INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Supersaturated Drug Delivery System: An Approach To Enhance The Bioavailability

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ARTICLE INFO

Received: 03 Feb 2024
Accepted: 05 Feb 2024
Published: 06 Feb 2024
Keywords:
Supersaturation, Bioavailability, Solid dispersion, pH.
DOI:
10.5281/zenodo.10625380

ABSTRACT

An innovative technique for medication delivery is the supersaturated drug delivery system, which uses the drug's supersaturated condition in the gut to increase the drug's bioavailability. Low bioavailability, when taken orally, is caused by weak bases decreasing solubility as pH rises. Some excipients were utilized to stop or postpone the precipitation that occurs when there is change in pH. The purpose of this study is to analyze SDDS with a focus on its prospects for the future and its current advancements. This review's objectives were to compile the most recent findings on supersaturated drug delivery systems (SDDS). The most recent developments in SDDS, including the formulation of characteristics, are thoroughly explored. This review paper aims to give a thorough understanding of the biopharmaceutical foundation of the supersaturated drug delivery system. Because of their higher solubility and enhanced saturation, supersaturated drug delivery systems improve drug absorption as well as its bioavailability. This reviews the scientific and technological advancements in systems.

INTRODUCTION

The BCS Class II drugs are very permeable but have limited solubility. The breakdown of these drugs may be a rate-limiting stage in the absorption process, even while permeability does not limit absorption.

Super saturable formulation

When super saturable formulations come into contact with the aqueous environment of the gastrointestinal tract, they can cause a supersaturated drug concentration. For medications to be absorbed in the intended amount of time, supersaturation needs to be created and sustained. Several variables affect formulation performance, including the compound's physicochemical characteristics, the methods of processing employed, and the drug's propensity to generate and retain a supersaturated solution. 1

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Saturated Drug Delivery System:

A maximum limit to the drug solubility may be reached in a saturable drug delivery system. This system usually functions within the drug's solubility limit; adding more medicine will not cause it to dissolve or absorb it more readily. Several variables, including pH, temperature, and the inclusion of additional excipients, may have an impact on the solubility limit. In a saturated drug delivery system, the medication is pre-dissolved to the fullest extent possible in the solution. When the solution reaches saturation, the medication will no longer dissolve in the specified conditions. Sometimes reaching a saturated condition is desirable, particularly if it guarantees a steady state and predictable medication concentration. Amorphous solid dispersions (ASDs), nanoparticulate systems, and lipid-based delivery systems are examples of supersaturated drug-delivery systems (SDDS) that are frequently employed to improve the solubility and oral bioavailability of poorly water-soluble medications. For a long enough duration until absorption happens through the intestinal membranes, supersaturation keeps the drug concentration in the gastrointestinal (GI) lumen above its equilibrium solubility. The supersaturated drug delivery method can improve bioavailability by increased Solubility, Improved Dissolution Rate, and Enhanced Absorption. Supersaturation functions as a driving force for the absorption of medicines by passive diffusion.

However, precipitation results from the nucleation and crystal formation of medicines in their supersaturated state, further limiting their absorption. Precipitation inhibitors are therefore used to prevent medications from precipitating too soon in the gastrointestinal tract. 2-9

Supersaturation

Supersaturation is the driving force for crystallization comprising two steps –

- Nucleation
- Crystal growth.

The degree of supersaturation or supersaturation index (SI) is calculated by the equation:

Degree of supersaturation (SI)=Csol /Ceq

Where,

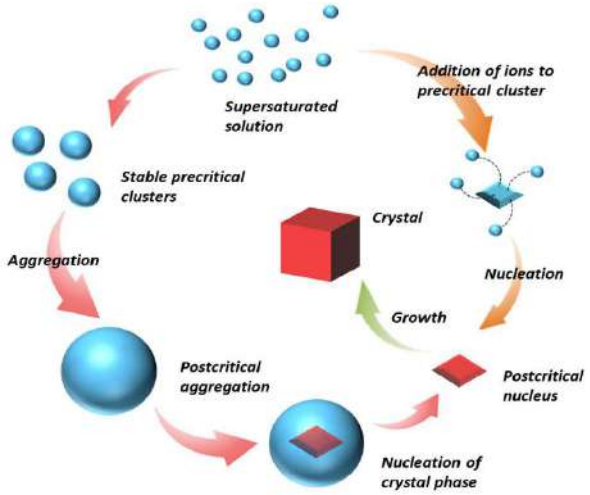
Csol is the drug concentration in the solution and

Ceq is the drug in equilibrium solubility.

A solution can be defined by the value of SI as undersaturated (S < 1), saturated (S = 1), and supersaturated (S > 1). Both the solvent shift method and the pH shift method can be used to study supersaturation. Drop by drop, a concentrated drug solution in an organic solvent or at a pH at which the drug is soluble is added to the precipitation medium (relevant media, simulated gastric/intestinal fluid), and the drug begins to precipitate until equilibrium is reached due to a change in solubility. Supersaturation assay can be done both in the presence and absence of polymer and evaluate the capacity of polymers to inhibit precipitation.10

Crystallization

The process of solute mass transitioning from a liquid to a solid form is called crystallization. The process of crystallization starts with nucleation, which is the arranging of tiny ions and molecules for crystal growth. Crystal growth starts when the number of nuclei grows to a critical value and creates small crystals at first before growing into bigger crystals.11



The crystallization process is divided into two distinct stages/processes:

- Nucleation
- Crystal growth.

Growth and nucleation happen simultaneously, with the relative contributions of the two processes determined by the external environment. As a result, the system always contains a polydisperse mixture of particle ages and sizes. Many compounds can crystallize into a variety of polymorphs or crystal shapes; the polymorph that forms may just be kinetically preferred and not always the most stable. The solute solubility, the degree of supersaturation, the rate at which supersaturation is formed, diffusivity, temperature, and the sensitivity of surfaces toward nucleation all influence the rate and process of crystallization. 12,13

Crystal growth is generally considered to occur in the following four stages

1. Molecules are transported by bulk diffusion to the developing surface, where they are captured on the crystal face terrace.
2. Molecules adsorbed on the terrace migrate to the step-through surface diffusion, where they are caught.
3. Molecules adsorbed on the step migrate to the kink site and integrate into the crystal's kink structure.
4. Transfer of solvent molecules from the desolvated molecules in the preceding steps, as well as the reaction's generated heat.14

Nucleation

The process of solute molecules separating from the solution—known as the "birth of small nuclei"—is the first step in nucleation. Supersaturated solutions tend to crystallize and move toward equilibrium.

Nucleation is further divided into

- Primary and
- Secondary nucleation.

Primary nucleation lacks a crystalline surface whereas secondary nucleation occurs in the presence of a surface and is affected by environmental and processing conditions. 11

Kinetic of Solubility Studies.

Kinetic solubility tests are conducted using distilled water and a shaking water bath equipment running at 100 rpm to maintain a temperature of 370± 0.5°C. An excess of 20 mg of solid was added to 15 mL of water, and up to six hours later, aliquots of one millilitre were taken out at prearranged intervals. All of the samples were immediately centrifuged for 10 minutes at 15,000 rpm. The supernatant is then extracted, diluted, and HPLC can be used to determine the drug content.38

Precipitation inhibitors

When PPIs are present, it is typical for crystal habits to change. It has been demonstrated that the selective adsorption of the polymer to distinct crystal faces is the cause of the change in crystal habit. Moreover, Guo et al. discovered that several polymeric additives were efficient in preventing calcium oxalate monohydrate from crystallizing or dissolving. AMG 517 generated an amorphous drug when precipitated in the presence of HPMC, whereas crystalline drug precipitated in the presence of PVP. This is the sole known instance in which the presence of a PPI led to the development of an amorphous drug precipitate.15,16

Crystallization Inhibition Studies

UV-extinction measurements are used to estimate the nucleation induction time of nevirapine in the presence and absence of dissolved polymer. The investigations on crystallization inhibition were conducted on supersaturated nevirapine solutions (500 µg/mL) that contained either 0.1% PVPVA or 0.05% HPMC-AS, without any polymer. By utilizing a UV dip probe to quantify the induction time, which is the total of the real nucleation induction time plus the time needed for the crystals

to grow to a detectable size, the formation of crystals was identified from the increase in extinction at 400 nm.17

Polymeric precipitation inhibitors

For uses in oral drug delivery, PPIs seek to keep the medication in a supersaturated, thermodynamically unstable state (metastable) for a long enough duration to permit absorption. Because of this, their impacts are often kinetic and only serve to slow down the precipitation process by preventing nucleation or crystal formation. On the other hand, changes in the thermodynamic (equilibrium) features of the system are less frequent. PPIs major method of action is consequently not via co-solvency and they do not often promote equilibrium solubility. In contrast, surfactants, for example, are also capable of avoiding drug precipitation but normally do so via increases in drug solubility arising from micellar solubilization.

Polymeric Precipitation Inhibitor screening techniques

A method that creates a supersaturated aqueous phase where precipitation can happen and an analytical approach to measure the amount of material that precipitates over time are needed to screen possible inhibitors of polymeric precipitation. 18

Solid dispersion

Drug molecules or solid-state micro-fines dispersed in an inert, biocompatible crystalline, or amorphous carrier are known as solid dispersions.35

Advantages of Solid Dispersion

1. Particles with smaller sizes are produced during the preparation of solid dispersions, increasing their surface area and dissolving rate. The end outcome is increased bioavailability.
2. The process of producing solid dispersions improves wettability. Solubility rises with improved wettability. In this case, the carriers are mostly responsible for increasing the particles' wettability.
3. It has been discovered that particles in solid dispersions have a greater porosity level. The medication release profile is accelerated by the solid dispersion particles' enhanced porosity. The carrier characteristics also affect increased porosity.
4. Drugs are shown as supersaturated solutions in solid dispersions, which are regarded as metastable polymorphic forms. As a result, giving medications in an amorphous state makes the particles more soluble. 36

Disadvantages of Solid Dispersion

1. Poor scale-up for manufacturing.
2. Laborious and expensive methods of preparation.
3. Reproducibility of physicochemical characteristics.
4. Difficulty in incorporating into the formulation of dosage forms.
5. Stability of the drug and vehicle. 37

Transmission Electron Microscopy Analysis

Transmission electron microscopy (TEM) is used to assess the size and shape of the generated SD. The foundation of TEM investigation is the passage of electron beams through incredibly thin nanoparticulate materials. Using negative materials like phosphotungstic acid/uranyl acetate, homogeneous sprays of drug-loaded or drug-unloaded SDs (with a 0.5% w/v concentration) were applied to formvar-coated copper grids, and the results were monitored after the SDs had completely dried by air. To ensure that the samples would not break under the instrument's vacuum, sample fixation was done. 19

Scanning Electron Microscopy (SEM)

A scanning electron microscope usually operating at an acceleration voltage of 15 kV and with appropriate magnification at room temperature can be used to study the morphology and surface topography of the prepared SDs. In short, the

samples are placed on silicon wafers with a diameter of 5 mm, and then Au was sputter-coated in an argon atmosphere. Specimens need to be electrically grounded to avoid the buildup of an electrostatic charge at the surface and electrically conductive, at least on the surface, to be imaged in the SEM. Therefore, before being exposed to electron scanning, the optimized, SDs were Au-coated. 20,21

In Vivo Studies

Supersaturation is difficult to measure in vivo directly, particularly in humans, unless the supersaturating medication is aspirated into the gastrointestinal tract. The majority of researchers use oral drug delivery followed by blood concentration measurements to assess supersaturation in biological bodies. Intestinal perfusion is utilized in several animal supersaturation experiments.

Oral Absorption

Rats and dogs are the most often utilized pharmacokinetic study animals. Studies on the bioavailability of supersaturate formulations have also been conducted on pigs and rabbits. Although it is simple to raise rats, it is difficult to give them a solid, supersaturable diet. Before gavage, supersaturate SMEDDS could be uniformly combined with water. For ASD and mesoporous material-based dosage formulations, it is recommended to choose dogs or pigs for oral administration. For instance, oral gavage of pre-emulsified supersaturate SMEDDS formulations was regularly administered to Sprague-Dawley and Wistar rats, and blood samples are taken at predetermined intervals. Hard pills can be given orally to the dogs, and within 24 hours, blood samples are taken. It was observed that supersaturate ASD increased 1.8-fold in the AUC.

Intestinal Perfusion

Intestinal perfusion may give rise to a method for measuring drug supersaturation in the gastrointestinal system in addition to providing access to regularly used permeability and absorption data. To replicate the actual state in vivo, the perfusate should use bio-relevant media. Furthermore, because the effluent would dilute and disrupt the supersaturation, the intestinal perfusion study on supersaturation should be carried out in a single pass rather than in circulation. The gastrointestinal system could be perfused in various sections, correspondingly. For instance, in situ single pass jejunal perfusion studies were performed on Sprague-Dawley rats. In order to measure drug flux via the relevant isolated portion of the rat's jejunum without the interference of hepatic first-pass metabolism, mesenteric blood can be simultaneously drawn.

To replicate the upper gastrointestinal tract, the intestinal infusion can be used in conjunction with an in vitro dissolving device. For example, the fluid in the duodenum chamber of the GIS was utilized to perfuse C57BL/c mice from the proximal jejunum.

Intestinal Content Aspiration

The most direct method of accessing the supersaturation and precipitation process in the human gastrointestinal system is to aspirate the intestinal content with dissolved medication for concentration assessment. The double-lumen polyvinyl catheters can be inserted through the mouth or nose, placing them in the stomach's antrum and the small intestine's duodenum. Utilizing fluoroscopic imaging, the catheter positions can be verified. In a similar method, one can slowly the impact of key GI circumstances (fasted state, fed state and fasted state with simultaneous proton pump inhibitor) on the intraluminal dissolution and supersaturation behavior. It is suggested to introduce a fiber optic detecting technology into endoscopes or other in situ instruments for intestinal content detection. It goes without saying that the fiber optical probe needs to be modified to be both flexible and long

enough to fit through the gastrointestinal tract. 22-31

Estimation of drug content

A formulation corresponding to dose of the drug was weighed and appropriately diluted using deionized water. The amount of drug in each formulation will be computed based on the measured absorbance.

Differential Scanning Calorimetry

To produce appropriate thermograms, differential scanning calorimetry can be carried out using a Differential Scanning Calorimeter. An empty aluminium pan is used as a reference, and the precisely weighted sample is placed. Under nitrogen flow, the experiment is run at a scanning rate of 300C/min in the 50–3500C range.

Infra-red spectrum

Using an infrared spectrophotometer, infrared experiments were conducted to rule out interactions between the drug and the carrier utilized in the formulation of the solid dispersion using the potassium bromide disc method.

Dissolution Studies

The purpose of the in vitro dissolution experiments is to assess how quickly solid dispersions dissolved in comparison to pure drugs and physical mixes. The test was run in a USP paddle device with 900 ml of phosphate suitable medium at 370 + 10 C and suitable pH .32

Stability Studies.

The physical stability of ASSD formulations and binary Amorphous Solid dispersions under ambient conditions in closed containers shall be assessed. The samples are analyzed using DSC to find the melting endotherm in the event that such crystallinity was detected in the amorphous formulations, and by polarized light microscopy to detect birefringence, which indicates the presence of crystallinity in amorphous formulations.38

Drugs used in the supersaturated drug delivery along with precipitation inhibitors 33,34

Sr No.	Precipitation inhibitors	Model drug	References
1	PEG 6000, PVP, HPMC	Tacrolimus	Yamashita et al.
2	PEG 6000, PVP, HPMC	Paclitaxel	Gao et al.
3	HPMC H SOL	Candesartan, Cilexetil	Tang, B et al.
4	Eudragit EPO	Trimethoprim, sulfamethoxazole	Dokania, S et al.
5	SOL SLS	Chlorthalidone	Herpin, M.J et al.
6	Saccharin	Griseofulvin	Chavan, R.B et al.
7	HPMC	Magnolol, AMG009	Pinto et al.
8	PVP K17	Indirubin	Chen et al.
9	PVP	Carbamazepine	Zhang et al.
10	HPMCAS	Butyl paraben	Tajarobi et al.

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HOW TO CITE: Manoj R. V., Parthasarathi K. Kulkarni, Nagendra R., Venkatesh K. , Supersaturated Drug Delivery System: An Approach To Enhance The Bioavailability, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 2, 145-153. https://doi.org/10.5281/zenodo.10625380