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SELF-NANOEMULSIFYING METAPROLOL DRUG DELIVERY SYSTEM: FORMULATION AND IN VITRO CHARACTERIZATION.

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ABSTRACT

The oral administration route remains the best choice for drug delivery owing to its safety, patient compliance and capacity for self-administration. In addition to being the most convenient route of administration, oral delivery has been limited owing to the numerous barriers present at the gastro-intestinal (GI) tract. The self-emulsifying formulations can be administered as water-free pre-concentrates those in situ form nanoemulsions in the fluids of the gastrointestinal tract. Self-nano emulsifying drug delivery systems (SNEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug that form fine oil-in-water nanoemulsion when introduced into aqueous phases under gentle agitation.

KEY WORDS: Formulation, Oral, Metaprolol, Nanoemulsion

INTRODUCTION

In recent years, substantial attention has been focused on lipid-based formulations to increase the oral bioavailability of poorly water-soluble medicinal molecules. Active lipophilic ingredients are often added to inert lipid vehicles like oils, surfactant dispersions, emulsions, liposomes, self-emulsifying formulations, nano-emulsifying systems, and microemulsifying systems. Most improve solubilization and permeation by increasing drug surface area. Lipids are used to increase the solubility and oral bioavailability of BCS class II and IV drugs. Most improve solubilization and permeation by increasing drug surface area [1]. Lipids are used to increase the solubility and oral bioavailability of BCS class II and IV drugs. Since self-emulsifying drug delivery systems (SEDDS) are physically stable lipid solutions or dispersions, they are one of the lipid formulations that represent an attractive alternative to orally administered emulsions [4, 26]. This is because SEDDS are one of the lipid formulations that make up self-emulsifying drug delivery systems. Mixtures of natural or synthetic oils, solid or liquid surfactants, and, alternatively, one or more hydrophilic solvents and co-solvents/surfactants are what make up SEDDS [2].

These mixtures are isotropic in nature. Candidates for this formulation concept include pharmaceutical substances that have adequate solubility in mixtures of lipids, surfactants, and co-solvents (or co-surfactants) [6]. SEDDS are able to disperse easily throughout the gastrointestinal tract, and the agitation that is required for the self-emulsification–dispersion process is provided by the digestive motility of the stomach and intestine. SEDDS are usually liquid or soft gelatin capsules [7, 26]. Solid dosage forms are preferred over liquid preparations due to manufacturing ease, patient convenience, accuracy, and stability. Combining lipid-based drug delivery systems with solid dosage forms overcomes the drawbacks of liquid formulations. Some attempts were made to solidify liquid SEDDS [3].

Metaprolol is a naturally long-acting beta-blocker, and according to the Biopharmaceutical Classification System, it is a drug that has low solubility [10]. However, in the essential drug list maintained by the World Health Organization, it is presented in an immediate-release dosage form. Patients suffering from heart failure, hypertension, and ischemic heart diseases have been the subjects of research on metaprolol, which is now commercially available in 3.125-, 6.25-, 12.5-, and 25-mg tablet strengths [4].

SNEDDS are useful for pre-dissolving poorly water-soluble compounds and filling capsules. Pre-dissolving the compound overcomes the rate-limiting step of particulate dissolution in the GI tract. The drug may precipitate in the GI tract if a hydrophilic solvent is used

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(e.g. polyethylene glycol). If the drug is dissolved in a lipid vehicle, there is less chance of precipitation in the GI tract, as partitioning kinetics favour the drug remaining in the lipid droplets [5].

METHODOLOGY

Solubility studies [6]

An excess amount of Metoprolol was added to various oils, surfactants and cosurfactants, and mixed by vortexing. The mixture was kept at ambient temperature for 72 hr to attain equilibrium. The equilibrated sample was centrifuged at 1000 rpm for 10 min to remove the insoluble drug. An aliquot of the supernatant was diluted with methanol and CNZ was quantified by UV spectroscopy.

Screening of oils [7]

`The oils were selected on the basis of their tendency for self-emulsification. The oils selected for this investigation were oleic acid, castor oil, olive oil and soyabean oil. The oils and surfactant (tween 80) were mixed in a ratio of 1:1. The mixture was then checked for self-emulsification by adding 1 mL from each mixture to 5 mL of water and followed by agitation. The turbid solution obtained was observed under microscope for emulsion formation.

Preparation of self nanoemulsifying systems [8]

A series of SNEDDs were prepared using oleic acid as the oil, Tween 80 as surfactant and Capmul MCM C-8 as the cosurfactant. In all the formulations, the amount of Metoprolol was kept constant. Accurately weighed Metoprolol was placed in beaker and oil, surfactant, and co surfactant were added. The components were mixed by gentle stirring with magnetic stirrer and the resulting mixture was heated at 40°C, until the drug was completely dissolved. The homogenous mixture was stored at room temperature until further use.

Characterization of SNEDDS [9]

Robustness to dilution

Robustness to dilution was studied by diluting the formulation with 100 times volumes of various dissolution media viz. 0.1N HCl and phosphate buffer (pH 6.8). The diluted nanoemulsions were stored for 12 h and observed for any signs of phaseseparation or drug precipitation.

Determination of emulsification time

Self-emulsifying formulations can be graded for self-emulsification time, dispersibility and appearance. Visual assessment criteria for self nanoemulsion formed from different formulation.

Characterization of SNEDDS

Transmission electron microscopy

The nanoemulsion globules were visualized by Transmission Electron Microscope (TEM) (MORGAGNI 2680 FEI, (Holland). Samples were dried on carbon-coated grid and negatively stained with aqueous solution of phosphotungstic acid. After drying the specimen was viewed under the microscope.

Droplet size analysis

The droplet size and zeta potential of the emulsions was determined at 25°C by dynamic light scattering (DLS).

Zeta potential analysis

Zeta potential analysis with Zetasizer Nano-ZS (Malvern Instrument Limited, UK) by monitoring at a scattering angle 173°C. The nanometric size range of the globule was retained even after 100 times dilution with water which proves the compatibility of the system with excess water.

Drug loading efficiency

50 mg formulation was taken and to it methanol was added to make up the volume to 100 ml. The resultant solution was analysed spectroscopically following suitable dilution. The drug loading efficiency was determined by the following formula:

Drug loading efficiency

Amount of drug known in amount of formulation/initial drug load×100.

Stability study

The physical stability study of the various SNEDDS formulations was performed at 4°C, 25°C and 45°C for 60 days. The SNEDDS was evaluated by visual inspection for physical changes such as color and drug precipitation.

In-vitro dissolution study

Dissolution profiles of the SNEDDS were investigated using the dialysis bag method according to dissolution apparatus 2 in USP 24 in 0.1N HCl and Phosphate buffer (pH 6.8) (900 mL). The formulation was placed in dialysis bag (MWCO 12000, Medicell International, UK) held to the bottom of the vessel using copper sinkers.

The temperature was maintained at 37±0.5°C during the study. At regular time intervals, 3 ml samples were withdrawn and replaced with equal volumes of fresh medium. The withdrawn samples were analysed spectrophotometrically for the drug content.

RESULTS AND DISCUSSION

Preparation and Evaluation of SEDDS

Construction of ternary-phase diagram

Upon examining the different combinations of HCO-40, Transcutol HP, and MCT, no phase separation was observed upon storage for 72 h at ambient temperature. Visual observations of the dispersion

experiment, using 0.1 N HCl, were demonstrated in the phase diagram, From the results, it was deduced that an increase in HCO-40 content increased the clarity of the produced emulsion. Also, it showed that the particle size increased upon increasing MCT content. This could be explained by the fact that the surfactant stabilizes the O/W interface and its concentration increased at the interface upon decreasing the oily content. That attributed to a decrease in the emulsion particle size thus a more clear-appearing emulsion was produced. That increasing HCO-40 to Transcutol ratio at a constant MCT percentage increased the emulsification time. This may be due to the increase in system viscosity and formation of gel-like structure that decreased waterpenetration into the system.

Determination of metaprolol saturated solubility in differentsystems

It was noticed that increasing Transcutol percentage resulted in an increase in metaprolol solubility (Fig. **6**). There was a non-significant decrease in the solubility upon increasing MCT percent from 10% to 20% (p>0.05). Type (A) systems were able to dissolve 3.125, 6.25, and up to 12.5 mg metaprolol per 100 mg system.

Preparation and evaluation of carvedilol SEDDS

None of the prepared systems showed any precipitation within the storage period. Figure 7 shows the effect of 12.5% *W*/*W* metaprolol addition on systems classified as type (A). Systems with a high HCO-40 percentage produced emulsions having finer particle size, which indicates better stability. Also, it can be noted that systems containing 20% Miglyol produced emulsion with larger particle size than systems containing 10% Miglyol. Generally, it was observed that incorporation of 12.5% *W*/*W* carvedilol into systems classified as type (A) mostly increased particle size of the formed emulsions.

Time needed to measure 90% metaprolol was chosen as the emulsification time. Tested systems were emulsified within the first 2 min except systems 0, 1, and 2. These systems were considered as the most viscous systems, as they contained the highest percentage of HCO-40. After 4 min, detected metaprolol was higher from system 2 in comparison to system 1 (p=0.023). This could be explained by the fact that presence of Transcutol increased systems hydrophilicity and thus water penetration into the gel like structure. No precipitation of metaprolol was observed throughout the experimental period.

Metaprolol as a basic drug, dissolves in the acidic pH of the stomach (ionized form). However, precipitation in the higher pH environment of the small intestine (site of absorption) may occur, eradicating any advantage gained in dissolving the drug in the stomach. To verify the possibility of drug precipitation under intestinal conditions, emulsification test was done in pH 6.8. There was efficient self-emulsification and dispersion of metaprolol within tested pHs (1.2 and 6.8). Within 2 min, medicated system 9 dissolved 89.4±1.4% and 86.4±0.7% metaprolol in pH 1.2 and 6.8, respectively (p=0.115). The results of detected metaprolol upon testing system 9 in phosphate buffer (pH 6.8) showed a great improvement in comparison to metaprolol powder (0.2± 0.0%). This indicates that the improvement of metaprolol dispersion after incorporation within the SMEDDS is observed within acidic and basic media regardless its intrinsic solubility.

Formulation dispersion–drug precipitation test

Presence of high percentage of co-solvent (Transcutol) in systems 20, 27, and 35 increased carvedilol precipitations in the performed test regardless their classification as type A, B, or C, respectively. Drug precipitation upon dilution could be attributed to the relationship between drug solubility and co-solvent concentration, which is commonly approximated to a logarithmic relationship. It was noticed that systems containing 20% oil were more susceptible to metaprolol precipitation than systems containing 10% oil (1 *vs*. 2, 4 *vs*. 5, 8 *vs*. 9, and 13 *vs*. 14 having p=0.001, p<0.001, p<0.001 and p<0.001, respectively). Consequently, it was concluded that maintaining metaprolol within the emulsion structure is privileged to co-solvent presence under constant surfactant content. It should be mentioned that metaprolol precipitation may not only be due to the decrease in its solubility upon SEDDS dilution but also it may be due to phase separation of the formed emulsion.

Systems 4, 8, 13, 14, 20, 27, and 35 were excluded from this study as they retained less than 70% of the initial drug content at the end of the formulation dispersion–drug precipitation test, while systems 0, 1, and 2 needed more than 2 min for the emulsification process. On the other hand, system 5 contains more surfactant than system 9 which is expected to be more toxic. Accordingly, in order to improve metaprolol equilibrium solubility, system 9 was chosen for further studies. Each of the selected polymers (HPMC 5cp, HPMC 15cp, and MC 15cp) was added to system 9 in 5%, 10%, or 15% (*W*/*W*). Addition of such polymers enabled the retainment of metaprolol in the aqueous media by increasing its stability (77% increased to 98–102% according to the polymer type and concentration). Similar results were obtained with Itoh, Gao, and co-workers who proved that the addition of polymeric materials to SEDDS inhibited drug crystallization.

Preparation and Evaluation of Simple Liquisolid Powders and Tablets

Liquisolid powders having an angle of repose (θ) close to 25°, an HR less than 1.25, and a CI between 5%

and 18% were considered as powders with acceptable physical properties. Liquisolid powders LS9-22, LSH15-22, and LSM15-20 showedacceptable physical properties. They were chosen to be compressed into liquisolid tablets, using 11 mm concave punch, as they passed the lowest weights of unit dose within powders with acceptable physical properties in the following types of loaded liquid: SNEDDS-9, SNEDDS-9/5% HPMC 15cp, and SNEDDS-9/5% MC 15 cp, respectively.

Accordingly, different polymers changed the physical properties of liquisolid powders differently. Liquisolid powders adsorbing HPMC 15cp showed better physical properties than MC 15 cp followed by HPMC 5 cp.

Tested simple liquisolid tablets confirmed the accepted criterion for weight variation, drug content, friability, hard- ness, and disintegration. Tested liquisolid tablets dissolved about 90% of metaprolol within 45 minutes. It was noticed that the dissolution profile of metaprolol from the tested tablets was improved if compared to that of the powder form. Liquisolid tablets improved metaprolol dissolution profile as they introduced carvedilol into the dissolution media in a nanoemulsion. Presence of metaprolol within the nanoemulsion increased the release surface area thus increasing its diffusion into the dissolution media.

Particle size analysis is presented in SNEDDS-9 demonstrated a monodisperse system with a mean diameterof 17.9 nm. Simple liquisolid tablet particle size analysis revealed two peaks; one corresponds to the nanoemulsion. System while the other represents some insoluble nanoparticles in the tablet components. Liquisolid tablets LS9-22, LSH15-22, and LSM15-20 produced a nanoemulsion with mean diameter of 26.6, 17.0, and 27.4 nm, respectively. Processing SNEDDS into liquisolid tablet did not affect the nanoparticle size after emulsification in 0.1 N HCl..

Figure 1: Ternary-phase diagrams between HCO-40, Transcutol, and MCT.

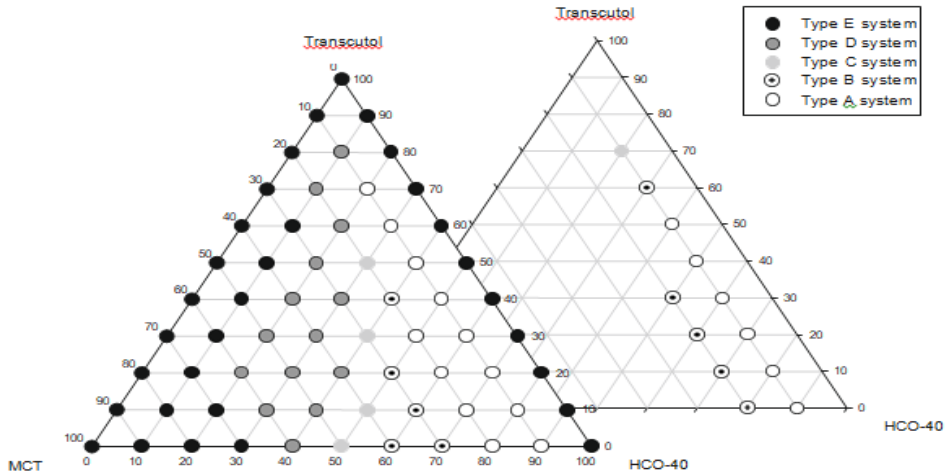


Figure 2: Time required for emulsification of systems (A and B), presented in minutes

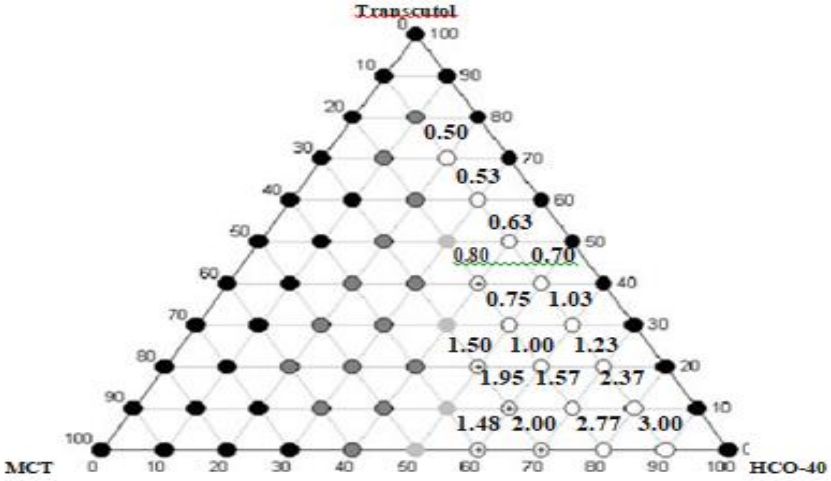


Figure 3: Saturated solubility of metaprolol in different systems composed of HCO-40, Transcutol, and MCT in different ratios

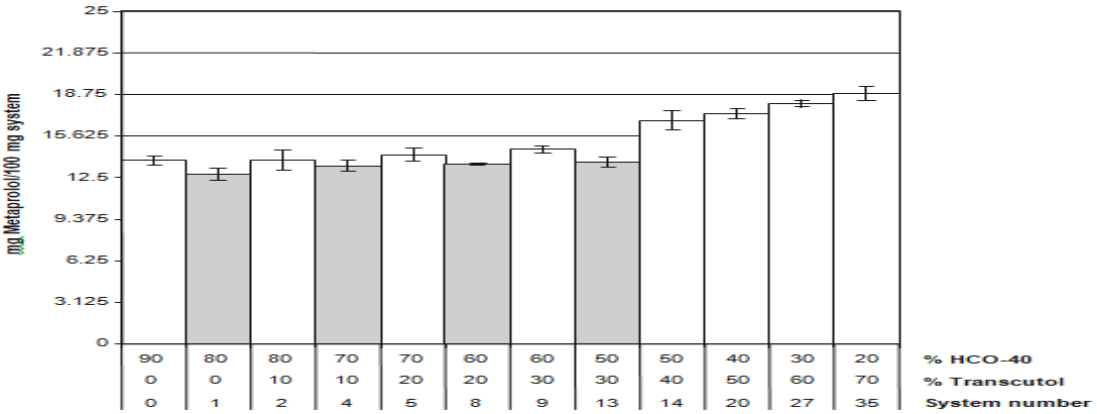


Figure 4: Percentage of detected metaprolol in 0.1 N HCl as a function of time.

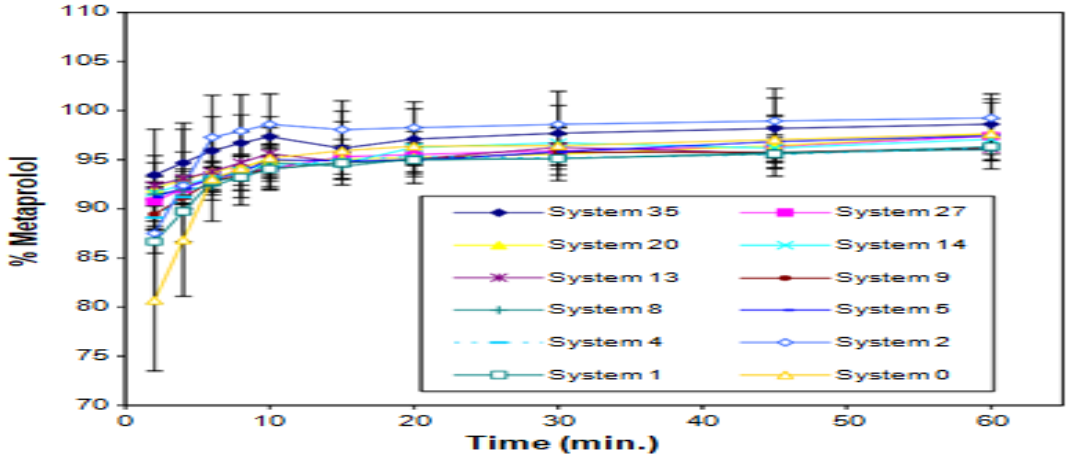


Figure 5: Formulation dispersion–drug precipitation test for different SEDDS

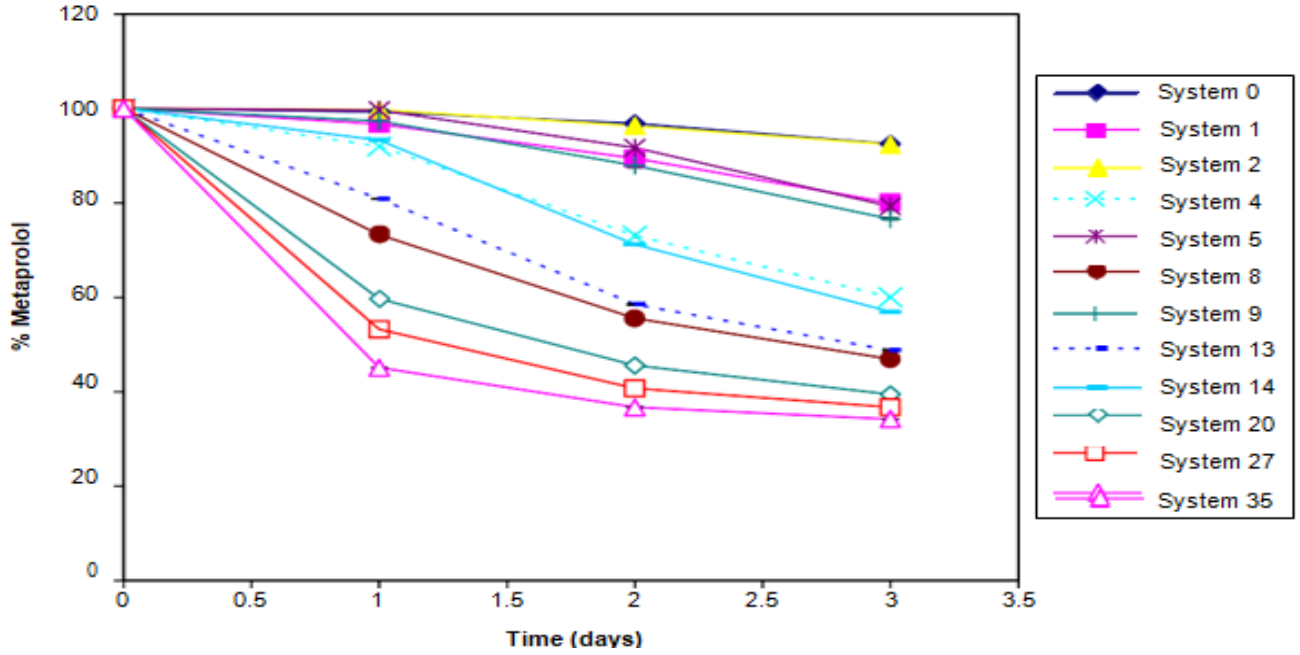


Figure 6: Dissolution profiles of Metaprolol from different liquisolid tablets compared to Metaprolol powder

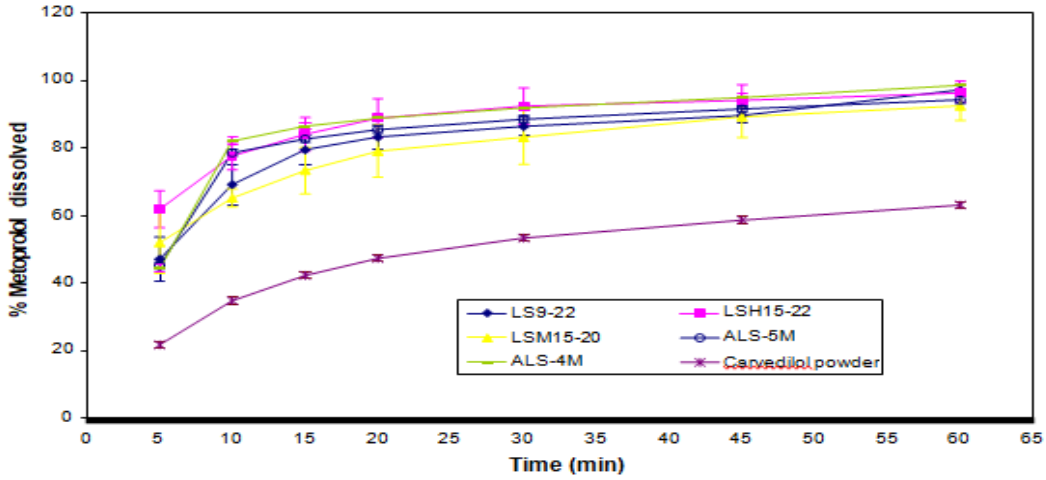
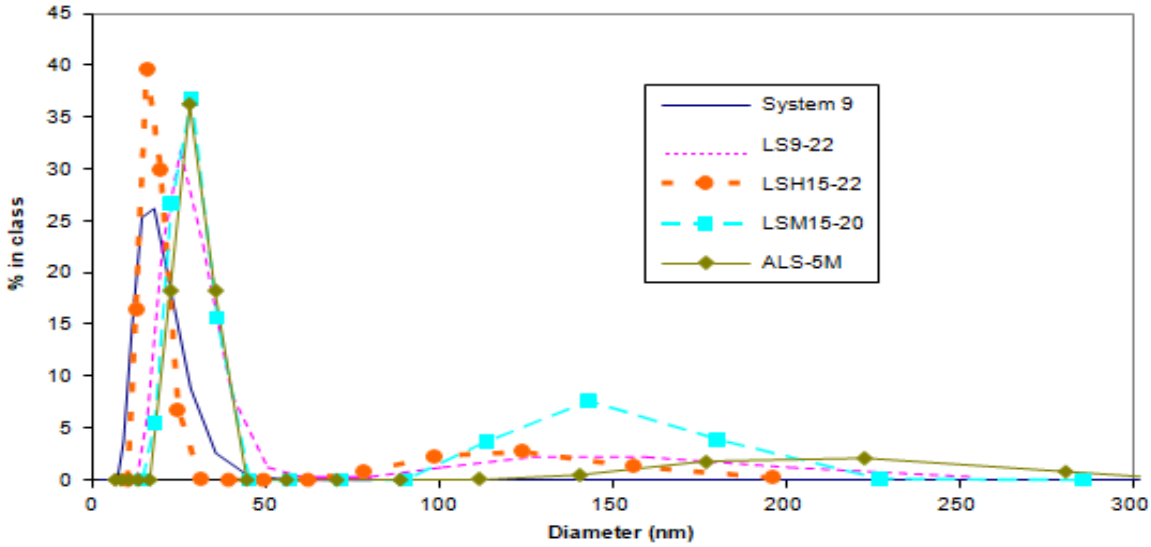


Figure 7: Particle size distribution of emulsified system 9 and liquisolid tablets dispersed in 0.1 N HCl



Preparation and Evaluation of Liquisolid Powders and Tablets

Powders containing adsorbent of Aeroperl: MCC in 3:17, 1:4, and 1:3 weight ratios showed acceptable physical properties regardless the order of adsorbent addition. Powders designed to contain 52.5 mg of SNEDDS-9/5% HPMC 15cp within 200-mg unit weight were successfully prepared. They were compressed using single punch machine having 9-mm concave or flat punch. Flat punch produced significant increase in tablets hardness at 95% level of significance. Accordingly, flat punch was used during further study.

Tested tablets had shown acceptable hardness and disintegration time. After mixing Aeroperl with SNEDDS-9/5% HPMC 15cp, mixing with MCC did not produce homogenous mixture easily. Tablets prepared by adding MCC as an adsorbent followed by Aeroperl were chosen for further study as they were easier to formulate. They showed acceptable weight variation, drug content, friability, and dissolution profile (Fig. 10). Nevertheless, ALS-5M was superior to ALS-4M in its disintegration time (4.7±0.3 min) and hardness (4.0±0.4 kg).

Liquisolid tablet, ALS-5M, particle size analysis revealed three peaks; one corresponded to the nanoemulsion system while the others represented some insoluble nanoparticles in the tablet components. It produced a nanoemulsion with a mean diameter of 28.4 nm. Processing SNEDDS into liquisolid tablets containing granulated SiO_2 was also able to retain the nanoparticle size of the nanoemulsion.

Study of P-gp inhibition Activity

The calculated IC_{10} value of SNEDDS was 0.60µg/ml, while IC_{50} value of paclitaxel was 435.32

ng/ml. The concomitant treatment with both formula and paclitaxel resulted in an inhibition in the cell growth and a potential downshift in the dose–response curve of paclitaxel, in a way that depressed the IC_{50} value of paclitaxel to306.54 ng/ml. That decrease in IC_{50} indicated presence of P-gp inhibition activity which may lead to a decrease in from the intestinal cells with absorption.

CONCLUSION

In this study, combination of HCO-40, Transcutol HP, and MCT in variable ratios showed rapid emulsification in aqueous media. Meanwhile, systems which form nanoemulsion and are able to retain the drug in a solubilized form after dispersion in aqueous media will be preferred as a carrier for poorly water-soluble drugs. In addition, they were able to introduce the SNEDDS into the dissolution media where it was efficiently transformed into nanoemulsion by the gentle agitation provided in the dissolution experiment. Modifying silicon dioxide physical form from amorphous into granulated improved the physical properties of both liquisolid powders and tablets.

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