AJPCR_11563_RA

ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 9, Issue 4, 2016

Online - 2455-3891
Print - 0974-2441

Research Article

FORMULATION AND EVALUATION OF NEUSILIN® US2 ADSORBED AMORPHOUS SOLID SELF-MICROEMULSIFYING DELIVERY SYSTEM OF ATORVASTATIN CALCIUM

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Received: 06 March 2016, Revised and Accepted: 10 May 2016

ABSTRACT

Objective: The objective of the present study was to improve the dissolution profile of poorly water-soluble atorvastatin calcium (ASC), via formation of its solid self-microemulsifying drug delivery system (SSMEDDS).

Methods: The SSMEDDS was prepared using oleic acid, Tween 80 and propylene glycol as an oil phase, surfactant, and co-surfactant, respectively. Initially, the solubility of ASC was examined in different oils, surfactants and co-surfactants, and pseudo-ternary phase diagrams were constructed subsequently to optimize the ratio of the excipients having greater microemulsion region. The liquid self-emulsifying batches of ASC were developed with the optimized excipients and evaluated for droplet size, zeta potential, percentage transmittance, self-emulsification time assessment, dispersibility test, and drug release. Neusilin® US2 was employed as an adsorbent to transform optimized liquid emulsifying batch A1 to solid formulation. The solid formulation was characterized by particle size analysis, differential scanning calorimetry, X-ray powder diffractometry, scanning electron microscopy, and *in vitro* drug release.

Results: The characterization studies revealed the transformation of crystalline ASC to amorphous form in solid adsorbed batch. The drug release studies demonstrated remarkable improvement in dissolution profile of ASC from its liquid as well as SSMEDDS as compared to pure drug.

Conclusion: The development of SSMEDDS could be a reliable and alternative approach for improvement of dissolution performance of ASC.

Keywords: Atorvastatin, Self-microemulsifying, Amorphous, Formulation, Neusilin® US2.

INTRODUCTION

Recently, particulate drug delivery system has become one of the promising approaches to improving the physicochemical and biopharmaceutical characteristics of poorly water-soluble drug molecules. The physicochemical properties such as solubility and dissolution are the key factors controlling the bioavailability and therapeutic efficacy of drugs [1]. The rate and extent of absorption of poorly water-soluble drugs are primarily solubility and dissolution rate limited [2]. As these physicochemical factors are influenced by particle size, shape, and morphology of drug particles; modification of particulate properties of a drug molecule would be expected to overcome the solubility problems to develop a successful dosage form with enhanced physicochemical and therapeutic effectiveness [3]. Consequently, physical state modification through particle size engineering to control physicochemical and biopharmaceutical characteristic has attracted much attention of researchers in drug product development. This process is associated with particle size reduction of a drug molecule to micron and/or nano size to achieve the better therapeutic outcome.

According to Noyes and Whitney equation, the dissolution rate of drug particles can be improved by increasing the surface area of the powder particles [4], which in turn can be achieved through particle size reduction to micron size [5]. Many strategies including jet-milling [6], ball milling [7], high pressure homogenization [8], spray drying [9,10], freeze drying [11], complexation [12], solid lipid nanoparticles [13], and self-emulsifying drug delivery systems (SEDDSs) [14] have been implemented for the reduction of particles size of drug powder to obtain desired transport properties. Among these strategies, self-microemulsifying drug delivery systems (SMEDDSs) have been recognized as one of the efficacious solubilization methods owing to their ability to improve oral bioavailability of poorly water-soluble drugs [15,16].

SMEDDS is generally considered as isotropic mixtures of oils, surfactants, and co-surfactants/co-solvents, which spontaneously emulsify to produce homogeneous, transparent/translucent and stable oil in water (o/w) emulsion on gentle agitation in aqueous media [17]. Peroral administration of these formulations results into the formation of microemulsions in gastrointestinal tract (GIT) with mild agitation provided by gastric mobility [14,17]. Such formulation provides increased surface area due to a large number of drug loaded small droplets leading to improved absorption of drug particles from GIT [18]. The development of successful SMEDDS formulation depends on the proper choice of emulsifying components, solubility behavior of the drug in various components, construction of pseudo-ternary phase diagram for optimization of emulsifying region, and droplet size of the microemulsion [19].

However, the conventional SMEDDS are associated with manufacturing limitations leading to high production costs, difficulty in use, incompatibility problems with shells of soft gelatin capsules and storage problems [3]. Therefore, it is desirable to transform liquid SMEDDS into solid SMEDDS (SSMEDDS) using a suitable solid carrier to overcome certain limitations of liquid SMEDDS. Spray drying, adsorption or trituration of liquid SMEDDS along with solid carriers such as dextran, gelatin, lactose, silicon dioxide (Aerosil®), and/or magnesium aluminometasilicate (Neusilin® US2) can afford SSMEDDS with expected outcomes [3,20]. Thus, considering the importance of SSMEDDS in drug delivery, this technique has been exploited to improve the dissolution properties of poorly water-soluble atorvastatin calcium (ASC) in the present work.

ASC is a selective and competitive 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor used as an antihyperlipidemic agent [21]. It is used to decrease cholesterol and triglycerides levels in patients with hypercholesterolemia and mixed dyslipidemia and in

the treatment of homozygous familial hypercholesterolemia [22]. It is a poorly water-soluble compound with an absolute bioavailability of 14%, therefore, being classified as biopharmaceutics classification system Class II drug [22]. Although usefulness of SEDDSs aiming to improve dissolution and bioavailability of ASC have been reported recently [21,23], in this article, as a proof of concept, formation of Neusilin® US2 adsorbed amorphous SSMEDDS of ASC has been attempted with the objective of characterization and assessment of dissolution profile.

Initially, solubility studies of ASC in different excipients were performed, and pseudo-ternary phase diagrams were constructed to obtain optimum emulsification region. The liquid batches were formulated with the optimized ratios of excipients and evaluated for droplet size, zeta potential, percentage transmittance, self-emulsification time, dispersibility test, and drug release in 0.1 N HCl and phosphate buffer (pH 6.8). Subsequently, optimized liquid emulsifying batch was transformed to the solid formulation using Neusilin® US2 as an adsorbent and characterized by particle size analysis, differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), and scanning electron microscopy (SEM). The SSMEDDS was also further evaluated for *in vitro* dissolution performance in 0.1 N HCl and phosphate buffer (pH 6.8).

METHODS

Materials

ASC was generously gifted by Abbott Healthcare Pvt. Ltd. Mumbai, India. Labrafac CC, Labrafac PG, and Capryol 90 were gift samples from Gattefosse, Mumbai, India. Neusilin® US2 was kindly gifted by Fuji Chemicals, Japan. Tween 80, Tween 60, Tween 20, polyethylene glycol 400, Propylene glycol, Span 20, Span 60, Span 80, oleic acid, castor oil, and cottonseed oil (all AR grade) were purchased from Loba Chemie Pvt., Ltd., Mumbai, India. All other chemicals were of analytical grade. Double distilled water was used for all experimental procedures.

Solubility determination

Solubility determinations of ASC were carried out in various excipients as follows: An excess but weighed amount of ASC was added to 2 ml of each vehicle taken in screw cap vial and shaken for 72 hrs in a rotary flask shaker at a room temperature (25±0.5°C). The samples were taken out at 72 hrs and centrifuged at 3,000 rpm for 10 minutes to separate the supernatant. Aliquots of supernatant were then withdrawn and filtered through Whatman filter paper 41. The filtrate was suitably diluted with methanol and analyzed spectrophotometrically (Shimadzu 1800, Japan) at 246 nm [21,24]. Vehicles, which showed the highest solubility, were then used for the preparation of SMEDDS batches.

Construction of pseudo-ternary phase diagrams

The pseudo-ternary phase diagrams consisting of oil, surfactant, and co-surfactant were obtained at room temperature by water titration method. On the basis of solubility determinations, oleic acid, Tween 80, and propylene glycol were selected as an oil phase, surfactant, and co-surfactant, respectively. The surfactant and co-surfactant were mixed in different weight ratios (1:1, 2:1, 3:1). For each phase diagram, oil and specific surfactant mixture (Smix) ratios were mixed thoroughly in different weight ratios from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1) in different vials. Each mixture was then slowly titrated with distilled water, visually examined for transparency and phase diagrams were constructed. Clear and isotropic mixtures were considered to be within microemulsion region [25].

Preparation of liquid batches of SMEDDS

For the preparation of different series of SMEDDS, an accurately weighed ASC (10 mg) was dissolved in oleic acid and then added surfactant and co-surfactant in a glass vial. The mixture was mixed by gentle stirring using vortex mixer and placed on magnetic stirrer until ASC was completely dissolved. The mixture was stored at room temperature until further use [26].

Determination of droplet size, polydispersity index, and zeta-potential measurement

The mean droplet size, zeta potential, and polydispersity index of emulsion globules were determined using nanoparticle size analyzer (Horbia SZ-100, Kyoto, Japan). For droplet size analysis, the dispersed formulation was measured after 100 dilutions with double distilled water. Light scattering was monitored at 25°C at 90° angle. For determination of polydispersity index, 1 mL of SMEDDS was dispersed in 100 mL distilled water at 37°C. The resultant emulsion was prepared by gentle agitation for 10 minutes using a magnetic stirrer [27].

Determination of cloud point

The cloud point was determined for assessing the stability of microemulsion at body temperature. The formulation containing 10 mg ASC was diluted with 50 mL of distilled water in beaker and placed on a water bath. The temperature of beaker was gradually increased until the diluted formulation showed cloudiness [27].

Determination of emulsification time and % transmittance

The emulsification time was determined according to the United States Pharmacopeia (USP)-II dissolution apparatus. 1 mL of each formulation was added dropwise to 500 mL purified water at 37°C, and gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. The emulsification time was assessed visually [27].

Percentage transmittance of SMEDDS diluted with 100 times with distilled water was checked against distilled water spectrophotometrically (Shimadzu 1800, Japan) at 650 nm [28].

Drug content determination

The drug content was determined by dissolving SMEDDS formulation equivalent to 10 mg drug in 50 mL of methanol and mixed well with shaking for two to three times. 0.1 mL of this solution was diluted with fresh methanol, and drug content was determined spectrophotometrically (Shimadzu 1800, Japan) at 246 nm [29].

Dispersibility tests

Self-emulsification efficiency of SMEDDS was examined using a standard dissolution apparatus II. 1 mL of each sample was added to 500 mL of distilled water at 37°C sand gently agitated by a standard stainless steel dissolution paddle rotating at 50 rpm. The grading system was followed to assess visually the *in vitro* performance of the formulation [30].

Dissolution studies

The dissolution studies were carried out using USP dissolution test apparatus (DS 8000 LABINDIA, LABINDIA Analytical Instruments, Pvt. Ltd., Mumbai, India), according to USP type II. Pure drug or liquid SMEDDS containing 10 mg ASC was filled in hard gelatin capsule shell and placed in a dissolution vessel containing 900 mL of 0.1 N HCl and phosphate buffer (pH 6.8) (pH meter EQ-614A Equiptronics, Equiptronics Analytical Instruments, Pvt. Ltd. Mumbai, India) separately at 50 rpm, maintained at 37±0.5°C. 5 mL of aliquots were withdrawn periodically by previously programed autosampler and replaced by fresh dissolution medium. The samples were immediately filtered through Whatman filter paper 41; suitably diluted and analyzed spectrophotometrically (Shimadzu 1800, Japan) at 242.7 and 240 nm for 0.1 N HCl and phosphate buffer, respectively [22,23,28].

Conversion of liquid SMEDDS into SSMEDDS

The optimized liquid batch was transformed into free flowing powder by adsorption technique using Neusilin® US2 as a solid carrier. Liquid SEDDS (Batch A1) containing ASC was added dropwise on Neusilin® US2 in 1:0.5 ratio contained in broad porcelain dish. After each addition, mixture was homogenized using glass rod to ensure a uniform distribution of formulation. The resultant mass was passed through sieve no. 120, dried at ambient temperature and stored in desiccators until further analysis [25,30].

Characterization of SSMEDDS

Particle size analysis

The particle size analysis of SSMEDDS was performed using a nanoparticle size analyzer (Horbia SZ-100, Kyoto, Japan). The powder formulation was dispersed in double distilled water and mean particle size was measured. Light scattering was monitored at 25°C at 90° angle.

DSC

Thermal properties of pure ASC and SSMEDDS were recorded on a DSC 82E, Mettler Toledo, Switzerland. Approximately 2 mg of each sample was heated in a pierced aluminum pan from 30°C to 300°C at heating rate of 10°C/minute under a stream of nitrogen at a flow rate of 50 mL/minutes.

XRPD

The physical state of pure drug and SSMEDDS was characterized using X-ray diffractometer (PW 1729, Philips, The Netherlands) with Cu as an anode material; operated at a voltage of 46 kv and current of 40 mA. The sample was analyzed in the 2θ angle range of 10-60°.

SEM

The morphology of ASC and SSMEDDS were evaluated by JEOL, JSM-6360, Tokyo, Japan, operated at an acceleration voltage of 15 kV, and microphotographs were examined at ×550, ×2000, and ×10000 magnifications.

In vitro dissolution studies of SSMEDDS

Based on drug content determinations, SSMEDDS formulation containing 10 mg equivalent of ASC was filled in a hard gelatin capsule. The dissolution was carried out using USP II dissolution test apparatus (DS 8000 LABINDIA, LABINDIA Analytical Instruments, Pvt. Ltd. Mumbai, India) at 37±0.5°C in a 900 ml of 0.1 N HCl and phosphate buffer (pH 6.8) (pH meter EQ-614A EQUIPTRONICS, EQUIPTRONICS Analytical Instruments, Pvt. Ltd. Mumbai, India), separately, maintained at 50 rpm. The samples were withdrawn at appropriate time intervals by previously programed autosampler, filtered through Whatman filter paper 41, and analyzed spectrophotometrically (Shimadzu 1800, Japan) at 242.7 and 240 nm for 0.1 N HCl and phosphate buffer, respectively.

RESULTS AND DISCUSSION

Solubility determination

The selection of proper vehicles on the basis of solubility of a drug in various vehicles is an important aspect in designing SMEDDS formulation. The vehicles (oil, surfactant, and co-surfactant) used for the formation of SMEDDS should have high solubilization capacity for a drug to avoid drug precipitation during the formulation process of SMEDDS and after dilution in GI lumen [22,27]. The results of solubility determinations of ASC in various vehicles are shown in Fig. 1.

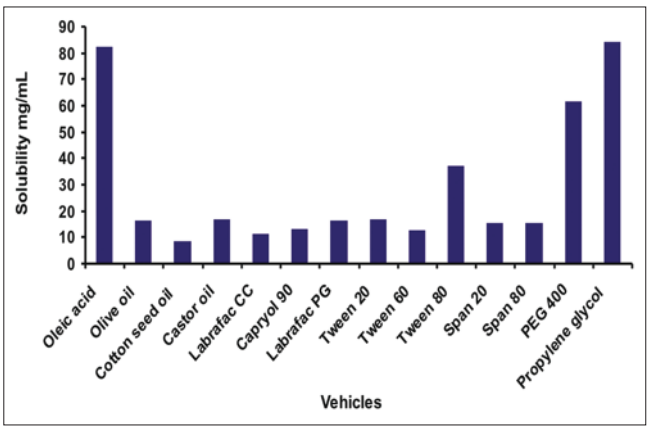

Fig. 1: Solubility of atorvastatin calcium in various excipients

From the results obtained, oleic acid, Tween 80, and propylene glycol were selected as an oil phase, surfactant, and co-surfactant, respectively, due to their highest solubilizing capacity for ASC as compared to other vehicles screened. The significance of the oil phase is to facilitate self-emulsification and absorption of the lipophilic drug from GIT. The non-ionic surfactant Tween 80 having high hydrophilic-lipophilic balance (HLB) value HLB 15 promotes self-microemulsion formation, whereas co-surfactant/co-solvent propylene glycol dissolves the high amount of hydrophobic drug and provides equal distribution of the drug in the formulation. This helps to prevent the precipitation of the drug in GI lumen and for prolonged existence of drug molecules [31].

Construction of pseudo-ternary phase diagrams

The pseudo-ternary phase diagrams were constructed to identify self-microemulsifying region and to choose appropriate proportions of oil, surfactant, and co-surfactant/co-solvent for the development of SMEDDS. Upon introduction into aqueous media, SMEDDS form fine oil - water emulsions with only gentle agitation. This is attributed to reduction in interfacial energy and generation of mechanical barrier to coalescence due to preferential adsorption of surfactant and co-surfactant at the interface. The spontaneous nature of an emulsion formation is attributed to decrease in the free energy required for the emulsion formation; consequently resulting in gain in thermodynamic stability of the microemulsion [22,28,31-33]. Therefore, selection of excipients in their proper proportions is an important criterion for the development of SMEDDS. The selected excipients, *viz.,* oleic acid, Tween 80, and propylene glycol from the solubility studies were further subjected for phase behavior studies. There combinations of surfactant and co-surfactant (Smix 1:1, 2:1, 3:1) were used for the present study. Fig. 2 shows phase diagrams of various combinations of excipients studied.

A combination of Tween 80 and propylene glycol in the ratio 2:1 displayed wider microemulsion area than other two ratios (Fig. 2). The larger the size of the microemulsion region, the greater is the self-emulsification efficiency [28,31]. In the Smix ratios 1:1 and 3:1, the microemulsion area was observed to be smaller and distinguishable. The low concentration of propylene glycol as a co-surfactant would probably prevent its incompatibility with capsule shells. Thus, Smix ratio 2:1 of surfactant: Co-surfactant was found to be optimum and used further for the formation of different batches of SMEDDS in different proportions with oleic acid as an oil phase as shown in Table 1.

Evaluation of liquid SMEDDS

The prepared liquid SMEDDS were evaluated for droplet size, polydispersity index, cloud point, self-emulsification time, % transmittance, and drug content. The results of evaluation studies are shown in Table 2. Zeta potential of optimized formulation was determined further.

The self-emulsification performance of the SMEDDS is based on the particle size of emulsion droplet as it influences drug release and rate and extent of absorption of the drug through GIT remarkably [22,31]. The decrease in droplet size may lead to more rapid absorption of drug resulting in enhancement of drug bioavailability [34-36]. As shown in Table 2 and Fig. 3, the particle sizes of emulsion droplet of all

Table 1: Composition of various liquid SMEDDS formulations

Serial number	ASC (mg)	Formulation code	Percentage of oleic acid	Percentage of Smix 2:1
1	10	A1	5	95
2	10	A2	10	90
3	10	A3	15	85
4	10	A4	20	80

Smix: Mixture of surfactant and co-surfactant, i.e., Tween 80 and propylene glycol in 2:1, SMEDDS: Self-microemulsifying drug delivery system, ASC: Atorvastatin calcium

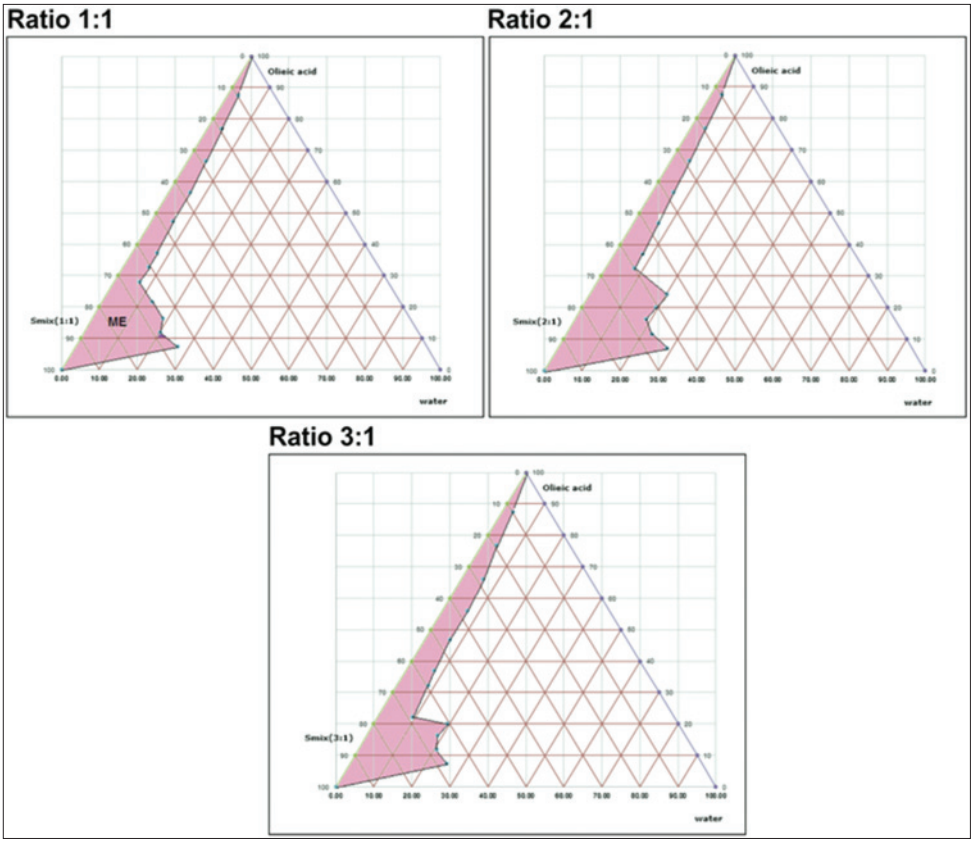

Fig. 2: Pseudo-ternary phase diagrams of self-emulsifying drug delivery system composed of oleic acid (oil phase): Tween 80 (surfactant): Propylene glycol (co-surfactant/co-solvent) dispersed with water, Smix: Mixture of surfactant and co-surfactant in 1:1, 2:1 and 3:1 ratios, Pink-colored area represents microemulsion region

Table 2: Evaluation parameters of SMEDDS formulations

Parameters/formulation code	A1	A2	A3	A4
Droplet size (nm)	386.4	423.6	928.9	1617.4
Polydispersity index	0.302	0.357	0.547	0.573
Cloud point (°C) [a]	79±5.3	72±5.5	68±3.8	72±4.2
Self-emulsification time (second) [a]	55±4.0	88±6.0	141±2.0	195±3.0
% Transmittance[a]	99.11±0.26	62.23±2.10	57.23±0.85	32.30±0.36
% Drug content[a]	96.59±0.43	92.42±0.38	91.95±0.06	86.79±0.60

[a]Mean±SD (n=3), SD: Standard deviation, SMEDDS: Self-microemulsifying drug delivery system

formulations were found to be within the range of 386.4-1617.4 nm. It could be observed that decreasing the lipid proportion and increasing the proportion of Smix ratio led to decrease in the globule size of the emulsion. The uniformity of droplet size in the formulation could be examined by determination of polydispersity index [31,37] which was found to be less than 1 in case of all formulations. However, the droplet sizes of batches A1 and A2 have experienced the narrower size of distribution than those of A3 and A4 batches (Fig. 3).

Thus, the emulsion droplets of A1 and A2 batches were more uniform as compared to A3 and A4 formulations.

Could point determination is again a crucial factor as far as the storage stability of an emulsion formulation is concerned. It is the temperature above which the formulation clarity turns into turbidity or cloudiness. Hence, the cloud point of the formulation should be greater than over 37°C to prevent the phase separation and instability of formulation. The cloud point of the formulation is affected by type and proportion of the surfactants/co-surfactants, oils, and their mixing ratio used in the formulation [27]. The cloud points of all formulation were determined in the rage of 68±±3.8-79±±5.3°C which was sufficiently at the high side.

The assessment of efficiency of SMEDDS formulation can be measured by its self-emulsification time. It could be expected that SMEDDS should disperse completely and rapidly on dilution with aqueous phase under mild agitation [28]. From the data obtained, it was clear that as the proportion of Smix was increased, the self-emulsification time decreased.

It might be attributed to the presence of a higher proportion of surfactant in the formulation which might have promoted the emulsification process, eventually, resulting in rapid emulsification rate [38].

The optical clarity of the SMEDDS was examined quantitatively by measuring the amount of light of given wavelength transmitted by the solution (% transmittance). The solutions would be considered optically clear if higher transmittance values were obtained since turbid or cloudier solutions would scatter more of the incident radiation, eventually lowering the transmittance [39]. The results of % transmittance revealed that the value of percentage transmittance was increased by increasing surfactant concentration. If the lipid content in the formulation was increased, then the turbidity was found to be increased resulting in lowering of % transmittance. The maximum %

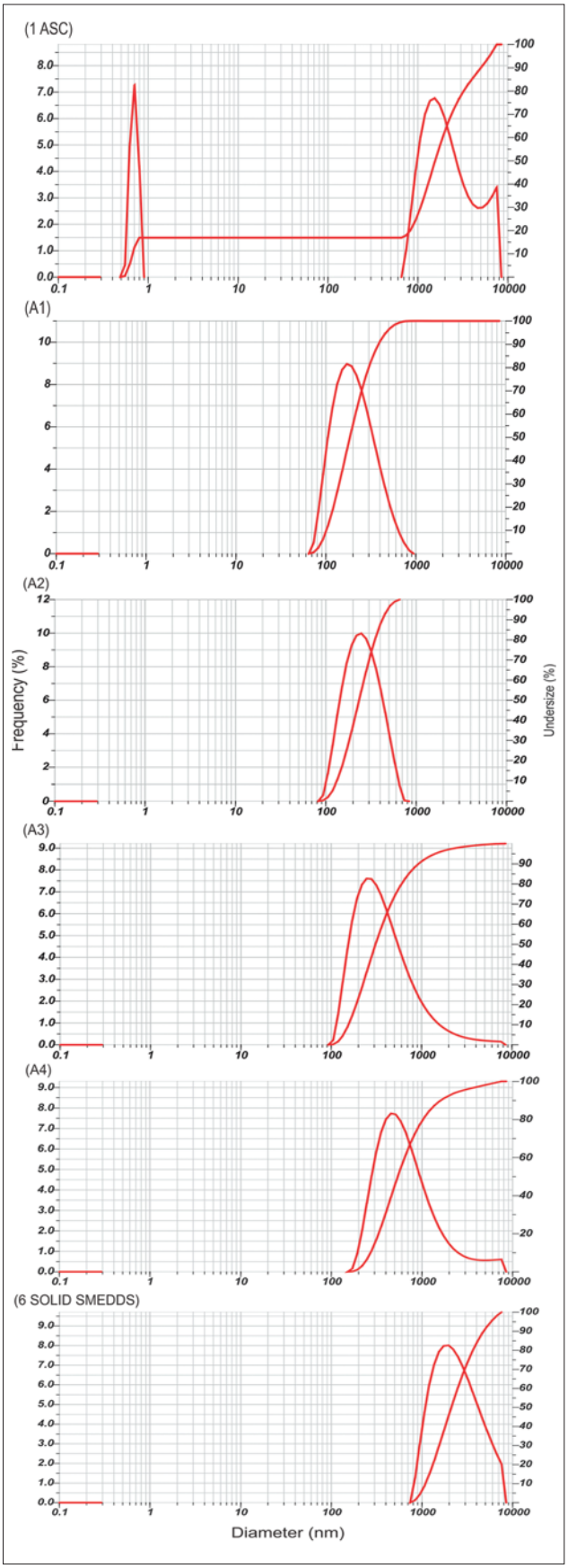

Fig. 3: Droplet size distributions of liquid self-microemulsifying drug delivery system (SMEDDS) and particle size analysis of pure atorvastatin calcium and solid SMEDDS, A1-A4 liquid SMEDDS

transmittance was obtained for A1 formulation batch indicating the presence of the finest dispersion state of droplets in the microemulsion.

The drug content of all formulations was found to be in the range of 86.79 ± 1.92-96.59±2.21%.

Zeta-potential analysis of liquid SMEDDS

According to the data obtained for the evaluation parameters of prepared SMEDDS, the optimized formulation batch A1 was subjected for zeta-potential analysis. The stability of the colloidal system is related to the charge of oil droplets and its magnitude of zeta potential which may directly or indirectly influence absorption. Higher positive or negative zeta-potential values prevent flocculation of dispersion by repelling similar charged particles and confer electrical stability to the dispersion. On the contrary, lower positive or negative values of zeta potential promote attraction between the dispersed particles which results in their aggregation imparting instability to the dispersion. The particles with zeta-potential values more positive and more negative than +30 mV and −-30 mV, respectively, are generally considered stable. The zeta potential of batch A1 (Fig. 4) was found to be −36.7 mV indicating formation of a stable microemulsion. The negative value of zeta potential indicates negative charge on the droplets [22,31,40].

Dispersibility studies

As shown in Table 3, the dispersibility of emulsions was assessed visually by applying grading systems after dilution in the ratio of 1:500 with distilled water. The microemulsions A1 and A2 were rapidly forming and appeared as bluish and slightly bluish in color, whereas A3 and A4 were slow forming with oily, dull, and grayish-white appearance. It could be observed that increasing the concentration of lipid phase decreased the stability of the formulation. On the contrary, the clarity of microemulsions was found to be increased on increasing the surfactant content in the formulation [26,27]. From the results, the optimized formulation batch A1 was considered for further studies.

Dissolution studies of liquid SMEDDS

The dissolution profile of pure ASC and all batches of SMEDDS are shown in Fig. 5.

It has been reported that pure ASC shows pH-dependent solubility [28,41,42]. Therefore, dissolution was performed in two different media, i.e., 0.1 N HCl and phosphate buffer (pH 6.8).

According to the results obtained, a significant enhancement in dissolution profile of ASC was noticed from its SMEDDS formulations tested in both the media. The formulations A1 and A2 have shown above 90% drug release within 30 minutes in 0.1 N HCl and phosphate

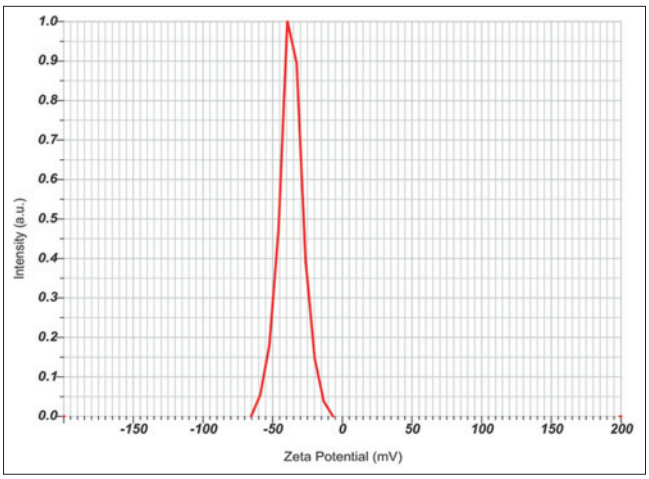

Fig. 4: Zeta-potential analysis of optimized liquid self-emulsifying drug delivery system A1

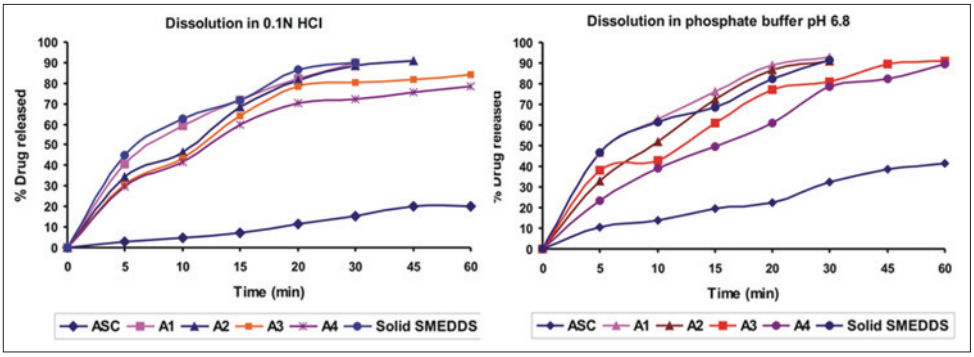

Fig. 5: Dissolution profiles of pure atorvastatin calcium, liquid, and solid self-emulsifying drug delivery system in 0.1 N HCl and phosphate buffer (pH 6.8) at 37±0.5°C

Table 3: Grading system for visual assessment of SMEDDS formulations

Serial number	Formulation code	Grades	Observation
1	A1	A	Rapidly forming (within 1 minute) microemulsion, having a clear or slight bluish
2	A2	B	Rapidly forming, slightly less clear emulsion, in bluish color
3	A3	D	Dull, grayish-white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 minutes)
4	A4	D	Dull, grayish-white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 minutes)

SMEDDS: Self-microemulsifying drug delivery system

buffer, whereas the drug release from formulation A2 in 0.1 N HCl was found to be 89% within the same time. Although the release of pure ASC was very poor in both the media during the entire period of dissolution, it was almost double in phosphate buffer than 0.1 N HCl indicating its pH dependent solubility behavior.

As the pKa of ASC is 4.46, the solubility of ASC has been reported to be higher in the medium of pH greater than or equal to 6 or pH value equal or greater than pKa +1 of ASC [26,42].

The enhanced dissolution profile of ASC from SMEDDS could be ascribed to the spontaneous formation of microemulsion with a small droplet size, which allowed a faster rate of drug release into the aqueous phase. Further, rapid dispersion of microemulsion with increased solubility of ASC might have contributed for enhanced dissolution of ASC from SMEDDS. Thus, the absorption and oral bioavailability of ASC would be expected to be higher from the SMEDDS formulation as a result of greater availability of dissolved ASC [22,23,31]. As the liquid SMEDDS batch A1 showed higher dissolution profile as compared to other batches examined, it was optimized and further formulated into SSMEDDS by adsorption technique using Neusilin® US2.

Characterization of SSMEDDS

Particle size analysis

The mean particle size of ASC was found to be 5036.2 nm d (90) with a polydispersity index of 0.722 (Fig. 3). The particle size of SSMEDDS was measured to be 4804.08 nm. However, no uniform distribution of particles was noticed. Thus, the particle size was increased when liquid SMEDDS was converted into SSMEDDS when adsorbed on Neusilin® US2. However, the particle size of SSMEDDS was found to be less than pure ASC.

DSC

DSC curves of pure ASC and SSMEDDS are shown in Fig. 6.

DSC curve of ASC displayed broad endotherm at 119.05°C and a sharp endotherm at 169.76°C corresponding to the loss of water and melting of ASC, respectively, indicating its crystalline nature [43]. DSC curve of SSMEDDS showed a broad peak at 84.24°C due loss of adsorbed moisture and a complete disappearance of melting endotherm of ASC. These results pointed out that ASC was no longer present in the crystalline state and was converted into amorphous form in SSMEDDS formulation.

XRPD

The XRPD patterns of pure ASC and SSMEDDS are shown in Fig. 7.

A crystalline nature of ASC was depicted by the appearance of sharp XRPD peaks at 9.13°, 10.19°, 12.07°, 16.65°, 19.32°, and 22.54° at a diffraction angle of 2θ with sharp and prominent peak intensities [43,44]. A significant decrease in the degree of crystallinity with hallow diffraction pattern was noticed in diffractogram of SSMEDDS. From these observations, it could be suggested that ASC was transformed completely into amorphous disordered phase of molecular dispersion state after adsorption on a solid carrier Neusilin® US2. It has been well documented that Neusilin® US2 has ability to transform crystalline substances into stable amorphous form on co-grinding or adsorption resulting in strong physical interaction [45,46]. Thus, the results of physical characterization studies of SMEDDS were in full agreement with the literature.

SEM

Fig. 8 shows images of microscopic examination of pure ASC and SSMEDDS.

Pure ASC appeared as large, rod-shaped irregular crystals or occasionally agglomerated in bundles as reported earlier [43]. The surface morphology of SSMEDDS revealed the appearance of amorphous and somewhat spherical granules with smooth surface deposited on solid carrier Neusilin® US2. From the SEM images, it could be concluded that the SSMEDDS of ASC exerted an amorphous form, thus contributing to improved dissolution rate of the drug [9].

Drug content determination

The drug content of SSMEDDS was determined as reported previously and was found to be 92.52 ± 1.83% w/w.

Dissolution studies of SSMEDDS

The dissolution profile of ASC and SSMEDDS in 0.1 N HCl and phosphate buffer (pH 6.8) is shown in Fig. 5. As could be seen from the Figure, SSMEDDS has shown more than 90-91% drug release within 30 minutes in both the media. Three was no significant difference

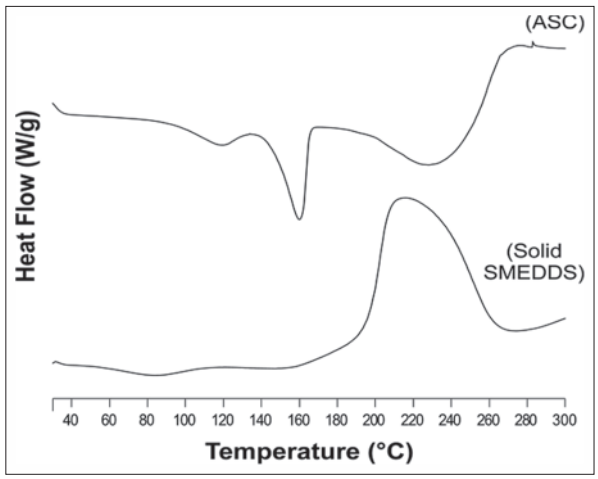

Fig. 6: Differential scanning calorimetry thermograms of pure atorvastatin calcium and solid self-emulsifying drug delivery system

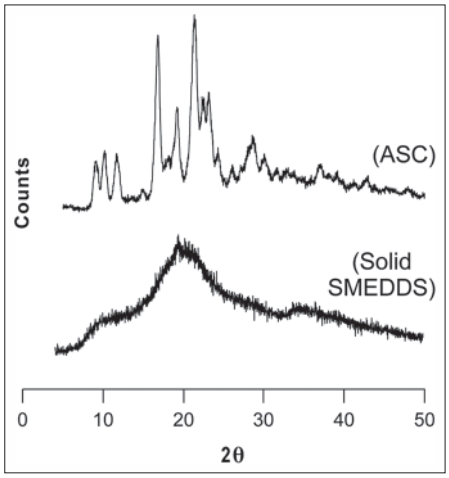

Fig. 7: X-ray powder diffractometry patterns of pure atorvastatin calcium and solid self-emulsifying drug delivery system

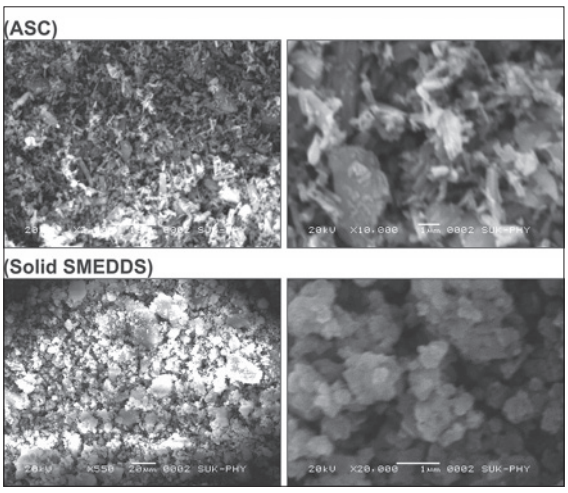

Fig. 8: Scanning electron microscopy images of pure atorvastatin calcium and solid self-emulsifying drug delivery system

(p>0.05) found between the dissolution profile of ASC from optimized liquid SMEDDS A1 and SSMEDDS. These results indicated that self-microemulsifying property of the formulation remained unaffected even after solidification with Neusilin® US2. The faster dissolution from the formulation could be attributed to the presence of the drug insolubilized state in the formulation and upon exposure to the dissolution medium, it resulted in the formation of smaller droplets size that could dissolve rapidly in the dissolution medium [26]. In addition to that, drug amorphization with enhanced physical stability due to hydrogen bonding interactions between silanol groups and metal ions on the surface of the porous Neusilin® US2 might have contributed significantly for rapid release of ASC from SSMEDDS [47].

CONCLUSIONS

Present studies demonstrated the successful transformation of liquid optimized SMEDDS of ASC into the solid stable amorphous form using Neusilin® US2 with faster dissolution rate. The results indicated that both optimized liquid and SSMEDDS of ASC were physicochemically equivalent from dissolution point of view. It could be concluded that Neusilin® US2 could be employed successfully as a potential carrier for the development of SSMEDDS of ASC suggesting an alternative approach with improved dissolution profile of ASC.

ACKNOWLEDGMENTS

The corresponding author is grateful to the Department of Science and Technology, New Delhi, India, for research grant in the form of Fast Track Scheme for Young Scientists (SR/FTP/ETA-53/2011). The authors are thankful to Abbott Healthcare Pvt. Ltd., and Gattefosse, Mumbai, Maharashtra, India, for providing gift samples of drug and excipients, respectively. The authors are also thankful to Fuji chemicals, Japan, for providing Neusilin® US2 to carry out the research work. The analytical facilities provided by Shivaji University, Kolhapur, and Sinhgad College of Pharmacy, Vadgaon, Pune, Maharashtra, India, are gratefully acknowledged. All the authors express their sincere gratitude toward Principal, Government College of Pharmacy, Karad, Maharashtra, India, for providing laboratory facilities and constant encouragement.

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