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Enhancement of dissolution and bioavailability of Eprosartan mesylate by forming Nanosuspension

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ABSTRACT

Eprosartan mesylate (EM) is a poorly aqueous soluble drug belonging to BCS-class II suffers from low bioavailability Issues (13%). The present study involves an effort for improving dissolution and thus the bioavailability of EM using nanosuspension approach. And the Further Evaluation of solubility and dissolution were performed using some analytical tools that are infrared spectroscopy, differential scanning calorimeter, X-ray diffraction study respectively. Where saturation solubility shows 20 fold increases in solubility when formulated as nanosuspension. So the nanosuspension prepared using SLS, PVPK-30 and pluronics F-68 showed improved dissolution. Hence Nanosuspension formulation capable sorted as a promising approach for improving the dissolution of Eprosartan mesylate.

Materials and methods: Eprosartan mesylate, Ethyl Cellulose, Sodium Lauryl Sulphate, Triacetin, .Benzyl alcohol, PVP-K30

Keywords: Eprosartan Mesylate, Solid dispersion, Nanosuspension Technique, Dissolution, Bioavailability, Characterization.

INTRODUCTION

Eprosartan mesylate(EM), chemically *(E)*- 4-({2-Butyl-5-2-carboxy-2-(thiophen-2- methyl) eth-1-en-1-yl-1 *H*-imidazol-1-yl} methyl) benzoic acid, is an anti-hypertensive drug which prevents the vasoconstriction and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle.[1]Eprosartan is of BCS class II drug having poor solubility, and low dissolution rate in the aqueous gastrointestinal fluids often cause insufficient bioavailability approximately 15%. EM has Tmax around 1-2 h, and protein bound capacity approximately 98%. Vd is 308 lit (at steady state), metabolized to inactive

ingredients and terminal elimination half-life is 5-9 h [2, 3]. After oral dosing, approximately 90% is recovered in feces and approximately 7% in urine [2-4]. Due to extensive hepatic first pass metabolism in the liver and very low solubility, the resultant bioavailability lies about 13% [5]. Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bioavailability.[6] During the past few years, there has been a great pace in using solubility enhancement techniques for the improvement of the dissolution rate and subsequently the bioavailability of poorly water soluble drugs. Several techniques like nano-materialization, [7]salt formation,[8]liquisolid compaction,[9]liposome formation,[10] solid dispersion,[11] hydrotropic,[12] Therefore, a high dose of 800 mg is often prescribed for the management of hypertension and other cardiac complications, which often precipitates adverse or side-effects. EM bounds extensively with plasma proteins (98%) and having a mean terminal elimination half-life of 20 hr at 600 mg oral dose [13]. EM undergoes little metabolism by oxidative and hydrolytic processes and about 90% of unchanged drug gets eliminated in feces. The roles of CYP450 are enzyme forms in drug metabolic processes are quite limited. The metabolized products are very minute and are generally inactive [14].

METHODS

Drug content estimation

The SDs equivalent to 10 mg of EM were accurately measured and dissolved in 10 mL of phosphate buffer (pH 6.8 and 7.4). The absorbance was recorded at 233 nm using a UV spectrophotometer (UV-1800, Shimadzu, Japan).

Phase solubility evaluation of EM

An excess amount of quantity of EM was placed in empty small conical flask containing 10 ml of phosphate buffer (6.8 and 7.4). The tubes were sonicated (Transonic Digital S, USA) for 10 minutes at 25°C and the reactant mixture was stirred vigorously using a vortex mixer (V-Mixer Scientific, India) for 5 min to facilitate solubilization of EM in solvent. The reactant mixture was further agitated continuously on a rotary shaker cum incubator (MVTEX, India) at 40°C for 24 hr. After reaching equilibrium, the dissolved EM content in solvent was separated by centrifuging at 10,000 rpm for 5 min and clear supernatants obtained were filtered, suitably diluted and analyzed spectro-photometrically at 233 nm.

Phase solubility study

The phase solubility studies were carried out according to the method reported by Higuchi and Connors.20 An excess amount of EM was added to the screw capped vials containing 20 ml of an aqueous solution of hydrophilic polymers (PEG-4000, Eudragit E-100, PVP K-30, Poloxamer-407, and Eudragit L-100) at various concentrations (5-100 mM) placed in an orbital shaking incubator and agitated for 24 hr at 37°C. After reaching the equilibrium, the supernatant solutions were filtered suitably by Whatmann filter paper (No.41) and after appropriate dilution; solutions were analyzed by UV spectroscopy at 233 nm.

Formulation of Eprosartan Mesylate as Nanosuspension

Emulsion diffusion technology was opted to prepare the EM nanosuspension, where water is partially miscible with organic solvent benzyl alcohol. To obtain this state of emulsion high intensity probe sonicator was used. The process comprises of two steps, Initially EM dissolved in Benzyl alcohol prepared and in next step, various aqueous solution of different stabilizer such as PLURONIC F68(NP) & SLS and PVP K30(NPS) are made. Then EM solution of benzyl alcohol mixed into aqueous solution of stabilizer under ultrasound to obtain the course emulsion &then water also added into same sonication condition to dilute the emulsion. Water causes complete diffusion of the internal phase into the external phase, leading to instantaneous formation of a nanosuspension by precipitation of EM drug particles.

Stabilization with SLS and PVP K30 (NPS)

0.1 % aqueous solution of stabilizer SLS and PVPK30 with ration of 1:1 was prepared. EM solution of benzyl alcohol prepared by dissolving 100mg of EM into 4 ml of benzyl alcohol which was further injected into 0.1% aqueous solution of stabilizer SLS and PVPK30 and sonicated for 3 min at 50% amplitude (Pulse: Pulse of 30 sec followed

by 3 sec relaxation.). This coarse emulsion was again diluted with 150 ml water and sonicate for 3 min at 15^0C.To maintain the temperature ice bath was used. (Sonics and materials Inc.,Vibra Cell, Model VCX 750, Connecticut, USA)

Stabilization with PLURONIC F68 (NP)

Aqueous solution of 0.5% Pluronics F68 was prepared. Accurately weighed 100 mg of EM was dissolved in 4 ml benzyl alcohol. This EM solution rapidly injected into 32 ml aqueous solution of 0.5% Pluronics F68 with probe sonicator for 3 min at 50% amplitude to form coarse emulsion. This emulsion was diluted with 150 ml water and further sonicated for 3 min at 15^0C.

Lyophilization of Nanosuspension

Considering high boiling point of benzyl alcohol, 205^0C, spray drying was not suitable to spray dry nanosuspension. Hence freeze drying i.e. Lyophilization technical was feasible to obtain solid matrix from nanosuspension. Therefore, these samples of nanosuspension (SLS and PVP K30(NPS) based & PLURONIC F68(NP) based) were quickly frozen and lyophilized by dissolving 1 g of mannitol for 24 hours at room temperature at pressure 180 millitorr by using freeze dryer (Virtis, Benchtop K). Lyophilized Nanosuspension with SLS & PVP referred as Lyo NSP and containing Pluronic F68 is referred as Lyo NP & in below text

EVALUATION OF NANOSUSPENSION

Appearance

The prepared Nano suspensions and lyophilized Nano suspensions were inspected visually for color, free flowing nature and presence of any foreign particles.

pH

pH of optimized batches of Nano suspensions and lyophilized Nano suspensions was determined in triplicates using a calibrated pH meter. About 10 ml of nanosuspension was subjected for pH measurement using pH meter. (Toshniwal Instruments Ltd, India)

Drug content

Samples of optimized batches of Nano suspensions and lyophilized Nano suspensions were assayed by dissolving 10 mg of powder in 10 ml of methanol. The solutions were filtered, diluted with distilled water and their drug content was determined (in triplicates) spectro-photometrically at 233 nm, using UV spectrophotometer.

Particle size analysis

Nano suspensions were characterized for average particle size (measurements were performed in triplicates) using laser diffraction technique (Malvern Mastersizer 2000 SM, Malvern Instruments Corp., U.K). Laser obscuration was kept 1%. Particle size distribution is given by d (0.9), d (0.5) and d (0.1) which is the particle size diameters determined at 90th, 50th and 10th percentile of particle undersized, respectively.

Redispersibility of lyophilized nanosuspensions

Lyophilized powders were redispersed in distilled water and analyzed for average particle size using laser diffraction technique (Malvern Mastersizer 2000 SM, Malvern Instruments Corp., U.K). (All measurements were performed in triplicates and their average was considered).

Zeta potential determination

The surface charge of the particles was assessed in triplicates by zeta potential measurements using the Malvern zetasizer (Malvern Instruments, UK). The zetasizer measures the electrophoretic mobility of the particles, which was converted into the zeta potential using the Helmholtz –Smoluchowski equation built into the Malvern zetasizer software. The samples were analyzed as such without any dilution.

Diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS)

The DRIFTS spectra of pure drug and lyophilized products were obtained, after appropriate background subtraction; using an FTIR spectrometer (FT/IR-4100,Jasco, Japan). The sample was mixed with dry potassium bromide and was scanned from 4000–400 cm−1, Jasco spectra manager ver.2 was used for data acquisition and analysis.

Powder X-ray diffraction patterns (PXRD)

PXRD patterns of pure drug and lyophilized nanosuspensions were recorded using an X-ray

Brucker AXS diffractometer (Model: D8 Advance, USA) with Cu line as the source of radiation. The samples were analyzed in the 2θ angle range of 5 to50^0. The range and the chart speed were 1 x 10 3CPS and 10 mm/ 02θ, respectively.

Saturation solubility study

Saturation solubilities of pure drug, nanosuspensions and lyophilized nanosuspensions were determined by equilibrating excess liquid/powder in distilled water and phosphate buffer (pH 6.8) for 24 hours on a mechanical stirrer at room temperature. The samples were filtered through 0.45µm membrane filter. The resulting filtrate was collected and assayed for drug content (in triplicates) spectro-photometrically at 233 nm.

Dissolution /In vitro Release studies

The dissolution studies of pure drug, nanosuspensions and lyophilized nanosuspensions were performed using USP type II dissolution test apparatus (Electroplax TDT-08L, Mumbai, India). The samples equivalent to 40 mg of EM were placed in the dissolution vessel containing 900 ml phosphate buffer (pH 6.8) maintained at 37±0.50C and stirred at 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through 45 µ filter, concentration of EM was determined spectro-photometrically at 233 nm. Analysis of data was done using PCP-Disso software (V3, Poona College of Pharmacy, and Pune, India.).

RESULTS AND DISCUSSION

Selection of the Solvent for Nanosuspension Preparation

A drug which is appropriate applicant for nanosuspension preparation by emulsion diffusion method should be very poorly soluble in water (<10-3 to 10-4 mol/l) and well soluble in organic solvent. The solubility of EM in water, partially water miscible solvents and the solubility of selected organic solvents in water are presented in Table 1.

Table 1. Solubility testing of EM in partially water miscible solvents

Sr. No.	Solvent	Approximate EM solubility (mg/ml)	Reported solubility of solvent in water (w/w%)
1.	Water	0.10 ± 0.03	
2.	Triacetin	0.9 ± 0.5	7.1 (Trotta et al. 2001)
3.	Ethyl acetate	2.1 ± 0.5	7.7 (Yeo et al. 2003)
4.	Benzyl alcohol	29 ± 2	3.5 (Yeo et al. 2003)

*Mean ± S.D., n=3 S.D. Standard deviation

EM is very poorly soluble in water (0.10 ± 0.03 mg/ml) and well soluble in organic solvent. So Emulsion diffusion which is one of the techniques to prepare stable nanosuspension was chosen for the study. In this method surface energy of the system increases during the process of crystallization. In addition, the water solubility of organic solvent is a determining factor affecting the precipitation process. EM dissolves well in ethyl acetate and benzyl alcohol, both of which are partially water miscible.

The solubility of EM in triacetin is very low and thus triacetin less appropriate for the preparation of nanosuspensions.

Small particles, which spontaneously aggregate to decrease surface energy, were stabilized by a layer of surfactant or / and protective polymer. Ethyl acetate has higher water solubility than benzyl alcohol, but benzyl alcohol is a better solvent for EM and was therefore selected for the preparation of nanosuspensions. Ultrasonication is used to prepare emulsion and suspension by diluting emulsion.

Impact of Stabilizers on Nanosuspension Formation

The stabilizer or mixture of stabilizers should show enough affinity for the droplet surface to allow preparation of emulsion and for the particle surface in demand to stabilize the nanosuspension. Hence the choice of stabilizer is specific to each drug applicant and each formulation procedure play important role. In initial experiments, different stabilizers were screened in different

concentrations for nanosuspension preparation by solvent diffusion method [5-9].

When the impact of different stabilizers was explored, the emulsions were prepared with a fixed concentration of the drug. Three different stabilizers such as, SLS, PVPK30 and Pluronics F68were tried. SLS formed nanosuspension with particle size range of 200 to 300 nm. But this suspension was not steady after 15 days due to increase in particle size. As reports suggest that combination of stabilizers was chosen over one single stabilizer for long term stabilization of nanosuspension, groupings of these stabilizers were tried. The particle size of nanosuspension stabilized with 0.1% SLS: PVPK30 (1:1) was significantly less than suspension stabilized with SLS & PVPK30 individually. Use of mixture of SLS and PVPK30 was based on rationale of electrostatic and stearic stabilization as reported by Rainbow, where both steric and electrostatic mechanisms are enabled by mixing non-ionic and ionic surface modifiers, which therefore complement each other. The suspension stabilized with 0.5% Pluronics F68 resulted into minimum particle size i.e. 192 nm (Table 2). So, this batch was selected for further study.

Important role of stabilizer is that they can build a substantial mechanical & thermodynamic blockade at the interface that lessens cohesive forces between individual emulsion droplets. Nonionic surfactants like Pluronic F68 bid an advantage over other polymers in that they have a higher adsorption potential on the droplet surface and act as a steric barrier, preventing close contact of droplets and later particles than an equal-chain-length polymer. Ionic surface modifiers like SLS formed electrostatic repulsive layer to avoid aggregation of particles in the process of size reduction. Both ionic as well as non-ionic stabilizers would prevent Ostwald's ripening in nanosuspensions. But non-ionic stabilizers arrested crystal growth only while ionic stabilizers inhibited both nucleation and crystal growth of nanoparticles.

Appearance &pH study

Appearance &pH of pure EM, nanosuspensions and lyophilized products are shown in table 2. As reported by nanosuspensions with neutral pH are compatible for oral delivery, present results are in agreement with this report.

Table 2: Comparative evaluation of appearance, pH

Batch	Appearance	pH study (pH ± SD)*
Pure drug suspension	White and turbid	_
NP	Translucent with light blue tint	6.85 ± 0.55
NSP	Translucent with light blue tint	7.06 ± 0.22
lyoNP	White and free flowing	7.09 ± 0.06
lyoNSP	White and free flowing	7.18 ± 0.31

Percentage of Drug Content

Percentage Drug content of all the optimized batches done by assay method &is shown in Table 3. In case of NP and NSP, some amount of drug must have remained in soluble form in the stabilizer solution, and some was loosed in processing. Therefore, all the batches were found to be in between 89 to 94%.This was confirmed by testing solubility of EM in respective concentrations of stabilizer solutions.

Table 3: % Drug Content of Optimized Batches by UV Spectroscopy

Sr. no.	Batches	Drug content (% ± SD) *
1.	NP	92.47 ± 3.17
2.	NSP	94.76 ± 2.67
3.	Lyophilized NP	93.11 ± 4.27
4.	Lyophilized NSP	89.94 ± 3.69

* Mean ± SD, n=3

Particle Size Analysis

Particle size and particle size distribution analysis was done by laser diffraction (LD) technique is mentioned in Table 4. As per laser diffraction (LD) technique, liquid nanosuspensions showed d90 having size less than 1 µm particles size with less than 1 uniformity. Nanosuspensions NP and NSP showed comparatively smaller nano sized particles (192±10nm and, 348± 15nm respectively) and were stable. So, these batches were selected for further studies.

Table 4: Particle size analysis of nanosuspensions by laser diffraction technique

Batches	Uniformity± SD*	d (0.9) µm ± SD
Pure drug	4.89 ± 0.57	22.847± 7.115
0.02%SLS+PVPK30 (1:1)	0.786±0.134	0.579±0.027
0.1%SLS+PVPK30 (1:1) (NSP)	0.832±0.098	0.357±0.018
0.02% SLS + Soya lecithin (1:1)	0.674±0.126	0.661±0.009
0.1% SLS+soyalecithin(1:1)	0.852±0.037	0.711±0.043
0.25% PVPK30	1.063±0.904	0.667±0.078
0.5% PVPK30	0.853±0.218	0.595±0.070
0.05% SLS	0.643±0.230	0.284±0.009
0.1% SLS	0.895±0.192	0.383±0.016
0.25% Soya lecithin	0.879±0.020	0.834±0.018
0.5% Soya lecithin	0.861±0.146	0.772±0.048
0.25% Pluronic F-68	0.937±0.085	0.505±0.025
0.5% Pluronic F-68r (NP)	0.319±0.093	0.194±0.030

Redispersibilityof Lyophilized Nano-suspensions

For ease of handling, packaging and storage, solid dosage forms are preferred over liquid formulations. Hence, lyophilization techniques were used to convert liquid nanosuspensions into dry powders. But these dry powders must be redispersible to original liquid nanosuspensions on dilution with a suitable media. Particle size distributions of lyoNP and lyoNSP after redisposing dry powders in distilled water are shown in table No.5.

Table No.5: Particle size distributions of lyoNP and lyoNSP

Batches	d (0.5) µm ± SD*	d (0.9) µm ± SD*	Uniformity ± SD*
lyoNP	0.249 ± 0.078	0.518 ± 0.036	0.814 ± 0.035
lyoNSP	0.379 ± 0.057	0.661 ± 0.021	0.858 ± 0.049

After dispersion, dry powders showed submicron particle size and uniformity similar to that of respective nanosuspensions (NP and NSP). Increase in particle size was observed due to lyophilization. But particles were still below 650nm size range. Thus, lyophilization technique successfully incorporated nanosuspension into solid matrix.

Zeta Potential Determination (ZP)

Zeta potential of a nanosuspension is critical parameters. It is characteristic associated with double layer on the surface of colloidal particles of nanosuspension which indicate the physical stability of nanosuspension as testified. Zeta potential of pure drug suspension and optimized batches of nanosuspensions shown in table 6. Dispersion shows instability when particles having low zeta potential values signifying that there no force available to prevent the magnetism of particles is coming together. All particles with massive positive or negative zeta potential have ability to resist each other and maintain their stability in dispersion. Zeta potential value is estimated by using electrophoretic technique. Negative sign in zeta potential of NSP was due to anionic nature of SLS. From zeta potential values it was confirmed that batch NSP was stabilized by combined electrostatic and steric effect and batch NP was stabilized by steric effect [10-14].

Table No.6: Zeta potential of pure drug suspension and optimized batches of nanosuspensions

Batch	Zeta potential determination (mV ± SD)*
Pure drug suspension	+16.1 ± 0.4
NP	-28.4 ± 0.8
NSP	-31.6 ± 0.3

Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFTS)

IR spectra of pure EM, lyoNP and lyoNSP are shown in figure.1 FTIR analysis was performed to study any possible interactions between drug, carrier and lyoprotectant. The spectrum of EM was characterized by peaks at 3650 cm-1 (OH stretching), 3290cm–1 (NH stretching), 2927 cm–1 (aliphatic CH stretching), 1830 cm–1 (ester stretching), 1703 cm–1 (acetate stretching) and 1527-1446 cm–1 (C=C stretching). IR spectra of lyoNP and lyoNSP also showed similar peaks indicating absence of any interaction of EM with excipients after lyophilization of nanosuspensions. IR spectra of lyoNP and lyoNSP exhibited few peaks other than those for EM were due to presence of mannitol.

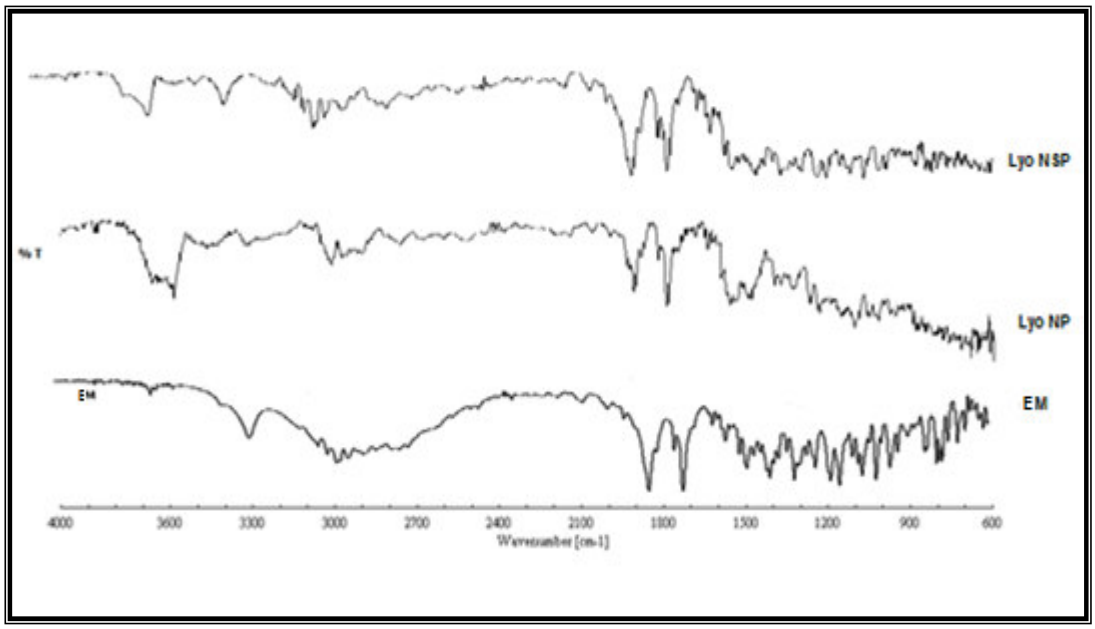


Figure 1: FTIR spectra of pure EM, lyoNP and lyoNSP

Stretching of peaks shows crystallinity of formulation needed to describe hydrophilicity and attraction of forces for solubilization of drug from the formulation. Sharp peak shows more crystallinity and a broad peak gives the indication to amorphous nature and hydrophilicity.

Powder X-ray diffraction analysis (PXRD)

PXRD patterns of pure EM, lyoNP and lyoNSP are shown in figure.2 PXRD analysis is a technique used to find crystalline/amorphous nature of drug nanoparticles. XRPD of pure EM indicated with few distinctive peaks in the region of 5to 400 (2θ) at 7.100, 15.130, 18.950, 20.820, 22.100 24.950, and 29.600 indicating that pure EM is highly crystalline in nature. Intensity of these peaks was reduced in the PXRD spectrum of the lyophilized nanosuspensions (lyoNP and lyoNSP).

The crystalline nature of drug particles is reduced as a result of nanoprecipitation, ultrasonication and freeze drying. Reduction in crystalline status of drug would improve its solubility. Other peaks observed in the PXRD spectra of lyophilized nanosuspensions could be ascribed to the presence of excess amount of cryoprotectant.

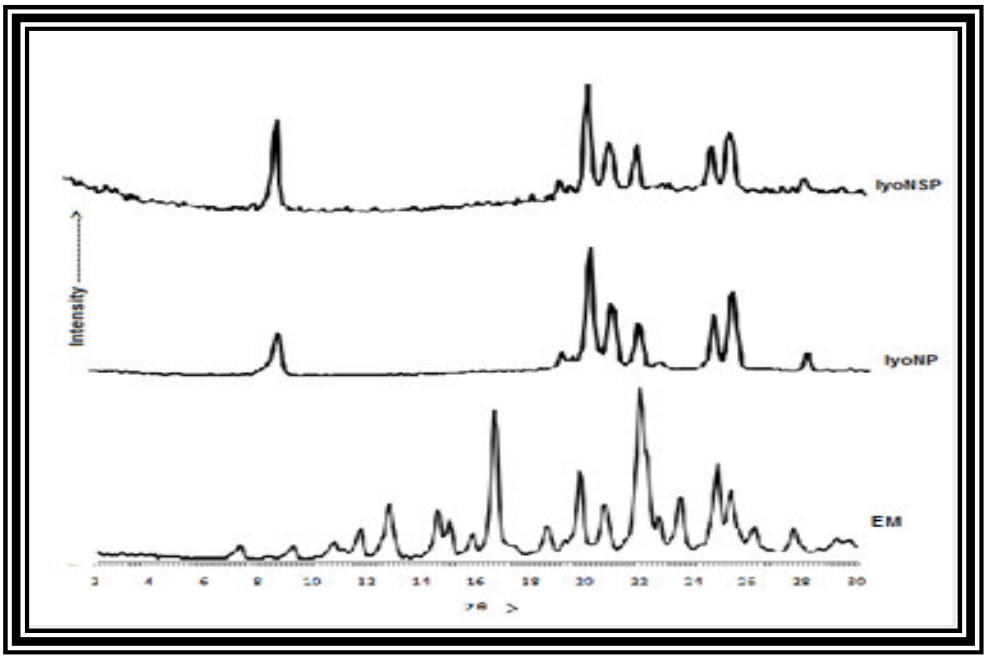


Figure 2: PXRD patterns of EM, lyoNP and lyoNSP

Saturation solubility study

Comparative saturation solubility study of different batches helps to identify the improvement in drug solubility. Saturation solubilities of different formulations are shown in table 7. It is reported that reducing the particle size down to the submicron range increases the saturation solubility of EM. So, saturation solubility of drug was improved around 20-fold when formulated as nanosuspensions (NP and NSP). Lyophilized nanosuspensions showed lower solubility improvement compared to liquid nanosuspensions due to particle size enlargement during lyophilization.

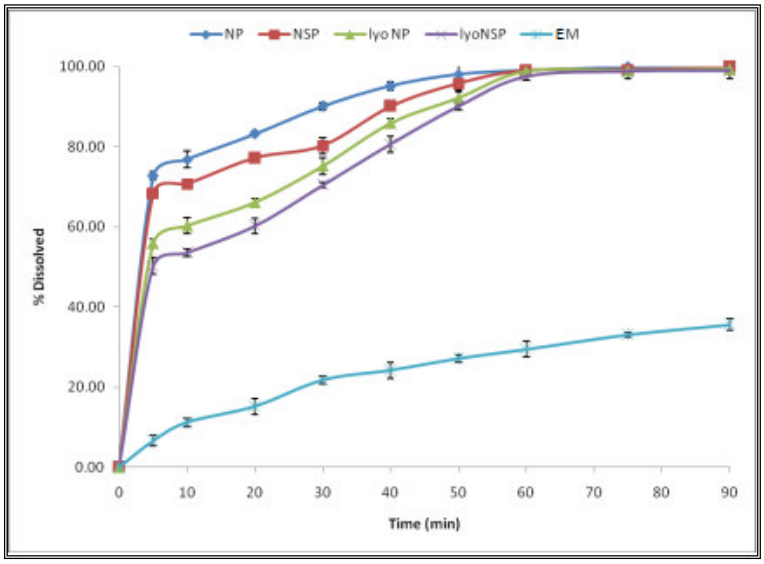
Table 7: Saturation solubility of different batches of nanosuspensions

Sr. No.	Batch	Saturation Solubility in distilled water (mg/ml ± SD)*	Saturation Solubility in phosphate buffer pH 6.8 (mg/ml ± SD)*
1	Pure Drug	0.11 ± 0.04	0.19 ± 0.09
2	NP	2.24 ± 0.34	2.82 ± 0.13
3	NSP	1.67 ± 0.13	2.56 ± 0.11
4	Lyophilized NP	1.59 ± 0.17	1.73 ± 0.26
5	Lyophilized NSP	1.89 ± 0.11	1.78 ± 0.19

Dissolution study

Dissolution profiles of different formulations are shown in figure 3. Pure EM showed poor dissolution pattern. EM was characterized by only 28.89 % drug release within 60 min. When formulated as a nanosuspensions (NP and NSP), its dissolution rate was significantly ($p<0.05$) enhanced. This must be attributed to the increased surface area of the drug and possible better contact between nanosuspensions and dissolution medium. According to Noyes –Whitney equation, an increase in saturation solubility and decrease in particle size lead to an increased dissolution rate (Patrawale et al 2004). Nanosized particles can improve saturation solubility and solution due to the vapour pressure effect. Moreover, the drug

nanoparticles diffusional distance is decreased, which cause an increased concentration gradient. The increase in concentration gradient and surface area will produce increase in the dissolution kinetics as compared to a micronized formulation. So, formulation of poorly water-soluble drugs as nano-sized drug particles had a dramatic effect on dissolution rate and drug solubility. Lyophilized products showed lower drug release compared to nanosuspensions. This must be attributed to increase in particles size during lyophilization. In first 10 min, nanosuspensions presented about 75 % in solution and lyophilized products presented about 65%. % drug release studies are in agreement with result of saturation solubility study.



* Mean ± SD, n=3

Figure 3: Dissolution profiles of pure EM, nanosuspensions and lyophilized products

CONCLUSION

EM nanoparticles may be prepared using an emulsion-diffusion method with Pluronic F68, PVPK30 and SLS stabilizer followed by lyophilization Ultrasound uniformly mixes organic and aqueous phase resulting in formation of stable emulsion which on dilution produces stable suspension. Ultrasound strengthens mass transfer and initiates important phenomenon cavitation. This effect brings extensive benefits to crystallization process, such as reduction of crystal size, embarrassment of agglomeration which can help in manipulation of crystal size distribution. Nanosuspension prepared under high intensity ultrasonication successfully resulted into nanosized, uniformly dispersed stable nanosuspension. Nano-sized EM dissolved much more rapidly than micronized. PXRD results showed decrease in crystalline nature of drug particles as a result of nanoprecipitation, ultrasonication and lyophilization. Clearly, these findings indicated the suitability of emulsion diffusion techniques for preparation of nano-sized poorly water-soluble drug with significant improvement of the in vitro dissolution rate, and thus possibly improve their oral bioavailability.

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