World Journal of
Drug Delivery

IDAAM Publications

World J Drug Deliv 2023; 1(1): 28-33

REVIEW ARTICLE

Review on classification and factors influencing the design of sustained release formulations

AFRIN N NAIKAWADI, JAMEEL AHMED S MULLA*

Department of Pharmaceutics, Shree Santkrupa College of Pharmacy, Ghogaon, Karad, Dist: Satara, MS– 415111, India

***Author for Correspondence:** *Email:* jameelahmed5@rediffmail.com

ARTICLE DETAILS

Article history:
Received on 25 September 2022
Modified on 26 October 2022
Accepted on 29 October 2022

Keywords:
Sustained Release,
Controlled Drug Delivery System,
Oral Drug Delivery System,
Pharmacokinetics,
Conventional Drug Therapy.

ABSTRACT

Pharmaceutical innovation and research are putting more and more emphasis on delivery methods that maximise therapeutic outcomes while minimising negative effects. One of the cutting-edge subfields of controlled medication administration is the oral drug delivery system. The most significant benefit of such a dose form is patient compliance. Sustained release dosage forms are designed to release a medicine at a set rate in order to keep the drug concentration constant for a set amount of time with the fewest side effects. By eliminating fluctuations in the therapeutic concentration of a medicine in the body, sustained release formulations are also offering a promising technique to reduce side effects of medication.

INTRODUCTION

The oral route of administration is the greatest of all the drug administration routes. This is due to benefits such as low manufacturing costs and ease of usage, administration, and so on. Many studies on rapid and unique delivery have been conducted over the years. Long years ago any drug delivery system's goal is to achieve a therapeutics at a precise location to keep the desired drug concentration [1]. To release drugs over an extended period of time the oral drug delivery method is the mostly used route of administration among all the options for systemic drug delivery via various routes that have been investigated. The route's popularity may be due to its ease of administration and its the conventional idea that by administering the medicine orally. The drug's effectiveness is linked on how well it is absorbed into the food that is consumed every day (Howard and Loyd, 2005). S.R. (sustained release)/(Since their first appearance.) Controlled dispersion (C.R). Among all the ways that have been investigated for the systemic distribution of pharmaceuticals via diverse pharmaceutical products of varied dose forms, oral drug delivery has long been recognised as the most frequently used route of administration. The majority of pharmaceutical experts nowadays are working to create the ultimate DDS [2]. The benefit of a single dose for the length of treatment would be a feature of the ideal system, as would direct medication delivery to a specific location. Scientists have succeeded in creating a system that comes close to being ideal, and this inspires them to create controlled release systems. The primary goal of the design of an oral sustained drug delivery system (DDS) should be to increase predictability and reproducibility in the control of drug release, drug concentration in the target tissue, and optimization of a drug's therapeutic effect by regulating its release in the body with a smaller and less frequent dose. Regular administration of a therapeutic agent that has been prepared to maintain its stability, activity, and bioavailability is a common component of conventional pharmacological therapy. The majority of medications can be successfully formulated using traditional procedures. Some medications, however, must be localised to a specific place in the body, have a narrow therapeutic range, exhibit extreme solubility issues, and call for tight adherence or long-term administration. In these situations, a continuous drug administration approach is preferred to maintain constant plasma drug levels [3]. By localizing the

drug to the site of action, lowering the dosage needed, or ensuring consistent drug delivery, sustained or sustained delivery systems aim to reduce the frequency of dosing or increase the effectiveness of the medicine. Therefore, a sustained release dosage form is a dosage form that releases one or more medications systemically or to a specific target organ continuously in a predetermined pattern for a set amount of time. Greater control over plasma drug levels, reduced dosing frequency, less adverse effects, and enhanced effectiveness are all provided by sustained release dosage forms [4].

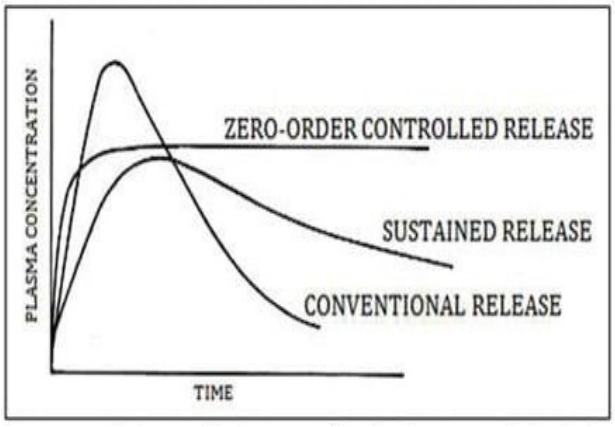

Figure 1: Drug plasma concentration- time profile4

Advantages [5, 6]

- Medicinal concentrations keep the rate at the same levels.
- Blood drug concentration is constant.
- Reduction in the dosage's administration frequency.
- Cost-effective and easy to manufacture [5].
- Accumulation of drug is reduced as the frequency of Administration is less.
- The deficiency in treatment can be improved.
- Compliance problems of the patients are reduced.
- Bioavailability should be increased while local side effects should be minimized [6].

Disadvantages [7, 8]

- When compared to traditional dose forms, the cost of manufacture is expensive, and the poor *in vivo* and *vitro* correlation [7].
- The potential of first-pass metabolism has grown [8].

Classification of Sustained Release Formulations: [9 - 12]

1. Dissolution Sustained Systems:

For medications with high water solubility, a substance that naturally keeps the medication from dissolving quickly while also sufficiently reducing the pace at which salt or a derivative is formed. In general, these gadgets are utilized in Enteric-coated dose forms are processed. Stomach protection from medication side effects A coating that dissolves in natural or alkaline water, similar to aspirin, is used. It causes a drug's release to be delayed. Release from the dosing process until the intestine's pH falls below 7 [9].

2. Diffusion Sustained Release [10]**:**

The passage of drug molecules from a higher concentration to a lower concentration is referred to as a diffusion sustained system. The formula for calculating drug flow is:

$J = - D \, dc/dx$

D = diffusion coefficient in area/time
dc/dx = change in concentration 'c' with distance

3. pH– Independent Formulations:

Maintain the constant pH, help to make pH independent drug release substitutes such as amino acid salts, citric acid, phthalic acid, phosphoric acid and tartaric acid applied to the formulation. Preparation of buffered sustained release formulation is generally done by combining a simple or acidic product with a single or more buffering agents, granulating with suitable pharmaceutical excipients, and covering with permeable film forming polymer with gastrointestinal fluid [11].

4. Ion Exchange:

By using ion exchange resin for continuous drug delivery is appealing because drug release is largely determined by the ionic environment of drug-containing resins and is less affected by environmental factors. Zero order release kinetics can be affected by factors such as enzyme concentration and pH at the absorption site.

5. Changed Density:

Because not all of the drug contents are released in the GIT, the usage of the medication is limited. To overcome this, several approaches to increase the resident time in the GIT have been devised [12].

Factors Influencing Design and Act of SR [5, 13, 14, 20]:

1) Biological Factors:

a. Half-life:

The usual goal of an oral SR product is to maintain therapeutic blood levels over an extended period of time. To achieve this, drug must enter the circulation at approximately the same rate at which it is eliminated. The elimination rate is quantitatively described by the half-life ($t_{1/2}$). Each drug has a unique characteristic elimination rate, which is the total of all processes that permanently remove the drug from the bloodstream, including metabolism, urine excretion, and all other processes. Therapeutic compounds with short half-life are generally are excellent candidate for SR formulation, as this can reduce dosing frequency. In general, drugs with half-lives shorter than 2 hours like furosemide or levodopa are poor candidates for SR preparation. Compounds with long half-lives, more than 8 hours are also generally not used in sustaining form, since their effect is already sustained. Digoxin and phenytoin are the examples [5, 20].

b. Absorption:

The rate of release must be substantially slower than the rate of absorption because the goal of creating an SR product is to exert control over the delivery system. The maximum half-life for absorption should be around 3–4 hours if we consider that most medications transit through the GI tract within 8–12 hours. Otherwise, the device will leave the potential absorptive regions before the drug release is finished [13].

c. First Pass Effect:

Drugs with a significant first pass impact have a slower release rate. The bioavailability is impacted by the delayed release rate [14].

d. Adverse Effects:

The drug release may be prolonged, which could result in unwanted side effects. Because their activity is already long-lasting, compounds with large half-lives (more than 8 hours) are rarely used in sustaining form. Examples include phenytoin and digoxin [5, 20].

2) Chemical and Physico-Chemical Properties

a. Molecular Size and Diffusivity:

During its duration in the body, a medication must disperse through a number of biological membranes. Many extended-release methods require medications to pass through a rate-controlling polymeric membrane or matrix in addition to biological membranes. A drug's so-called diffusivity (diffusion coefficient D), which refers to its capacity to disperse through polymers, depends on the molecular size of the drug (or molecular weight).

$$\textbf{Log D} = -sv \log u + kv = -sM\log M + km$$

It can be used to empirically connect log D to some function of molecular size for the majority of polymers [13].

b. Aqueous Solubility:

The quantity of a substance still in solution in a given volume of a solvent that also contains undissolved substance is known as its solubility. It is a compound's thermodynamic characteristic. The amount of drug in the G.I. tract's solution, or the drug's intrinsic permeability, determines the fraction of the drug that is absorbed into the portal blood. A drug needs to dissolve in the aqueous phase near the administration site before partitioning into the absorbing membrane in order to be absorbed. A drug's aqueous solubility affects its rate of dissolution, which in turn determines its concentration in solution and, consequently, the force that propels diffusion through membranes. The Noyes-Whitney equation demonstrates that aqueous solubility and dissolution rate are connected [14].

c. Partition Coefficient:

Partition coefficient is referred to as the drug's fragment in the neighboring aqueous phase from the oil phase. Drugs that pass across biological membranes may have a higher bioavailability if the partition coefficient of the drug alters the membrane's hydrophobicity. For oral controlled release drug delivery systems, drugs with lower partition coefficient are unacceptable, whereas drugs with higher partition coefficient are likewise unacceptable. Because once they enter the lipid membrane they cannot be partitioned out of the membrane [20].

Polymers used in Sustained Release Formulation [18-24]:

The use of polymers is growing in significance for medication delivery. Polymers are used in pharmaceutics for a variety of purposes, from tablet binders to viscosity and flow regulators in liquids, suspensions, and emulsions [18].

Table 1: Characteristics of sustained release drug suitable for formulations [15]

Parameters	Criteria
Molecular size	< 1000 Daltons
Aqueous Solubility	More than 0.1 mg/ml for pH 1 to pH 7.8
Apparent partition coefficient	High
Absorption mechanism	Diffusion
General absorbability from all GI segments	Releases should not be influenced by pH and enzymes

Table 2: Pharmacokinetic parameters for drug selection [16, 17]

Parameters	Comment
Elimination half-life	Between 2 to 8 hrs
Absolute bioavailability	Should be 75% or more
Absorption rate constant (Ka)	Must be higher than release rate
Apparent volume of distribution (Vd) required for design	Larger Vd and MEC, Larger will be the required dose
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration (Css)	The lower Css and smaller Vd, the loss among of drug required
Toxic concentration	Apart the value of MTC and MEC safer the dosage form

Polymers can be employed as film coatings to improve drug stability and change the characteristics of drug release while masking a drug's unpleasant taste. Examples of polymers are [19]:

- Polyethylene glycol (PEG)
- Polyvinyl alcohol (PLA)
- Polyacetic acid (PLA)
- Polyglycolic acid (PGA)
- Polyanhydrates
- Tragacanth
- Cellulose acetate
- Guar gum
- Xanthangum

Features of an Ideal Polymer System [25-31]:

- It ought to be adaptable and have a variety of mechanical, physical, and chemical qualities.
- It should be non-toxic and have good mechanical strength and should be easily administered.
- It should be inexpensive and easy to fabricate.
- It should be inert to host tissue and compatible with environment.

The Selection of Polymers was based on a Set of Criteria [32-36]:

- The polymer should be soluble and simple to work with synthesis.
- Its molecular weight should be limited.
- It must be compatible with biological systems environment.
- It ought to be biodegradable.
- It should be able to create strong drug polymer linkage.

CONCLUSION

The goal of a sustained release drug delivery formulation is for the medicine to release at the optimum rate over time. A long length of time in order to keep the therapeutic concentration in blood plasma at the moment, the For long-term release, use the oral method of administration. More people are aware of the medicine delivery technique. Lower dose due to limited flexibility a higher frequency of use, and a higher level of patient compliance The design of a sustained-release medication delivery system for oral administration system is influenced by a number of factors, including drug's physico-chemical characteristics, type of drug mechanism of delivery, ailment being treated, and patient condition, length of treatment, and existence of Food, gastrointestinal motility, and drug interactions are all factors to consider. We can come to a conclusion.

The low cost of an oral sustained release drug delivery system has made it easier to replace oral conventional drug delivery systems on the market. Moreover the low cost of an oral sustained release drug delivery system has made it easier to replace oral conventional drug delivery systems on the market.

REFERENCES

[1] Shukla AK, Kumar M, Bishnoi RS, Kachawa VS, Jain CP. Dosage from design of sustained release drug delivery systems: An overview. Asian Journal of Biomaterial Research. 2017; 4(3):1-7.

[2] Remington JP, Beringer P. Remington: The science and practice of pharmacy, 2005.

[3] Bose S, Kaur A, Sharma SK. A review on advances of sustained release drug delivery system. Int. Res. J. Pharm. 2013; 4:1-5.

[4] Robinson JR, editor. Sustained and controlled release drug delivery systems. M. Dekker; 1978.

[5] Kumar AR, Aeila AS. Sustained release matrix type drug delivery system: An overview. World J Pharma pharm Sci. 2019 Oct 24; 8(12):470-80.

[6] Moghal M, Islam M, Ahmed I, Islam M, Rahman H, Development and optimization of sustain release matrix tablet of Ambroxol HCl using central composite design, Indian Journal of Pharmaceutical Education and Research, 2010; 44(1): 2-35

[7] Narwate BM. Sustained release dosage form: a concise review. International journal of pharmaceutics and drug analysis. 2017 May 2:153-60.

[8] Hoffman A. Pharmacodynamic aspects of sustained release preparations. Advanced drug delivery reviews. 1998 Sep 7; 33(3):185-99.

[9] Patil H, Patel N, Patil V, Rane B, Gujrathi N, Pawar S. A review on sustained release drug delivery system. International Journal of Pharmaceutical, Chemical and Biological Sciences. 2014; 4(3):470-8.

[10] Banker GS and Anderson NR. The Theory and Practice of Industrial Pharmacy: Tablet, Lachman, (3rded) Varghese Publishing House, Bombay, 1990, 293-303

[11] Patnaik AN, Nagarjuna T, Thulasiramaraju TV. Sustained release drug delivery system: a modern formulation approach. International Journal of Research in Pharmaceutical and Nano Sciences. 2013; 2(5): 586-601.

[12] Jethara SI. Sustained Release Drug Delivery Systems: A Patent Overview. Aperito J Drug Design Pharmacol 2014; 1: 104.

[13] Parashar T, Soniya SV, Singh G, Tyagi S, Patel C, Gupta A. Novel oral sustained release technology: a concise review. Int J Res Dev Pharm Life Sci. 2013 Feb; 2(2):262-9.

[14] Mamidala RK, Ramana V, Sandeep G, Lingam M, Gannu R, Yamsani MR. Factors influencing the design and performance of oral sustained/controlled release dosage forms. Int. J. Pharm. Sci. and Nanotech. 2009 Nov 30; 2(3):583-94.

[15] Pareek SP, Kumawat S, Sharma V, Sharma D, Rathore DS, Agarwal M. Review on sustained release technology. Int J Pharm Bio Sci Archive. 2019; 7(6):29-38.

[16] Yadav IK, Singh HP, Singh RP, Tiwari PK, Chandra D, Jaiswal D, Jain DA. Formulation, evaluation and optimization of aceclofenac sustained release matrix tablets. International Journal PharmTech Research. 2010; 2(1): 592-98.

[17] Semalty M, Semalty A, Bisht T. Triple layered Aceclofenac tablets of Xanthan gum and guargum: A comparative study. International J Pharm SciNanotechnol 2012; 5: 1621. 2012; 1626.

[18] Gandhi KJ, Deshmane SV, Biyani KR. Polymers in pharmaceutical drug delivery system: a review. International journal of pharmaceutical sciences review and research. 2012; 14(2):57-66.

[19] Raizada A, Bandari A, Kumar B. Polymers in drug delivery: a review. Int. J. Pharm. Res. Dev. 2010 Oct 8; 2(8):9-20.

[20] Mulla JA, Mabrouk M, Choonara YE, Kumar P, Chejara DR, du Toit LC, Pillay V. Development of respirable rifampicin-loaded nano-lipomer composites by microemulsion-spray drying for pulmonary delivery. Journal of Drug Delivery Science and Technology. 2017 Oct 1; 41: 13-9.

[21] Mabrouk M, Bijukumar D, Mulla JA, Chejara DR, Badhe RV, Choonara YE, Kumar P, du Toit LC, Pillay V. Enhancement of the biomineralization and cellular adhesivity of polycaprolactone-based hollow porous microspheres via dopamine bio-activation for tissue engineering applications. Materials Letters. 2015 Dec 15; 161: 503-7.

[22] Mabrouk M, Chejara DR, Mulla JA, Badhe RV, Choonara YE, Kumar P, Du Toit LC, Pillay V. Design of a novel crosslinked HEC-PAA porous hydrogel composite for dissolution rate and solubility enhancement of efavirenz. International journal of pharmaceutics. 2015 Jul 25; 490(1-2):429-37.

[23] Chejara DR, Mabrouk M, Badhe RV, Mulla JA, Kumar P, Choonara YE, du Toit LC, Pillay V. A bio-injectable algin-aminocaproic acid thixogel with tri-stimuli responsiveness.

Carbohydrate polymers. 2016 Jan 1; 135: 324-33.

[24] Mulla JAS, Aralelimath VR, Tipugade O, Shinde SS, Tetgure NG, Mulla AA, Gavali DD. Formulation and Evaluation of Teneligliptin-Loaded Mucoadhesive Microspheres. Indian Journal of Novel Drug Delivery. 2020Oct-Dec; 12(4): 222-227.

[25] Nokano M, Ogata A, *In vitro* release characteristics of matrix tablets, Study of Karaya gum and Guar gum as release modulators, Ind. J. Pharm. Sc, 68, 6, 2006, 824-826.

[26] Michael B, Alulton E. Fluidized-bed Granulation: A Chronology. 1991.1437–63.

[27] Potekar PM, Mulla JAS, Doijad RC. Gastro-Retentive Drug Delivery Systems: A Review. Indian Journal of Novel Drug Delivery. 2017: 9(3):159-166.

[28] Mulla JAS andKarande BS. Microemulsion Based Hydrogel Formulation for Topical Drug Delivery - A Concise Review. Indian Journal of Novel Drug Delivery. 2021Apr-Jun;13(2): 63-69.

[29] Nikam GG, Mulla JAS. Design, Development and Characterization of Fast Dissolving Oral Film of Clonazepam. Indian Journal of Novel Drug Delivery. 2020Jan-Mar; 12(1): 48-54.

[30] Mulla JAS.Drug Delivery and Therapeutic Approaches to Prostate Cancer. Indian Journal of Novel Drug Delivery. 2018; 10(3): 98-109.

[31] Mulla JS, Khazi IM, Sharma NK. Solid Lipid Nanoparticles: Measures of Characterization. Indian Journal of Novel Drug delivery. 2011; 3(4): 259-264.

[32] Hargel L, Yu A. Modified release drug products. Appl. Biopharm. Pharmacokinet. 4th ed. McGraw Hill; 1999:169–71.

[33] Mulla JS, Khazi IM, Sharma NK, Hiremath SP, Jamakandi VG. Solid Lipid Nanoparticles: Methods of Preparation. Indian Journal of Novel Drug delivery. 2011; 3(3): 170-175.

[34] Mandal S, Ratan GN, Mulla JS, Thimmasetty J, Kaneriya A. Design and *In Vitro* Evaluation of Gastro Retentive Sustained Release Tablets of Tizanidine Hydrochloride. Indian Journal of Novel Drug delivery. 2010; 2(4): 144-152.

[35] Mulla JS, Khazi IM, Jamakandi VG. Solid lipid nanoparticles: Potential Applications. Indian Journal of Novel Drug Delivery. 2010; 2(3): 82-87.

[36] Jamakandi VG, Mulla JS, Vinay BL, Shivakumar HN. Formulation, characterization, and evaluation of matrix-type transdermal patches of a model antihypertensive drug. Asian Journal of Pharmaceutics (AJP). 2009; 3(1).