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Review Article

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Polymer as precipitation inhibitor of weak base drug: An update and brief review

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ABSTRACT

Precipitation due to supersaturation phenomenon and intraluminal solubilization behavior is mainly faced on reducing bioavailability, particularly for weak base drugs. Incomplete and extend of absorption can be avoided by modification of drug-excipient interaction namely polymers. This interaction is proposed to stabilize the amorphous form of drug through reducing nucleation followed by crystal growth. Therefore, polymers can be utilized to inhibit the precipitation phenomenon through their interaction with poorly water-soluble and weak base drugs. However, until to date, there was no recent updates on the use of polymer for precipitation inhibitor of weak base drug. This review discussed the brief and recent updates on polymer as precipitation inhibitor of weak base drug during intraluminal solubilization behavior namely mechanism, factors, and polymer application.

Keywords: Polymer precipitation inhibitor, polymer, solubility, supersaturation, weak base drug

INTRODUCTION

In general, drugs that have low solubility and permeability are categorized in biopharmaceutical classification system Class 2.[1] Several techniques and developments have been proposed for eliminating those limitations particularly the solubility using nanocrystal and lipid-based formulations. Those methods were widely used for solubility enhancement and had dramatic improvement.[2,3] However, due to the natural behavior of physiological conditions through intraluminal solubilization behavior, supersaturation promotes precipitation of poorly water-soluble drug particularly for weak base.[4-6] Weakly basic and poorly soluble drugs have solubility depend on pH gradient during transition from the stomach to the intestine. When weak base drugs reach the intestine, they have higher pH than that of in gastric. Equilibrium phenomenon due to supersaturation and pH shifting promotes precipitation and the solubility decreases because saturated condition is achieved. Hence, it faces a great consideration of precipitation in weak base drugs affected by pH shifting due to intraluminal behavior.[7,8] However, supersaturation themself can be applied for solubility enhancement of weak base drugs that have low solubility. Increasing the bioavailability of drugs can be achieved by designing into supersaturated formulation.[9] Amorphous form is an effective strategy due to easy to provide supersaturation effect. The dissolution rate can be increased dramatically by converting the stable crystalline drug into a high energy form, such as the metastable polymorph form, namely, amorphous system.[10-12] The molecular mobility of the amorphous form may decrease due to decreasing intermolecular interactions between drugs and polymers. In addition, the amorphous state can reduce the stability and transform into a crystalline state, hence reducing dissolution.[13] Precipitation of weak base during intraluminal solubilization behavior frequently occurs that produces crystalline or amorphous precipitates. Therefore, it affected on extend of drug absorption and reduces the amount of drug absorbed so that the drug decreases.[5,8]

Several techniques were proposed to inhibit precipitation phenomenon during intraluminal solubilization behavior thermodynamically and kinetically. The thermodynamic

mechanism is intended to increase the solubility and reduce the degree of supersaturation. Meanwhile, the kinetics mechanism is to prevent precipitation from supersaturation. The effectiveness of kinetic mechanism is more than that of thermodynamic to inhibit the precipitation phenomenon. According to that method, polymer can be applied and play a fundamental role on kinetic stabilization through precipitation inhibitor known as polymer precipitation inhibitor (PPI).[14] Polymers are a versatile material that have been widely used in solubility enhancement or targeted drug delivery properties. By maintaining the supersaturation phase through drug-polymer interaction, polymer acts as precipitation inhibitor, thereafter the precipitation does not occur in a certain period of time.[14,15] Thus, the soluble drug in supersaturated condition can be absorbed easily.

Several polymers can be applied for PPI and it was mainly dominated by semisynthetic polymers, for example., hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), and copolymer methacrylate (Eudragit types). By interaction between polymer and drug, for example., hydrogen bonds, hydrophobic interactions, or ionic bonds. Polymer can inhibit precipitation through decreasing the hydrodynamic boundary layer and crystallization rate. Polymer can also reduce the effective drug diffusion coefficient, which affects the crystallization rate. It can be adsorbed on the crystal surface, which can inhibit precipitation.[16] Some supersaturated formulations use polymers to maintain the supersaturation phase thereby slowing down the precipitation. Supersaturated formulation can be applied, for example., amorphous solid dispersion, lipid based formulation, or nano-emulsion.[17] Therefore, small concentrations of polymers have a great potential for increasing of dissolution rate by preventing nucleation or crystallization upon intraluminal solubilization behavior. Hence, this review focused on supersaturation behavior, PPI, and recent updated of the use and application of frequent PPI in pharmaceutics.

METHOD

The data were retrieved from PubMed, Scopus, and Google Scholar databases published after 2000. We used the following free-text search as keywords terms in "All field" with keywords such as "polymer and inhibit and precipitat," "polymer and inhibit and supersaturate," "polymer and inhibit and drug," "polymer and precipitation and inhibitor." The criteria for eligibility articles selected were about pharmaceutical field. Article type used includes journal and review article that manually check to identify the potentially relevant articles to this review.

PRECIPITATION OF WEAK BASE DRUGS

Supersaturated phase can promote drug precipitation that is formed from nucleation and crystal growth [Figure 1]. The amorphous state promotes enhancement the solubility above the saturated solubility (thermodynamic solubility). This phenomenon is kinetically unstable, thus it called as kinetics solubility. The soluble drug appears in molecular drug dispersion in appropriate solvent. Regarding the supersaturation phase, the precipitation will occur when the drug reaches the highest energy gaps and lead to metastable

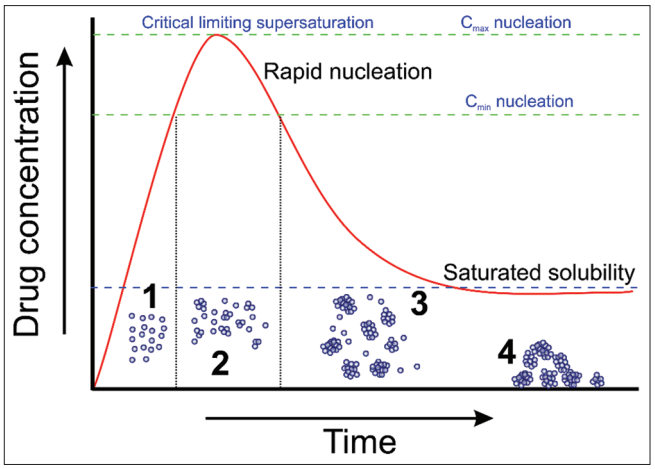

Figure 1: Phases in supersaturation-precipitation phenomenon. Soluble phase in molecular dispersion (1), nucleation (2), crystal growth after nucleation (3), and precipitation (4)[20]

phase. The precipitation process is divided into two stages i.e., nucleation stage and followed by crystal growth stage. The first stage is accumulating the small nuclei bodies in the solution till occur the aggregation thereby the size of nuclei is larger than the critical size. Thereafter, molecules growth are periodically organized and followed by crystal skeleton forming, which is the second stage.[15,18] Those are simultaneously influenced by physical conditions. The solute solubility determines the rate and mechanism of crystallization, degree of supersaturation, speed of supersaturation, diffusivity, temperature, and reactivity of the nucleation surface.[14] The crystal growth is also observed after the nuclei is detected. This phenomenon will be followed by precipitation. This precipitation process gains some consequences particularly the unabsorbed drug due to molecular size and not in soluble form. Another consequence is extending of absorption and reduces the bioavailability of poorly water-soluble drug.[19]

Several strategies can be used to inhibit precipitation by selecting excipients that inhibit precipitation, for example., polymers (HPMC, PVP, or Eudragit), surfactants (sorbitan polyester, sodium dodecyl sulfate, Kolliphor, and Span), or cyclodextrin derivatives.[21] Saturated drug formulations, for example., salt/multicomponent crystal or amorphous solid dispersions are suitable for amorphous or polymorphic precipitated drugs because they increase solubility. For crystalline precipitated from the supersaturation phase, a controlled release is an appropriate way to increase drug absorption by maintaining drug concentration in the small intestine below the critical nucleation concentration. The use of water-soluble polymers can be applied inhibit precipitation through supersaturation phenomenon.[4] Understanding the small intraluminal solubilization behaviors, supersaturation, and precipitation particularly for weak base drugs is important for predicting the pharmacokinetic profile.[22]

PPI

Inhibitor precipitation aims to maintain the supersaturation phase for preventing precipitation at predetermined time. Thermodynamic inhibition increases the solubility by reducing

the degree of supersaturation, for example., the inclusion of solubilizing agents such as co-solvents, surfactants, and cyclodextrins. Kinetics inhibition is an approach to increase the solubility through slowing or inhibiting drug precipitation in the supersaturation phase i.e. the inclusion of a polymer that acts as PPI.[15] However, drug and polymer interaction might have thermodynamic inhibition due to their molecular interaction. In general, stability of supersaturation of thermodynamic inhibition is greater than that of kinetic inhibition. The mechanism of precipitation inhibitor consists of decreasing the degree of supersaturation by increasing solubility to reduce nucleation and crystal growth, increasing viscosity thereby reducing molecular mobility then reducing nucleation and diffusion coefficient thereby reducing crystal growth, increasing interfacial energy of liquid clusters thereby reducing nucleation, changing the adsorption layer on the surface of crystal medium then followed by modification of crystal habit, and changing the level of solvation at the surface of the liquid crystals.[21]

The supersaturated formulation aims to increase the solubility of the drug. The amorphous drug delivery system can increase many drug's solubility along with different physicochemical properties.[22] This concept can be explained through the theory of "spring" and "parachute" [Figure 2]. The curve of the high energy form that the drug produces in a supersaturated solution is known as a "spring." The formulation can induce supersaturation in the gastrointestinal tract. Supersaturated drug delivery includes the delivery of drugs in solutions such as co-solvent systems, lipid-based formulation, and delivery of high energy solids that can accelerate dissolution and increase solubilities, such as amorphous forms, crystalline salts, and co-crystals.[21] Supersaturation solutions are induced by two factors, i.e., high energy or dissolving rapidly in solid form and highly concentrated solutions. The existence of supersaturation can induce precipitation, hence in order to maintain the supersaturation phase, precipitation inhibitor is required by inhibiting nucleation or crystal growth followed by formation a curve known as from "spring" become a "parachute."[15] In addition, the molecular interaction between drug and precipitation inhibitor also gives a stable

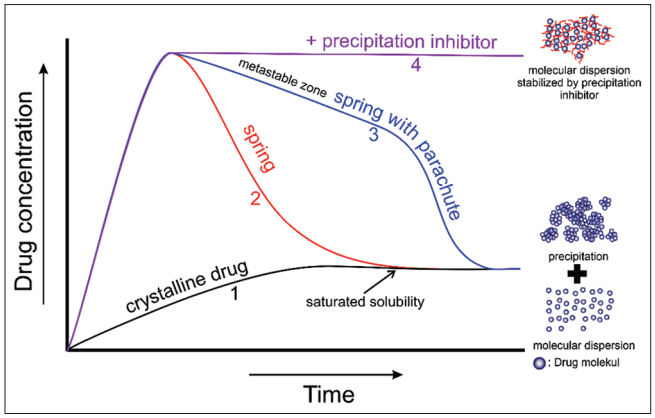

Figure 2: Supersaturation phenomenon of drug delivery system observed in different systems. Drug in stable crystalline form (1), amorphous system (2), amorphous system with inadequate precipitation inhibitor (3), and drug along with adequate precipitation inhibitor (4)[14]

molecular dispersion system. Either spring or parachute effect has a combination between molecular dispersion and precipitation when the thermodynamic solubility is reached due to metastable kinetics. However, the precipitation was also mostly inhibited by molecular interaction between PPI and drug, for example., through ionic interaction.[23]

The ability of polymers to inhibit precipitation depends on the interactions between drugs and polymers in solution. These interactions can be divided into four categories, which are stabilizing supersaturation, forming hydrogen bonds, increasing solubility, and changing out crystals.[14] The polymers that have been widely studied are cellulose-derived polymers and synthetics such as HPMC, PVP, and Eudragit. Polymers can inhibit precipitation by decreasing the hydrodynamic boundary layer's crystallization rate formed with hydrogen bonds, hydrophobic interactions, or ionic bonds. The polymer can also reduce the drug diffusion coefficient significant which affects the crystallization rate. Polymers can be adsorbed on the crystal surface which can inhibit precipitation.[16] On the other hand, ionic interaction between drug and polymer can enhance and maintain the supersaturation degree by enhancing solubility of drug.[23]

HYDROXYPROPYLMETHYLCELLULOSE

HPMC was reported to be able to inhibit precipitation by prolonged the duration of the supersaturation phase and increasing zafirlukast concentration during the supersaturation phase[24] and inhibiting the crystallization of pazopanib.[25] HPMC could inhibit precipitation in supersaturated drug preparations, several studies have been conducted on supersaturated drug formulations. The use of HPMC could inhibit precipitation in solid dispersion amorphous dosage forms. HPMC inhibited dipyridamole precipitation by delayed the initiation time and precipitation rate.[26] HPMC has more significant effects than PVP to increase the dissolution of dipyridamole.[27] HPMC as a hydrophilic polymer could delay precipitation in lipid-based formulations,[28] maintained the highest concentration of tacrolimus in the S-SEDDS dosage form by increased the wetting and stabilized the metastable phase of the active substance.[29] In the formulation of S-SMEDDS, HPMC could inhibit precipitation by increased the solubility capacity of saquinavir. The drug concentration in the intestinal fluid was longer in the supersaturated SMEDDS preparation than that of SMEDDS, thereby increasing the lymphatic absorption of saquinavir.[30] HPC-L (hydroxy propyl cellulose-L) and phosphoric acid were able to increase the solubility and dissolution rate of Raloxifene HCl in the S-SMEDDS dosage form.[31]

Type of HPMC that has significant effect was HPMC E50 which has a role in intermolecular interactions and a steric barrier to the prevention of dipyridamole precipitation. The mixture of PVP K90 and HPMC E50 also increased dissolution rate but the effect was not significant.[27] Another study was also reported similar results that HPMC and PVP could enhance the supersaturation generation of ciprofloxacin in complex with sodium dextran sulfate.[32] HPMC-AS could increase solubility and prolong the supersaturation of dipyridamole and griseofulvin. Griseofulvin formulation with HPMC-AS polymer could enhance the drug capacity higher. HPMC and

HPMC- acetate succinate (HPMC-AS) almost completely inhibited precipitation of pioglitazone particles surface. Polymers not only slow down the precipitation in medium but also act as inhibitors for precipitation of solid surface.[7] The combination of dipyridamole with HPMC-AS and HPC-SSL (hydroxypropyl cellulose) could increase its dissolution speed so that increased drug absorption in the gastrointestinal tract.[33] The HPMC-AS and tocopheryl polyethylene glycol (TPGS) combination could improve itraconazole AUC by 1.8 times higher than that of the single HPMC-AS.[17] The other type of HPMC such as HPMC-E5 could increase albendazole solubility as well as the bioavailability.[34] In addition, combination of HPMC and shellac has been reported that it could enhance the degree of supersaturation of loratadine.[35]

PVP

PVP can interact by hydrogen bonds with drugs via a nitrogen or carbonyl groups on the pyrrole ring. The use of PVP polymers can increase the drug concentration in solution well as its bioavailability.[36] Hydrogen bonding is responsible for molecular stability.[37] PVP could inhibit precipitation in supersaturated drug preparations, several studies have been conducted on supersaturated drug formulations.[37] PVP could significantly reduce the crystallization rate with a low concentration of 0.01% in the bicalutamide solution without changing the form of polymorphs through PVP adsorption of crystals in solution.[38] PVP was reported to be able to inhibit zafirlukast precipitation in the amorphous form by prolonged the supersaturation phase and increasing drug concentration during the supersaturation phase.[24] The addition of PVP polymer could be useful for maintaining the supersaturation phase of itraconazole formulated with the liquid-solid technique by increased stability, increasing the flow rate of the liquid-solid powder, and increasing the wetting ability of the liquid-solid tablets.[39] PVP had a better ability than HPMC and PVA to increase the dissolution of celecoxib in the solid dispersion amorphous dosage form.[40]

Fornells *et al*. (2018) have conducted a study used 16 drugs and several types of PVP (K-12, K-17, K-25, K-29/32, K90). The drugs tested included: bendroflumethiazide, bupivacaine, haloperidol, maprotiline, cyproheptadine, papaverine, dibucaine, isoxicam, propanolol warfarin, ketoprofen, diclofenac sodium, benzthiazide, olanzapine, pindolol, and tetracaine. Diclofenac and ketoprofen only interacted with PVP type K. Warfarin was able to interact with all types of PVP to increase warfarin solubility by 20 times. The effect of PVP did not significantly affect the solubility of most of the weak base drugs, 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.[36]

PVP-17 could slow down indirubin precipitation in S-SMEDDS[37] and cyclosporine in S-SEDDS.[41] PVP-K90 could decrease the precipitation rate of dipyridamole solid dispersion.[22,27] The mixture of PVP K90 and HPMC E50 also increased the dissolution rate of dipyridamole in the amorphous form of solid dispersion, but the effect was not significant.[27] Several studies have reported that PVP was not more effective for some of active drug substances. PVP K17 as a hydrophilic polymer was not effective to delay nucleation or growth of tacrolimus crystals in S-SEDDS dosage form under non-sink conditions.[29] PVP did not have a good ability to prevent precipitation and maintain the supersaturation phase after the amorphous phase of BMS-817399 undergoes separation.[42]

POLY METHACRYLATE

Eudragit is a brand name for polymethacrylate co-polymers. Different substitution is available for different functionality and purposes. Eudragit can inhibit precipitation in solution of supersaturated drugs. Several studies have been carried out on supersaturated drug formulations. Eudragit E100 could inhibit dipyridamole precipitation in the form of solid dispersion by inhibited the initiation time and precipitation rate, whereas Eudragit S100 only delayed the initiation time and acts effectively as a stabilizer.[22] The formulation of indomethacin into a solid dispersion amorphous dosage form with Eudragit could increase dissolution even though it causes crystallization at acidic condition. A combination with HPMC could increase drug release, increased drug solubility, and inhibited precipitation by the presence of HPMC.[43] In a lipid-based formulation, Eudragit RL100 was able to delay fenofibrate precipitation.[28]

Research has been conducted by Sunnam *et al*. (2020), polymer screening based on quantitative supersaturation to show differences in activity on nucleation and growth of atorvastatin crystals. This can to estimate the effect on induction time and crystal growth. The interaction of atorvastatin with Eudragit EPO was stronger than that of PVP K30 and resulted to become stronger nucleation inhibitor effect. Eudragit EPO had the potential to maintain the supersaturation phase so as to increase the transmembrane permeability.[13]

PHYSICAL CHEMICAL INTERACTIONS OF POLYMERS AND DRUGS

The effect of precipitation inhibition is usually kinetic and only slows down the deposition process through inhibition of nucleation or crystal growth compared to the thermodynamic mechanism.[14] There are factors that affect the chemical physics interactions between drugs and polymers in inhibiting precipitation: [14,18]

Effect of Hydrogen Bond Formation

PPIs can form stable intermolecular hydrogen bonds with drugs and then inhibit precipitation. Raghva *et al*. (2001) used hydrocortisone acetate (HA) and several polymers to determine the interactions. The mechanism of drug interaction with HMPC and PVP was through hydrogen bonding between drugs and polymers. HA had 3 carbonyl and 2 hydroxy functional groups which can interact through hydrogen bonds with cellulose polymers. The hydrogen bonds could inhibit nuclei form then precipitation did not occur. HPMC has more hydroxy groups than PVP, hence that HPMC was more useful to inhibit precipitation. The nucleation process depends on the hydrogen bonding from the drug or polymer functional groups.[16] Xie *et al*. (2010) used the drug salbutamol and

several polymers to determine its interactions. The interaction between salbutamol and PVC through the formation of hydrogen bonds. There were 3 hydrogen bonds formed from hydroxy group and amine of salbutamol with a carbonyl group and a nitrogen atom of PVP. The carbonyl group of PVP could interact easier with salbutamol because interaction with nitrogen was no steric barrier.[44]

Effects of Hydrophobic Interactions

Gao *et al*. (2009) have been used HPMC type E and type K showed a hydrophobic interaction. The hydrophobic interaction between the drug and polymer functional groups could determine the polymer adsorption on the primary surface of the nuclei of the drug. This process was a critical step for determining effectiveness in inhibiting precipitation. The hydrophobic properties were representative by methyl group substitution. HPMC type E has a methyl substitution of 29%, while type K had a methyl substitution of 22%. The greater the methyl substitution, the higher the hydrophobic interaction tendency. Therefore, HPMC type E has better PPI capability than type K.[45]

The hydrophobicity of polymers has an effect to alter nucleation. This effect influences the ability of polymer to mix with the pre-nucleated drug aggregates. It is assumed that polymers influence nucleation through blocking the solute molecules from solute clusters formed which are the rate-limiting step of the 2-stage nucleation model. Nucleation inhibitors are effective if they easily interact with the solution and have a strong affinity for the solution. Hence, polymers having hydrophobicity similar to solutes have benefit to enhance specific interactions with drugs.

Effect of Molecular Weight

Xie *et al*. (2010) have been used PVP K10 to K40 that showed effect of molecular weight on the ability to inhibit precipitation. The greater molecular weight indicated that the PVP concentration was higher than the pyrrolidone groups interacting with the crystal surface. This interaction had a greater adsorption tendency and then the inhibitory effect was stronger.[44] The greater the molecular weight of the polymer, the stronger the interaction with the drug molecule. This effect could be attributed to increase in viscosity or the number of functional groups of the polymer chain.[14]

Steric Barriers Effect

The steric hindrance effect of bulk groups in the polymer molecule helps in inhibiting precipitation by stabilize the drug in the micro-hydrophilic environment of the polymer. Cellulose polymers containing bulk methyl and propyl groups contribute effectively to inhibit the crystallization of itraconazole.[18] Feng *et al*., have been using TPGS 1000 succinate (TPGS) as precipitation inhibitor. The result was TPGS has ability to provide steric hindrance that leads to delay crystal growth by absorbing into the surface of small particles.[17]

Effect of Viscosity

The effect of viscosity on the inhibition of crystal growth by preventing material diffusion into the media. The crystal growth rate in a specific medium is directly proportional to the diffusion rate of the specific component.[18] Increasing the viscosity of the aqueous medium will decrease the rate of drug diffusion from the solution to the crystal nuclei or surface, inhibiting crystallization, during the nucleation and growth phases.[14] The rheology behavior of solution polymers, such as HMPC and EHEC that has a high viscosity and highest network associations can modification of dendrite-like growth of NF hydrate crystals.[46] Effect of Rigidity.

Polymer rigidity can affect its ability to inhibit precipitation. Polymers with the rigid structure are more effective to adsorbed on the crystal surface compared to flexible structures, and thus, they can better inhibit precipitation.[18] The presence of rigid-planar structure can significantly influence the effectiveness of precipitation inhibitors. Knowledge about adsorption behavior on drug surface would help in exploring the mechanisms of crystal growth inhibition, including the forming of barier for surface diffusion or the blocking of active growth sites for incorporation of drug molecules into crystal lattice.[47]

Effect of Temperature

The bond between the drug and the polymer decreases at higher temperatures because the intermolecular interactions between the molecules are weak.[14] The temperature mainly influences the mobility of polymer structure and drugs, thereafter it decreases the affinity of drug-polymer interaction High temperature lead to increase the drug solubility due to weakens intermolecular bonding.[48] In other hand, the increasing of temperature enhanced the rate of calcium carbonate precipitation due to the presence of magnesium and sulfate ions lead to a change on the effect of magnesium solution on kinetics of $CaCO_3$ precipitation and caused the magnesium ions incorporation in the $CaCO_3$ lattice.[49]

Dielectric Constant

Lowering the dielectric constant would decrease the interaction between the polymer and the drug molecule and usually increase drug solubility due to drug-solvent affinity.[14] Finally, hydrogen bonding between drug and polymer is greater where there are more hydrogen bonding sites on the polymer.[48] Mutasim *et al*., have been found that the lowering the dielectric constant would increase the velocity of crystal growth in NaCl solution studied.[50]

Hydrophilicity or Hydrophobicity Properties

Raina *et al*. (2015) reported about polymers with different levels of hydrophilic and hydrophobic properties. Polymers that are effective as precipitation inhibitors must be able to interact in both phases, which are the amorphous precipitation phase of the drug and the aqueous phase. Polymers with hydrophilic or hydrophobic intermediate properties, for example., HPMC, HMPC AS, and PVP VA (PVP vinyl acetate) could be good precipitation inhibitors. Polymers have affinity with the drug phase and the aqueous phase, which can be interpreted from the polymer's solubility. On the other hand, polymers that were more hydrophilic or more hydrophobic, for example., PVP, poly acrylic acid, poly 2-vinyl-pyridine, carboxymethyl

cellulose acetate butyrate and, did not have a good ability to inhibit crystallization. This was because the affinity was only higher for one phase while the other phases had less affinity.[51] Knopp *et al*. (2015) used PVP, HMPC, and PVA polymers with dipyridamole solid dispersion showed that the maximum concentration achieved by the drug combination with the polymer PVP> HPMC> PVA. This indicated that the maximum concentration obtained correlated to the hydrophilicity of the polymer. The maximum concentration could increase the degree of supersaturation which affected the drug to crystallize spontaneously. However, the highest maximum concentration did not give the best performance yield.[40]

PPIs have been widely used in drug development to stabilize the amorphous form of drugs by reducing the rate of nucleation or crystal growth or reducing and preventing the nucleation processes that played a fundamental role in crystal formation and growth. The stabilization of the supersaturation system in the presence of polymer addition depended on the ability of the polymer to inhibit nucleation and crystal growth.[52] Polymers could also inhibit precipitation in supersaturation solutions by maintaining the supersaturated drug concentration for a long period of time.[53] In some cases, polymer-drug interactions could affect drug precipitation by a variety of mechanisms, but some negate each other.[14]

CONCLUSION

Supersaturation phenomenon naturally promotes the formation of precipitation of poorly water-soluble and weak base drugs during intraluminal solubilization behavior. Interaction between polymers and those drugs can be utilized and used to reduce the precipitation and maintain the drug in supersaturation followed by further process, i.e., absorption. Several polymers, HPMC, PVP, and Eudragit types, have been widely applied for addressing the precipitation issue through intermolecular interaction between drug and polymers along with several mechanisms. For further practical application, the formulation of poorly water-soluble weak base drugs should be considered regarding the supersaturation effect. Therefore, it should be elucidated preliminary in order to enhance bioavailability and avoid the extend of absorption followed by incomplete absorption of poorly water-soluble weak base drugs.

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