Insoluble Polymers in Solid Dispersions for Improving Bioavailability of Poorly Water-Soluble Drugs

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Abstract: In recent decades, solid dispersions have been demonstrated as an effective approach for improving the bioavailability of poorly water-soluble drugs, as have solid dispersion techniques that include the application of nanotechnology. Many studies have reported on the ability to change drug crystallinity and molecular interactions to enhance the dissolution rate of solid dispersions using hydrophilic carriers. However, numerous studies have indicated that insoluble carriers are also promising excipients in solid dispersions. In this report, an overview of solid dispersion strategies involving insoluble carriers has been provided. In addition to the role of solubility and dissolution enhancement, the perspectives of the use of these polymers in controlled release solid dispersions have been classified and discussed. Moreover, the compatibility between methods and carriers and between drug and carrier is mentioned. In general, this report on solid dispersions using insoluble carriers could provide a specific approach and/or a selection of these polymers for further formulation development and clinical applications.

Keywords: solid dispersion; controlled release; nano-sized solid dispersion; dissolution enhancement; insoluble carrier

1. Introduction

In the last few decades, solid dispersions (SDs) have been involved in the development of the majority of new drugs to improve dissolution rates and controlled release because these newly discovered drugs are poorly water-soluble [1–5]. The limited solubility of these drugs could lead to low oral availability, potential toxicity, low half-lives, and difficult formulations [6–9]. To achieve high absorption, drugs need to be dissolved in the gastrointestinal tract [10,11]. Therefore, poorly soluble drugs often result in low absorption and oral bioavailability [10,12–17].

Recent studies have shown that hydrophilic polymers, such as hydroxypropyl methylcellulose, polyvinylpyrrolidone, hydroxypropyl cellulose, and polyethylene glycol, are commonly used in the formation of SDs [18–30]. Moreover, ternary SDs of these polymers have also been utilized to further improve drug bioavailability [31–41].

In addition, insoluble carriers have also been exploited in many formulations of SDs. By taking advantage of hydrophobic interactions between polymers and poorly water-soluble drugs, the polymer may easily change the drug crystallinity into an amorphous state via molecular interactions, enhancing dissolution [42–48]. Moreover, the insoluble property of carriers in various dissolution media might be applied to overcome the low bioavailability of drugs with pH-independent solubility. The poor
solubility of certain polymers can also be utilized in the development of controlled-release SDs or even nano-sized SDs. This review, therefore, provides insight strategies for using insoluble carriers in SDs to improve drug dissolution and bioavailability. Figure 1 describes general approaches and key applications for using insoluble carriers in SDs.

![Figure 1](image_url)  
**Figure 1.** General approaches and key applications for using insoluble carriers in solid dispersions (SDs).

### 2. Fundamental Properties and Physicochemical Characterization of SDs

Generally, SDs can be defined as the dispersion of a poorly water-soluble drug(s) in a carrier or a mixture carrier [49]. A crystalline drug can be transformed into the amorphous form once it is dispersed in polymers [50,51]. In addition, various advantages of SDs, including wettability improvement, reduced size, and porosity of particles, contribute to the dissolution enhancement and bioavailability of poorly water-soluble drugs [52]. In certain circumstances, the molecular interaction has a crucial role in the formation of the amorphous forms of drugs and maintains the stability of SDs.

However, physical stability may prevent further development of SD products. Under storage conditions, an amorphous drug in an SD can recrystallize under thermodynamic and moisture conditions [53]. Fortunately, more homogeneous amorphous SDs lead to the longer physical stability of formulations [54]. Compared to hydrophilic polymers, better hydrophobic interactions between an insoluble carrier and poorly water-soluble drugs probably result in more homogenous SDs. Moreover, hydrophobic carriers might also help to prevent moisture adsorption. Therefore, the use of insoluble carriers may be a good strategy to improve the long-term stability of SDs. With regard to chemical stability, both hydrophilic and hydrophobic compounds can protect the dispersed molecules in SDs at a certain level (e.g., against oxidative degradation) [55]. However, drug molecules, which are susceptible to pH in the gastrointestinal tract, can be degraded if an SD is fabricated from hydrophilic polymers. In contrast, insoluble carriers appear useful in chemical stability by preventing drug release in the medium, which can degrade the model drug [56].

Physicochemical characterization of SDs is an important factor in determining successful formulations and the mechanism of drug release. First, the level of drug crystallinity in SDs can be evaluated via techniques such as powder X-ray diffraction and different scanning calorimetry [57]. Second, the molecular interactions can be characterized by infrared spectroscopy, Raman spectroscopy, nuclear magnetic resonance spectroscopy, X-ray photoelectron spectroscopy, molecular modeling, quantum chemical calculation, and water vapor sorption [58,59]. Third, scanning electron microscopy, atomic force microscopy, and transmission electron microscopy are usually utilized to observe the morphologies of SDs and nano-sized particles [26,58]. The details of those methods can be found in prominent reviews [57–59].
3. Insoluble Carriers at Low pH Levels in SDs

3.1. Dissolution Improvement in Alkaline Environments and for Colonic Delivery

Although the use of enteric coating materials as a carrier in SDs can inhibit drug release at low pH levels, an improvement in drug dissolution in neutral and alkaline media can be obtained with amorphous SDs. Figure 2 describes the ability to incorporate poorly water-soluble drugs in SDs using insoluble carriers at low pH levels. For instance, Eudragit® S, which dissolves above a pH of 7, successfully changes dipyndamole to an amorphous state in an SD by the solvent method [60]. Dipyndamole is a weakly basic drug with a pH-dependent solubility that causes incomplete absorption in the gastrointestinal tract [60]. Therefore, amorphous SDs of dipyndamole significantly increase drug dissolution at pH levels above 7 to improve drug bioavailability [60]. This study also confirmed that dipyndamole and Eudragit® S interact via hydrogen bonding of carboxylic groups and nitrogen atoms [60]. Similarly, Eudragit® S100 has also been shown to be a promising material in SDs of berberine hydrochloride for colonic delivery [61]. In vitro cytotoxicity tests in human colon cancer cells (HCT116 and SW480) have suggested antitumor activity enhancement, which indicates the potential application of SDs with Eudragit® S100 for colon cancer therapy [61].

![Dissolution improvement in alkaline environments](image)

**Figure 2.** The ability to incorporate poorly water-soluble drugs in SDs using insoluble carriers at low pH levels.

The utilization of enteric coating agents in SDs is a potential application for weakly basic drugs with pH-dependent solubility [62,63]. For example, itraconazole is soluble in gastric fluid, but it is likely precipitated after entering the small intestines due to the pH change, leading to low bioavailability [63]. To prevent soluble drugs from dissolving in the stomach, enteric coating agents are used in SDs [62,63]. Moreover, amorphous SDs can increase drug absorption in the small intestine, where higher absorption is observed compared to the stomach [63–65]. Overhoff et al. successfully used hydroxypropylmethylcellulose phthalate in SDs containing itraconazole with the mentioned purposes [63]. In this study, amorphous SDs were fabricated by the solvent method using ultra-rapid freezing [63].

Anionic enteric coating polymers, such as Eudragit® L100 and Eudragit® L100-55, can be applied for delivering cationic drugs in SDs [66]. Maniruzzaman et al. indicated that the amide groups of propranolol HCl and diphenhydramine HCl molecularly interact with the carboxyl group of polymers via hydrogen bonding, resulting in the formation of amorphous drugs in SDs by hot-melt extrusion [66]. In this study, hot-melted extrusion played an important role due to its facilitative ability to enhance the interaction between drugs and polymers in SDs, increasing drug solubility [66–69]. However, preparations of SDs with Eudragit® L100-55 should carefully take into account the temperature during the process because the resulting SDs could be degraded at temperatures below 180 °C [70,71].

3.2. Effects of Enteric Coating Polymers and Preparation Methods on Amorphous SDs

The formation of amorphous SDs with enteric coating materials depends on the drug properties, the type of carrier, and the preparation methods. Figure 3 illustrates factors from enteric coating polymers affecting amorphous SDs. Indeed, in an investigation by Hasegawa et al., the effects of six enteric coating agents on two poorly water-soluble drugs (griseofulvin and phenytoin) were analyzed, but only hydroxypropylmethylcellulose phthalates (HP-50 and HP-55) formed amorphous SDs with...
these drugs [72]. Drugs were still in crystal form when Eudragit® L, Eudragit® S, cellulose acetate phthalate, and carboxymethyl ethoxy ethyl cellulose were used [72]. In a study on MK-0364 SDs, Sotthivirat et al. showed that hydroxypropyl methylcellulose acetate succinate was more effective than hydroxypropylmethylcellulose phthalates and Eudragit® L100-55 in enhancing the dissolution of a poorly water-soluble drug [73]. Moreover, hot-melt extrusion has been demonstrated as a suitable approach for preparing SDs using hydroxypropyl methylcellulose acetate succinate [74,75]. Surfactants have been recommended to be incorporated in SDs to reduce the high temperatures during the hot-melt extrusion processes, which may cause the degradation of both drug and polymers [76].

![Illustration of factors from enteric coating polymers affecting amorphous SDs.](image)

The effectiveness of SDs developed from enteric coating polymers depends on the miscibility between drug and polymer [77]. It has been noted that excessive drug loading in SDs results in drug domains that do not interact with polymer matrices [77]. Amorphous drugs are easily transformed into drug crystals once these domains are exposed to the dissolution medium [77]. Therefore, miscibility and drug recrystallization must be considered in SD formulations with enteric coating agents [77]. The preparation method certainly affects the miscibility in SDs [78]. In an investigation of amorphous SDs of lumefantrine, Song et al. showed that more favorable acid-base interactions were observed in SDs by spray-drying compared to hot-melt extrusion because of their exposure to the solution [78].

To improve stable, amorphous SDs, Shah et al. suggested a method to precipitate SDs (so-called solvent controlled precipitation) [79]. Eudragit® L100, Eudragit® L100-55, Eudragit® S100, hypromellose acetate succinate, and hypromellose phthalate 50 were used as carriers in this study [79]. Briefly, a poorly water-soluble drug and a polymer were dissolved in an organic solvent, which was then precipitated into the aqueous medium [79]. Based on the insoluble properties of the enteric coating agents, the aqueous medium was maintained between pH 1 and 3 to minimize the solubility of the polymers; therefore, the drug was dispersed in the inner carrier and precipitated into microparticles [79]. The precipitates were isolated and dried to form microprecipitated bulk powder with the characteristics of an amorphous SD [79]. By using this technology, enteric coating polymers prevented nucleation, protected against moisture, and maintained supersaturation, immobilizing the amorphous drug in SDs [79]. The authors proposed that the insolubility in medium and possible ionic interactions were the results of the stabilization of the amorphous SDs [79].

Further development of an efficient screening method was also proposed by the same group for the selection of polymer type, drug loading, and solvent in the development of SDs using microprecipitated bulk powder [80]. Specifically, the authors suggested a 96-well platform composed of miniaturized co-precipitation screening (including mixing drugs and enteric polymers in organic solvents, controlled precipitation, isolation, drying, and high throughput characterization) [80]. Practically, solvent-controlled precipitation has been demonstrated as an efficient method for improving the human bioavailability of poorly water-soluble drugs [81]. Vemurafenib has been chosen to prepare
the microprecipitated bulk powder, increasing the human bioavailability five-fold compared to the crystalline drug [81].

Ternary SDs are effective strategies for further enhancing the dissolution of poorly water-soluble drugs [68,82–85]. Enteric coating polymers have been investigated by this approach [86,87]. Ohyagi et al. combined hypromellose and Eudragit® L 100 (or a methacrylic acid copolymer) and showed that the resulting ternary SDs had improved dissolution compared to those of single-polymer SDs [86]. Differential scanning calorimetry and solid-state NMR confirmed that the hydroxyl groups (HPMC) and carboxyl groups (enteric coating polymers) interacted to form the intermolecular interactions that led to dissolution enhancement [86]. Therefore, the authors suggested that this strategy is likely a powerful approach to create SDs for poorly water-soluble drugs [86].

3.3. Nano-Sized SDs from Enteric Coating Polymers

Duarte et al. developed a solvent-controlled precipitation method to produce nano-SDs of carbamazepine by using microfluidization [88]. A similar precipitation process was proposed in which the precipitates were spray-dried to form nano-SDs of approximately 100 nm [88]. The authors compared the results from these SDs with those obtained with amorphous SDs prepared by spray-drying but without precipitation process [88]. The higher dissolution rate and bioavailability of the nano-SDs demonstrated that particle size played a key role in improving the bioavailability of carbamazepine [88].

Electrospinning has also been used as an alternative approach to prepare nano-sized SDs with enteric coating polymers [89]. Balogh et al. utilized Eudragit® FS 100 in SDs of poorly soluble spironolactone by electrospinning and hot-melt extrusion to produce nanofibers and amorphous SDs, respectively [89]. Both methods showed impressive dissolution enhancement at a pH 7.4 [89]. However, drug release in the gastric fluid was higher in the case of the electrospun samples compared to the extruded SDs due to the large surface area of the nanofibers [89]. In general, Eudragit® FS 100 was demonstrated to be an excellent carrier in SDs, and hot-melt extrusion was recommended for colon-targeted delivery of poorly water-soluble drugs with this polymer [89].

Although hydroxypropylmethylcellulose acetate succinate has been shown to be a promising carrier in SDs, it is difficult to process using electrospinning [90–92]. However, this process has been used successfully to produce nanofibers of spironolactone by adjusting the conductivity in a study by Balogh et al. [90]. This study indicated the importance of solution conductivity in electrospinning with hydroxypropylmethylcellulose acetate succinate because the drug dissolution from nanofibers was dependent on the adjusted conductivity [90]. Compared with other hydrophilic polymers (i.e., hydroxypropyl methylcellulose and polyvinylpyrrolidone K-30), hydroxypropylmethylcellulose acetate succinate is less effective in improving the dissolution of darunavir [93].

Hassouna et al. proposed a combination of the emulsification-diiffusion method and freeze-drying to prepare ibuprofen-loaded Eudragit® L100-55 nanoparticles, resulting in amorphous SDs [94]. The encapsulation of the drug in Eudragit® L100-55 nanoparticles not only sustained drug release but also stabilized the amorphous state during storage [94].

4. Water-Insoluble Carriers for SDs

4.1. Sustained Release and Stability Improvement

Figure 4 illustrates the applications of water-insoluble carriers for SDs. For example, Eudragit® RS 100 and RL 100 have been utilized in sustained-release SDs because they are insoluble at physiological pH values but can swell and become permeable to water [95–97]. By formulating misoprostol in SD matrices with these polymers, drug release could be slowed, and drug stability can be protected from degradation by water [96]. Interactions via hydrogen bonding and channel formation are attributed to the drug release pattern [98,99]. Compared to nanoparticles with the same Eudragit® RS 100 polymer in their formulations, diclofenac sodium–Eudragit® RS100 SDs are shown to have a slower drug release rate [97].
In addition to aiding in sustained drug release, Eudragit® RS 100 and RL 100 are also used in a photoprotective strategy [100]. Although the SDs do not transform the drug from its crystalline form, drug release is prolonged, and the photosensitive compound diflunisal is protected due to the dispersion of the drug in the polymers in a molecular or microcrystalline form [100].

Amorphous SDs with Eudragit® RS PO are developed for transdermal films because a high concentration of the released drug may enhance skin permeability [101]. However, hydrophilic excipients (e.g., gelucire, xanthan gum) are suggested to be incorporated into transdermal systems to allow water sorption and create triggered drug delivery systems [101].

4.2. Dissolution Improvement

Due to the low wettability of water-insoluble carriers, the amorphous SDs from these polymers have shown a lower dissolution rate compared to water-soluble polymers [102,103]. Therefore, Ngo et al. developed hydrophilic-hydrophobic polymer blends in SDs to enhance dissolution [83,104]. Specifically, zein was used as an insoluble carrier and combined with hydroxypropyl methylcellulose to modulate molecular interactions and drug crystals [83,104]. Compared to the single polymer-based SDs (zein or hydroxypropyl methylcellulose), this combination resulted in a high reduction of drug crystallinity, high wettability, and good performance of molecular interactions [104]. The use of hydrophobic polymers in SDs might facilitate molecular interactions with poorly water-soluble drugs for changing drug crystals to amorphous forms [104]. In the case of the limited dissolution rate of very poorly soluble drugs, the addition of surfactant in this polymer blend was part of a strategy to decrease drug recrystallization and increase wettability [83].

4.3. Controlled Release of SDs with Water-Insoluble Carriers

Under certain circumstances, dissolution enhancement and sustained release are required to improve the bioavailability of a poorly water-soluble drug. For example, Yang et al. proposed a system including two main parts: (1) SDs to improve the dissolution rate of nitrendipine and (2) the presence of Eudragit® RS PO in the SDs to sustain drug release [105]. Specifically, the drug and Eudragit® RS PO were dissolved in an organic solvent, which was then incorporated with Aerosil to form microspheres [105]. The drug release from the microsphere SD could be modulated by altering the amount of Eudragit RS PO [105].

In a concept similar to microsphere SDs, Huang et al. used Eudragit® RL and ethylcellulose blends to control nifedipine release [106]. This study indicated that these SDs exhibited good stability because of molecularly stable interactions via hydrogen bonding between the drug and the Eudragit® RL and ethylcellulose blends [106]. However, it has been noted that the internal structure of the microspheres and the state of nifedipine would change if high drug loading occurs in the formulations [107]. The presence of excessive amounts of drugs would form drug reservoirs, resulting in a change in the drug release kinetics [107].
5. Hydrophobic Substitution of Polymers in SDs

To interact with poorly water-soluble drugs, hydrophobic polymers can be substituted on polymers. This substitution would lead to the formation of a new material that can be used in SDs to enhance drug solubility and bioavailability. Orienti et al. investigated the substitution of polyvinyl alcohol with triethylene glycol monoethyl ether for preparing progesterone SDs [108]. Given the presence of the amphiphilic tetraethylene moiety in the substituted polymer, the solubility of progesterone increases with increasing polymer concentration, which improves the chance of interactions forming between the hydrophobic parts of the polymers and the drug [108].

In addition to the amphiphilicity of the new polymer, the substituted polymer concentration strongly affects the physicochemical properties of the drug. For instance, in an investigation of the effect of hydroxypropyl methylcellulose acetate succinate on the crystallization suppression of four model drugs (carbamazepine, nifedipine, mefenamic acid, and dexamethasone), a lower concentration of substituted succinoyl has resulted in a strong suppression of drug crystallization [109]. However, a high substituted succinoyl concentration has been recommended to increase the drug dissolution rate due to its high hydrophilicity [109].

In an effort to create unique material for SDs, a zein-hydroxypropylmethylcellulose conjugate has been proposed to enhance the dissolution of poorly water-soluble drugs [110,111]. In fact, the conjugates from these materials have shown amphiphilic properties and formed self-assembled nanoparticles during a dissolution test [110,111]. Therefore, the conjugate not only acts as a carrier to change drug crystallinity to an amorphous state but also encapsulates a poorly water-soluble drug in nano-size particles in dissolution media, resulting in enhanced dissolution [110,111]. Moreover, these studies have also indicated that the conjugated material is suitable for different model drugs in different gastrointestinal tract environments [110,111].

6. Conclusions

Substantial strategies for using insoluble carriers in SDs include pH-sensitive carriers, water-insoluble carriers, and hydrophobic substitution of polymers. In addition to improving the drug dissolution rate, these insoluble carriers in SDs could be utilized to control drug release or target delivery in the colon in the same formulations with poorly water-soluble drugs. The application of advanced nanotechnology in SDs containing insoluble carriers has shown promising approaches and materials in recent studies. Moreover, the improved stability of SDs containing insoluble carriers compared to other polymers has been reported in some cases [112]. With regard to the evaluation of SDs containing enteric coating polymers, the selection of in vitro dissolution conditions should be considered carefully. For example, one investigation demonstrated that the in vitro performance of an amorphous SD of celecoxib in fasted state simulated intestinal fluid with a pH of 7.4 was more representative of the in vivo performance of the SD than the in vitro performance in fasted state simulated intestinal fluid with a pH of 6.5 [113].

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