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EXPLORING THE ROLE OF POLYMER PRECIPITATING INHIBITORS IN SUPERSATURATED SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM -AN OVERVIEW

Naishan*[1], N. S. Ganesh[1], Vineeth Chandy[1], N. Keerthana[1]

[1*]Department of Pharmaceutics, T. John College of Pharmacy, Banglore-560083, Karnataka, India.

ABSTRACT

The incorporation of particular polymers into lipid-based formulations, such as self-nano emulsifying drug delivery systems, can sustain drug supersaturation after vehicle dispersion and/or digestion. Precipitation due to supersaturation and intraluminal solubilization behaviour has a significant impact on bioavailability, particularly for weak basic drugs. As a result, bioavailability improves. By interactions with poorly water-soluble and weak base drugs, polymers can be used to limit precipitation. This review presents an overview of the different types of precipitation inhibitors, drug precipitation mechanisms, describes the mechanisms by which precipitation may be inhibited, evaluation of supersaturated drug delivery system where PPI's are incorporated, role of polymer precipitation inhibitors and recent applications of snedds.

KEYWORDS

Self-Emulsifying Drug Delivery System (SEDDS), Supersaturated Self-Nanoemulsifying Drug Delivery Systems (S-SNEDDS), Self-Microemulsifying Drug Delivery System (S-SMEDDS) and Polymer precipitation inhibitors.

Author for Correspondence:

Naishan,
Department of Pharmaceutics,
T. John College of Pharmacy, Banglore-560083,
Karnataka, India.

Email: naishankm123@gmail.com

INTRODUCTION

The increasing number of poorly water-soluble compounds resulting from current drug development programmes necessitates a new territory in medicine administration. Among these approaches, lipid and surfactant-based drug delivery systems, particularly self-emulsifying drug delivery systems (SEDDS), are promising[1]. The self-emulsifying formulation is an isotropic combination of medication, lipids, surfactants, and co-solvent that produces a superfine emulsion when agitated in the GI tract[2]. SEDDS are classified into two

categories based on the size of the globules generated during dispersion: SMEDDS and SNEDDS[3].

SMEDDS are formulations that produce a transparent oil-in-water or water-in-oil microemulsion with a globule diameter of 250nm. SNEDDS have transparent droplets with a size between 20 and 200nm[4]. SNEDDS is a competent, well-designed, and patient-acceptable approach for sparingly soluble pharmaceuticals because it improves solubility, dissolution patterns in the GI tract, permeability, and absorption[5].

SNEDDS is thermodynamically stable and consists of the medication and SNEDDS preconcentrate (combination of oil, surfactant, and co-surfactant)[6]. It enhances drug delivery by increasing the permeability or transport of less permeable medicines, decreasing the activity of intestinal efflux transporters, reducing drug degradation in physiological milieu, and boosting drug absorption via the intestinal lymphatic pathway[7].

The extent of drug solubility in excipients used for SNEDDS formulation determines the dosage of drug loading. The solubilizing capacity of SNEDDS is diminished due to a decrease in lipid content, which causes drug precipitation. Drugs that are highly soluble in surfactants or co-surfactants than lipophilic phase precipitate quickly as the solvent capacity of these excipients decreases with dilution. Hence, the majority of SNEDDs formulations contain drugs lower than equilibrium solubility. The presence of high concentrations of hydrophilic surfactants also aids in drug precipitation. To overcome this drawback, S-SNEDDS comprising hydrophilic precipitation inhibitors (PIs) were studied[8].

These S-SNEDDS achieve a metastable saturated state, which prevents drug precipitation in the GI tract. This mechanism involves the incorporation of water-soluble polymeric PIs (PPIs), resulting in a prolonged precipitation time in compared to the mean absorption time[9].

ADVANTAGES OF SUPERSATURATED SNEDDS[10-12]

S-SNEDDS retards the precipitation of crystalline drugs on GIT due to precipitation inhibitors.

S-SNEDDS has high loading dose (150%-200% of equilibrium solubility of drugs) compared to snedds (50%-90% of equilibrium solubility of drugs).

S-SNEDDS has more bioavailability compared to SNEDDS

S-SNEDDS requires low amount of surfactant and it is less toxic and has more half-life.

S-SNEDDS has large surface area for enhanced drug solubilization and dissolution.

S-SNEDDS iscost effective, ease to manufacturing and scale up.

S-SNEDDS formulation with optimal droplet size and zeta potential improves oral absorption.

S-SNEDDS is promising approach for poorly soluble and permeable drug candidates belong to BCS class of II, III and IV.

PRECIPITATING INHIBITORS

For supersaturating formulations, nucleation of the generated supersaturated solution would be highly probable, if the formulation was not stabilised by addition of PIs. If the precipitation process is arrested for physiologically relevant time periods, the supersaturated state can be sustained long enough for enhanced absorption[13]. Surfactant, polymers and cyclodextrins have been investigated as excipients that can sustain the supersaturated state[14]. Polymeric PIs and non-polymeric PIs are the two major types of precipitation inhibitors. Most PIs are polymers. As a result, they may be categorised as polymeric PIs(PPIs)[15].

PPIs are classified into two types: surface-active and non-surfaceactive. Surface-active PPIs include cremophor EL, polyethylene glycol 1000 succinate (TPGS), D-tocopherol and poloxamers. Concentrations exceeding critical micelle concentration (CMC) are primarily responsible for the precipitation inhibitory effect of surface-active PPIs, and they may also enhance the drug's solubility in equilibrium state. Surface-active PPIs can improve the bioavailability of poorly water-

soluble drug's by maintaining supersaturation and providing high equilibrium solubility. If surfactants are adsorbed on a surface of a nucleus, however, there may be an undesired increase in nucleation rate. Surfactant reduces the interfacial tension between the surface and the solvents. PPIs (non-surface active) are further classified into cellulosic and non-cellulosic. CMC, HPMC, MC, acetate phthalate, alginic acid, cellulose, hydroxyl ethyl cellulose, HPC, Na-CMC, HPMC-AS, and arabic gum are cellulosic PPIs; poly(vinylpolypyrrolidone), polyvinylpyrrolidone vinyl acetate, polyvinyl alcohol and Eudragit are non-cellulosic PPIs. Utilizing PVP and its derivatives to prevent precipitation of pharmaceuticals manufactured as supersaturated solid particles and SDDSs has been found to be an effective technique[16].

SURFACTANTS AS PRECIPITATION INHIBITORS

Surfactants are well known for their capability of increasing drug solubilization and decreasing the degree of supersaturation. Some of the surfactants, such as Pluronics, TPGS, SDS, Cremophor® RH40 and Tween® 20, have also been explored for their capability to delay precipitation from supersaturated solutions[17]. Surfactants have the ability to reduce supersaturation and so limit precipitation by increasing the solubility of the API. For surfactants this can occur via micellar solubilisation and complexation, respectively. As a result, surfactants often been called as thermodynamic precipitation inhibitors[18].

CYCLODEXTRINS AS PRECIPITATION INHIBITORS

Cyclodextrins are hydrophobic inside and hydrophilic outside, they can form complexes with hydrophobic substances to increase concentration. Cyclodextrins such as 2-hydroxypropyl-β-cyclodextrin (HPβCD) and sulfobutylether-β-cyclodextrin (SBEβCD) are well known for their solubilizing capability and have been widely used in oral bioavailability enhancement formulations. Cyclodextrins can form inclusion complexes with a variety of hydrophobic drugs, increasing their solubility and decreasing supersaturation, resulting in decrease in the rate of nucleation and crystal growth[19].

Thermodynamically, Cyclodextrins improve the apparent saturation solubility while decreasing the amount of supersaturation. Kinetically, they may also interact with the growing crystal through hydrogen bonding to crystal-associated site. The accumulation of cyclodextrin in the unstirred water layer can enhance viscosity and diffusion resistance. Moreover, cyclodextrins can increase the cohesive nature of water, which may impact induction time and nucleation, resulting in stable supersaturated solutions that do not precipitate drugs[20].

POLIMER PRECIPITATING INHIBITORS

Polymeric precipitation inhibitors (PPI) are incorporated into the SNEDDS actual formulation to inhibit drug precipitation. The PPI blocks the nucleation process that is required for crystal formation and growth, which retard drug precipitation out of the solution and maintains a metastable supersaturated state for a certain period[21]. Polymers function by delaying the process of nucleation and crystal growth by interacting with dissolved API molecules as well as interacting with and adsorption onto growing crystals[22].

S-SNEDDS reduce drug precipitation in the GI tract by achieving a metastable saturated state. S-SNEDDS reduce drug precipitation in the GI tract by achieving a metastable saturated state. This approach incorporates water-soluble polymeric PIs (PPIs), resulting in a longer precipitation time compared to the mean absorption period. PPIs that are often utilised include polyvinyl pyrrolidone, hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose, hydroxypropyl methylcellulose acetate succinate (HPMCAS) and MC polymers. Few drugs precipitate in an amorphous state and show markedly quick post-precipitation disintegration when tested *in vitro*. This indicates that precipitation of such drugs improves bioavailability[23].

Hydroxypropyl methylcellulose (HPMC)

HPMC is a propylene glycol ether of methyl cellulose, hydroxypropyl, and methyl that is ether-bonded to an anhydrous glucose ring[24]. In a wide range of formulations, including solid solution/dispersion and lipid-based formulations, HPMC has been demonstrated to be an effective drug precipitation inhibitor. HPMC has more hydroxyl groups, and the linkage is stronger, which effectively inhibits drug precipitation[25]. HPMC decrease drug precipitation and improve oral absorption in various solid dispersion formulations[26]. For several drugs, the inhibitory effect of HPMC on drug precipitation in the S-SEDDS formulation with a variety of formulation components has also been confirmed.A significant increase in oral bioavailability has been reported using lipid formulations including HPMC as a precipitation inhibitor. The inhibitory effect of HPMC on drug precipitation varied depending on the type of HPMC used[27].

Hydroxypropyl Methyl Cellulose Acetate Succinate (HPMCAS)

HPMCAS has also been proposed as an effective drug precipitation inhibitor for a wide variety of drugs. HPMCAS was the most effective at maintaining drug supersaturation was shown to be the most potent inhibitor in spray-dried dispersions among all the investigated excipients[28]. The greater inhibition of HPMCAS is due to two properties: first, it is partially ionised above pH 5, allowing for the formation of stable nanosized amorphous drug-polymer aggregates; and second, it contains hydrophobic regions, which provide site for drug molecule association. The formation and maintenance of nanosized drug–polymer aggregates has been identified as a key factor, providing a reservoir from which the drug can dissolve and maintain the supersaturated free-drug concentration[29].

Polyvinylpyrrolidone (PVP)

PVP is a water-soluble polymer generated by the polymerization of the monomer N-vinylpyrrolidone. PVP is a non-toxic, inert, temperature-resistant, pH-stable, biocompatible, and biodegradable polymer that can help with the encapsulation and distribution of both hydrophilic and lipophilic drugs[30]. PVP and drugs can establish hydrogen bonds byusing a nitrogen or carbonyl group. It is another polymer precipitation inhibitor that is widely employed. PVP adsorption of crystals in solution may significantly reduce the crystallisation rate with a low concentration of 0.01% in the Bicalutamide solution without modifying the morphology of polymorphs.[31]

The effect PVP did not significantly affect the solubility of most of the weak base drug, depending on the structure of the drug. In acid drugs, PVP has an obvious effect in two ways: maintaining supersaturation by stabilizing the amorphous form or increasing the degree of supersaturation for a single component but only in a short time. The solubility effect for all drugs depends on the type and PVP concentration[32].

MECHANISM OF PRECIPITATION INHIBITION BY PPI's

In order to attain greater bioavailability from supersaturating drug delivery formulations, supersaturation must be maintained by preventing drug precipitation with PIs[31]. The drug precipitation process is divided into two different phases: nucleation and crystal formation. The precipitated solute molecules concentrate and form tiny nucleus bodies inside the solution during the first stage. These nuclei bodies combine and become larger than their critical size, resulting in crystal growth beginning. Crystal growth is the process by which molecules assemble themselves on a regular basis to form the framework of crystals. The inhibitory effect of precipitation inhibitors is influenced by the inhibitor, drug, and medium properties. Drug precipitation can be suppressed thermodynamically or kinetically. Precipitation by thermodynamic approach is achieved by increasing drug solubility, thus decreasing the degree of supersaturation (DS) which leads to the reduction in crystallinity. Examples of excipients capable of inducing thermodynamic inhibition are cyclodextrins, polymers and cosolvents. On the other hand, by

inhibiting drug precipitation in a supersaturated state where polymers are used as PIs, kinetic inhibition is accomplished. The general mechanisms of precipitation inhibition through PPI are hydrogen bonding, hydrophobic interactions, steric hindrance and polymer rigidity. The other factors related to polymer supersaturation inductions depend upon the molecular weight of PPIs used and solution viscosity[32].

Hydrogen bonding between drug and polymer

Hydrogen bonding interaction between drug and polymer could inhibit the growth of crystals as well as the nucleation process. It has been seen that if the drug has hydrogen bond donor sites (hydroxyl, amide group) is always interacted with acceptor site such as PVP, which inhibits the precipitation through the formation of hydrogen bond interaction between polymer-drug[33].

Hydrophobicity and rigidity

Hydrophobicity and rigidity of polymer are affecting the precipitation process. Generally, that moderate hydrophobic polymer are more effective than highly hydrophobic polymer or highly hydrophilic polymer due to weak adsorption of polymer to the drug crystal surface[34].

Molecular weight and steric hinderance

Polymer adsorption capacity depends on the molecular weight of polymer. It has been investigated that high molecular weight polymer are the efficient choice for supersaturated solution[35]. It was shown that PVP 2000 seen less crystal inhibiting capacity than PVP due to low molecular weight and the PVPK90 has a better inhibiting effect than PVP K12, PVPK29 and PVPK32[36].

EVALUATION OF SUPERSATURATED DRUG DELIVERY SYSTEM

Better knowledge and regulation of supersaturation is desirable for improved *in vivo* performance and bioavailability. In an early stage, researchers concentrated on the fundamental phenomena of supersaturation, almost solving difficulties *in vitro* such as *variable* behaviour at different pH levels and drug-polymer interactions. Yet, the genuine intraluminal situation in which supersaturation occurs in vivo differs significantly, even between fasting and feeding states[37].

Subsequent studies sought to imitate the true in vivo condition and mediate the decision to meet the biomimetic environment. This section depicts the supersaturation biomimetic mechanisms that are at work in distinct study aspects *in vitro*, *in vivo*, and *insilico*.

In vitro Studies

Biorelevant Media

Biorelevant media are an essential component of the biomimetic environment for studying supersaturation. They are made up of simulated physiological compositions and, as a result, are drug product-independent media. Solubility and supersaturation in mediums are important in the physiological environment because solubility impacts absorption. The selection of biorelevant medium may have an impact on the behaviour of supersaturating formulations[38].

Biomimetic Apparatus

Another key aspect of supersaturation environment research is biomimetic equipment. The most often used techniques for drug dissolving are USP dissolution machines, although they are ineffective at simulating transportation or absorption. A range of *in vitro* apparatus has been created by researchers to imitate physiological settings for supersaturating process investigation[39].

In vivo Studies

Supersaturation is difficult to measure *in vivo*, particularly in humans, unless the supersaturating medication is aspirated into the gastrointestinal system. The majority of researchers assess supersaturation in biological bodies by administering the medication orally and monitoring the drug blood content. Some supersaturation studies conducted on animals applied intestinal perfusion[40].

Different types of *in vivo* studies are conducted they are:

Oral absorption

Intestinal perfusion

Intestinal content aspiration

Insilico studies

As computer science advances, a lot of tools for doing insilico investigations emerges. GROMACS, Gaussian, and Materials Studio are utilised for molecular modelling, and Gastro Plus TM, Simcyp® and GI-Sim are employed for pharmacokinetics simulations, for supersaturation and precipitation inhibitory mechanism research. With the assistance of such expert software packages, researchers may study intermolecular interactions and anticipate the influence of polymer on the API, allowing them to properly pick the optimal excipients for SNEDDS. Moreover, mathematical models can aid in the prediction of supersaturation and *in vivo* absorption[41].

Insilico studies can be conducted by:

Molecular modelling

Pharmacokinetic simulation

ROLE OF POLYMER PRECIPITATON INHIBITORS

Altering bulk solution properties such as surface tension (where decreasing surface tension moves crystallization from diffusion control to surface nucleation control) and solubility (where increasing solubility reduces supersaturation and the likelihood of nucleation)[42].

Changing the adsorption layer at the crystal–solution interface, including the properties of the hydrodynamic boundary layer surrounding the crystal, potentially decreasing the rate of diffusion of drug molecules to the crystal nuclei[43].

Adsorbing to the crystal surface interface, thereby blocking crystal growth by blocking access of the solute molecules to the crystal terrace[44].

Adsorbing onto the growth terraces and thereby disrupting the growth of steps across the surface, blocking access of adsorbed molecules to the terrace steps and/or kinks[45].

Adsorbing into surface imperfections causing rough surfaces to become flat, therefore eliminating growth spots.

RECENT APPLICATIONS IN SUPERSATURATED SNEDDS

Controlled-release technology in S-SNEDDSs

The use of S-SNEDDSs is primarily intended to increase the absorption of poorly water-soluble medicines, it would also be ideal to give sustained-release action in the case of low-dose pharmaceuticals with short biological half-lives that require frequent administration[46].

Improvement in solubility and bioavailability

Nowadays, the majority of APIs produced remain difficult problems for formulation development. Numerous methods, such as chemical modification, innovative drug delivery systems, salt creation, and others, are being used or investigated to improve solubility. Supersaturated medication delivery devices are one intriguing method that is now gaining consideration. When medication concentrations above equilibrium solubility in gastrointestinal fluids, a supersaturation condition is sustained long enough to be absorbed, improving bioavailability[47].

Improve the Solubility and Bioavailability of Anti-Cancer Drugs

The BCS Class II medications entrectinib and pemigatinib, which have low solubility and high permeability, make it difficult to obtain the ideal dissolution kinetics from the dose form. Especially for medications with poor gastrointestinal solubility and high permeability, drug release is an important and constricting stage in oral drug bioavailability. As a result, the model pharmaceuticals' dissolving properties may be improved by formulating into S-SNEDDS by improving its release and solubility by S-SNEDDS technology[48].

S-SNEDDS given through ocular route

Econazole nitrate (ECO) is an antifungal medication that is poorly water soluble. Because of its limited aqueous solubility, it is ineffective for ocular therapy. The ocular supersaturated self-nanoemulsifying drug delivery systems (S-SNEDDS) use hydroxypropyl methylcellulose as a precipitation inhibitor to increase drug solubility by preventing precipitation after injection[49].

Solidification of S-SNEDDS

The right solid excipients for the solidification of S-SNEDDSs should be adapted exactly because of their crucial consequences for not only the physicochemical features of the S-SNEDDS formulation but also *in vivo* drug absorption from the formulation. Water-insoluble mesoporous silica and Microcrystalline cellulose (MCC), water-soluble polysaccharide, or polymer or protein-based solid carriers are commonly utilised as solidification excipients. After solidification process they can be formulated as different solid dosage forms.

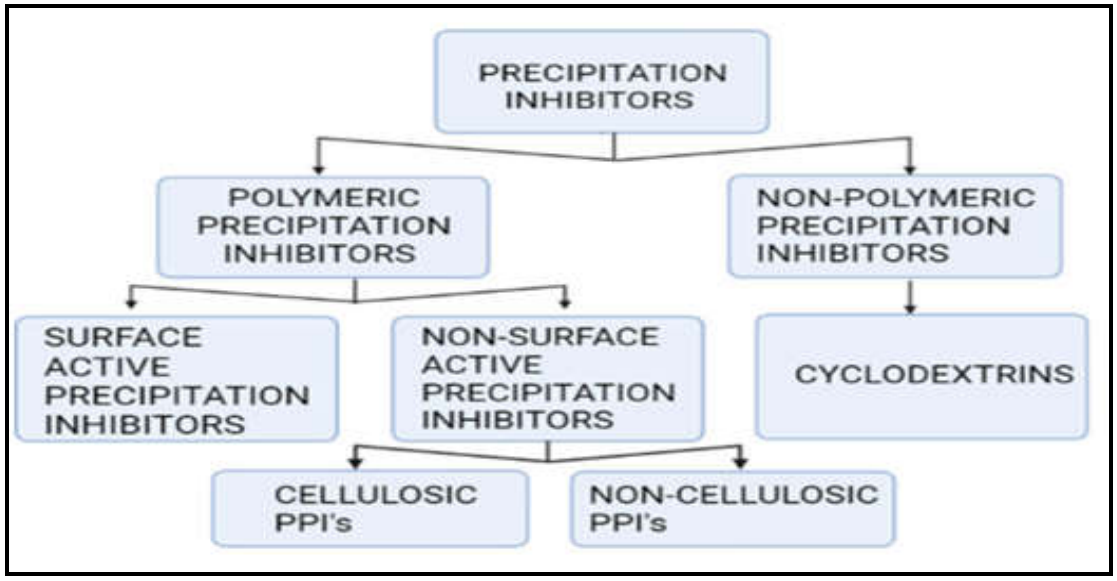

Figure No.1: Classification of precipitation inhibitors

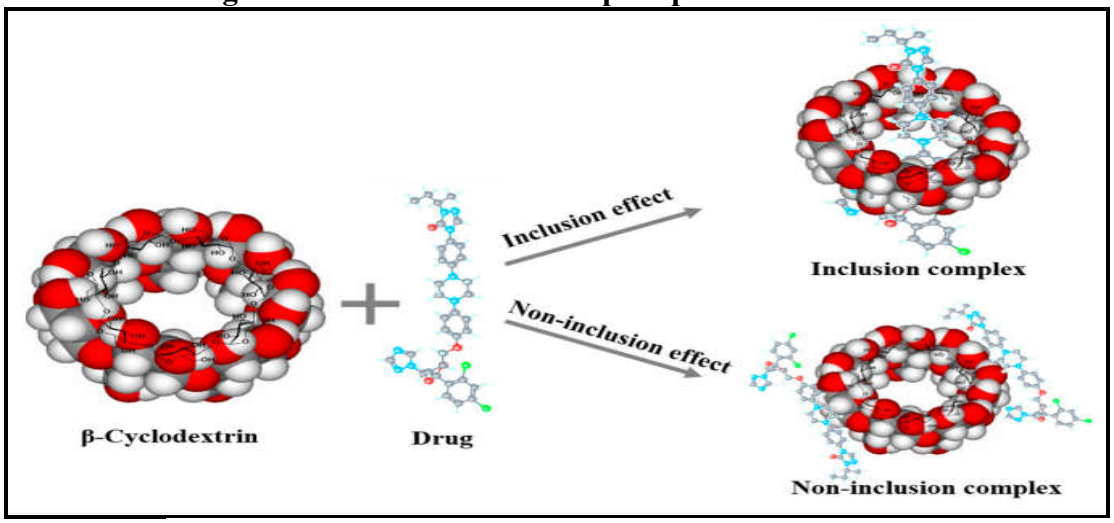

Figure No.2: Illustration of inclusion complexes and non-inclusion of cyclodextrins

CONCLUSION

Supersaturable-SNEDDSs are a potential strategy for improving the bioavailability of poorly water-soluble medicines by inducing and stabilising a supersaturated drug state in the GI fluid via PIs. This method solves the major drawbacks of conventionally solubilized SNEDDSs. To employ S-SNEDDS for a target medication, it is necessary to first understand the process of precipitation via drug supersaturation. Based on this technique, it may be able to limit precipitation and extend supersaturation by taking into account the numerous parameters that govern precipitation.

Continued exploration and development of innovatively improved S-SNEDDS technology, as well as advancement of current characterization and assessment methodologies, will lead to a more in-depth understanding of the mechanisms that control the supersaturation and absorption of poorly water-soluble drugs. This will improve the therapeutic potential of a large variety of difficult, weakly water-soluble medications still to be found.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

REFERENCES

1. Sokkula S R, Gande S. A comprehensive review on self-nano emulsifying drug delivery systems: Advancements and applications, *International Journal of Pharmaceutical Sciences and Drug Research,* 12(5), 2020, 576-583.
2. Fatouros D G, Karpf D M, Nielsen F S, Mullertz A. Clinical studies with oral lipid based formulations of poorly soluble compounds, *Therapeutics and Clinical Risk Management,* 3(4), 2007, 591-604.
3. Kale A A, Patravale V B. Design and evaluation of self-emulsifying drug delivery systems (SEDDS) of nimodipine, *AAPS Pharmscitech,* 9(1), 2008, 191-196.
4. Kang B K, Lee J S, Yuk S H, Khang G, Lee H B, Cho S H. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs, *International Journal of Pharmaceutics,* 274(1-2), 2004, 65-73.
5. Elgart A, Cherniakov I, Aldouby Y, Domb A J, Hoffman A. Improved oral bioavailability of BCS class 2 compounds by self nano-emulsifying drug delivery systems (SNEDDS): The underlying mechanisms for amiodarone and talinolol, *Pharmaceutical Research,* 30(1), 2013, 3029-3044.
6. Savale S K. A review-self nanoemulsifying drug delivery system (SNEDDS), *International Journal of Research in Pharmaceutical and Nano Sciences,* 4(6), 2015, 385-397.
7. Date A A, Desai N, Nagarsenker M. Self-nanoemulsifying drug delivery systems: formulation insights, applications and advances, *Nanomedicine,* 5(10), 2010, 1595-1616.
8. Bandyopadhyay S, Katare O P, Singh B. Development of optimized supersaturable self-nanoemulsifying systems of ezetimibe: Effect of polymers and efflux transporters, *Expert Opinion on Drug Delivery,* 11(4), 2014, 479-492.
9. Gao P, Akrami A. Characterization and optimization of AMG 517 supersaturatable self-emulsifying drug delivery system (S-SEDDS) for improved oral absorption, *Jour of Pharl Sci,* 98(2), 2009, 516-528.
10. Dash R N, Mohammed H, Reddy A V. Solid supersaturatable self-nanoemulsifying drug delivery systems for improved dissolution, absorption and pharmacodynamic effects of glipizide, *Jour of Dru Deli Sci and Tech,* 28, 2015, 28-36.

11. Reddy M S, Sowjanya N. Formulation and *in-vitro* characterization of solid self nanoemulsifying drug delivery system (S-SNEDDS) of Simvastatin, *Journal of Pharmaceutical Sciences and Research,* 7(1), 2015, 40-48.
12. Krishnaiah Y S. Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs, *J Bioequiv Availab,* 2(2), 2010, 28-36.
13. Xu S, Dai W G. Drug PIs in supersaturating formulations, *International Journal of Pharmaceutics,* 453, 2013, 36-43.
14. Warren D B, Benameur H, Porter C J, Pouton C W. Using polymeric precipitation inhibitors to improve the absorption of poorly water-soluble drugs: A mechanistic basis for utility, *Journal of Drug Targeting,* 18(10), 2010, 704-731.
15. Dannenfelser R M, He H, Joshi Y, Bateman S, Serajuddin A T. Development of clinical dosage forms for a poorly water soluble drug I: Application of polyethylene glycol–polysorbate 80 solid dispersion carrier system, *Journal of Pharmaceutical Sciences,* 93(5), 2004, 1165-1175.
16. Sirvi A, Kuche K, Chaudhari D, Ghadi R, Date T, Katiyar S S, Jain S. Supersaturable self-emulsifying drug delivery system: A strategy for improving the loading and oral bioavailability of quercetin, *Journal of Drug Delivery Science and Technology,* 71, 2022, 103289.
17. Brewster M E, Vandecruys R, Peeters J, Neeskens P, Verreck G, Loftsson T. Comparative interaction of 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin with itraconazole: Phase-solubility behavior and stabilization of supersaturated drug solutions, *European Journal of Pharmaceutical Sciences,* 34(2-3), 2008, 94-103.
18. Price D J, Ditzinger F, Koehl N J, Jankovic S, Tsakiridou G, Nair A, Holm R, Kuentz M, Dressman J B, Saal C. Approaches to increase mechanistic understanding and aid in the selection of precipitation inhibitors for supersaturating formulations–a PEARRL review, *Journal of Pharmacy and Pharmacology,* 71(4), 2019, 483-509.
19. Zhou J, Yu G, Huang F. Supramolecular chemotherapy based on host-guest molecular recognition: a novel strategy in the battle against cancer with a bright future, *Chemical Society Reviews,* 46(22), 2017, 7021-7053.
20. Loftsson T, Vogensen S B, Brewster M E, Konradsdottir F. Effects of cyclodextrins on drug delivery through biological membranes, *Journal of Pharmaceutical Sciences,* 96(10), 2007, 2532-2546.
21. Dash R N, Mohammed H, Humaira T. Design, optimization, and evaluation of ezetimibe solid supersaturatable self-nanoemulsifying drug delivery for enhanced solubility and dissolution, *Journal of Pharmaceutical Investigation,* 46(2), 2016, 153-168.
22. Brouwers J, Brewster M E, Augustijns P. Supersaturating drug delivery systems: The answer to solubility-limited oral bioavailability? *Journal of Pharmaceutical Sciences,* 98(8), 2009, 2549-2572.
23. Thomas N, Holm R, Garmer M. Supersaturated self-nanoemulsifying drug delivery systems (super-SNEDDS) enhance the bioavailability of the poorly water-soluble drug simvastatin in dogs, *AAPS J,* 15(1), 2013, 219-227.
24. Singh R, Thorat V, Kaur H, Sodhi I, Samal S K, Jena K C, Sangamwar A T. Elucidating the molecular mechanism of drug-polymer interplay in a polymeric supersaturated system of rifaximin, *Molecular Pharmaceutics,* 18(4), 2021, 1604-1621.
25. Yamashita K, Nakate T, Okimoto K, Ohike A, Tokunaga Y, Ibuki R, Higaki K, Kimura T. Establishment of new preparation method for solid dispersion formulation of tacrolimus, *International Journal of Pharmaceutics,* 267(1-2), 2003, 79-91.

26. Engers D, Teng J, Jimenez-Novoa J, Gent P, Hossack S, Campbell C, Thomson J, Ivanisevic I, Templeton A, Byrn S, Newman A. A solid-state approach to enable early development compounds: Selection and animal bioavailability studies of an itraconazole amorphous solid dispersion, *Journal of Pharmaceutical Sciences,* 99(9), 2010, 3901-3922.
27. Gao P, Guyton M E, Huang T, Bauer JM, Stefanski K J, Lu Q. Enhanced oral bioavailability of a poorly water soluble drug PNU-91325 by supersaturatable formulations, *Drug Development and Industrial Pharmacy,* 30(2), 2004, 221-229.
28. Curatolo W, Nightingale J A, Herbig S M. Utility of hydroxypropylmethylcellulose acetate succinate (HPMCAS) for initiation and maintenance of drug supersaturation in the GI milieu, *Pharmaceutical Research,* 26(6), 2009, 1419-1431.
29. Friesen D T, Shanker R, Crew M, Smithey D T, Curatolo W J, Nightingale J A. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions: an overview, *Molecular Pharmaceutics,* 5(6), 2008, 1003-1019.
30. Kurakula M, Rao G K. Pharmaceutical assessment of polyvinylpyrrolidone (PVP): As excipient from conventional to controlled delivery systems with a spotlight on COVID-19 inhibition, *Journal of Drug Delivery Science and Technology,* 60, 2020, 102-146.
31. Lindfors L, Forssen S, Westergren J, Olsson U. Nucleation and crystal growth in supersaturated solutions of a model drug, *Journal of Colloid and Interface Science,* 325(2), 2008, 404-413.
32. Fornells E, Fuguet E, Mane M, Ruiz R, Box K, Bosch E, Rafols C. Effect of vinylpyrrolidone polymers on the solubility and supersaturation of drugs; a study using the Cheqsol method, *European Journal of Pharmaceutical Sciences,* 117, 2018, 227-235.
33. Singh D, Singh M, Tharmatt A, Tiwary A K, Bedi N. Polymeric precipitation inhibitor as an effective trigger to convert supersaturated into supersaturable state *in vivo*, *Therapeutic Delivery,* 10(9), 2019, 599-608.
34. Raghavan S L, Trividic A, Davis A F, Hadgraft J. Crystallization of hydrocortisone acetate: Influence of polymers, *International Journal of Pharmaceutics,* 212(2), 2001, 213-221.
35. Chen Z Q, Liu Y, Zhao J H, Wang L, Feng N P. Improved oral bioavailability of poorly water-soluble indirubin by a supersaturatable self-microemulsifying drug delivery system, *International Journal of Nanomedicine,* 7, 2012, 1115-1125.
36. Park H, Ha E S, Kim M S. Current status of supersaturable self-emulsifying drug delivery systems, *Pharmaceutics,* 12(4), 2020, 365.
37. Bandyopadhyay S, Katare O P, Singh B. Development of optimized supersaturable self-nanoemulsifying systems of ezetimibe: Effect of polymers and efflux transporters, *Expert Opinion on Drug Delivery,* 11(4), 2014, 479-492.
38. Gan Y, Baak J P, Chen T, Ye H, Liao W, Lv H, Wen C, Zheng S. Supersaturation and Precipitation applicated in drug delivery systems: Development strategies and evaluation approaches, *Molecules,* 28(5), 2023, 2212.
39. Enright E F, Joyce S A, Gahan C G, Taylor L S. Impact of phospholipid digests and bile acid pool variations on the crystallization of atazanavir from supersaturated solutions, *European Journal of Pharmaceutics and Biopharmaceutics,* 153, 2020, 68-83.
40. O'Dwyer P J, Box K J, Dressman J, Griffin B T, Henze L J, Litou C, Pentafragka C, Statelova M, Vertzoni M, Reppas C. Oral biopharmaceutics tools: Recent progress from partnership through the pharmaceutical education and research with regulatory links collaboration, *Journal of Pharmacy and Pharmacology,* 73(4), 2021, 437-446.

41. Li J, Spivey N, Silchenko S, Gonzalez-Alvarez I, Bermejo M, Hidalgo I J. A differential equation based modelling approach to predict supersaturation and *in vivo* absorption from *in vitro* dissolution-absorption system (idas2) data, *European Journal of Pharmaceutics and Biopharmaceutics,* 165, 2021, 1-2.
42. Pellett M A, Castellano S, Hadgraft J, Davis A F. The penetration of supersaturated solutions of piroxicam across silicone membranes and human skin *in vitro*, *Journal of Controlled Release,* 46(3), 1997, 205-214.
43. Raghavan S L, Trividic A, Davis A F, Hadgraft J. Crystallization of hydrocortisone acetate: Influence of polymers, *International Journal of Pharmaceutics,* 212(2), 2001, 213-221.
44. Ziller K H, Rupprecht H. Conteol of crystal growth in drug suspensions: 1) Design of a Conteol unit and application to acetaminophen suspensions), *Drug Development and Industrial Pharmacy,* 14(15-17), 1988, 2341-2370.
45. Gu C H, Chatterjee K, Young Jr V, Grant D J. Stabilization of a metastable polymorph of sulfamerazine by structurally related additives, *Journal of Crystal Growth,* 235(1-4), 2002, 471-481.
46. Rehman F U, Shah K U, Shah S U, Khan I U, Khan G M, Khan A. From nanoemulsions to self-nanoemulsions, with recent advances in self-nanoemulsifying drug delivery systems (SNEDDS), *Expert Opinion on Drug Delivery,* 14(11), 2017, 1325-1340.
47. Sharma A, Arora K, Mohapatra H, Sindhu R K, Bulzan M, Cavalu S, Paneshar G, Elansary H O, El-Sabrout A M, Mahmoud E A, Alaklabi A. Supersaturation-based drug delivery systems: Strategy for bioavailability enhancement of poorly water-soluble drugs, *Molecules,* 27(9), 2022, 2969.
48. Reddy M R, Gubbiyappa K S. A comprehensive review on supersaturable self-nanoemulsifying drug delivery system, *System (BCS),* 14(8), 2021, 4-5.
49. ElKasabgy N A. Ocular supersaturated self-nanoemulsifying drug delivery systems (S-SNEDDS) to enhance econazole nitrate bioavailability, *International Journal of Pharmaceutics,* 460(1-2), 2014, 33-44.

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