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Review Article

An Overview Unsustained Release Formulations Using Solid Dispersion as Solubility Enhancement Technique.

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ABSTRACT

Biopharmaceutical classification system is important for determining the bioavailability of the drug. Drugs that dissolve slowly in water can be effectively solid-dispersed to increase their bioavailability. The bioavailability issue can be due to insufficient solubility of permeability. The poorly water-soluble medication dissolves more quickly when combined with the water-soluble carriers used to make solid dispersion. The review paper concentrates on the preparation techniques, benefits, drawbacks, and characterization of solid dispersion. Pharmaceuticals with sustained release have recently emerged as a very practical tool in medical practise, providing patients with a variety of real and perceived benefits. By minimising fluctuations in Using the therapeutic dose of the medicine in the body, sustained release is another promising reduction technique side effects. The major methods for creating tablets with a sustained release matrix are wet granulation, direct compression, or dispersion. In this review paper got the information about various polymers and different methods which are used for the formulate the sustained release tablet.

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INTRODUCTION

The simplest and easiest way of administering drugs is through oral route. Over other types of dosage forms the oral dosage forms have many advantages like accurate dosage, less bulk, greater stability and easy production is possible. Formulating poorly soluble chemicals for oral delivery is currently one of the biggest issues facing formulation scientists in the pharmaceutical industry.¹ The formulation of up to 50% of orally delivered medicinal compounds suffers from issues linked to their high lipophilicity and low solubility, which affects nearly 40% of novel chemical entities. After oral delivery, a medicine must dissolve in the stomach fluid in order to be absorbed into the systemic circulation.² The explanation for the medicine's limited bioavailability, however, is that it is a chemical that is weakly water soluble and dissolves slowly in gastric fluid with water. Such medications' One can improve solubility by mixing them with a hydrophilic carrier substance to create a substance known as a solid dispersion.³ By enabling continuous, regulated distribution and/or directing the medicine to the targeted place, new drug delivery systems play an important role in increasing the therapeutic effectiveness of included pharmaceuticals. Any drug delivery system's goal is to quickly

and sustainably achieve the desired by administering a therapeutic dose of the medicine to the desired location, The body's medication concentration is decreased The body's medication concentration is decreased. Prolonged release a solid dispersion method may improve bioavailability and be appropriate for formulations with prolonged release. Drugs with low bioavailability may benefit from continuous solid dispersion, which can effectively distribute them there while maximising their bioavailability and sustained action.⁴ A medicine that is not well soluble in water will take longer to dissolve in gastrointestinal fluid than it does to absorb into the digestive system.⁵ It can be assumed that traditional dosage forms, such as capsules and tablets, quickly release their active components into an absorption pool. In particular for those medications that require reasonably constant blood levels, spanning a considerable amount of time sustained release formulations were developed to avoid the need for numerous dosage regimens while achieving a prolonged therapeutic impact by continually releasing drug over an extended length of time after administration of a single dose.⁶

Solid Dispersion

To improve the absorption of medications that were poorly water-soluble, Sekiguchi et al. invented the idea of solid dispersion as early as 1961. It included melting the physical combinations of the pharmaceuticals and

the medication precipitated in water in a finely split form when the water-soluble carriers broke down, creating eutectic mixtures. Later, Goldberg et al. showed that some of the drug could also be molecularly transmitted in the matrix, generating solid solutions, while other researchers claimed that the drug could be incorporated in the matrix as amorphous materials.

Solid dispersion refers to the dispersion of one or more active compounds in an inert excipient or matrix, where the active chemicals may be present in finely crystalline, solubilized, or amorphous states. Considering these elements, Chiou and Riegelman defined solid dispersion.⁷

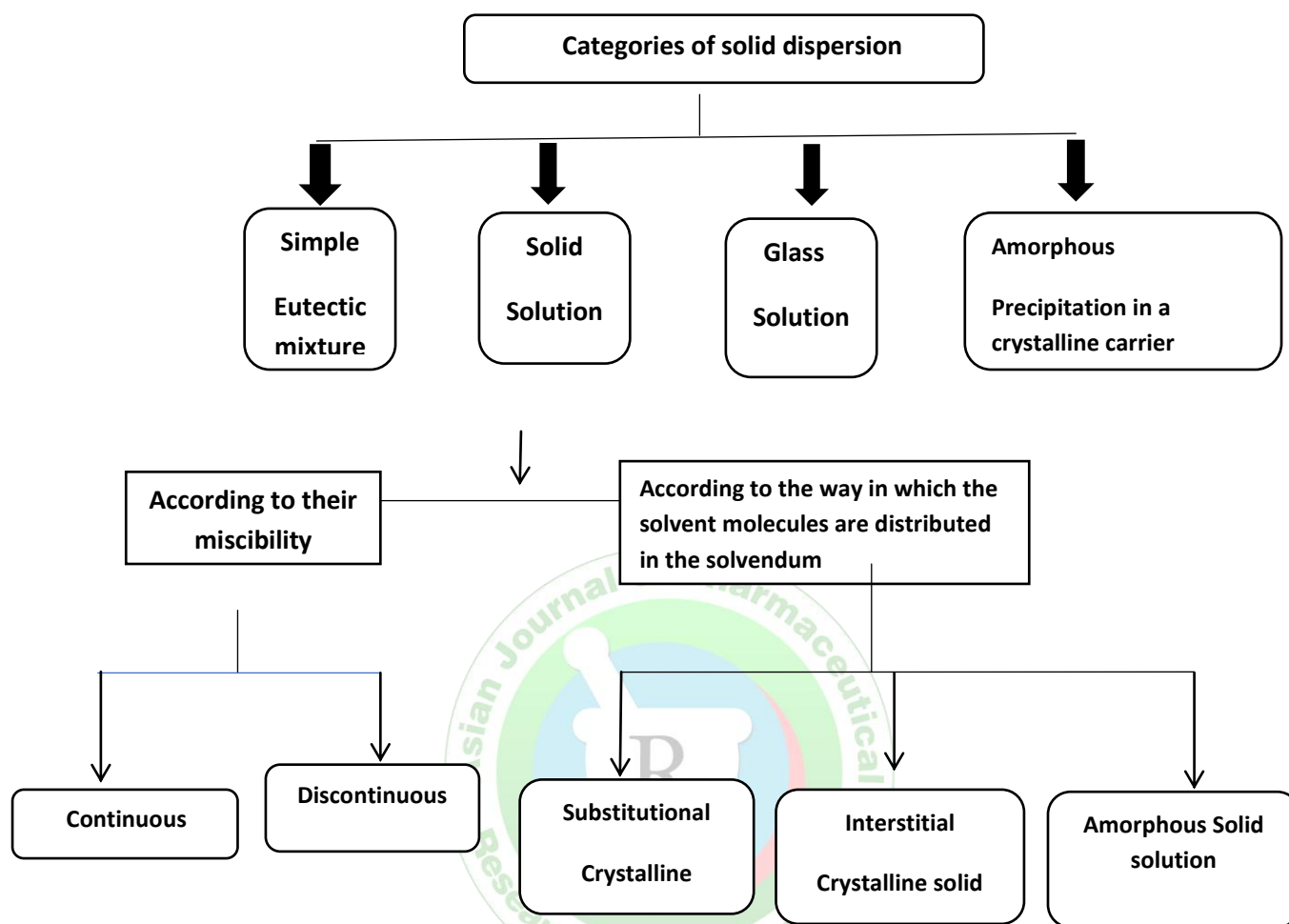


Figure: Categories of Solid Dispersion⁽⁸⁾

Types of solid dispersion

1. Depending on the carrier
2. Based on the way their molecules are arranged

Depending on the carrier, there are three generations of solid dispersion that can be identified.

First generation carriers:

acids are all crystalline carriers. They have the drawback of creating a thermodynamically in a state of liquid more crystalline solid dispersion that is stable and a slower drug release.⁽⁹⁾

Second generation carriers:

Polyethylene glycol, Polyvinylacetate, Polymethacrylate, and Povidone, and cellulose derivatives are examples of amorphous carriers.⁽¹⁰⁾

Third generation carriers:

Poloxamer 408 and Tween 80 are surface-active self-emulsifying carriers, as are Gelucire 44/14. With the use of these carriers, high polymorphism purity and improved in vivo bioavailability were successfully created.⁽¹¹⁾

Based on the way that their molecules are arranged

1) Eutectics Mixtures:

A simple eutectic combination consists of two chemicals that are completely miscible but only slightly miscible in the solid state. It is produced by quickly cooling a melt that fuses two components. that are totally miscible in liquid but hardly miscible in a solid-solid solution..^(12, 13, 14)

2) Amorphous solid solution:

The main difference between this and the drug precipitates out in an amorphous form in simple eutectic mixture.^(12,15,16)

3) Solid solution:

Solid solutions are similar to liquid solutions in that they only include one phase, regardless of the number of constituents. In the once the drug is broken down in a solid, the Particle size of the medication has been decreased to its molecular dimensions, and the rate of dissolution is governed by the carrier's rate of dissolution.^(12,16)

A) Continuous solid solution:

In a continuous solid solution, all ratios of the components are miscible. This implies, theoretically, that the molecules of the two components' individual molecules have stronger bonds than the molecules of the other

two components combined. Such solid solutions have not yet been documented in the pharmaceutical industry. ^(12,17)

B) Discontinuous solid solutions:

Each component is soluble within the second component to a certain extent, constrained in discontinuous solid solutions. According to Goldberg et al., the phrase "solid solution" should only be used when the mutual solubility of the two components surpasses 5% due to practical issues. ^(12,17)

C) Substitutional solid dispersions:

Only when the size of the solute molecules differs from the size of the solvent molecules by around 15% or less is substitution possible. The solute molecules in traditional solid solutions can either replace the solvent molecules within a crystal lattice or fit into the spaces between the solvent molecules due to the crystalline structure of the solution. ^(18,12)

D) Interstitial solid solutions:

In interstitial solid solutions, the dissolved molecules fill the gaps within a crystal lattice between the solvent molecules. Amounts of the solvent molecular diameter to the solute molecular diameter should not be greater than 0.59. ^(12,17)

4. Glass solution and suspensions:

Glass carriers dissolve the solute in a homogenous glassy system known as a glass solution. Glass suspensions are a mixture of which glass solvent is suspended with precipitated particles. Glass suspension and solution have substantially lower lattice energies ^(12,17,16)

Method of preparation of Solid dispersion

1) Melting method:

The "melting and fusion" technique involves mixing a medication physically with a water-soluble carrier, heating it until it melts. The fluid is melted first, then quickly solidifies in an ice bath while being stirred vigorously. After that, the resulting solid mass is pulverised, crushed, and sieved. ⁽¹⁹⁾

2) Solvent Evaporation Method

In an organic solvent, the drug and carrier are entirely dissolved before the solvent is evaporated. The resulting An object is crushed, strained, and dried. Ex. Solvent evaporation-based solid dispersion of ofloxacin with PEG ⁽²⁰⁾

3) Lyophilization technique:

With this technique, mass and heat are transferred away from the product that is being prepared. This method was put forth as an alternative to the solvent evaporation method. This particular molecular mixing method uses a shared solvent to simultaneously dissolve the carrier and the medication. To obtain a lyophilization molecular dispersion, this was followed by being frozen and sublimed. ^(21,22)

4) Kneading method:

A properly measured mixture and drug carrier is moistened with solvent and thoroughly mixed for a while in a glass mortar. The resulting paste is sieved and dried. It was used to make solid dispersions of, for instance, furosemide and crospovidone. ⁽²³⁾

5) Co-grinding:

A blender is used to physically combine the medicine and carriers at a specific pace. Then it is loaded into a ball mill chamber that vibrates. At room temperature, It is ground and gathered into a powder. This approach was used to create a solid dispersion of ex chlordinazepoxide and mannitol. ⁽²⁴⁾

6) Co-precipitation method:

The carrier is dissolved in water, the drug is in an organic solvent, dissolved, and then the aqueous carrier solution is added to the organic drug solution. The medication and carrier are co-precipitated to produce microscopic particles upon the addition of non-solvent. The resulting solid dispersion of microparticles is filtered and dried ⁽²⁵⁾

7) Spray drying

In this procedure, the medication and lipid carrier are carefully weighed out and then dissolved in methanol to produce a transparent solution. With the aid of a dryer, this solution is sprayed there on a lab size, creating a solid dispersion. ⁽²⁶⁾

8) Melting Solvent method:

It combines two techniques, involving the medication being dissolved in an appropriate solvent, mixing it with a molten carrier, and then cooling ¹⁵. The bulk that has solidified is broken down, ground up, and sieved. The benefit of this approach is that it lowers the maximum temperature and causes less thermolabile drug degradation ⁽²⁷⁾

Advantages of solid dispersion

Particles produced via solid dispersion have smaller particle sizes, which improve their surface area and speed up the dissolution process. Consequently, bioavailability is raised. ⁽²⁸⁾

The carrier utilised in the dispersion of solids significantly contributes to the particles' improved wettability. Increased solubility due to improved wettability raises bioavailability. ^(29,30)

Drugs are presented in solid dispersion as supersaturated solutions, which are regarded as metastable polymorphic forms. This enhances the particles' solubility by giving the medication an amorphous shape. ^(30,31)

Disadvantages of solid dispersion

- Their volatility is a significant drawback. As they age, they exhibit changes in crystallinity and a decrease in the rate of dissolution.
- Compared to physical combinations, solid dispersions are more susceptible to deterioration from temperature and moisture.
- Tackiness makes handling challenging ⁽³²⁾

Need of Solid Dispersion:

Solid dispersion formulations are relatively sophisticated drug delivery systems that demand a significant increase in time, effort, and money for development as compared to traditional tablet and capsule dosage forms.

Therefore, a careful in-vitro evaluation of the NCE's biopharmaceutical properties and the relevance of these findings to the projected in vivo formulation performance should be used to determine whether solid dispersion is required and whether other, more straightforward methods like salt production or particle size reduction could produce the requisite bioavailability increase.

Horter and Dressman characterised a weakly water-soluble medication a situation when the average passage time via the GIT's absorbent areas is longer than the dissolving time of a single dose in the GI fluids.

Therefore, intake of inadequately water-soluble substances is controlled by the rate of dissolution in the GIT and the solubility in GI fluids, which is dosage dependent. If the drug's component size or surface area is held constant, the fraction of the dose absorbed will decrease as there is a rise in dose, whereas if the dose size is held constant, the fraction of the dose absorbed will increase with a reduction in particle size or an increase in particle surface area. A typical tablet or capsule dosage form may still be possible if it is established that complete absorption of the dose can be achieved by lowering the particle size, for example, to between 2 and 5 micrometres (within the range of standard manufacturing capacity) ^(7, 33)

Sustained Release:

This category consists of any medication delivery device that offers delayed drug release over a long length of time, typically eight to twelve hours. Any dose type that releases medication slowly over time or indicates that the system is capable of exerting some real therapeutic control is said to be sustained release. The majority of the time, sustained release systems fall short of achieving zero order type release, but they do their best to imitate it by slowly releasing the drug use in first order.

Most methods typically approximate the optimum method of delivering an exact dose of medication at action location for an exact amount of time.

In other words, Drug withdrawal from the system is equal to the dosage of the medicine entering the system. This approximation is accomplished by preserving a constant concentration in the body or an organ over a prolonged period of time. The elimination process takes into account every type of metabolism and excretion, including faeces, perspiration, entero-hepatic recycling, and urine excretion. Due to the fact that most pharmaceuticals have a set rate of elimination. The plan is to continue delivering rugs at this rate for a while. This is represented mathematically as following,

$$\text{Rate in} = \text{Rate out} = \text{kelim} \times C_d \times V_d$$

Where,

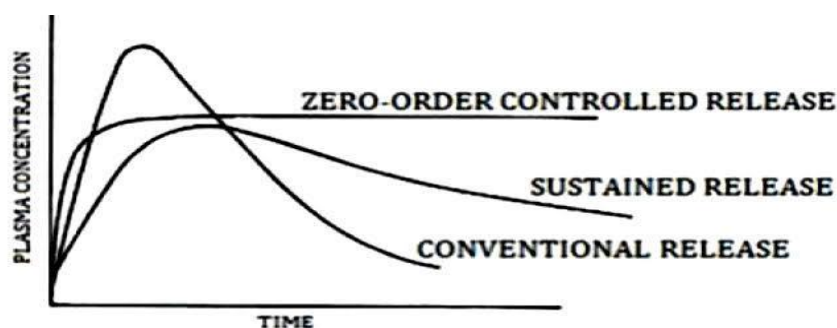
C_d is the desired drug level

V_d is the volume of distribution

Kelim is the rate constant of drug elimination from the body. ^(34,35)

Designing of Sustained Release Drug Delivery System

Due to its pleasant dosage form, layout, and attention to the needs of the patient, the oral route of administration is the most practical. Drugs taken orally are typically meant to permeate the overall circulation and perfuse to different bodily tissues; targeting is typically not a major consideration. Because of this, sustained release techniques are typically used. Before creating a sustained-release dosage form, it is important to consider a number of factors, such as the GIT's pH levels, gastrointestinal motility, and the impact of the enzyme system on both the dosage form and the drug. Figure 1 shows the plasma drug concentration profiles for three different formulations: traditional tablet or capsule, sustained release formulation, and zero order sustained release formulation. ⁽³⁶⁾



Plasma Drug Concentration Profile for Formulation of Sustained Release, Zero Order Controlled Release, and Conventional Release

Sustained Release solid dispersion tablet

Sr No	Drug	Polymer	Method of preparation	Comment	References
1.	Verapamil HCl	Carbopol, ethyl cellulose	Direct Compression Method	Better dissolution and absorption profile resulting in improved patient compliance	37
2.	Ziprasidone hydrochloride	Guar gum HPMC	Direct Compression Method	Ziprasidone hydrochloride from the sustained release solid dispersion tablets revealing the fickian drug transport mechanism.	38
3.	Carvedilol	HPMC K15 potato starch	Direct Compression Method	Release of carvedilol was markedly reduced when HPMC concentrations rose.	39
4.	Nintedanib	HP K4M, K15M, and K100M	Direct Compression Method	Compared to the reference, nintedanib sustained-release capsules had superior bioavailability and a sustained-release action.	40
5.	Ibuprofen	HPMCK100M HPMCK4	Direct Compression Method	Reduce the dosing frequency and improve the patient compliance.	41
6.	Glimepiride	Hydroxyl propyl methyl cellulose and ethyl cellulose	Direct Compression Method	The faster dissolution rate of the drug from the solid dispersion is attributed to the marked reduction in the crystallinity of the drug.	42
7.	Ibuprofen	Manlikara Zapota gum	Wet granulation	Manlikara Zapota Gum is a polymer that delays release. Drug distribution via the intestine is possible with it.	43
8.	Aceclofenacs	HPMC/guar gum	Wet granulation	Drug release was retarded with an increase in polymer concentration due to the gelling property of polymers	44
9.	Nilvadipine	hydrogenated soybean oil hydroxypropylcellulose	wet granulation	Without any re-crystallization, the release of NiD from DCMTs was successfully maintained.	45

10.	Losartan	polyethylene oxide	Direct Compression Method	The resulting SD-SR tablet revealed pH independent and linear release of 2 hours of LST in stomach fluid and continuously in intestinal fluid for 12 h	46
11.	Pelubiprofen	Eudragit® RL and Eudragit® RS, methacrylic resins	Blended mixture	<i>in vivo</i> absorption of SRSD was well-correlated with <i>in vitro</i> dissolution data, creating a high standard IVIVC A.	47
12	Ondansetron	Hydroxypropyl cellulose, Ethyl cellulose	Melt-granulation	The current study is its demonstration of the feasibility to continuously manufacture ready-to-compress melt granules of OND by a twin-screw extruder that can be processed into tablets to provide pH-dependent/pH-independent sustained release of the drug.	48
13.	Glipizide	Xanthumgum,,Guargum	Direct Compression Method	It was found that drug release rate decreased with the amount of polymer increased in formulation.	49
14	Lovastatin	HPMC K100M	Direct Compression Method	The sequence of swelling seen in these polymers (HPMC) might reflect the rates at which the preparations were able to absorb water and expand, according to the results of a research on water absorption (swelling) and erosion.	50
15	Metoclopramide	Eudragit RSPO, Eudragit RLPO and Guargum	Direct Compression Method	Increase the bioavailability and simultaneously decrease the dosing interval as well as dosing amount.	51
16.	Zidovudin	Sodium CMC, HPMC, EudragitL155, Xanthan gum	Wet granulation	It has also good drug entrapment efficiency stable Formulation could be developed by incorporating both hydrophilic and hydrophobic polymers in a definite proportion so that sustained release profile is maintained for an extended periods of time.	52
17.	Rabeprazole	HPMC-E15, Carbopol934, and sodium carboxymethyl cellulose	Wet granulation	Without anticholinergic or H2blocking activity, the inhibition of stomach acid secretion is dosage dependant. lower dosages with improved bioavailability and reduced dosing frequency	53
18.	Metformin hydrochloride	Eudragit RSPO, gum copal, gum damar,	Wet granulation	According to drug release data to the Korsmeyer equation, erosion and diffusion may be the mechanism of drug release.	54
19.	Nifedipine	HPMCE5 HPMCK100, Eudragit	Wet granulation	It was found that increasing the viscosity of the polymer has a delaying impact on the release from the matrix of the polymer.	55
20.	Baclofen	HPMC K4M, sodium alginate, HPMC K15	Wet granulation	Increasing the amount of HPMC and sodium alginate in solid matrix tablet decreased the release rate of the drug.	56
21.	Atenolol	HPMC,Sodium Carboxy Methyl Cellulose and Guar Gum	Wet granulation	CMC successfully sustains the release of Atenolol HCl for the period of 12 hrs. swelling study matrices containing a minimum Sodium CMC achieve higher Swelling Index.	57
22.	Levosulpiride	HPMC, HPC, and CMC sodium	Direct Compression Method	It can be concluded that the drug release could be further prolonged if the polymers are used in combination because of their possible interaction and subsequent cross-linking.	58
23	Flurbiprofen	Xanthan gum, Karaya gum, HPMC K- 100, Ethyl cellulose	Wet granulation	The developed sustained-release tablets of Flurbiprofen could perform superior to conventional dosage forms, leading to improve efficacy and better patient compliance.	59
24	Tramadol Hydrochloride	Gum Kondagogu HPMC	Wet granulation	Tramadol HCl dosage form could reduce the dosing frequency and improve patient compliance	60
25	Quetiapine Fumarate	HPMC K100M HPMC K15M Karaya gum and Xanthum gum, Guar gum	Direct Compression Method	The research study provided useful information for the formulation scientists on formulation, characterization during development of controlled drug delivery systems of Quetiapine Fumarate using these polymers	61
26.	Captopril	HPMC K100, ethyl cellulose and sodium CMC	Direct Compression Method	The efficacy of captopril as the first choice of the drug with antihypertensive action after oral dosing is limited to only 6-8 hrs. Therefore, clinical use requires captopril to be taken three times daily.	62

27.	Repaglinide	HPMC (K4M, K100M, K15M) Croscarmellose	Wet Granulation	Repaglinide sustained release matrix tablets were successfully prepared by using various grades of HPMC as polymer to retard the release and achieve the retard dissolution profile.	63
28	Aceclofenac	Xanthan gum, Ethyl cellulose	Direct Compression Method	With repeated administration of standard Aceclofenac, the sustained release tablets are anticipated to minimise both the frequency of administration and the dose-dependent adverse effects.	64
29.	Diclofenac Sodium	HPMC K4M and acacia gum	Direct Compression Method	The drug polymer ratio was found to influence the drug release, as the polymer level increased, the drug release rates were found to be decreased.	65
30	Oxprenolol Hydrochloride	Carrageenan, Oryza Sativa and Gum	Direct Compression Method	The study reveals that the sustained release of Oxprenolol Hydrochloride is possible for choosing the Oryza sativa (natural polymer) as matrix former also shows anomalous diffusion.	66

Rationale for sustained release:

- Drugs that are frequently repeated at predetermined intervals in order to maintain therapeutic levels in the blood or blood tissues.
- Achieved uniform medication response utilising various dose combinations and dosage intervals.
- However, when the therapeutic effect is sustained for the necessary length of therapy at the lowest frequency of administration, the dose regimen of an oral medication may be considered to be optimal.
- Side effects are caused when a dose is administered often. ⁽⁶⁷⁾

Advantages of sustained release drug delivery system

- Greater patient comfort and compliance because medication is administered less frequently
- Less variation at the steady-state level, which leads to better illness condition control.
- Greater safety margin for drugs with high potency as a result of improved plasma level management.
- Maximum medication utilisation allowing for a reduction in the overall dose given.
- Lower health care costs due to more effective therapies and shorter treatment times

Disadvantages of sustained release drug delivery system

- Lower systemic availability compared to typical, immediate-release dose forms.

This might be because

- Unfinished release
- Site-specific absorption, pH-dependent solubility, increased instability, enhanced first-pass metabolism, etc.

- Insufficient in vivo-in vitro connection.
- The potential for dosage dumping.
- In cases of toxicity, poisoning, or hypersensitivity reactions, retrieval of the drug is challenging.

CONCLUSION

It can be difficult to improve a drug's bioavailability when it is poorly soluble. Because the drug has poor aqueous solubility, it has dissolution issues that reduce in vivo absorption and, in turn, bioavailability. As a result, the drug is unsuitable for oral consumption, necessitating the need for solubility enhancement for such a drug candidate. The most straightforward and effective method for improving a drug's aqueous solubility is solid dispersion.

The composition of sustained-release matrix tablets, their benefits and drawbacks, and the various polymers utilised to create such systems were the main topics of this review paper. The conclusion of the above discussion is that matrix tablets are useful for overcoming patient compliance issues and dose form effectiveness in eliciting desired

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