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

Human Journals
Review Article
May 2023 Vol.:27, Issue:2

A Review on Formulation of Sustain Release Tablets

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

Varsha S. Katore*, Soniya V. Katore, Sachin B.Somwanshi

Pravara Rural Education Society's College of Pharmacy (For Women) Chincholi Sinner, Maharashtra, India.

Submitted: 23 April 2023
Accepted: 29 April 2023
Published: 30 May 2023

Keywords: Oral Drug Delivery System, sustained release dosage forms.

ABSTRACT

Oral ingestion is most convenient and commonly employed route of drug delivery due to its ease of administration, least aseptic and flexibility in the design of dosage form. Sustained drug release formulations are quite helpful in treating chronic diseases. The design of oral sustained release delivery systems is subjected to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug. DDS depends on various factors such as, physicochemical properties of drug, type of delivery system, disease being treated, and patient condition, and treatment duration, presence of food, gastrointestinal motility, and co-administration of other drugs sustain release system includes any drug delivery systems that achieves slow release of drug over prolong period of time. Now a days the technology of sustained release is also being applied to veterinary products also. 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. The release of the drug through such system includes both dissolution controlled as well as diffusion controlled mechanisms, Most of drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration.

INTRODUCTION

The development of oral sustained release formulation is an attempt to control the release of drug from the gastro intestinal tract (GIT) and maintain an effective drug concentration in the systematic circulation for a long time. After an oral administration such a drug will retain in the stomach, which will eventually release the drug in a controlled manner so that the drug could be supplied continuously to its absorption sites in the GIT [1]. Oral drug delivery systems are matrix based requiring fewer unit operations, less machineries, reduced number of personnel and processing time, increased product stability and production rate [2]. An ideal controlled drug delivery system is that which delivers the drug at a specific rate locally or systemically for a specified period of time with minimum fluctuation in plasma drug concentration, reduced toxicity and maximum efficiency. In present scenario conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Oral drug delivery is the most preferred and convenient route of drug administration due to high patient compliance, cost effectiveness, least sterility constraints, flexibility in the design of dosage form and ease of production [3]. The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release (SR) dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ [4]. 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 Sustained drug delivery, greater attention is being paid on development of oral sustained release drug delivery systems. The goal in designing sustained release drug delivery system is to reduce the frequency of the dosing, reducing the dose & providing uniform drug delivery. So, Sustained 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 organ 1-3. Sustained release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery [5].

Various Mechanisms of Medicament Release

1) Diffusion is rate limiting Diffusion is driving force where the movement of drug molecules occurs from high concentration in the tablet to lower concentration in gastro intestinal fluids.

2) This movement depends on surface area exposed to gastric fluid, diffusion pathway, drug concentration gradient and diffusion coefficient of the system.

3) In practice, we can follow either of the two methods.

4) The drug is formulated in an insoluble matrix; the gastric fluid penetrates the dosage form and dissolves the medicament and release the drug through diffusion.

5) The drug particles are coated with polymer of defined thickness so as the portion of drug slowly diffuse through the polymer to maintain constant drug level in blood.

Dissolution is rate limiting the drugs with poor water solubility (BCS class 2 and 4) are inherently sustained release forms. While for water soluble drugs, it's possible to incorporate a water insoluble carrier to reduce dissolution of the drug particles are coated with this type of materials e.g. Polyethylene Glycol. One may skip the use of disintegrating agent to promote delayed release doses form.

Osmotic pressure is rate limiting Osmosis is a phenomenon in which the flow of liquid occurs from lower concentration to higher concentration through a semi permeable membrane which allows transfer of liquid only. The whole drug is coated with a semi permeable membrane with a hole on one end of tablet made by a laser beam. The delivery rate is constant provided that the excess of drug present inside the tablet. But it declines to zero once the concentration drops below saturation. Release is controlled by ion exchange Ion exchangers are water insoluble resinous materials containing salt forming anionic or cationic groups. While manufacturing, the drug solution is mixed with resin and dried to form beads which are tableted. The drug release depends upon high concentration of charged ions in gastro intestinal tract where, the drug molecules are exchanged and diffused out of the resin into the surrounding fluid. This mechanism relies upon the ionic environment of resin and not pH or enzyme on absorption site [6].

Polymers used in sustained release tablet

The polymers most widely used in preparing matrix system include both hydrophilic and hydrophobic polymers.

a) Hydrophilic Polymers: Hydroxyl propyl methyl cellulose (HPMC), hydroxyl propyl cellulose(HPC), hydroxyl ethyl cellulose (HEC), Xanthan gum, Sodium alginate, poly(ethylene oxide), and cross linked homopolymers and copolymers of acrylic acid.[7 -9]

b) Hydrophobic Polymers: This usually includes waxes and water insoluble polymers in their formulation[10].

c) Natural polymers: Xanthan Gum, Guar Gum, Sodium Alginate, Pectin, Chitosan [10].

d) Biodegradable polymers: Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters [11].

e) Non-biodegradable polymers: Polyethylene vinyl acetate (PVA), Polydimethylsiloxane (PDS), Polyether urethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC) [12].

ADVANTAGES OF SUSTAIN RELEASE DOSAGE FORMS

1) Reduce the toxicity by slowing drug absorption.[13]

2) It maintains a therapeutic concentration over a prolonged period. [14]

3) Reduction in frequency of intakes.

4) Reduce side effects.

5) Uniform release of drug over time. [14]

6) Better patient compliance [15]

7) The total amount of drug administered can be reduced, thus:

- Maximizing availability with minimum dose;
- Minimize or eliminate local side effects;
- Minimize or eliminate systemic side effects;
- Minimize drug accumulation with chronic dosing. [15]

DISADVANTAGES OF CONVENTIONAL DOSAGE FORMS

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.

3. A typical peak-valley plasma concentration time profile is obtain which makes attainment of steady-state condition difficult.

4. The fluctuations in drug levels may lead to precipitation of adverse effect especially of a drug with small Therapeutic Index whenever over medication occur [16, 17].

Classification of Oral Sustained or Controlled Release Systems

The controlled release systems for oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. Depending upon the manner of drug release, these systems are classified as follows:

1. Continuous release systems

2. Delayed transit and continuous release systems

3. Delayed release systems. [18]

A. Diffusion controlled release systems[19] In this type of systems, the diffusion of dissolved drug through a polymeric barrier is a rate limiting step. The drug release rate is never zero-order, since the diffusional path length increases with time as the insoluble matrix is gradually exhausted of drug. Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems.

B. Dissolution-controlled release systems [20] The drug present in such system may be the one Having elevated aqueous solubility and dissolution rate Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across the aqueous boundary layer.

C. Dissolution and diffusion controlled release systems [21] In such systems, the drug core is encased in a partly soluble membrane. Pores are thus created due to dissolution of parts of the

membrane which permit entry of aqueous medium into the core and hence drug dissolution and allow diffusion of dissolved drug out of the system.

Formulation strategy for oral SRDDS [22]

1. Diffusion Sustained System

2. Dissolution Sustained System

3. Methods using ion exchange

4. Methods using osmotic pressure

5. pH independent formulation

6. Altered density formulation

FACTORS AFFECTING SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Physicochemical factor: [23]

Dose size: In general, a single dose which contains drug about 500mg-1.0g is considered maximal for a conventional dosage form Compounds which having large dosing size that can sometimes be given in multiple amounts or formulated into liquid systems Same criteria also hold for sustained release dosage form. Ionization, pka and aqueous solubility: Most drugs are weak acids or bases. While the drugs which are in unchanged form permeate across lipid membranes, therefore pka of the compound and absorptive environment relationship is important Delivery systems that are dependent on diffusion or dissolution will equally be dependent on the solubility of the drug in aqueous media.

Partition Coefficient: To produce therapeutic effect in another area of body, when a drug is administered to the GI tract, it must cross a variety of biological membranes. It is common to consider that these membranes are lipidic; therefore the partition coefficient of oil soluble drugs is important in determining the effectiveness of membrane barrier penetration. Compounds which are lipophilic in nature having high partition coefficient are poorly aqueous soluble and it retain in the lipophilic tissue for the longer time. In case of compounds with very low partition coefficient, it is very difficult to penetrate the membrane in case of the compound which having very low partition coefficient, resulting in poor bioavailability.

Stability: The drugs which are orally administered subjected to both acid base hydrolysis and enzymatic degradation. For a drug in solid state degradation will continue at a reduced rate

thus, this is the preferred composition of delivery for problem cases. For the dosage forms that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial. This is also true for systems that delay release until the dosage form reaches the small intestine. Compounds which are unstable in small intestine may show decreased in bioavailability when administered from a sustaining dosage form. This is because more drugs are delivered in the small intestine and these drugs are subjected to degradation.

Biological factor [24]**:**

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 from and Sustained 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.

Therapeutic index: If the dose of a drug in the conventional dosage form is high, then it is less suitable candidates for SRDDS. This is because the size of a unit dose Sustained release oral formulation would become too big to administer without difficulty.

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 SRDDS.

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 SR drug delivery system.

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 SR delivery system. It should be of first order kinetics.

METHODS OF PREPARATION

1. Direct Compression In this method, finely powdered materials are compressed directly without changing the physical and chemical properties of the drug [3].

2. Wet Granulation In this method weighed quantities of drug and polymer are mixed with sufficient volume of the granulating agent. After enough cohesiveness was obtained, the mass is sieved and dried at 40°C and kept in a dessicator. Lubricants and Glidants are added and the tablets are compressed using a tablet compression machine [3].

3. Melt Granulation In melt granulation, meltable substance act as liquid binding agent and hence does not require the use of organic solvents. This substance can be added in the molten form over the substrate, which is then heated above its melting point. Various lipophilic binders such as Glyceryl Palmitostearate are used in melt granulation technique[3].

Evaluation Parameters

Pre Compression Parameters

1. Bulk density (Bd): It is the ratio of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. Bulk density is expressed in gm/cc and is given by,

$$Db = M / Vo$$

Where, Db = Bulk density (gm/cc)

M = mass of powder (g)

Vo= bulk volume of powder (cc)

2. Tapped density (Dt):- Ten grams of powder was introduced into a clean, dry 100ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$$Dt = M / Vt$$

Where, Dt = Tapped density (gm/cc)

M = mass of powder (g)

Vt= tapped volume of powder (cc)

3. Compressibility index:- The compressibility of the powder was determined by the Carr's compressibility index.

Sr. No.	Carrs index	Flow properties
1	5-15	Excellent
2	12-15	Good
3	18-21	Fair to possible
4	23-30	Poor
5	33-38	Very poor
6	≥40	Very very poor

4. Hausner ratio:

Hausner ratio = tapped density/bulk density

Values of Hausner ratio; < 1.25:

Good flow >1.25:

Poor flow If Hausner ratio is between 1.25-1.5, flow can be improved by addition of glidants.

5. Angle of repose (θ): It is defined as the maximum angle possible between the surface of pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of funnel. The angle of repose was then calculated using the formula,

$$\tan\theta = h/r \quad \theta = \tan^{-1}(h/r)$$

Where, θ = angle of repose,

h = height of pile,

r = radius of the base of the pile.

6. Total Porosity: Total porosity was determined by measuring the volume occupied by a selected weight ofa powder (bulk) and the true volume of the powderblend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces,

Porosity (%) =V bulk-V/V bulk x 100

7. Flow rate: Flow rate of granules influences thefilling of die cavity and directly affects the weight of the tablets produced.

Post Compression Parameters

1. Thickness and diameter: Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm.

2. Hardness: The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw.

• Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet.

• Hardness was expressed in Kg/cm^2.

• Friability (F): Tablet strength was tested by Friabilator USP EF-2.

• Preweighed tablets were allowed for 100 revolutions (4min), taken out and were dedusted. The percentage weight loss was calculated by rewriting the tablets.

The % friability was then calculated by, D.

3. Weight variation test:- The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The USP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the USP test if not more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit.

$$PD = Wavg \ X \ Winitial/Waveg \ X100$$

Where, PD = Percentage deviation,

Wavg = Average weight of tablet,

Winitial =individual weight of tablet.

4. Uniformity of drug content:- Five tablets of various formulations were weight individually and powdered. The powder equivalent toaverage weight of tablets was weighed

and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 262.4 nm after suitable dilution using a UV/Visible Spectrophotometer (UV-1800).[25]

CONCLUSION:

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 various factors influencing the designs.

REFERENCES:

1 .Samira Karim, Mohiuddin Ahmed Bhuiyanand Md. Sohel Rana Formulation and *In vitro* Evaluation of Glimepiride Sustained Release Tablets: Comparison with Immediate Release Tablets Received: June 30, 2015; Published (Web): July 21, 2015

2. Reddy, R. K., Mutalik, S. and Reddy, S. Once-daily sustained-release matrix tablets of nicorandil: formulation and *in vitro* evaluation. AAPS Pharm. Sci. Tech. 2003.

3. Agarwal P, Semimul A. A comprehensive review on sustained release matrix tablets: a promising dosage form. Universal Journal of Pharmaceutical Research. 2018; 3(6): 53-58.

4. Sudhir Karna*, Shashank Chaturvedi, Vipin Agrawal, Mohammad Alim, Formulation approaches for sustained release dosage forms: a review, vol 8, issue 5, 2015 ISSN - 0974-2441.

5. *Ratnaparkhi M. P., Gupta Jyoti P. Review Article Sustained Release Oral Drug Delivery System International Journal of Pharma Research & Review, Mar 2013; 2(3):11-21.

6. International Journal of Science and Research (IJSR) ISSN: 2319-7064 SJIF (2019): 7.583 Volume 9 Issue 11, November 2020. www.ijsr.net Licensed Under Creative Commons Attribution CC BY Sustained Release Oral Dosage Form Krishan Kant1 , Archana Rautela2 Gyani Inder Singh Institute of Professional Studies, Dehradun, India.

7. Kumar S, Kant S, Prashar B. A review on sustained release drug delivery system. Int J Inst Pharm life Sci. 2012:2(3):356-376.

8. Oyeniran Taiwo Opeyemi, Obanewaopeyemi Adegbenro. Development and characterization of direct compressed matrix mini tablets of naproxen sodium. Univ J Pharm Res. 2018; 3(5): 7-11.

9. Kumar N, Roy Mahasweta, Kumar B, Puri Pooja, Hasan M. Formulation and Evaluation of Sustained Released Metformin HCl Tablet Using Natural Polymers. Int J Pharmacy Pharm Res. 2016:6(2):217-237.

10. Prajapati B, Patel R, Patel D, Shah P. Metformin hydrochloride sustained release tablet using different matrixing tablet, e-Journal of Science and Technology (eJST). 2013:4(8):61-72.

11. Singh S, Virmani T, Virmani R, Kumar P, Mahlawat G. Fast dissolving drug delivery systems: formulation, preparation techniques and evaluation. Univ J Pharm Res. 2018; 3(4): 60-69.

12. Singh A, Rajput DS, Gopalrao AA, Chauhan D, Mafidar R, Bhowmick M, Rathi J, Mathur R, Design and characterization of sustained release matrix tablets of metformin hydrochloride using combination of hydrophilic polymers. J Drug Deliv Therap. 2018; 8(2):96-101.

13. D. Nagendrakumar, Keshavshetti G G and ShardorA G, An overview: Matrix tablets as sustained release Recent Research in Science and Technology 2013, 5(4): 36-45 ISSN: 2076-5061.
14. Chein Y.W. Oral Drug delivery and delivery systems. In: Novel drug delivery systems. Marcel Dekker, Inc., New York, 2002; 50; 3rd edition: 139-96.
15. Vyas S, P, Khar R K. Controlled Drug delivery: Concepts and Advances. Concepts And Advances.1st ed. Vallabh Prakashan, 2002, p, 156-189.
16. Jantezen GM Robinson JR, Sustained and control release drug delivery system. In Banker GS, Rhodes CT, editors. Modern Pharmaceutics. 3rd edition New york: Marcel dekker Inc; 1996. p. 575-09.
17. Gennaro Alfonso R. Extended Release Dosage Forms. In: Remington: The Science and Practice of Pharmacy. Lippincott Williams and Wilkins, U.S.A, 2000; vol 1; 20th edition: 660-63.
18. Chang R. K., Robinson J. R., Sustained drug release form tablets & particles through coating, In: Liberman H.A., Lachman L.S., Chwartz J.B.," Pharmaceutical Dosage Form: Tablets" vol 3, 2nd edn., Marcel Dekker, New York, 2015; 199-287.
19. Sahilhusen I J, Mukesh R P, Alpesh D P. Sustained Release Drug Delivery Systems: A Patent Overview. Aperito J Drug Designing and Pharmacology 2014; 1(1): 1-14.
20. Shalin A M, Gaikwad P D, Bankar V H, Pawar S P. Sustained release drug delivery system: a review. Int J Phama Res Dev., 2011; 2(12): 147-60.
21. Gandhi A, Hari Kumar SL. Recent Trends in Sustained Release Drug Delivery System.
22. Jain N. K. Controlled and Novel Drug Delivery. CBS Publiser, New Delhi, 1-2, 2002: 676-698.
23. Robinson J R, Lee V H. Controlled drug delivery. 2nd ed. Marcel Dekker, 1987, 4 -15.
24. Devraj, Bhatt D C. Studies on enteric coated sustained timed-release tablets of Metronidazole. J. Chem. Pharm. Res, 2(2), 2010, 226-232.
25. International Journal of Science and Research (IJSR) ISSN: 2319-7064 SJIF (2019): 7.583 Volume 9 Issue 11, November 2020. www.ijsr.net Licensed Under Creative Commons Attribution CC BY Sustained Release Oral Dosage Form Krishan Kant1, Archana Rautela2
26. Aulton, ME. (2002). Pharmaceutics-The science of dosage form design, 2nd Ed., Churchill Livingstone, London. Pp. 322-334.
27. Indian pharmacopoeia (2007) volume 2, 44-45.