AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Recent Advancements in Solubility and Dissolution Enhancement of Simvastatin: A Review

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ABSTRACT

A drug should be present in dissolved or solublized state before producing its therapeutic effect however in current market more than 40% drugs are poorly soluble in water. Such drugs exhibit poor dissolution rate and slow absorption throughout the gastrointestinal tract which leads to irregular bioavailability. Thus various techniques has been adopted for solubility and dissolution enhancement of poor water soluble drugs thereby bioavailability. Solubility plays an important role in achieving the desired plasma drug concentration. In this review article various techniques like solid dispersion, SLNs, SEDDS, dried emulsion were discussed for solubility and dissolution rate improvement of BCS class II anti hyperlipidemic drug Simvastatin. Amongst various method described in this review, solid dispersion was found to be most used technique by researcher as it provide ease in preparation and efficiency in terms of resolving the solubility and dissolution problems associated with Simvastatin.

Keywords: solubility, surfactant, polymers, solid dispersion

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Received 15 February 2013, Accepted 22 February 2013

Please cite this article in press as: Sav A *et al* Recent Advancements in Solubility and Dissolution Enhancement of Simvastatin: A Review. American Journal of PharmTech Research 2013.

INTRODUCTION

Solubility and dissolution rate are the key evaluating factors for poorly water soluble drugs to define their bioavailability. Due to limitation of these factors, they show poor absorption throughout gastro-intestinal tract often results into insufficient bioavailability besides having good permeation through the epithelial cell [1] As per European pharmacopoeia, it revealed that more than 40% of the drug substances have aqueous solubility below 1mg/ml and the 32% have an aqueous solubility below 0.1mg/ml [2, 3]. This presents bigger challenge in front of formulation scientist in industries to develop a suitable dosage form for such poorly water soluble drugs [4].

Various method have been reported for solubility and dissolution rate enhancement of BCS class II drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization and hydrotropy [5]. This review is prepared to provide a brief idea about various methods adopted for solubility and dissolution improvisation of Simvastatin and finally development of a suitable oral dosage forms.

Simvastatin (SIM) is an antihyperlipidemic agent given in the strength ranging from 5-40 mg by oral route. It has poor bioavailability (< 5%) due to limited solubility and short biological half life (3h). Its chemical structure is given in figure 1. It is a synthetic methyl derivative of lovastatin, fermented product of *Aspergillus terreus*. It metabolized to β- hydroxyl acid form, a major metabolite which inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in the biosynthesis of cholesterol[6]. SIM is available as white, crystalline and non-hygroscopic powder. It is practically insoluble in water (30 µg/mL), and 0.1 M HCl (60 µg/ml). This review avoids discussion of basic details about solubility such as definition and various methods used for solubility enhancement. We have directly focused on methods and results obtained by various scientists who worked in the area of solubility and dissolution rate enhancement thereby bioavailability of SIM in last few years.

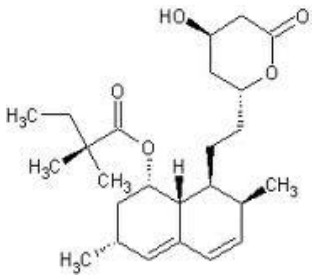

Figure1. Chemical Structure of Simvastatin

SOLID DISPERSION (SD)

Kneading method:

Kumar *et al* worked on solid dispersion preparation by kneading method. SIM and hydrophilic carrier poloxamer 188 were mixed in weight ratio of 1:2, 1:5 and 1:8 using a glass mortar and pestle. Kneaded for 30 min using small volume of ethanol-water mixture to give a thick paste and dried at 45 °C temperature. Dried solid mass was powdered and sieved through 30 mesh and finally 60 mesh to get uniform particle size. Solid dispersed drug showed increase in water solubility with increase in carrier concentration as compared to plain drug. Dissolution efficiency was also increased by two fold with solid dispersion prepared from the drug polymer ratio 1:8.This results suggested that Poloxamer 188 [(Poly (ethylene glycol)-block-poly (propylene glycol)-block-poly (ethylene glycol)] imparts some hydrophilic property to SIM that results into enhanced solubility and dissolution rate [7]

Cogrinding and Spray drying

Pattewar *et al* has studied the effect of natural polymer chitosan and synthetic polymer HPMC E3LV on solubility of SIM. They have prepared the solid dispersion in weight ratio of 1:1 to 1:9 following two method, co grinding mixing and co solvent evaporation by spray drying. Mixture of drug and polymers was co-grinded for 5min, in ceramic mortar and sieved through 100 # mesh. In case of co solvent evaporation method, SIM with chitosan solution was prepared in 1:1, 1:2, 1:6 and 1:9 ratio. The solution for spray was prepare by dissolving 1g of drug in 40 ml of methanol and 1g of Chitosan in 1% acetic acid and both the solutions were mixed to produce clear solution. Solvent was evaporated using spray dryer (LU-222, Advanced, Labultima, India) with an inlet temperature 120 °C and outlet 80 °C, feed pump speed 10 ml per minute and aspiration 45 %. SIM with HPMCE3LV solutions were prepare by dissolving 1g of drug in 70 ml of methanol and 1g of HPMCE3LV in 30 ml of distilled water and spray dried. An immediate release tablet formulation was prepared using sodium starch glycolate as super disintegrant, citric acid, sodium bicarbonate and lactose as release enhancer.

Dissolution test of tablets were performed in pH 1.2 HCl buffer and pH 7 buffer with USP dissolution apparatus II at 50 rpm and 37 ± 0.5 °C. Results indicate solubility improvement by several folds and dissolution efficiency (% DE) increase by two folds with drug and carrier ratio 1:6. Co grinding mixing was found to be showed better results as compared to co solvent evaporation method. It also suggested that natural polymer chitosan has better property in terms of solubility enhancement of the chosen drug as compared to HPMC E3 LV. DSC and XRD studies reveals about decrease in crystalline state of pure SIM and SEM studies showed conversion of crystal rod shape plain Simvastatin into irregular size and shape. The change in

percent crystallinity of SIM and increase in surface wettability of drug are the two main mechanisms for solubility improvement[8].

Solvent evaporation

Shinde *et al* worked on solid dispersion preparation based on PEG 6000. They have prepared SIM and PEG 6000 solid dispersion in weight ratios of 1:1, 1:2 and 1:3% w/w with the help of little ethanol containing hydrophilic adsorbant Aerosil® 200 in a constant proportion. The solvent was removed under reduced pressure to get solid mass. Solubility studies showed increase in solubility with increase in proportion of both the carriers. Mechanism for these results involves good wetting property associated with PEG 6000 and very finer size of Aerosil® 200 with larger surface area made immediate interaction of solid dispersed products and solubilizing media. *In-vitro* dissolution studies for plain SIM and SDs were carried out in USP Apparatus 2, media containing 900 ml of 0.01 M phosphate buffer pH 7.0 with 0.5% SLS at 37 ± 0.5° C and stirred at 50 rpm. SDs showed 90.68% drug release in 90 min as compared to plain which exhibited 27% drug release in 2h. The improved dissolution was attributed to a reduction in particle size of the drug, its rapid deposition on the surface of the carrier and improved wettability. As the proportion of carriers increase, more surfaces will be available for adsorption of drug crystals on evaporation of solvent, this leads to an increase in interfacial area of contact between the drug particles and dissolution medium. The affinity between the hydrophilic inert carriers and dissolution fluids also aids in rapid penetration of dissolving fluid into drug particles. FTIR results indicate absence of any chemical incompatibility between drug and excipients. DSC, Powder X ray diffractogram confirms the decrement in drug Crystallinity in solid dispersed form. SEM study showed change in the physical form of SIM from crystal needle shape to round to irregular shape [9].

Boddupalli *et al* adopted solvent evaporation method for SIM solid dispersion preparation. They evaluated the effect of super disintegrants like Sodium Starch Glycolate (SSG), Cross Povidone (CP) and Cross Carmalose Sodium (CCS) on solubility and dissolution enhancement of SIM. Drug and super disintegrant was dissolved weight ratio of 1:1 in minimum quantity of acetone and evaporated using rota evaporator. Studies found that highest dissolution rate was observed with solid dispersion prepared with cross povidone 90.36% drug release at the end of 3h where as plain SIM showed 14.49% drug release in same time. Dissolution study with super disintegrant SSG showed 74.7% and CCS 75% drug release. Dissolution study was performed using USP apparatus type 2 with 900ml dissolution medium (distilled water with 0.25% SLS) at 37 °C±0.5°C at 100rpm for 3h. A suitable tablet dosage was developed and evaluated for

dissolution rate and similarity factor (f2). Similarity value was found to be more than 50 indicating the similar drug release profile between all the tablet formulations. FTIR study confirms absence of any chemical interaction and X ray diffractograms showed transition of crystalline drug into amorphous phase. It concludes that increase in dissolution rate was due to increase in surface hydrophilicity of hydrophobic drug in presence of hydrophilic super disintegrants [10].

Pandya *et al* worked upon solubility and bioavailability enhancement of SIM by co-solvent evaporation method. They followed two methods for solvent evaporation, rota evaporation and spray drying. For rota evaporation, the solution was prepared by dissolving 2 g of SIM in 100 ml methanol and 2g HPMC K3LV in 60 ml distilled water then both the phase was mixed to give clear solution. Solvent was evaporated for 30 min in rota evaporator. In case of spray drying, 2g SIM in 70 ml methanol and 2 g HPMC K3LV in 30 ml distilled water mixed to give clear solution. Then spray dried at inlet temperature 110°C and outlet 60°C, feed pump speed 10 ml per minute and aspiration 45%. Dissolution study of co-solvent-evaporated mixtures and SIM was performed in a capsule using pH 1.2 HCl buffer and pH 7 (SLS, 0.5%) buffer with USP dissolution apparatus I at 50 rpm and 37±0.5°C. Aqueous solubility study indicated 15-20 folds increase water solubility of co solvent evaporated SIM as compared to plain SIM. At the end of 30 min of dissolution, plain SIM showed about 27% cumulative drug release, spray dried showed 88% and rota evaporated SIM showed 73% cumulative drug release. Therefore spray dried method was concluded as better method than rota evaporation for dissolution enhancement. *In vivo* hypolipidemic activity was studied in albino rats (wistar strain). Spray dried SIM showed 3.3 folds decrease in cholesterol level and rota evaporated SIM also showed significant decrease in cholesterol level. DSC and XRD studies confirmed presence of amorphous SIM in solvent evaporated system. Hence studies prove that HPMC K3LV can be employed for the dissolution rate enhancement of poor water soluble drug [11].

Rio *et al* described the surface solid dispersion method (SSD) for solubility and dissolution enhancement of SIM. For SSDs preparation hydrophilic carriers Sodium starch glycolate (SSG) and croscarmellose sodium (CCS) were used in the ratios of 1:1, 1:2, and 1:3. Co evaporation method adopted for SSD preparation. 1 g of simvastatin was dissolved in a minimum amount of ethanol in which hydrophilic carrier was suspended. The mixture was continuously stirred at 100 rpm using an electronic stirrer at room temperature until all the solvent evaporated. The in vitro dissolution study was carried out in USP Apparatus 2 containing 900 ml of 0.01 M phosphate buffer pH 7.0 with 0.5% SLS at 37 ± 0.5° C and stirring at 50 rpm. SIM showed pH dependent

solubility. Solubility in aqueous buffer was increases with increase in carrier proportion due to increase in wettability, reduced drug particle size with increase surface area and solvent evaporation leads to an increase in interfacial contact with dissolving medium. Solubility performed in biorelevant media like fasted-state simulated intestinal fluid (FaSSIF) and fed-state simulated intestinal fluid (FeSSIF) showed much higher solubility because, being a lipophilic molecule it get entrapped in lipophilic micellar core of surfactant like sodium taurocholate and lecithin present in the media. CCS was found to be as better solubilize (1:3) than SSG. Dissolution study indicated that SSD prepared with CCS (1:3) showed 99.68% drug release after 90 min whereas SSD with SSG (1:3) exhibits 93.21% drug release after 120 min. In vivo pharmacodynamic study showed 64.06% decrease in total cholesterol, a 59.70% decrease in TG, and 77.96% and 25.72% decreases in LDL and VLDL, respectively [12].

Kneading and Melt fusion method

Mandal *et al* have prepared SIM solid dispersion following two method, fusion and inclusion with HP-β-cyclodextrin by kreanding method. PEG 4000 and PEG 6000 were used as hydrophilic carriers. SDs were prepared in 1:1, 1:3, 1:5 ratio with PEG 4000 or PEG 6000 by melt fusion method. SIM- HP-β-cyclodextrin inclusion complex was prepared by kneading method. In kneading method, 1:1 molar ratio of Simvastatin and hydroxypropyl-β-cyclodextrin were wetted in a glass mortar for 20 min, and then kneaded with 50% (v/v) alcohol for 45 min. The pasty mass obtained was dried at 60 ^{o}C. The dried mass was passed through sieve 80 and stored. Physical mixtures were also prepared in same ratios. Dissolution studies were performed using USP apparatus II containing dissolution medium 900 ml of phosphate buffer (pH6.8) maintained at a temperature of 37±0.5 ^{o}C, stirring at 50 rpm. Phase solubility studies showed a linear increase in Simvastatin solubility as a function of PEG 6000 concentration with maximum solubility 3.5 folds as compared to plain SIM at 5%w/w polymer concentration. Pure simvastatin was characterized by only 29.52% drug release after 3 h. Drug release from SDs and inclusion complexes was found to be higher than the dissolution rate of drug alone. Physical mixture, also demonstrated higher dissolution profile which may be due to an improved wettability of the drug particles. Dissolution of SDs was 66.44% using PEG 6000 after 3h whereas SD prepared by with HP-β-cyclodextrin (1:1) released completely within 60 min. Solid dispersion prepared with HP-β-CD showed the highest improvement in wettability and dissolution rate as compared to fusion method. This improvement was observed due to several reasons like formation of soluble inclusion complex, amorphous state of drug and better wettability and reduction of particle size.

Solid state characterization indicated SIM was present as amorphous material when it was inside the HP-β-CD matrix without any chemical interaction [13].

Microwave assisted fusion and kneading method

Parmar *et al* worked on solid dispersion preparation by melt fusion and inclusion complex. They selected two hydrophilic carrier poloxamer 407 and gelucire 44/14. Solid dispersions were prepared in weight ratios of 1:1, 1:2, 1:3, 1:4, 1:5 by direct heating in porcelain dish (fusion) and inclusion complexation with β-cyclodextrin by kneading with water in a mortar pastel. Microwave heating was also studied for solid dispersion by fusion method. In this, drug and polymer mixture in different ratio were heated for several periods 2, 4, 6, 8 and 10 min and cool for 24h. Amongst all the three polymers used, gelucire 44/14 was found to be showed better solubility at 1:5 ratio as compared to poloxamer 407 and β-cyclodextrin. Microwave induction fusion method was demonstrated better results than melt fusion and inclusion with β-cyclodextrin in terms of solubility and dissolution rate [14].

Solvent evaporation and melt fusion method

Jatwani *et al* used fusion and solvent evaporation method for solid dispersion preparation. Hydrophilic carriers used were Polyethylene glycol 6000, Sorbitol, and Gelucire 44/14 in combination or alone to increase its aqueous solubility. Solid dispersions were prepared in drug and single carrier in 1:1 ratio, drug +PEG 6000 + Sorbitol (1:1:1, 1:1:2, 1:2:1, 1:2:2) by the method and drug + PEG 6000 +Sorbitol + Gelucire 44/14 in 1:1:1:1 ratio by fusion method. Dissolution was performed in USP II Paddle type apparatus media containing 900 ml of phosphate buffer 7.0, at speed of 50 rpm at 37 ± 0.5 °C. Aqueous solubility profiles indicated 8-9 times increase solubility in presence of hydrophilic carriers as compared plain drug in distilled water. They observed that use of multiple carriers i.e. PEG 6000 and sorbitol showed higher percentage cumulative drug release from solid dispersion than with single carrier. They found solvent evaporation method more superior as compared to fusion for solid dispersion preparation because evaporation method produces drug particles with increase surface area, improved wetting and solubilization property. It also reduces the Crystallinity of drug more effectively than in fusion method [15].

Co grinding and Spray drying

Pattewar *et al* used Hydroxy propyl methyl cellulose E3LV (HPMCE3LV) synthetic polymer to enhance the solubility of SIM. Solid dispersion was prepared in ratio 1:1 to 1:9 w/w by co grinding method and spray drying. For spray drying, SIM with HPMCE3LV solution was prepared in drug and polymer ratio 1:1, 1:2, 1:6, 1:9 w/w and process carried out by using spray

dryer (LU-222, Advanced, Labultima, India). The solutions prepare by dissolving 1g of drug in 70 ml of methanol and 1g of HPMCE3LVin 30 ml of distilled water and mixed both solutions which produces clear solution. The solvent evaporated at inlet 120 ^{o}C and outlet 80 ^{o}C, feed pump speed 10 ml per minute and aspiration 45 %. An immediate release tablets were also formulated using sodium starch as super disintegrant and lactose as a filler. Solubility profile was highest with SD prepared by co grinding method in 1:6 ratios. Similarly dissolution efficiency was also get improved by twice fold as compare to SIM and marketed formulation. Dissolution test of tablets were performed using pH 1.2 HCl buffer and pH 7 buffer with USP dissolution apparatus II at 50 rpm and 37± 0.5^{0}C. The suggested mechanisms for solubility and dissolution increment due to surface active property of HPMCE3LV which reduces the contact angle and increase surface wetting of drug in dissolving media. Transition of crystalline form of drug to amorphous state was also contributing factors [16].

Spray drying

Rao *et al* explored two hydrophilic carriers PVP K30 and Poloxamer 188. They prepared the SDs in ratios of 1:1, 1:2 and 1:3 by dissolving in ethanol AR followed by spray dried using spray dryer (LU-222, Labultima, India). SIM showed 1.45 µg/ml water solubility, 14.5µg/ml in pH 1.2buffer and 24.4µg/ml in pH 7 buffers. They found that saturation solubility was increased with increase in amount of solid carriers i.e. with PVP K30 (1:3) 617.59% and with Poloxamer 188 increase was 1028.04%. The increase in percentage saturation solubility was higher in case of Poloxamer 188, this might be due better solubilizing ability of poloxamer 188 by micellar solubilization effect as it is composed of polyoxyethylene-polyoxypropylene polymeric chain and has ability to form a micelle after certain concentration. SIM showed higher solubility in biorelevant media. SIM Being a lipophilic drug easily can be entrapped in a lipophilic micellar core of surfactant. Dissolution studies were performed using USP apparatus II containing dissolution medium 900 ml 0.01M phosphate buffer (pH 7) with 0.5% SLS maintained at a temperature of 37±0.5 °C, stirring at 50 rpm. Pure drug showed poor drug release 46.82% after 3h whereas physical mixture showed some improvement in dissolution rate due to hydrophilic effect of polymer. The increase dissolution rate of SDs was found to be linear with increase in polymer concentration i.e. PVP K30 SD1 showed 75.67%, SD2 90.25% and SD3 99.23% drug release after 3h. In contrast to PVP K30, poloxamer 188 did not show significant effect on dissolution rate with increase in carrier concentration i.e. in 10 min SD1 showed 80.26%, SD2 85.34% and SD3 86.8% drug release. The SD prepared with poloxamer 188 showed 99.19% drug release in 1h whereas SD with PVP K30 required 3h for 99.23% drug release indicating the

superiority of poloxamer 188 over PVP K30 due to micellar solubilization effect of poloxamer 188. The degree of crystalinity of plain SIM was found to be 53.82% whereas this percent Crystallinity was decreased to 14.29% with PVPK30 SD and further decrease in percentages to 6.975% was observed with Poloxamer 188 SD. This can be attributed to fact that spray drying is an energy intensive process where solution was passes through a state of unsaturation to supersaturation in a short period of time and rapid evaporation of solvent from supersaturated atomized droplets interfere with crystallization process leading to amorphous state. Pharmacodynamic study performed in Triton WR 1399 induced hyperlipidemia in wistar albino rats showed two folds decrease in total cholesterol and triglyceride level in comparison to plain SIM. Therefore Poloxamer 188 has better option to be used as a carrier for solubility enhancement of poor water soluble drug [17].

Nanoprecipitation

Patil *et al* prepared solid dispersion by nanoprecipitation method using Eudragit L100 as self emulsifying polymer and poloxamer 407 as surfactant. Simvastatin nanoparticles were prepared by the controlled nanoprecipitation method by adding 5ml SIM solution in methanol into aqueous phase containing poloxamer under Mechanical stirring. The formed nanoparticles filtered and dried using rota evaporator under vacuum. For the optimized batch particle size was found to be 295 nm and zeta potential value -8.31 mV indicating the stability of nanodispersion drug. The dissolution performed in apparatus USP Apparatus II containing pH 6.8 phosphate buffer having pH 6.8 revealed about higher dissolution rate (90.67%) of nanodispersion prepared with polymer and surfactant ratio 1:3 after 60 min. Mechanism suggested was reduced particle size and amorphous state of drug. In vivo study of the optimized batch in rat model indicates that in 30 days, simvastatin lowered cholesterol (93.87% inhibition), triglyceride (139.49 % inhibition), and HDL (-22.04 % inhibition) and nanoparticle formulation resulted in a greater reduction of cholesterol (97.65% inhibition), triglyceride (145.11% inhibition), and HDL (-24.04 % inhibition) due to higher solubility and bioavailability of nanoprecipitates. Thus nanoprecipitation technique was successfully employed for solubility enhancement of SIM [18].

Sonoprecipitation

Wang *et al* produced simvastatin solid nanoparticle by Sonoprecipitation method. An apparatus (JY-92-II sonifier, Ningbo Scientz Biotechnology Co. Ltd., China) consisting of a probe and sonifier was used as a source of ultrasound and a power of 400 W was applied in the precipitation process. Stabilizers tried were F68, PVPK30 and HPMCE5. Method in brief, organic phase containing 0.5g SIM in 5 ml methanol and 500 µl of this solution was injected into

10 ml 0.2% aqueous stabilizer solution maintained at 3°C through a syringe under ultrasonic conditions at 400 W. The concentration ratio of drug to stabilizer was 5:2 (w: w). This process resulted in formation of milky simvastatin nanodispersions. An intermittent sonication was applied to the nanodispersions by sonication for 5 seconds at 5 seconds intervals for a total sonication time of 10 min. Solvent was removed under vacuum at room temperature. Then aqueous phase containing nanodispersion was filter through 0.1 µm microporous membrane and washed twice with distilled water. Finally dried to get solid nanodispersion and studied for saturation solubility and dissolution rate. The dissolution studies were performed using USP apparatus 2. 10 mg drug were placed in a dissolution vessel containing 900 ml pH6.8 buffer solution, maintained at 37 ± 0.5°C and stirred at 100 rpm. They have also studied the effect of particle size, effect of solvent, ratio of solvent/antisolvent ratio, effect drug of loading, effect of stabilizer and stabilizer concentrations. They found that amongst different solvent, methanol has better ability to give smaller particles. Stabilizers screening study shows that F68 allows the production of submicron-sized particles with the smallest diameter of 360 nm and narrowest PSD compared with other stabilizers. A 0.2% stabilizer (F 68) concentration was optimized as they found maximum reduction in particles size. The mechanism for their stabilization involves that stabilizers or polymers get adsorbed at surface of the drug particle creating a steric barrier during the process of anti solvent precipitation thereby preventing the crystal growth and agglomeration. They also found that increase in drug loading from 0.2% to 1% leads to nuclei growth and agglomeration. In results part they demonstrated that the saturation solubility and dissolution rate of Simvastatin nanocrystals were enhanced by 1 fold and 4 fold respectively as compared to with plain simvastatin and dissolution rate improvement with the decrease in particle size. Bioavailability study in wistar rat model showed that C_{max} and AUC $_{(0–24\ h)}$ values of simvastatin nanocrystal group were approximately 1.5 fold and 1.44fold greater than that of crude Simvastatin respectively. The T_{max} time was also reduced to 1.99h for simvastatin nanocrystal group as compared to 2.88 h for reference group. They have explained the fact for decrease in Crystallinity of drug nanocrstals that at a fast nucleation rate, the drug solute lacks sufficient time to be incorporated into the growing crystal lattice to form perfect crystals which leads to lower lattice energy. Second, the lower melting point can be attributed to the reduction in crystal size. Thus they successfully explored the Sonoprecipitation method for simvastatin nanocrystals preparation for the improvement of saturation solubility, dissolution rate and oral bioavailability [19].

Melt fusion method

Lai *et al* have investigated the potential application of glyceryl monooleate (GMO)/poloxamer 407 cubic nanoparticles as oral drug delivery systems to enhance the bioavailability of simvastatin. Cubic nanoparticles were prepared through fragmentation of the GMO/poloxamer 407 bulk cubic gel. GMO and poloxamer 407 were melted together in different weight ratios at 60°C, after which simvastatin was added and stirred continuously until total dissolution. This molten mass was vortex mixed with Milli-Q deionized water for 1 min to achieve a homogenous phase. An optically isotropic cubic-phase gel was formed after equilibration for 24–48 h at room temperature. This cubic-phase gel subsequently fragmentized with water to form a crude dispersion by intermittent probe sonication in a water bath at 25°C for 5 min. The crude dispersion was further homogenized through through a high-pressure homogenizer (Avestin Em-C3) at 689 bar and 25°C to obtain an opalescent dispersion of the cubic nanoparticles. Cryo-TEM microscopy was performed to check the cubic structure nanoparticles. After 24h equilibrium a clear and low viscous gel formed for the GMO/poloxamer 407 binary systems with a poloxamer 407 weight percentage over 4% (w/w). Maximum 8% drug was incorporated without any significant change in clear crystalline cubic gel. Beyond this level clear gel turned to translucent due to decrease in solubility of SIM in gel phase. The mean diameter of the cubic nanoparticles found within the range of 100–150 nm. However, GMO/poloxamer 407 ratio and theoretical Simvastatin loading did not have any significant effect on particle size. Drug entrapment was found more than 98% in each case due high affinity of Simvastatin to hydrophobic region of cubic phase. In vitro drug release was performed by dynamic dialysis method in a ZRS-8G release tester (Tianjin, China) according to the Chinese Pharmacopoeia Method III (the small beaker method). One ml of freshly made cubic nanoparticles suspension (equivalent to 0.8 mg drug) was put in the dialysis bag (Ø 16 mm, MWCO 14,000 Da) and sealed. The dialysis bags fitted in sinking were kept in beaker containing 70 ml release medium maintained at 37°C and at 100 rpm. Release medium was either simulated gastric fluids (SGF), 0.1M HCl solution containing 0.2% SLS, or fasted-state simulated intestinal fluids (FaSSIF). Plain Simvastatin showed more than 90% release at 1 h both in SGF and FaSSIF, while cubic nanoparticles showed less than 3% Simvastatin release in the same media at 10 h. This was possibly attributable to high affinity of simvastatin with the hydrophobic domain in the cubic phase which made it difficult to release from the nanoparticles. Pharmacokinetic study in beagle dogs showed that relative oral bioavailability of simvastatin cubic nanoparticles was 241% compared to simvastatin crystal powder. The enhancement of simvastatin bioavailability was might be due to facilitated absorption by lipids in the formulation [20].

Kneading and spray drying

Patil *et al* studied the effect of preparation methods on the solubility and dissolution of Simvastatin-β-cyclodextrin (β-CD) and hydroxypropyl β-cyclodextrin (HPβ-CD) inclusion complexes. The complexes were prepared by simple physical mixing, kneading and spray drying techniques. For kneading purposed 50% methanol and for spray drying mixture of isopropyl alcohol (IPA) and water was used. Spray drying condition was optimized to nozzle diameter 0.7mm, atomization pressure of 1.5kg/cm^2 with a feed rate of 3ml/min. The inlet temperature was kept at 80 ˚C and out let temperature 60 ˚C ± 2 ˚C. The vacuum in the system was 60mmwc and aspirator was 45%. Solid dispersion was prepared in drug polymer ratio 1:1 using both the polymers by different techniques. Dissolution study was performed using USP dissolution apparatus type (USPXX IV) 500 ml of 1.2 pH simulated gastric fluid (SGF) and 7.4 pH Buffer as dissolution media at 37˚C(± 0.5˚C) with a rotation of 50 rpm. Solid dispersion prepared by spray drying with β-CD and HP β-CD exhibited better aqueous solubility compared other method. Results obtained from in vitro drug release indicate that pain drug showed 14-35% drug release in both the medium where as solid dispersion prepared with HP β-CD by spray drying method showed complete more than 99% drug release. Thus spray drying method showed its superiority over other method. Similarly, HP β-CD gives better results than β-CD due to presence more complex forming structure. Increment in solubility and dissolution rate is attributed to reduction in particle size and presence of solubilized amorphous drug in solid dispersion [21].

Hot melt extrusion method

Tawde *et al* worked on novel polymeric solublizer Soluplus® for solubility enhancement of SIM. They prepared melt extrude in various ratios by melt extrusion process. They showed that solubility of SIM was increased just by incorporation soluplus® as a solublizer whereas 500 folds increase with melt extrudate of Soluplus® and SIM. They have also reported that addition of other hydrophilic polymer such as Kolliphor™ TPGS, Kolliphor™ P 118 and Kolliphor™ P 407 resulted in further increase solubility by 1400 fold. Solubility enhancement can be attributed due to reason, formation of amorphous state of drug molecule and secondly amphiphilic nature of Soluplus®. Thus Soluplus® can be act as powerful solubilizer for the drugs suffering from poor aqueous solubility such as SIM [22].

LIPID BASED FORMULATION

Solid Lipid Nanoparticle

Gambhire *et al* prepared SIM loaded solid lipid nanoparticle. SLN were prepared by pre-emulsion followed by ultrasonication method. Method in brief, lipid phase consist of 0.5g SIM

in 2.4g Compritol 888 ATO and Span 60 (3.6%) and aqueous phase contains poloxamer 188 (2%w/v) in distilled water. Both the phases were warm to a temperature at 70 °C then aqueous phase was added into lipid phase under homogenization condition 35000 rpm for 3 min. This coarse o/w emulsion further subjected to ultrasonication for 19 min to produce fine emulsion. The particle size analysis of the selected formulation was performed using Malvern Mastersizer 2000 MS. Stable simvastatin SLNs with a mean particle size of 245 nm and 72.52% entrapment was optimized. They suggested that high amount of drug could be incorporated in nanoparticle dispersion and percentage entrapment depends on amount of lipid, solubility of drug in lipid, process temperature and surfactant concentration. *In-vitro* release studies were performed using modified Franz diffusion cell. A dialysis membrane having pore size 2.4 nm, molecular weight cut off 12,000–14,000 was used with dialysis medium containing pH 7.0 buffer containing 0.5% sodium dodecyl sulphate in 0.01 M sodium phosphate. *In-vitro* drug release study indicated that % cumulative drug release from SIM-SLN highly retarded (37.08%) in 48h due to entrapment of drug in SLN matrix and the erosion of lipid has to take place for drug to be released in the medium whereas dispersion with plain drug showed 97.2% cumulative drug release. In contrast to this, the relative bioavailability of simvastatin hydroxy acid and simvastatin for SIM-SLN was 207.67% and 164.916% respectively which was higher in comparison with SIM suspension. This significant increase in relative bioavailability attributed to enhanced lymph flow due to triglycerides present in SLN and presence of lipase in intestinal wall and plasma. Lymph flow overpasses the first pass metabolism which is the major pathway for SIM metabolism and one of the reasons for poor bioavailability. FTIR study showed disappearance of SIM peaks in SLN due to entrapment of drug in lipid marix. Similarly, DSC endothermogram shifted to lower side due to low melting point of Compritol 888 ATO. Studies concluded that incorporation of lipid phase in oral formulation aids in bioavailability of lipophilic drugs [23].

Microemulsion

Srinivas *et al* has developed a novel microemulsion drug delivery system to enhance the solubility, dissolution rate and subsequently oral bioavailability SIM. Microemulsion was prepared using non ionic surfactant cremophore RH 40(HLB value 16), Transcutol p as co surfactant, (HLB 15), oleic acid and water. Pseudoternary ternary phase diagrams were constructed to using different ratio of surfactant to co surfactant (1:1, 2:1, 3:1) to find out the zone of microemulsion. The oil and water mixture was titrated with specified ratios of surfactant to co surfactant. For each phase diagrams at a specific ratio of surfactant/co surfactant, homogeneity of oil and drug, phase clarity and flow ability was observed visually. The

formulation composition containing oleic acid (18.70%), surfactant and co surfactant mixture in ratio 1:1 (48.30%), and water (32.90%) was optimized based on transparency and low viscosity of microemulsion. The mean droplet size of the formulation found to be 60.1 nm and zeta potential value determined using Nano Zeta sizer was negative charge(-75mV), an indicative of highly stable microemulsion. They have also evaluated other parameters like type of microemulsion (o/w or w/o) based on electro conductivity, refractive index and % transmittance to check the transparency and stability of microemulsion. They found that prepared microemulsion was of o/w type with refractvie index value same as water 1.83 and more than 99% transmittance. Stability study was performed by putting into empty hard gelatin capsules (size 0) at various intermediate and accelerated conditions for 3 and 6 month respectively. Formulation showed stability in terms of drug content, particle size and any other physical changes. The drug release from the optimized microemulsion and marketed tablet was determined according to USP dissolution apparatus type-II, 900 ml of phosphate buffer pH 5.5. Microemulsion filled in hard gelatin capsule and tablet were placed in the dissolution vessel and operated at 50 rpm at 37^{o}C. Studies observed that at the end of 1 h, the release of simvastatin from the microemulsion was significantly higher (98.62%) than that for marketed tablet (45.19%). This result may be attributed to effect of surfactant molecules on drug in dissolution medium. In Vitro intestinal permeation studies in male Sprague- Dawley rats shown that drug diffused at a faster rate from the microemulsion system than from the tablet dosage form due more lipophilic and small particle size nature of microemulsion. Hence this study suggested that incorporation of lipophilic drug in lipid based drug delivery system also have permeability advantages besides solubility enhancement [24]

SEDDS

Patil *et al* worked on self emulsifying drug delivery system for SIM. Various SEDDS formulations were prepared with a constant amount of simvastatin and varying ratios of surfactant to co surfactant. Simvastatin (200mg) was dissolved in 1:1 (V/V) mixture of Captex and Lauroglycol (oil) phase in stoppered glass vials. The then required amounts of Polyoxyl 35 castor oil (Cremophore® EL) and/or Capmul® MCM (C8/C10 mono-diglycerides) were added to the mixture and mixed well. These systems were warmed to 40 °C using a water bath for 30 min with intermittent shaking to ensure complete mixing. In vitro diffusion study was performed using the dialysis tubing in which 0.2ml SEDDS equivalent to 10 mg SIM was placed along with 0.8 ml dialyzing medium and both the end of tubing was tied with thread. This allowed to rotate freely in the dissolution vessel (USP 24 type II) that contained 900 ml dialyzing medium

(phosphate buffer pH 6.8) maintained at 37 ± 0.5 °C and stirred at 100 rpm. Pseudo ternary phase diagram was plotted to obtain optimum concentration of oil, surfactant and co surfactant ratio. Preliminary studies indicated that formulation prepared from combination of formulation A consists of Captex 355(0.5 ml), Lauroglycol 90 (0.5), Cremophor EL (1 ml), formulation B Captex 355(0.5 ml), Lauroglycol 90 (0.5), Cremophor EL (0.75 ml) and formulation C Captex 355(0.5 ml), Lauroglycol 90 (0.5) and Cremophor EL (0.5 ml) showed stability even after 500 fold dilution. Formulation A and B has low turbidity values for 14.21 NTU and 12.95 NTU respectively due to presence of adequate amount of surfactant. Formulation C was found to below instrument detection level due its fine droplet size. Mean particle size (124nm) obtained was higher with formulation C. In vitro diffusion profiles of formulation C showed 82.2% drug release after 12h against 69.3% and 48.9% from formulation B and A, respectively. This effect was observed due to lesser mean droplet size with larger surface area could easily diffuses through the dialyzing membrane. Formulation C was selected for in vivo studies in rat. Results showed significant reduction in plasma cholesterol and triglycerides level around 5-fold and 4-fold, respectively and high density liopoprotein-cholesterol concentration was markedly higher (2-fold) compared to reference Simvastatin suspension formulation after oral administration for 21 days of study. This enhanced pharmacodynamic performance could be contributed by combined effect of different mechanisms, like the solubilized form of drug, availability of large interfacial area for absorption, enhanced dissolution in the presence of surfactants, and increased cellular uptake of drug [25].

Dried Emulsion

Dixit *et al* studied on dried emulsion for solubility and dissolution enhancement of Simvastatin. SIM was incorporated in emulsion prepared using soybean oil and propylene glycol monocaprylate as oily phase and Tween 80 and Cremophor EL as surfactants and also their mixtures. Liquid emulsion prepared was adsorbed on colloidal silicon dioxide Aerosil® 200 in varying proportions to give free flowing powder. Optimized dried emulsion comprising combination of soybean oil and propylene glycol monocaprylate and Tween 80 and Cremophor EL showed 10 fold increases in dissolution rate as compared plain drug in pH 6.8 phosphate buffer. *In vivo* study in poloxamer F127 induced hyperlipidemic rat model showed significant reduction in the total cholesterol levels, from 439 mg/dl compared to 585 mg/dl of drug treated group. Significant increase in the high-density lipoprotein levels was also observed. DSC and XRD studies confirm the solubilized amorphous state of SIM in dried emulsion. Study also suggested that type and concentration of surfactant can affect the solubility and dissolution rate [26]

CONCLUSION

It has been observed that amongst various techniques available for solubility enhancement of poor soluble drug, solid dispersion preparation by different techniques well adopted method by most of the researcher for this purpose. Solid dispersion can be a good approach for solubility enhancement due to its ease preparation and good in efficiency. Beside solid dispersion, other approaches like lipid based formulation can be also employed for solubility and bioavailability improvement of Simvastatin.

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