

Sustained release drug delivery system: an overview

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Abstract:

Oral drug delivery is still the most used method for administering a variety of medications among all drug delivery systems. Because sustained release keeps the therapeutic concentration of the medicine in the body from fluctuating, it also offers a viable means of reducing pharmacological adverse effects. The main idea behind a continuous drug delivery system is to increase a medicine's utility, minimize side effects, and treat the disease by optimizing its biopharmaceutical, pharmacokinetic, and pharmacodynamic properties. Better patient compliance with sustained release drug delivery results from less frequent drug administration, less variation in steady-state drug levels, maximum drug utilization, a higher safety margin of a powerful drug, and lower healthcare costs through better therapy and a shorter treatment duration. The main objective of sustained release forms is to enhance medication therapy as determined by the weight of the benefits and drawbacks of using a sustained release system.

Keywords: Sustained release, Mechanism of drug release, conventional dosage form, Diffusion sustained system, Dissolution sustained system, Methods using Ion-exchange, Methods using osmotic pressure, pH-independent formulations, Altered density formulations.

Sustained Release Tablet:

A sophisticated type of medication delivery mechanism, sustained-release (SR) tablets are made to release the active pharmaceutical ingredient (API) gradually and under control. By keeping therapeutic drug concentrations in the bloodstream for a longer amount of time, these formulations hope to minimize side effects linked to peak plasma drug levels, increase patient compliance, and decrease the frequency of administration.(Pareek et al., 2019)

Traditional immediate-release tablets release the medication quickly, and in order to maintain therapeutic efficacy, several doses must frequently be taken daily. This frequent dose schedule, however, could cause variations in medication concentration, which could lead to hazardous or subtherapeutic consequences. By guaranteeing a constant and uninterrupted medication release, enhancing pharmacokinetics, and enhancing therapeutic results, sustained-release tablets overcome these difficulties.(Zalte & Saudagar, 2013)

A number of biological and physicochemical concepts form the foundation of the sustained-release medication delivery idea. These formulations control medication absorption and dissolution by the use of coatings, polymers, matrix systems, and other technologies. Depending on the formulation

design, the drug release mechanism may entail osmosis, diffusion, dissolution, or a mix of these mechanisms.(Gopinath et al., 2012)

CONVENTIONAL DOSAGE FORM DRAWBACK

1. Inadequate patient adherence: The likelihood of skipping a medication dosage.
2. Under or excessive medication may result from the inevitable changes in drug concentration.
3. When a typical peak-valley plasma concentration-time profile is attained, the standard dose form's drawback can be achieved.
4. Variations in drug levels, particularly those with a modest Therapeutic Index, are what lead to the development of negative effects whenever overmedication occurs. (Brahmankar D.M., 2009) (Kumar S.K.P., 2012) (Dusane A.R., 2011)

Rationale of developing Sustained release (Lachman L, 1986) (Joseph RR, 1887) (MS., 2008)

- To prolong the drug's duration of effect.
- To decrease the number of doses.
- To reduce variations in plasma levels.
- Increased use of drugs.
- Reduced negative consequences.

ADVANTAGES: (Kumar S.K.P., 2012) (Remington, 2006) (Chugh I., 2012)

1. **Patient compliance:** Chronic diseases that require long-term care are more likely to exhibit noncompliance since the effectiveness of medication therapy is dependent on the patient's capacity to adhere to the prescribed course of action. Knowledge of the illness process, patient trust in treatment, and patient comprehension of a rigorous treatment regimen are some of the elements that influence patient compliance. Moreover, the expense of therapy, the complexity of treatment plans, and any systemic or local adverse effects of the dosage type. A sustained release medicine delivery method can help alleviate this issue to a certain degree.
2. **Reduced 'see-saw' fluctuation:** The concentration of the drug in the tissue compartments and systemic circulation frequently exhibits a "see saw" pattern when the medicine is administered in a typical dosage form. The major determinants of these oscillations' magnitudes are drug kinetics, including dosing intervals, distribution, elimination, and absorption rates. Since recommended dose intervals are rarely shorter than four hours, the 'see-saw' pattern is more noticeable only for medications with biological half-lives subfour hours. A well-thought-out sustained release drug delivery system can significantly lower the frequency of drug dosages while maintaining a constant drug concentration in target tissue cells and blood circulation.
3. **Total dose reduction:** Under sustained release medication delivery systems, a less quantity of the entire drug is used to treat an illness. A reduction in systemic or local side effects is noted when the overall dosage of the medication is decreased. Increased economy would also result from this.

4. **Improvement of deficiency in treatment:** For a disease to be treated as effectively as possible, active medications must be transferred to the tissues and organs that require care. It is frequently essential to deliver doses significantly higher than those needed in the cells to reach the required therapeutically effective concentration. Unwanted toxicological and immunological consequences in non-target tissue could result from this, regrettably. Better control of the acute or chronic illness condition is achieved with a sustained release dose type.
5. **Economy:** The unique nature of these substances usually results in a higher initial unit cost for sustained release medications than for traditional dosage forms, but crucially, the average cost of treatment over an extended period of time may be lower.

DISADVANTAGES: (Pundir S., 2013) (Brahmankar D.M., 2009) (Remington, 2006)

1. When the formulation is flawed, dose dumping could happen.
2. Less room for dose modification.
3. The price is higher than for a traditional dose form.
4. Boost first-pass metabolic potential.
5. Patient education is required for appropriate medication.
6. A potential decrease in systemic accessibility.
7. Poor connections between in vitro and in vivo

ASSESSMENT REQUIREMENTS TO INCLUDE THE MEDICATION IN A SUSTAINED RELEASE DOSAGE FORM:

Certain physicochemical factors, namely the understanding of the drug's absorption process from the gastrointestinal (G.I.) tract, are included in the selection of the medication to be manufactured in sustained release dosage form. (Brahmankar D.M., 2009) (Bhargava A., 2013) (Chauhan M.J., 2012)

Physicochemical parameters for drug selection

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

Pharmacokinetic parameters for drug selection:

Parameters	Comment
Absolute bioavailability	Should be 75% or more
Apparent volume of distribution (Vd)	Larger Vd and MEC, Larger will be the required dose

Elimination half-life	Between 2 to 8 hrs
Absorption rate constant (K_a)	Must be higher than release rate
Total clearance	Not depend on dose
Elimination rate constant	Required for design
Therapeutic concentration (C_{ss})	The lower C_{ss} and smaller V_d , the loss among of drug required.
Toxic concentration	Apart the value of MTC And MEC safer the dosage form

Drug Release Mechanism in Sustained release tablet:

The controlled release of drugs from sustained-release tablets occurs through various mechanisms, which include:

- Diffusion-Controlled Release: The medicine releases progressively as it diffuses through a matrix or polymeric membrane.
- Dissolution-Controlled Release: A delayed release profile is achieved by incorporating the drug into a slowly dissolving carrier.
- Osmotic Pressure-Based Release: Osmotic pump systems work by allowing water to enter the tablet, dissolve the medication, and force it out through a hole that has been laser-drilled.
- Erosion-Based Release: As the tablet gradually erodes in the digestive system, the medication is continuously released. (Ainurofiq & Choiri, 2015)

The formulation and design of an oral sustained-release medication delivery system (VH., 1987) (NR., 1990) (Brahmankar D.M., 2009) (Rane M, 2010) (Sampath KP, 2010)

Because of its adaptability in terms of dosage form, design, and patient compliance, the oral mode of administration is the most popular. However, in this case, one must consider the different pH levels that the dosage form would experience while in transit, the motility of the gastrointestinal tract, and the enzyme system and how it affects the drug and the dosage form. To provide a delayed release of the medication into the gastrointestinal environment, the majority of oral sustained release systems rely on diffusion, dissolution, or a combination of the two processes. A sustained release delivery system should, in theory, release the medication through a zero-order mechanism, producing a blood level time profile that is comparable to that following an intravenous constant rate infusion.

Numerous classes of sustained drug delivery systems have been developed in an effort to provide sustained (zero-order) medication release.

1. Diffusion sustained system.
 - i) Reservoir type
 - ii) Matrix type
2. Dissolution sustained system.
 - i) Reservoir type.

- ii) Matrix type
- 3. Methods using Ion-exchange.
- 4. Methods using osmotic pressure.
- 5. pH-independent formulations.
- 6. Altered density formulations.

Diffusion sustained system:

The migration of drug molecules from an area of higher concentration to one of lower concentration is essentially depicted by the diffusion process. In the direction of decreasing concentration, Fick's law provides the flux of the drug J (in amount/area - time) across a membrane.

$$J = -D \frac{dc}{dx}$$

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

In common form, when a water-insoluble membrane encloses a core of drug, it must diffuse through the membrane.

The drug release rate dm/dt is given by

$$dm/dt = ADK\Delta C/L$$

Where: A = Area;

K = Partition coefficient of the drug between the membrane and the drug core.

L = Diffusion path length (i.e., thickness of coat).

ΔC = Concentration difference across the membrane.

Reservoir Type

A water-insoluble polymeric substance encloses a drug core in the system, which the drug partitions into the membrane and exchanges with the fluid around the particle or tablet. Other drugs then enter the polymer, diffuse to the periphery, and exchange with the surrounding media.

Matrix Type

The pace at which a solid drug diffuses, rather than the rate at which the solid dissolves, determines the rate at which the drug is released from an insoluble matrix. Higuchi has calculated the proper medication release equation for this system:

$$Q = D\epsilon / T [2A - \epsilon C_s] C_s^{1/2}$$

Where, Q = Weight in gms of drug released per unit area of surface at time t .

D = Diffusion coefficient of drug in the release medium.

ε = Porosity of the matrix. C_s = Solubility of drug in release medium.

T = Tortuosity of the matrix.

A = Concentration of drug in the tablet, as g/ml.

Dissolution Sustained Systems:

A medication with a slow rate of dissolution is naturally maintained, and for medications with a high water solubility, dissolution can be reduced by the creation of the proper salt or derivative. The manufacturing of enteric-coated dosage forms is where these systems are most frequently used. A coating that dissolves in alkaline or natural media is used to shield the stomach from the effects of medications like aspirin. This prevents the medication from leaving the device until it reaches the intestine's higher pH. Enteric-coated dose forms typically have a helpful role in guiding medication release to a specific location but are not genuinely sustaining in nature. The similar strategy can be used for substances that are broken down by the hostile environment in the stomach.

Methods Using Ion Exchange:

It is based on the idea that when ionic resins and a ionic solution are kept in contact, a drug resin complex is created. The medication from these complexes is released along with the excess Na^+ and Cl^- in the gastrointestinal system after being exchanged there.

$\text{Resin}^+ - \text{Drug}^+ + \text{Cl}^-$ moves to $\text{Resin}^+ - \text{Cl}^- + \text{Drug}^+$, whereas $\text{Resin}^- - \text{Drug}^+ + \text{Na}^+$ goes to $\text{Resin}^- - \text{Na}^+ + \text{Drug}^+$.

Typically, these systems make use of resin compounds made of cross-linked polymers that are insoluble in water. They have functional groups that produce salt in repeating locations along the polymer chain. The amount of cross-linking agent used to make resins determines the region of diffusion, length of the diffusional path, and rigidity of the resin, all of which support the rate of drug diffusion out of the resin. The drug resin complex can be coated using a microencapsulation technique to further maintain the release rate.

Methods Using Osmotic Pressure:

Water can be transported into a tablet, particle, or drug solution by enclosing it in a semi-permeable membrane. The drug solution can then be pumped out of the tablet via a tiny delivery aperture in the tablet coating.

Osmotically sustained systems come in two varieties:

Type A has a medication and an osmotic core, whereas

Type B has a flexible bag with an osmotic core encircling the drug.

pH– Independent Formulations:

Due to its relatively short transit time, the gastrointestinal tract presents certain unique challenges for the oral route of drug administration. These challenges limit the length of prolongation, and the chemical environment along the gastrointestinal tract also limits the design of dosage forms. Since the majority of medications are weak bases or weak acids, sustained release formulations' release is pH-dependent. Buffers, such as citric acid, phthalic acid, phosphoric acid, tartaric acid, or salts of amino acids, can be added to the formulation to help maintain a steady pH and enable pH-independent drug release. In order to create a buffered sustained release formulation, an acidic or basic medication is combined with one or more buffering agents, then granulated using the proper pharmaceutical excipients and coated with a polymer that forms a permeable film for gastrointestinal fluid. Buffering chemicals bring the fluid inside the stomach to a proper, constant pH when it passes through the membrane, resulting in a steady rate of drug release (for example, propoxyphene in a buffered sustained release formulation), which greatly improves repeatability.

Altered Density Formulations:

It makes sense to assume that a delivery system would be of limited use unless it stays close to the absorption site until the majority, if not all, of its medication content is released. In order to achieve this, a number of strategies have been created to extend the drug delivery system's residence time in the digestive system.

EVALUATION TEST FOR SUSTAINED-RELEASE TABLETS: (The Indian pharmacopoeia, 2010) (Haresh M, 2013) (Jain D., 2011)

Hardness:

Each batch of tablets was subjected to a hardness test using a Monsanto hardness tester, and average values were determined.

Thickness:

The micrometer screw gauge was used to measure the tablet thicknesses.

Weight variation:

Twenty tablets were weighed individually and then collectively, average weight of the tablets was calculated.

Friability:

The Roche friabilator was used to assess the tablets' friability; it rotates at 25 rpm for four minutes.

Content Uniformity:

The quantity of the medication was determined using the calibration curve method with a UV-Visible spectrophotometer.

In Vitro Dissolution Study:

Rotating Paddles equipment is typically used to determine drug release studies. Buffer is primarily employed as a dissolving medium. The bath's temperature is kept constant at 37°C, and the same amount of the drug-releasing dissolving media is replaced with a needed sample obtained on a regular basis. The drug's release quantities are measured with a UV spectrophotometer. Plotting the percentage release against time shows the drug dissolved at the designated time.

Challenges:

Despite their numerous advantages, sustained-release tablets present certain formulation and regulatory challenges:

- **Complex Manufacturing Processes:** Advanced methods are needed to provide consistent release kinetics and homogenous medication distribution.
- **Variability in Drug Absorption:** Drug bioavailability may be impacted by variations in stomach pH, motility, and enzyme activity.
- **Dose Dumping:** If a formulation error occurs, the drug may leak quickly and become hazardous.
- **Problems with Cost and Stability:** Expensive excipients and extensive stability testing are necessary for certain sustained-release formulations. (Karvekar & Khan, 2017)

A major development in pharmaceutical science, sustained-release tablets provide better treatment efficacy, patient adherence, and general health advantages. A thorough understanding of drug characteristics, excipients, and release processes is necessary for the development of these formulations. Newer and more advanced sustained-release systems are anticipated to improve the accuracy and efficacy of medicine therapy as drug delivery research advances. (Nigusse et al., 2021)

Conclusion:

It is evident from the discussion above that sustained-release formulations aid to improve patient compatibility and dosage efficiency. Furthermore, the cost of all of these is affordable. The dosage form is simple to adjust and extremely beneficial when it comes to antibiotics, since overuse can lead to resistance.

Reference:

- Gopinath, H., Vedanthan, C., & Kumar.B, P. (2012). Formulation and evaluation of acebrophylline sustained release matrix tablets. *Journal of Chemical and Pharmaceutical Sciences*, 5(2), 56–61.
- Pareek, S. P., Kumawat, S., Sharma, V., Sharma, D., Rathore, D. S., & Agarwal, M. (2019). *Review Article Issn : 2349-2678*. 3.
- Zalte, H. D., & Saudagar, R. B. (2013). JPPT Review Article. *International Journal Of Pharmacy And Biological Science*, 3(4), 17–29.
- Brahmankar D.M., Jaiswal S B., Biopharmaceutics and Pharmacokinetics: Pharmacokinetics, 2nd Edn, published by Vallabh Prakashan, Delhi 399-401,(2009)
- Kumar S.K.P., Debjit B., Srivastava S., Paswan S., Dutta AS., Sustained Release Drug Delivery system potential, *The Pharma innovation*.1(2):48-60,(2012)
- Dusane A.R.,Gaikwad P.D., Bankar V.H, Pawar S.P., A Review on Sustain release technology, *International journal research in ayurvedic and pharmacy*.2(6):1701 1708,(2011)
- Lachman L, Herbert AL, Joseph LK. 1986.The theory and practice of industrial pharmacy. 3rd edition. Bombay Varghese publishing house; p. 430-55.
- Joseph RR, Vincent HLL. 1987.Controlled drug delivery fundamentals and applications. 2nd edition revised and expanded. New York: Marcel Dekker Inc; p.3-56.
- Wani MS. 2008. Controlled Release System- A Review; 6 (1): www.pharmainfo.net/review
- Kumar S.K.P., Debjit B., Srivastava S., Paswan S., Dutta AS., Sustained Release Drug Delivery system potential, *The Pharma innovation*.1(2):48-60,(2012)
- Remington: The Science and Practice of Pharmacy,21st Edn, Vol 1, Published by: Wolter Kluwer Health (India):939-964,(2006)
- Chugh I., Seth N., Rana A.C., Gupta S.,Oral sustain release drug delivery system: an overview, *International research journal of pharmacy*.3(5):57 62,(2012)
- Pundir S., Badola A.,Sharma D.,Sustained release matrix technology and recent advance in matrix drug delivery system : a review. *International Journal of Drug Research andTechnology*,3(1):12-20, (2013)

Bhargava A., Rathore R.P.S., Tanwar Y.S., Gupta S., Bhaduka G., oral sustained release dosage form: an opportunity to prolong the release of drug, International journal Page28 advanced research in pharmaceutical and bio science.3(1):7-14,(2013)

Chauhan M.J., Patel S.A., A Concise Review on Sustained Drug Delivery System and Its Opportunities, Am.J. Pharm Tech Res. 2(2): 227-238,2012

Ainurofiq, A., & Choiri, S. (2015). Drug release model and kinetics of natural polymers-based sustained release tablet. *Latin American Journal of Pharmacy*, 34(7), 1328–1337.

Lee V.H. 1987. Controlled Drug Delivery Fundamentals and Applications: Influence of drug properties on design, Marcel Dekker, 2nd ed, INC, New York; p.16-29.

Banker GS and Anderson NR. 1990. The Theory and Practice of Industrial Pharmacy: Tablet, Lachman, 3rd ed, Varghese Publishing House, Bombay; p.293-03.

Rane M, Parmar J, Siahboomi A R. 2010. Hydrophilic Matrices for Oral Extended Release: Influence of Fillers on Drug Release from HPMC Matrices. *Pharma Times* - Vol 42 - No. 04.

Sampath KP, Bhowmik D, Tripath KK. 2010. Innovations in Sustained Release Drug Delivery System and Its Market Opportunities. *J. Chem. Pharm. Res*, 2(1): p.349-60.

The Indian pharmacopoeia, 6th Edn, Published by the Indian Pharmacopoeia Commission, Ghaziabad:187 198 (2010)

Haresh M, Thimmasetty J, Ratan G N, Formulation Development and In-vitro Evaluation of Sustained Release Matrix Tablets of Risperidone, *Inventi Impact Pharma tech* (1):28-34,2013

Jain D., Shukla S.B, Formulation and Evaluation of Sustained Release Matrix Tablets of Isoniazid. A Comparative Aspect Based on Polymer. *Inventi Rapid: NDDS* 2011; 2(1)

Karvekar, M., & Khan, A. B. (2017). A Brief Review on Sustained Release Matrix Type Drug Delivery System. *Journal of Pharmaceutical Research*, 16(3), 282. <https://doi.org/10.18579/jpcrk/2017/16/3/118769>

Nigusse, B., Gebre-Mariam, T., & Belete, A. (2021). Design, development and optimization of sustained release floating, bioadhesive and swellable matrix tablet of ranitidine hydrochloride. *PLoS ONE*, 16(6 June), 1–16. <https://doi.org/10.1371/journal.pone.0253391>