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Review Article

SOLID DISPERSION TABLETS IN IMPROVING ORAL BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

Recent advances in the field of conversion of solid dispersions of poorly water-soluble drugs in a wide range of hydrophilic or water-soluble carriers into solid dispersion tablets have shown great promise in improving solubility, dissolution rate and oral bioavailability of such drugs. Moreover, proper choice of tablet excipients during tableting of optimised solid dispersions can produce either fast/rapid or sustained drug release profile. Release kinetics have been found to follow either first-order kinetics or Higuchi model and release profiles in most of the cases have been found to be superior to that of conventional tablets or capsules. The present review aims to sum up the various studies on solid dispersion tablets and establish the novelty of this unique approach in the overall improvement of oral bioavailability of poorly water-soluble drugs in a simple and cost-effective manner.

Keywords: Carrier, Controlled release, Fast release, Fickian transport, First-order kinetics, Higuchi model, Solid dispersion, Superdisintegrant, Sustained-release, Tablet

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INTRODUCTION

For most therapeutic agents used to produce systemic effects, the oral route is the easiest, convenient, and most appropriate mode of drug administration due to high patient compliance, cost-effectiveness, least sterility constraints, flexibility in the design of dosage form, consistent production, simplicity of dosing and dosage precision [1-7]. However, poorly water-soluble drugs when administered orally, have shown low bioavailability since their bioavailability is largely dependent on the dissolution of the drug in the gastrointestinal fluids [8-11]. Approximately 40 % of the new chemical entities (NCEs) developed in the pharmaceutical industry suffer from poor water solubility. Therefore, one of the prime areas of current interest in dosage form development involves the enhancement of solubility, dissolution rate, and hence oral bioavailability of poorly water-soluble drugs [4, 12-21]. Salt formation, micronization, nanosuspensions, spray drying, hot-melt extrusion, lipid-based delivery systems, inclusion complexes, solubilization, supercritical fluid recrystallization, song crystallisation, micronization, and solid dispersions have commonly been used to increase the dissolution rate and, thereby, oral absorption and bioavailability of poorly soluble drugs [13, 22-31].

Solid dispersion refers to the group of solid products consisting of at least two different components, generally a hydrophilic carrier and a hydrophobic drug where the carrier can be either crystalline or amorphous [12, 32]. The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug, griseofulvin, and a water-soluble carrier, urea in the early 1960s [33, 34]. Solid dispersions hold great promise in increasing solubility, dissolution, absorption, bioavailability, and hence, the therapeutic efficacy of poorly water-soluble drugs in the dosage form. In a solid dispersion, the drug is dispersed molecularly in a solid-state in a solid carrier system [35-38]. The mechanisms of enhancement of solubility and dissolution rate by employing solid dispersion include reduction of the particle size of the drug to submicron size or to molecular size in the case where solid solution is obtained, improvement in wettability, and dispersibility, the transformation of a crystalline form of drug to its amorphous form, reduction in aggregation and agglomeration tendency of drug particles [5, 39-42].

Carriers play a major role in the formulation of solid dispersions as their properties exert a significant influence on the release profile of the dispersed drug [43-49]. They can be hydrophilic or hydrophobic in nature, depending on which there can be solid dispersions promoting rapid dissolution of poorly water-soluble drugs or dispersions with sustained-release characteristics resulting in an overall improvement in the bioavailability [45, 50-53]. Hydrophilic excipients like PVP, Gelucire,β-cyclodextrins, PEG 4000, PEG 6000, PEG 10000, mannitol, urea, lactose, sucrose, poloxamers, hydroxypropyl cellulose [HPC], hydroxypropyl methylcellulose [HPMC], etc as well as hydrophobic excipients like ethyl cellulose [EC], Eudragits, hydroxypropyl methylcellulose phthalate [HPMCP] have been employed as carriers in various studies to obtain solid dispersions of rapid and sustained-release profile [5, 8, 25, 54-60].

Several articles do exist focussing on the technique of solid dispersion in improving oral bioavailability but not a single review article could be found compiling various studies and investigations on solid dispersion tablets designed to produce either fast/rapid release or sustained release profile. In the literature, some studies on solubility enhancement strategies culminate with the identification of the best carrier and optimized drug: carrier ratio in solid dispersion, whereas others have proceeded towards the conversion of optimized solid dispersions into tablets with different release profiles with an ultimate aim to improve oral bioavailability. This article provides an update on solid dispersion tablets with fast and sustained release profiles with an overview of various carriers, excipients used, and also release characteristics to guide readers in the right direction.

Formulation of solid dispersion tablets

In the following sections, recent advances in the field of conversion of solid dispersions to solid dispersion tablets have been discussed and attempts have been made to compare release profiles thus obtained with the ones from conventional tablets. Complete knowledge on the manufacturing and characterization of solid dispersion tablets will provide a holistic view of the role of a novel technique of solid dispersion and its subsequent tableting in the overall improvement of oral bioavailability of poorly water-soluble drugs.

Fast dissolving solid dispersion tablets

Tadalafil solid dispersion was prepared by spray drying method using skimmed milk as a carrier. Fast dissolving tablets containing tadalafil solid dispersion were developed by direct compression using crospovidone, croscarmellose sodium, or sodium starch glycolate as superdisintegrant in different ratios with microcrystalline cellulose PH-102 along with directly compressible mannitol. Tablet with 4% w/w crospovidone demonstrated wetting time of 35 secs and released 99.73% drug in 30 min enabling fast dissolution of poorly water-soluble drug [61].

Solid dispersion of carvedilol in PEG 6000 and HPMC K100M was prepared by kneading method. The optimized solid dispersion was compressed into a tablet using crospovidone. Optimized formulation containing a higher concentration of superdisintegrant exhibited faster drug release in comparison to commercial product and the release mechanism was found to be super case II transport [62].

Solid dispersions of micronized glyburide in polyethylene glycol 6000 prepared by the cofusion method were compressed into tablets by direct compression containing 1:10 (w/w) drug: PEG 6000 cofused product. The tablets thus obtained exhibited the best performance with a 135% increase in drug dissolution efficiency at 60 min [63].

Ternary solid dispersions of domperidone with Gelucire 50/13 and Poloxamer 188 were successfully prepared by the fusion method. Ternary solid dispersion with 1:2:1.5 of drug: Gelucire 50/13: Poloxamer 188 was successfully incorporated into fast dissolving tablet by direct compression method. Fast dissolving tablet containing crospovidone as superdisintegrant (4% w/w) exhibited disintegration time of 19 s and approximating 100% drug release at 30 min in 0.1N HCl. Stability studies indicated the fast dissolving tablet containing ternary solid dispersion to be stable at accelerated environmental conditions for 1 mo [64].

Solid dispersion(SD) of ondansetron hydrochloride (OSH) was prepared by a solvent evaporation method using superdisintegrants like croscarmellose sodium (CCS), crospovidone (CP), sodium starch glycolate (SSG), and low substituted hydroxypropyl cellulose (L-HPC) respectively as carriers. The optimized SD formulation of drug and crospovidone in 1:3 ratio was converted into fast dissolving tablets (FDTs) which showed the fastest disintegration (3.22s), least wetting time (10.5s), and rapid dissolution (97.98% drug release in 30 min) [65].

A 4-fold increase in aqueous solubility was observed with solid dispersion of frusemide-containing drug: PVP-K30 in the ratio of 1:2. The optimized solid dispersion was converted into a tablet using different formulation excipients such as microcrystalline cellulose (MCC102) as binder, croscarmellose sodium as a disintegrant, magnesium stearate (0.5% w/w) as a lubricant that exhibited a better dissolution profile with respect to mean dissolution time (8.44 min) and dissolution efficiency in 30 min (42.54%) in simulated gastric fluid (pH 1.2) at 37 °C±0.5 than the marketed product and release followed Weibull and Korsmeyer models [66].

The solid dispersions of tenoxicamwere prepared with Kollidon CL and SLS, PVP K30 and Poloxamer 127 by using the solvent evaporation method. The optimized solid dispersion containing tenoxicam, Kollidon CL and sodium lauryl sulfate in the ratio of 1:3:1 exhibiting 99.11±5.17% drug release in 90 min in phosphate buffer pH 7.4 was converted into fast-dissolving tablets. The tablet containing gellangum(6%), fenugreek seed mucilage(10%), L-HPC(14%), aspartame(5%), mannitol(20%) and MCC(9.67%) produced maximum drug release of 99.68±1.52% in 10 min [67].

Solid dispersions containing nevirapine, urea, PEG 400 in the ratio of 1:2 exhibited99.68% and 98.58% drug release respectively in 60 min in 0.1N HCl buffer (pH 1.2). Nevirapine tablets were formulated employingsodium starch glycolate and croscarmallose sodium as a superdisintegrant, Aerosil, lactose, magnesium stearate by direct compression method. Optimized formulation containing SD (57%), croscarmallose sodium(2%), Aerosil (1.2%), lactose(38.7%), magnesium stearate(1.2%) showed 100% drug release at the end of 60th minute. The optimized tablet formulation followed the first-order release kinetics [68].

The fastest drug release was obtained from solid dispersions of nisoldipine in Poloxamer 407 with drug: carrier in the ratio of 1: 5. Cumulative drug release was found to be 99.13% in90 min in phosphate buffer (pH 6.8). Fast dissolving nisoldipine tablets were formulated using various proportions of sodium starch glycolate, croscarmellose sodium, and crospovidone as superdisintegrants, magnesium stearate, Aerosil, microcrystalline cellulose by direct compression method. Optimized formulation containing SD(60%), magnesium stearate(1%), aerosol(1%), microcrystalline cellulose(32%), croscarmellose sodium(6%) showed 99.6% drug release in 90 min [69].

The solid dispersion containing glimepiride and Gelucire 55/18 in the ratio of 1:5 was compressed as the immediate-release tablets by using croscarmellose sodium(CCS), microcrystalline cellulose PH 112(MCC PH112), lactose monohydrate, hydroxypropyl cellulose(HPC), sodium stearyl fumarate and magnesium stearate. Based on *in vitro* drug release data; formulation containing SD(16.86%), CCS(6.25%), MCC pH112(40.64%), lactose monohydrate(31.25%), HPC(3.13%), magnesium stearate(1.87%)was identified as the best formulation which produced 95% drug release within 30 min in phosphate buffer(pH7.8). Drug release followed first-order release kinetics [70].

Solid dispersions of irbesartan were prepared using Soluplus, PEG6000, and Kollidon as carriers. Solid dispersions of irbesartan containing drugs with Soluplus or Kollidon in the ratio of 1: 1 improved the aqueous solubility of irbesartan that showed the highest solubility (6.41 mg/10 ml) in 0.1N HCl buffer(pH 1.2). These dispersions were further formulated as fast dissolving tablets using croscarmellose sodium (CCS), SSG as superdisintegrants, MCC (Avicel pH-102), magnesium stearate, talc by direct compression method. The optimized formulations F4(drug: Soluplus)and F8 (drug: Kollidon)containing SD(30%)CCS(15%), MCC(53%), talc(1%), magnesium stearate(1%) showed 100% drug release within 50 min [71].

The optimized solid dispersion containing risperidone and β-cyclodextrin in the ratio of 1:3improved the dissolution of risperidone. Cumulative drug released was found to be 82% in 30 min in phosphate buffer (pH6.6). The optimized SD was formulated as fast dissolving tablets by using doshion P544 resin (C) as a taste masking agent, mannitol and aspartame as a sweetening agent with different superdisintegrants such as croscarmellose and crospovidone to improve bioavailability and hence better patient compliance. The optimized formulation F4 containing SD(8%), doshion-P544C(12.5%), mannitol(47.5%), camphor(2.5%), Ac-di-sol(4%), aspartame(10%), crospovidone(12.5%),magnesium stearate(1%), talc(1%), aerosil(1%) showed 100% drug release in 120 min in phosphate buffer (pH 6.8) [72].

Solid dispersion of azilsartan was developed using soluplus® as a novel solubility enhancer to observe the significant effect of independent variable i.e. concentrations of drug and soluplus on solubility (102.03±3.48 µg/ml). The optimized solid dispersion ASD2 containing 40 mg azilsartan and 80 mg of soluplus showed maximum drug release i.e. 99.82 % within 30 min in phosphate buffer (pH 7.8). Solid dispersion of azilsartan was compressed into an immediate-release tablet using 4% sodium starch glycolate as a superdisintegrant 0.5 % magnesium stearate as a lubricant [73].

Solid dispersion of piroxicam in Soluplus in the ratio of 1:4 enhanced drug solubility. The dispersion when converted into fast dissolving tablets containing microcrystalline cellulose, sodium starch glycolate (6% w/w), hydroxyl propyl methylcellulose, magnesium stearate, talc showed fast disintegration (68±1.5 sec), wetting time (29 sec), and drug release of 99.90% within 12 min in 0.1 N HCl (pH 1.2) [74].

Solid dispersion of thiocolchicoside (TCS) prepared by fusion method using Poloxamer 188 in the ratio of 1:6 was found to possess satisfactory solubility in distilled water (up to 0.78±0.04 µg/ml) and in 0.1 N HCl (up to 0.69±0.05 µg/ml). The release of TCS from the

prepared SDs followed first-order kinetics. The optimized solid dispersion compressed into tablet using SD(50%), lactose (20%), starch (6%), microcrystalline cellulose (20%), magnesium stearate (2%), talc (2%) showed drug release of 98.85% within 60 min in 0.1 N HCl [75].

Summarising the above studies on fast dissolving tablets from solid dispersions of poorly water-soluble drugs with various carriers, it can be concluded that compression of the optimized formulation into a tablet by direct compression, with the addition of different superdisintegrants can achieve a better drug release profile compared to conventional tablets.

Sustained release solid dispersion tablets

Controlled release floating capsules of ciprofloxacin solid dispersions were prepared by using mannitol and lactose as water-soluble carriers to improve the dissolution rate of the drug. A 3-fold increase in dissolution rate was observed with solid dispersion containing drug: lactose in the ratio of 1: 4. The optimized solid dispersion was converted into granules with ethyl cellulose and HPMC to form granules with controlled release behavior. The granules were filled into capsules and the capsules thus formed exhibited a floating duration of 6h [6].

Solid dispersion of ibuprofen in PEG 6000 was prepared by the melting-solvent method to increase the aqueous solubility. The solid dispersion was converted to a matrix tablet with the combination of hydrophilic swellable polymer, carbopol, and hydrophobic non-swellable polymer, ethyl cellulose. The cumulative drug release was found to be in the range of 68.76±3.04 to 95.33±2.34 % in 8 h. Development of swellable matrix tablets with ibuprofen solid dispersion in PEG 6000 provided better dissolution and absorption profile resulting in improved patient compliance [24].

Optimized tacrolimus-loaded fast-dissolving solid dispersions formulated with drug, hydroxypropyl-β-cyclodextrin (HP-β-CD) and dioctyl sulphosuccinate (DOSS)in the ratio of 5:40:4 (w/w) produced 700-fold, 30-fold and 2-fold enhancement in solubility, dissolution rate, and oral bioavailability, respectively. The formulation was converted into prolonged-release tablets with solid dispersion, HPMC, ethylcellulose and talc at the weight ratio of 20:66:112:2. No significant differences in AUC, Cmax, tmax and MRT values could be found between the prolonged-release tablets and commercial capsules when studied in beagle dogs. Thus the formulations may be assumed to be bioequivalent [76].

Free-flowing solid dispersion granules of poorly water-soluble losartan potassium were prepared by adsorbing the melt of the drug and Poloxamer 188 onto the surface of Aerosil 300 (fumed silicon dioxide), which were then compressed into solid dispersion-loaded sustained release matrix tablets with polyethylene oxide (PEO). Drug release was observed in gastric fluid (pH 1.2) for 2h and in intestinal fluid (pH 6.8) for 10 h. Therefore, a combination of approaches like solid dispersion and surface adsorption along with subsequent formulation of matrix tablets could improve the dissolution and release pattern of poorly soluble drugs like losartan potassium [77].

Self-emulsifying solid dispersions (SESD) of isradipine were prepared by melting method using surfactant and fatty acid in Poloxamer 407 (POX 407). Significant improvement in drug dissolution rate was observed. Then SESD were converted into controlled release matrix tablet by direct compression technique using HPMC that significantly increased oral bioavailability and extended plasma concentration compared with the marketed product [78].

Disintegration-controlled matrix tablet (DCMT) of nilvadipine was prepared from its solid dispersion granules containing low-substituted hydroxyl propylcellulose (L-HPC) as a disintegrant and adding hydrogenated soybean oil (HSO) as wax to control the release of nilvadipine (NiD) from DCMT. Drug release could be controlled either by increasing the amount of wax or decreasing the amount of L-HPC. It has been observed that drug release from DCMT was controlled solely by tablet disintegration and release followed the Hixson-Crowell model [79].

Nimodipine (NMD) solid dispersions(SD) were prepared using acombination of hypromellose acetate succinate (HPMCAS) and hypromellose phthalate (HP-55) as the carriers as well as HPMCAS as the single carrier by melting method to overcome the limitations associated with conventional NMD solid dosage forms such as poor bioavailability and limited clinical efficacy. Delayed-release tablets from NMD-SD were obtained by direct compression method. The tablets released less than 10% drug in the artificial gastric acid in the initial 2 h and more than 90% drug in 14 h in the artificial intestinal fluid [80].

Aqueous solubility of carvedilol was improved by solid dispersion in Poloxamer 407 and PVP K30. Sustained-release carvedilol tablets were developed from the solid dispersions using HPMC K 15M at various concentrations. Significant improvement was observed in the t_{50} value and drug release profile from sustained-release tablets of carvedilol solid dispersions [81].

Nintedanib solid dispersion was prepared by electrospraying technology with PVP K 30 and soybean lecithin to improve its dissolution behavior. Drug release from the solid dispersion was found to be>60% in 30 min and 100% in 60 min. The release of the nintedanib from its solid dispersion in sustained-release capsules was found to reach 93% in 12 h and followedRitger–Peppas model. *In vivo* studies in rats indicated higher bioavailability from sustained-release capsules in comparison to the commercial soft capsules or solid dispersions [82].

Ziprasidone hydrochloride solid dispersion was prepared by kneading method with PEG 6000 and β-cyclodextrinto to enhance the solubility and dissolution rate of the poorly soluble drug. The sustained-release matrix tablets were compressed from the solid dispersions using matrix polymers like guar gum and HPMC. The release of the drug from the sustained-release matrix tablets of ziprasidone hydrochloride solid dispersion followed Higuchi kinetics with Fickian transport [83].

Thus after summarising the various studies on sustained-release tablets from solid dispersions of poorly water-soluble drugs, it can be concluded that the development of such tablets with hydrophilic swellable polymers or a combination of swellable-hydrophobic polymers or gum or PEO, exhibited-extended release profile in simulated intestinal fluid for a period varying from 8-24 h and release kinetics usually followed Higuchi model. Therefore, sustained-release tablets of solid dispersions may be assumed to form matrix wherefrom drug release occurred in most cases via Fickian diffusion.

CONCLUSION

From the above discussion, it can be concluded that incorporation of either super disintegrants or hydrophilic swellable polymers or hydrophobic polymers into optimized solid dispersion formula with satisfactory enhanced solubility and dissolution profile can produce solid dispersion tablets with either fast or sustained release profile. Therefore, the problem of low oral bioavailability with poorly water-soluble drugs can be successfully overcome by the novel technique of conversion of solid dispersions into tablets.

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CONFLICT OF INTERESTS

No conflict of interest by authors.

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