. (c) Push–pull osmotic pump.

Methods for Preparation of Controlled Release tablets [13]

1) Wet Granulation Technique

Milling and gravitational mixing of drug, polymer and excipients. Preparation of binder solution Wet massing by addition of binder solution or granulating solvent, Screening of wet mass, Drying of the wet granules, Screening of dry granules, Blending with lubricant and disintegrant to produce "running powder", Compression of tablet.

2) Dry Granulation Technique

Milling and gravitational mixing of drug , polymer and excipients Compression into slugs or roll compaction, Milling and screening of slugs and compacted powder Mixing with lubricant and disintegrant Compression of tablet.

3) Sintering Technique

Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat. The sintering process has been used for the fabrication of sustained release matrix tablets for the stabilization of drug release.

Factors Affecting Drug Release: [14]

Various factors could be accounted for the drug release mechanism from hydrophilic matrices. These factors include ; geometry of matrix , particle size of polymers , matrix swelling ratio (which depend on polymer type and controls water and drug diffusion coefficients),polymer and drug concentration , Polymer viscosity, Polymer drug interaction, Tablet hardness and density, Effect of diluents chain length and degree of substitution on HPMC as well as drug characteristics.

Important Materials Used For Preparing Sustained Release Tablets:

- In Matrix, which are insoluble and inert Release retarding materials are Polyethylene, Polyvinyl Chloride, Methyl acrylate-methacrylate copolymer, Ethyl Cellulose.
- In Matrix, which are insoluble and erodible, Release retarding materials are Carnauba wax, Steryl alcohol, Stearic acid, Polyethylene glycol , Polyethylene glycol monostearate , Triglycerides.

- In Matrix, which is Hydrophillic, Release retarding materials are Methyl cellulose, Hydroxyethyl cellulose , Hydroxypropyl methycellulose, Sodium carboxymethylcellulose , Carboxypolymethylene, Sodium alginate, Galactomannose

Drug Selection Criteria:

- Molecular weight/ size should be less than 1000.
- Solubility should be lgreater than 0.1 μg/ml for pH 1 to pH 7.8
- PKa shold be Non ionized moiety > 0.1% at pH 1 to pH 7.8
- Apparent partition coefficient should be Diffusion.
- General absorbability should be from all GI segments
- Release Should not be influenced by pH and enzymes

CONCLUSION

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Modified release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. Now a days as very few drugs are coming out of research and development and already existing drugs are suffering the problem of resistance due to their irrational use specifically in case of drugs like antibiotics. Hence, change in the operation is a suitable and optimized way to make the some drug more effective by slight alteration in the drug delivery. Sustained Release is also providing promising way to decrease the side effect of drug by preventing the fluctuation of the therapeutic concentration of the drug in the body. There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and reduction in overall healthcare costs also.

REFERENCES

1. Agyilirah GA, Green M, Ducret R. Evaluation of the gastric retention properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablet. International J Pharmaceutics 1991; 75: 241-247.
2. Brahmankar DM. and Jaiswal SB. Biopharmaceutics and Pharmacokinetics a Treatise: Vallabh Prakashan, 1st ed. New Delhi: 1995.p. 336-337.
3. Lachman Leon, Lieberman Herbert A., Kanig Joseph L. The theory and practice of industrial pharmacy: Second edition, Varghese publishing house; Bombay, 1996.p. 171-196.
4. Hoffman F, Pressman JH, Code CF. Controlled entry of orally administered drugs: physiological considerations, Drug Development and Industrial Pharmacy, 1983. 9, 1077-1085.
5. Deshpande AA, Shah NH, Rhodes CT. Drug Development and Industrial Pharmacy, 1996; 22: 531-539.
6. LV Robles; AME Campos. Eur J Pharm Biopharm. 1997; 43:173-178.
7. Balasubramaniam J, Kumar MT. G Srinivas. Ind j pharm sci 2005; 67: 414-421**.**
8. S Bhansali; R Massodi. J of association of physicians of India 2005, 53, 441-445.
9. Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)
10. Navin Dixit et.al, Sustained Release Drug Delivery System, Indian J of Research in Pharmacy and Biotechnology 2013; 1(3): 305-310.
11. Sathish Ummadi et al,Overview on Controlled Release Dosage Form, International J of Pharma Sciences 2013; 3(4): 258-269.
12. Ansel H.C, Allen L.V, Popovich N.G. Pharmaceutical dosage forms and drug delivery systems. 7th ed; 2000: 230.
13. Lachman Leon, Lieberman Herbert A. Pharmaceutical Dosage Forms: Tablets. In: The Theory and Practice of Industrial Pharmacy. Lea and Febiger, U.S.A, 1991; 3rd ed: 293-345.
14. Sathish Ummadi et al, Overview on Controlled Release Dosage Form, International J of Pharma Sciences 2013; 3 (4): 258-269.