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Oral Bioavailability Enhancement of Acyclovir by Self-Microemulsifying Drug Delivery Systems (SMEDDS)

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Acyclovir is a potent anti-viral agent useful in the treatment of Herpes Simplex Virus (HSV) infections. Acyclovir exerts its anti-viral activity by competitive inhibition of viral DNA through selective binding of acyclovir to HSV-thymidine kinase. The main purpose of this work was to develop self-microemulsifying drug delivery system (SMEDDS) for oral bioavailability enhancement of acyclovir. Solubility of acyclovir was determined in various vehicles. SMEDDS is mixture of oils, surfactants, and co-surfactants, which are emulsified in aqueous media under conditions of gentle agitation and digestive motility that would be encountered in the gastro-intestinal (GI) tract. Pseudoternary phase diagrams were constructed to identify the efficient self-emulsifying region dilution study was also performed for optimization of formulation. SMEDDS was evaluated for its percentage transmittance, Assay of SMEDDS, phase separation study, droplet size analysis, zeta potential, electrophoretic mobility, and viscosity. The developed SMEDDS formulation contained acyclovir (50 mg), Tween 60 (60%), glycerol (30%) and sunflower oil (9%) was compared with the pure drug solution by oral administrating to male albino rats. The absorption of acyclovir from SMEDDS form resulted about 3.5 fold increase in bioavailability compared with the pure drug solution. Our studies illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds such as acyclovir by oral route.

Keywords self-microemulsifying drug delivery system; acyclovir; zeta potential; droplet size analysis; bioavailability

INTRODUCTION

Acyclovir is a potent antiviral agent. It is a synthetic nucleoside analogue active against herpes viruses. Acyclovir exerts its antiviral activity by competitive inhibiting of viral DNA through selective binding to HSV-thymidine kinase with about 200-fold greater affinity than for mammalian enzyme. The oral bioavailability of acyclovir ranges from 10 to 30% and decreases with increases dose. Peak plasma concentration average 0.4 to 0.8 μg/mL after 200 mg and 1.6 μg/mL after 800 mg doses (Frederick, 1995). The mean plasma half-life ($t_{1/2}$) of elimination of acyclovir is about 2.5 hr with a range of 1.5 to 6 hr (Frederick, 1995). Low bioavailability of acyclovir is due to poor absorption, which is related to its poor solubility in aqueous media (2.5 mg/mL at 37°C). Frequency of dosing is very high (200 mg five times a day).

It has been focused on enhancing the solubility of poorly water soluble drugs and improving bioavailability ability to administer them through oral route resulting in increasing their clinical efficacy. One of the popular approaches is the lipid-based delivery such as (1) solution and suspension (Yamaoka, Roberts, & Stella, 1983); (2) emulsion (Armstrong & James, 1980; Carrigan & Bates, 1973; Humberstone, 1997); (3) solid dispersion (Kincl & Rudel, 1986); (4) self-microemulsifying drug delivery system (Charman et al., 1992; Craig et al., 1993; Shah et al., 1994; Wakerly et al., 1986); (5) liposomes (Schwendener & Schott, 1996).

Among of theses approaches, self-microemulsifying systems are isotropic mixture of oils, surfactant and hydrophilic co-surfactant, which forms fine o/w emulsion, when introduce in the aqueous phase under condition of gentle agitation. That is the digestive motility of the stomach and intestine providing the agitation required for self-emulsification in vivo (Constantinides et al., 1995). The Spontaneous formation of an emulsion upon release in the GI tract advantageously presents the drug in a dissolved form and the small droplets size provides a large interfacial surface area for drug absorption (Charman et al., 1992; Jose & Kulkarni, 2002; Shah et al., 1994; Charman et al., 1998). For selecting a suitable self-emulsifying vehicle, it is important to assess:

a. the drug solubility in various components;
b. the area of self-emulsifying region in the phase diagrams;
c. droplet size distribution following self-emulsification (Kang, Lee, Cho, Jeong, Yuk, Khang, Lee, & Cho, 2004).

In this study various types of SMEDDS formulations were prepared using oil (sunflower oil), two surfactants (Tween 60, Tween 80), and co-surfactant (glycerol). The ability of SMEDDS to maintain the drug in solubilized form is generally

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influenced by the solubility of drug in oily phase. Surfactant or co-surfactant used for drug solubilization of drug in greater extent. Non-ionic with high HLB (HLB = 10) and subsequent hydrophilicity of surfactant necessary for the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous environment providing a good dispersing/self-emulsifying performance. The surfactants are amphiphlic in nature, and they are usually able to dissolve and solubilize even relatively high quantities of the hydrophobic drug. In SMEDDS generally co-surfactant of HLB value 10–14 is used. Hydrophilic co-surfactant is preferably which are known to reduce the oil/water interface and allow the spontaneous formation of microemulsion.

Various modes of enhanced drug absorption from the SMEDDS formulation can be hypothesized as follows:

- Drugs may be absorbed through lymphatic via chylomicron synthesis of the fatty components of the digestible oil phase of emulsion. A lipophillic drug, which preferably remains in the oil droplets, may in fact be absorbed via bile salt micelles along with metabolite of the lipid carrier.
- Bates and Sequeria suggested that inhibition of gastric motility caused by the presence of the lipid phase of emulsion might allow more time for dissolution and absorption of drug from lipid phase.
- Increase mucosal permeability via incorporation of lipid from mixed micelles and enhanced mesenteric lymph flow may be responsible for the enhanced drug absorption.
- A hydrophilic drug is less likely to be absorbed through the lymphatic (chylomicron) and instead may diffuse directly in to the portal supply. Hence, in this case, increase dissolution from the large surface area afforded by emulsion may be a contributing factor to enhanced absorption of drugs.
- A relatively less focused consideration is the presence of surfactant in formulation, which may also play a role in increasing the absorption of the drugs.

The objectives of this study were to develop and characterize the optimal formulation of SMEDDS containing acyclovir for to increase absorption leading to improvement in bioavailability, to reduce dose leading to reduction in dosing frequency, to achieve sustained release effect. Its bioavailability compared with pure drug solution in male albino rats. Mean droplet size of microemulsion was conducted by laser scattering particle size analyzer (Malvern instruments).

MATERIALS AND METHODS

Materials

Acyclovir was received as a gift sample from Alembic Limited, (Baroda, India). Tween 60 and sunflower oil were purchased from National Chemicals (Baroda, India). Glycerol, Tween 80, disodium hydrogen ortho-phosphate, sodium citrate, and sodium chloride were purchased from S.D. Fine Chemicals (Mumbai, India). Potassium dihydrogen ortho-phosphate was purchased from Allied Chemical Corporation (Baroda, India). Hydrochloric acid was purchased from Suvidhinath laboratories (Baroda, India). Octansulfonic acid (HPLC grade) was also received as a gift sample from Alembic Limited, (Baroda, India). Methanol (HPLC grade) was also from Alembic Limited, (Baroda, India). All other Chemicals were reagent grade.

Solubility Studies

The solubility of acyclovir in various oils (sunflower oil, soya bean oil, labrafil oil) surfactant (Labrafac CC), and co-surfactants (PG, PEG-600, glycerol) was determined, respectively. A total of 2 mL of each of the selected vehicle were added to each cap vial containing an excess of acyclovir (Ca. 500 mg) after sealing, the mixture was heated at 40°C in a water bath to facilitate the solubilization using a vortex mixer. Mixtures were shaken with shaker at 25°C for 48 hr. After reaching equilibrium, each vial was centrifuged at 3000 rpm for 5 min, and excess insoluble Acyclovir was discarded by filtration using Whatman filter. The free drug concentration of Acyclovir was quantified by UV spectroscopy. Table 1 shows the results of the solubility studies.

PseudoTernary Phase Diagram Study

The pseudoternary phase diagrams of oil (sunflower oil), surfactant: co-surfactant (Tween 60: glycerol and Tween 80: glycerol), and water were developed using water titration method. The mixture of oil and surfactant/co-surfactant at certain weight ratio were diluted with water in drop wise manner. For each phase diagrams at specific ratio of surfactant/co-surfactant (1:0.5, 1:1) was taken and prepared transparent and homogeneous mixture by magnetic stirring. Then, each mixture was titrated with water and visually observed for phase clarity and flow ability. After the identification of microemulsion region in the phase diagrams, the microemulsion formulations were selected at desired component ratios. In order to form the microemulsion, a series of SMEDDS were prepared. Figure 1 shows phase diagrams.

The Effect of Drug on the Phase Diagram

The following experiment was carried out to investigate the effects of acyclovir on the self-emulsifying performance of SMEDDS. The formulation amount of acyclovir (50 mg) was added to the boundary formulations of the self-emulsifying domain of the ternary phase diagrams. The self-emulsifying performance was visually assessed after infinite dilution using purified water.

Preparation Method for Self-Microemulsifying Drug Delivery System

A series of SMEDDS were prepared in each formulation with varying ratio of oil, surfactant, co-surfactant, and acyclovir. In all the formulations, the concentration of acyclovir was constant. Accurate quantity of the oil, co-surfactant, drug were mixed by gentle stirring for 15 min and vortex mixing, and the mixture was heated at 30–40°C till drug get solubilized. The mixture was cooled to ambient temperature. Then Tween 60 was added and stirred on the magnetic stirrer until stable mixture was formed.

Dilution Study

A total of 50 mg of acyclovir incorporated in SMEDDS formulation. 1 part SMEDDS of each solution was diluted with 10 parts of distilled water, 0.1 N HCl and Phosphate buffer 6.8 and observed. Observation of dilution studies is shown in Table 3.

Characterization and Evaluation of the Formulation

Percentage Transmittance (λ max 560 nm)

A total of 1 mL of the SMEDDS formulation was diluted 10 times and 100 times with distilled water. Percentage transmittance was measured Specrtophotometrically (Shimadzu, Japan) at 560 nm using water as a blank.

Determination of Drug Content in the SMEDDS of Acyclovir

Acyclovir from SMEDDS formulation was extracted in DMSO using Sonication technique. The DMSO extract of formulation was analyzed spectrophotometrically at 256 nm. The results are shown in Table 5.

Phase Separation Study

A total of 1 mL of SMEDDS was added to a glass test tube containing 5 mL distilled water at 25°C. After 1 min vortex mixing, mixture was stored for a period of 2 hr and any phase separation was observed visually.

Droplet Size Analysis

SMEDDS (1 mL) was diluted 10 times and 100 times with distilled water in beaker with constant stirring on a magnetic stirrer. The droplet size distributions of resultant microemulsion were determined after 1 hr by laser scattering particle size analyzer (Malvern Instruments). The results are shown in Figure 2.

Zeta-Potential Determination and Electrophoretic Mobility

SMEDDS (1 mL) was diluted 10 times and 100 times with distilled water in beaker with constant stirring on a magnetic stirrer. Zeta-potential and electrophoretic mobility of the resulting microemulsion was determined using the Zetasizer. (Malvern Instruments) The results are shown in Figure 3.

Viscosity Determination

SMEDDS (1 mL) was diluted 10 times and 100 times with the distilled water in beaker with constant stirring on magnetic stirrer. Viscosity of the resultant microemulsion and Initial SMEDDS was measured using Brookfield viscometer (DVIII +Rheometer). The results are shown in Table 6.

In Vivo Studies

In vivo study was approved and performed in accordance with the guideline of the animal ethics committee.

Experimental Procedure

The study was conducted in three groups consisting of six male albino rats weighing 225–250 g. One group of rat was for formulation; another group of rat was for control and third group was for plain drug solution.

Group I—six rats for plain drug solution

Group II—six rats for SMEDDS formulation of acyclovir.

Group III—six rats for placebo of SMEDDS formulation.

Analytical Method of Acyclovir Determination in Whole Rat Blood

A rapid, simple and sensitive reversed-phase high-performance liquid chromatographic (HPLC) method has been used for the measurement of acyclovir concentrations in whole rat blood and its use in bioavailability studies is evaluated. Unchanged acyclovir has been quantified without the introduction of an internal standard using the present method. Rat plasma proteins were selectively precipitated by the addition of 7% perchloric acid to spiked plasma samples or to the plasma samples obtained after acyclovir administration to rats and the mixture was spun at 2500 rpm for 10 min. The supernatant was directly injected into a Novaflex C column and detected at 254 nm. The mobile phase consisted of octane sulfonic acid buffer (pH 2.5) and methanol (92:08).

Calibration of Acyclovir in Rat Whole Blood

Blood was collected from retro-orbital plexus of rat in sodium citrate container. The containers used for the collection of blood were previously treated with 0.5 mL 2% sodium citrate solution. During collection, blood has been mixed thoroughly with sodium citrate solution in order to prevent blood clotting. Here, for calibration different concentration of acyclovir was used ranging from 0.5 μg/mL to 20 μg/mL. Each drug concentration ranging from 0.5 μg/mL to 20 μg/mL was spiked in 1 mL of blood. After spiking, the blood was immediately centrifuged at 2500 rpm at 4°C for 15 min, and plasma (clear supernatant) was separated. To 0.5 mL aliquot of plasma, 0.5 mL of freshly prepared 7% perchloric acid was added in a 2.0 mL Eppendorf Tube. It was thoroughly mixed by vortexing for 5 min. The precipitated plasma proteins were separated out by centrifuging this mixture at 2500 rpm for 10 min to get the drug in the supernatant. After centrifugation, supernatant was

collected. The samples were stored at −4°C before analysis. Acyclovir is stable in the plasma for 1 month at −4°C.

Frozen samples were thawed and brought to room temperature before they processed for analysis. Then the samples were transferred to the HPLC sample vial and the vials were arranged in the autosampler and programmed to inject 100 µL of sample into the chromatographic system. Calibration curve was done using different concentration of acyclovir and calibration curve is shown in Table 7 and Figure 4 (Bangaru, Bansal, Rao, & Gandhi,, 2000).

THE RESULTS AND DISCUSSION

Solubility Study

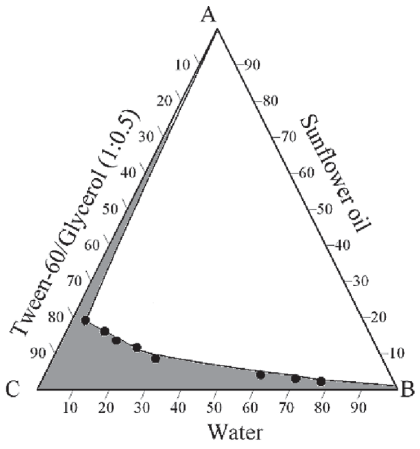
The SMEEDS formulations consisting of oil, surfactant, co-surfactant and drugs should be a clear and monophasic liquid at ambient temperature when introduced to aqueous phase and should have good solvent properties to allow presentation of the drug. The solubility of acyclovir in various vehicles is presented in Table 1. Sunflower oil and glycerol provided higher solubility than other vehicles so sunflower oil was selected as oil phase and glycerol was selected as co-surfactant for the optimal formulation, resulting in improved drug loading capacity (Kang et al., 2004).

PseudoTernary Phase Diagram Study

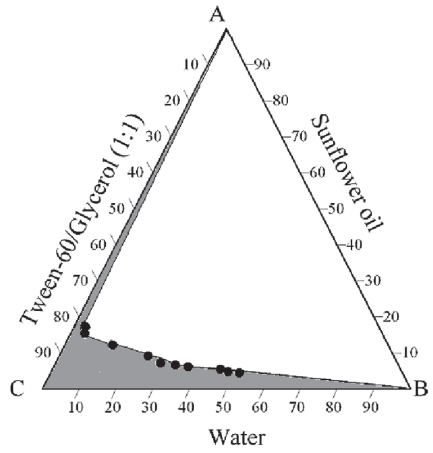
Phase diagrams constructed in the presence of acyclovir to obtain the optimum concentration of the oil, surfactant and co-surfactant. SMEDDS from fine oil-water emulsion with only gentle agitation upon its introduction in to aqueous media, since the free energy required to form a emulsion is very low, the formulation is thermodynamically spontaneous (Craig, Barker, Banning, Booth, 1995). Surfactant forms a layer around the emulsions droplets and reduces the interfacial energy as well as providing a mechanical barrier to coalescence. The visual test is measured the apparent spontaneous of emulsion formation. The series of SMEDDS were prepared and their self-emulsifying properties were observed visually. Pseudoternary phase diagrams were constructed to identify the self-emulsifying regions and to optimize the concentration of oil, surfactant and co-surfactant (Figure 1). Screening of the

TABLE 1
Solubility Studies in Various Vehicles

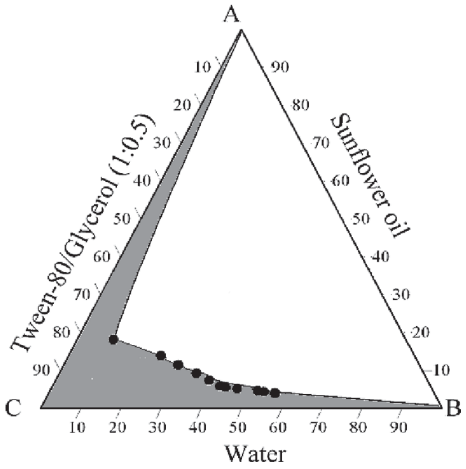
Name of vehicles	Solubility in mg/mL ± *SD*
Sunflower oil	4.333 ± 0.028
Soya bean oil	0.351 ± 0.007
Labrafil oil	0.431 ± 0.028
Labara CC	0.385 ± 0.0089
PG	1.645 ± 0.032
PEG-600	1.066 ± 0.025
Glycerol	152.9 ± 0.556



(A) Phase diagram of sunflower oil, Tween 60/Glycerol (1:0.5)



(B) Phase diagram of sunflower oil, Tween 60/Glycerol (1:1)



(C) Phase diagram of sunflower oil, Tween 80/Glycerol (1:0.5)

FIGURE 1. Pseudoternary phase diagram indicating the efficient self-emulsification region.

TABLE 2
Components of the Self-Microemulsifying Drug Delivery System of Acyclovir

Name of the Vehicle	Category
Sunflower oil	Oil phase
Tween 60	Surfactant
Glycerol	Co-surfactant

surfactant was based on the pseudoternary phase diagram. Here Tween 80 was formed clear gel so Tween 60 was used as a surfactant. Tween 60/glycerol was taken ratio with 1:0.5 required less percentage of surfactant then the ratio of Tween 60/glycerol was taken ratio with 1:1. After performing the solubility study and phase diagram study following components were selected for SMEDDS formulation. This was shown in Table 2.

The Effect of Drug on the Phase Diagram

It has been reported that the drug incorporated in the SMEDDS may have same effect on the self-emulsifying performance (Pouton, 1985). In the above experiment no significant difference were formed in self-emulsifying performance, when compared with the corresponding formulation without acyclovir. The results were similar to that of (Wei, Sun, Nei, & Pan, 2005).

Dilution Study

For the development of SMEDDS formulation, right blend of emulsifier is necessary to form stable Microemulsion. When 1 part SMEDDS of each solution was diluted with 10 parts of distilled water, 0.1 N HCl and phosphate buffer 6.8 pH (Table 3). It implies that the formulation C was more stable because there was no precipitation or cryalallization of drug.

TABLE 3
Observation of Dilution Study

Vehicles	A	B	C
Distilled water	Hazy within 4 Hrs.	Hazy within 6 Hrs.	Stable
0.1 N HCl	Hazy within 4 Hrs.	Hazy within 6 Hrs.	Stable
Phosphate buffer 6.8	Hazy within 4 Hrs.	Hazy within 6 Hrs.	Stable

Formulation A: 50 mg acyclovir, 9% sunflower oil, 57.6% Tween 60, 28.8% glycerol.

Formulation B: 50 mg acyclovir, 9% sunflower oil, 58.8% Tween 60, 29.4% glycerol.

Formulation C: 50 mg acyclovir, 9% sunflower oil, 60% Tween 60, 30% glycerol.

Dilution studies optimize the final formulation optimized formulation has been shown in Table 4.

TABLE 4
Optimized Formulation

Ingredients	Quantity	Category
Acyclovir	50 mg	Active ingredient
Sunflower oil	9%	Oil phase
Tween 60	60%	Surfactant
Glycerol	30%	Co-surfactant

TABLE 5
Drug Content of Acyclovir

Formulation	Percentage of Assay
Formulation: C	97.99% ± 1.91

Characterization and Evaluation of the Formulation

Percentage Transmittance (λ max 560 nm)

Percentage transmittance of microemulsion after 10 times and 100 times dilution was 98.62 and 98.85%, respectively, which was nearer to 100%. It indicates clear microemulsion was formed from the SMEDDS up to 100 times dilution with distilled water.

Determination of Drug Content

Drug content of the SMEDDA formulation was 97.99 ± 1.91, which was in the limit (Patil, Praveen, Shobha Rani, & Paradkar, 2004).

Phase Separation Study

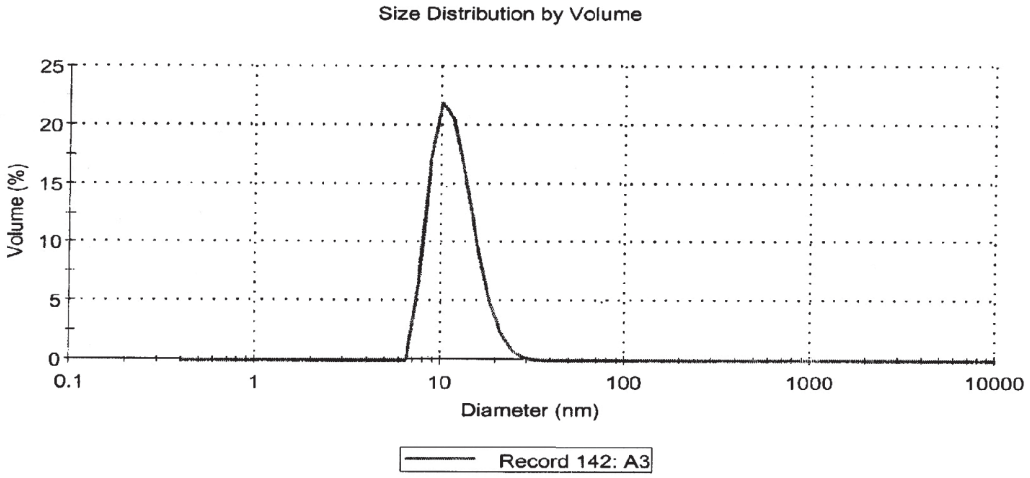
Phase separation study implies that, mixture of acyclovir, sunflower oil, Tween 60 and glycerol exhibited a negligible phase separation during the 2 hr period were used for subsequent study (Shengmiao, Chunshun, Dawei, & Zhongui, 2005).

Droplet Size Analysis

The average droplet size of the formulation was very low 17.87 nm. This was shown in the Figure 2(a) and (b). The SMEDDS was found to be clear transparent after the dilution with water and the preparation was stable for more than one weak. The results of droplet size are shown in Figure 2 (Shengmiao et al., 2005).

(A) Results

		Diam. (nm)	% Volume	Width (nm)
Z-Average (nm): 17.87	Peak 1:	12	99.99	3.443
PDI: 0.310	Peak 2:	391.2	0.01...	103.7
Intercept: 0.9605	Peak 3:	0	0	0



(B) Results

		Diam (nm)	% Int	Width (nm)
Z-Average size (nm): 17.87	Peak 1:	15.49	94.07	4.789
Polydispersity index: 0.310	Peak 2:	373.3	5.931	97.79
	Peak 3:	0	0	0

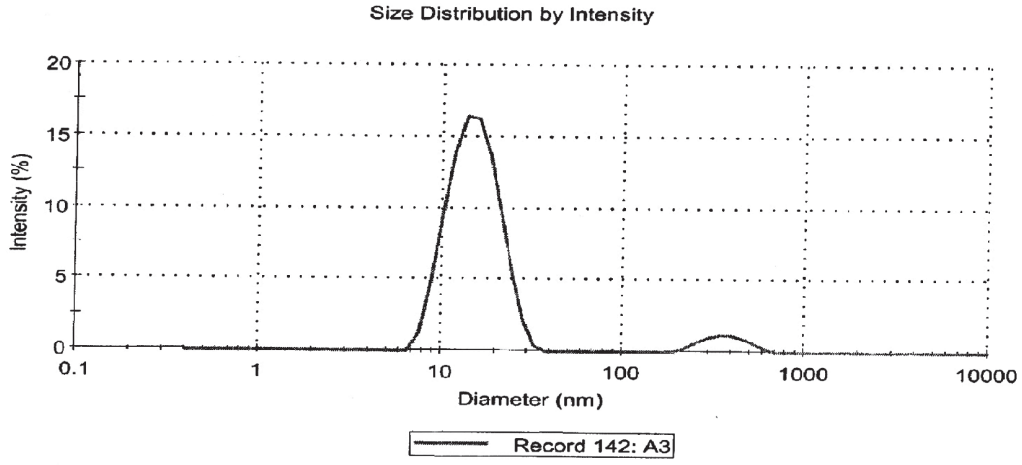


FIGURE 2. (A) Droplet size distribution by Volume (B) droplet size distribution by Intensity.

Zeta-Potential and Elecrtophoretic Mobility Determination

Zeta potential of the system was found to be neutral (−1.562 mV), which indicated the droplets of microemulsion having no charge. Elecrtophoretic mobility was also zero. (−0.1232 μm.cm/Vs) so which also indicated microemulsion droplets having no charge. The results of zeta-potential and electrophoretic mobility are shown in Figure 3 and are consistent with other findings (Wei et al., 2005).

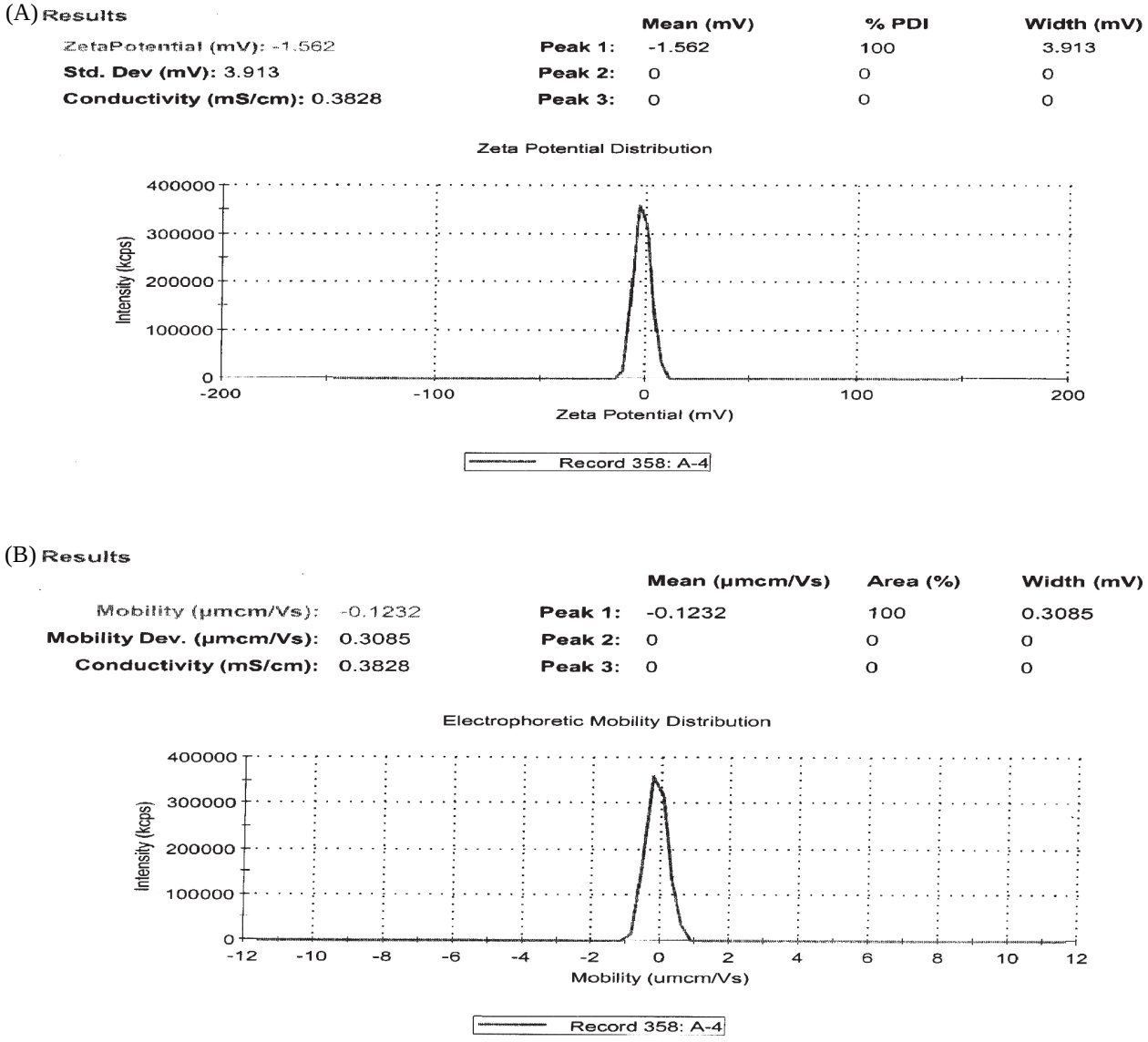


FIGURE 3. (A) Zeta potential distribution (B) electrophoretic mobility distribution

Viscosity Determination

Initial viscosity of SMEDDS was found very high (1244 cP), which was suitable for filling of SMEDDS in hard gelatin capsule without risk of leaking problem. When SMEDDS was diluted 10 times and 100 times with water, Viscosity of the system was decreased, which indicates that when SMEDDS formulation will be diluted with the stomach fluid its viscosity will be decreased and therefore absorption from stomach will befast. Table 6 show viscosity of SMEDDS formulation.

In Vivo Studies

SMEDDS formulation containing sunflower oil (9%), Tween 60 (60%), glycerol (30%), with the ratio (1:0.5) and plain drug solution were used for this study. Figure 4 present plasma concentration vs. time curve for acyclovir SMEDDS formulation and plain drug solution after oral administration in male albino rats. The corresponding means (± SD, n = 3). Pharmacokinetic parameters for both are presented in Table 7.

SMEDDS formulation of acyclovir shows higher C_{max} in blood as compared to plain solution. T_{max} of both plain drug solution and SMEDDS was 1 hr, which means that both plain drug solution and SMEDDS of acyclovir show same rate of absorption. AUC is an important parameter in evaluating bioavailability of drug from dosage form as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching the

TABLE 6
Viscosity of SMEDDS Formulation

Formulation: C	Viscosity	Temperature	Shear Rate
Initial SMEDDS	1244 cp	24°C	6 sec^{-1}
10 Times dilution with distilled water	1.92 cp	22.8°C	19.2 sec^{-1}
100 Times dilution with distilled water	0.72 cp	22.9°C	19.2 sec^{-1}

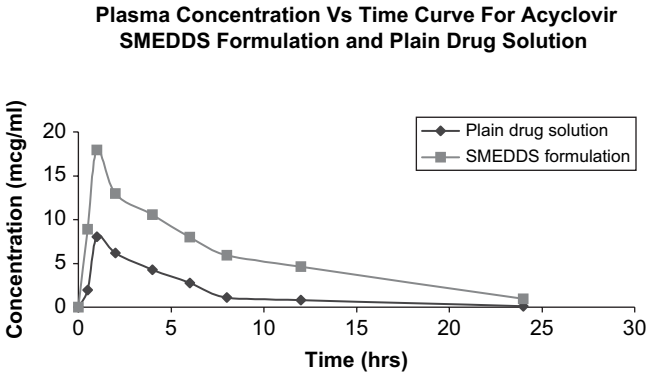


FIGURE 4. Plasma concentration level after oral administration of SMEDDS formulation of acyclovir and plain drug solution.

TABLE 7
Pharmacokinetic Profiles of Acyclovir After Administration in Rat

Sr. no.	Pharmacokinetic parameters	Group I	Group II
01	C_{max} (μg/mL)	8.05	17.96
02	T_{max} (hr)	1	1
03	K_{ele} (elimination rate constant)	0.1985	0.1838
04	Plasma Half life$t_{1/2}$ (hr)	3.49	3.77
05	AUC (0–24) (μg hr mL^{-1})	40.2025	133.06
06	AUC (0–∞) (μg hr mL^{-1})	40.69	140.4969
07	Clearance (1/hr)	786.35	227.7631
08	Volume of distribution (L)	3961.51	1239.262

systemic circulation after oral administration. AUC for SMEDDS formulation of acyclovir was higher (140.4969 μg hr mL^{-1}) than plain solution (40.2025 μg hr mL^{-1}). Higher amount of drug concentration in blood indicates better systemic absorption of acyclovir from SMEDDS as compared to plain solution. The evidence suggests the protective role of SMEDDS as a carrier system to deliver drug to the systemic circulation in the body.

SMEDDS formulation shows same half-life as compared to control group therefore no prolonged action was found in SMEDDS formulation. The results are similar to that of Shicheng, & Gursoy (2004); Patil et al. (2004); Araya, Tomita, & Hayashi (2005).

CONCLUSIONS

- The optimal formulation of SMEDDS containing acyclovir (high drug loading and smallest particle size) was as following 50 mg acyclovir, 9% sunflower oil, 60% Tween 60, 30% glycerol due to high affinity for the continuous phase and forming smallest particle size (17.87 nm). Zeta potential of the optimal system was neutral so we can conclude that system is stable
- From in vivo studies, we can conclude that developed SMEDDS formulation of acyclovir shows better bioavailability compared to control (plain drug solution). SMEDDS also shows higher rate and extent of absorption compared to control. Thus, there is improvement of oral bioavailabity of acyclovir was successfully achieved in SMEDDS formulation as delivery system.

However, further studies in higher animals and human being need to be performed before this formulation can be commercially exploited.

REFRENCES

Araya, H., Tomita, M., & Hayashi, M. (2005). The novel formulation design of self-emulsifying drug delivery systems (SEDDS) type O/W microemulsion II: stable gastrointestinal absorption of a poorly water soluble new compound, ER-1258 in bile-fistula rats. *Drug Metab. Pharmacokine*., *20*(4), 257–267.

Armstrong, N. A., & James, K. C. (1980). Drug release from lipid based dosage forms, Part 2. *Int. J. Pharm*., *6*, 195–204.

Bangaru, R. A., Bansal, Y. K., Rao, A. R. M., & Gandhi, T. P. (2000). Rapid, simple, and sensitive high-performance liquid chromatographic method for detection and determination of acyclovir in human plasma and its use in bioavailability studies. *J. Chromatogr. B, 739*, 231–237.

Carrigan, P. J., & Bates, T. R. (1973). Biopharmaceutics of drugs administered in lipid containing dosage forms I: GI absorption of griseofulvin in from an oil-in-water emulsion in the rat. *J. Pharm. Sci*., *62*, 1476–1479.

Charman, S. A. Chaman, W. N., Rogg, M. C. Wilson, T. D., Dutko, F. J., Puton, C. W. (1998). Self emulsifying drug delivery system: Formulation and biopharmaceutical evaluation of an investigational lipophillic compound. *Pharm. Res*., *9*, 87–93.

Constaantinides, P. P. (1995). Lipid microemulsion for improving drug dissolution and oral absorption physical and biopharmaceutical aspects. *Pharm Res.*, *12*, 1561–1572.

Craig, D. Q. M., & Barker, S. A., Banning, D., & Booth, S. W. (1995). An investigation into mechanism of size analysis and low frequency dielectric spectroscopy. *Int. J. Pharm*., *114*, 103–110.

Craig, D. Q. M., Lieveus, H. S. R., Pitt, K. G., & Storey, P. E. (1993). An investigation in to the physiological chemical properties of self emulsifying systems using low frequency dielectric spectroscopy, surface tension measurement, and particle size analysis. *Int. J. Pharm.*, *96*, 147–155.

Cui, S., Zhao, C., Chen, D., & He, Z. (2005). Self-microemulsifying drug delivery systems (SMEDDS) for improving in vitro dissolution and oral absorption of pueraria lobata isoflavone. *Drug Dev. Indust. Pharm.*, *31*, 349–356.

Frederick .G. H. (1995). *Acyclovir drug profile: Goodman & Gilman's The Pharmacological Basis of Therapeutics,* Hardman, J. G., Limbird, A. E., Eds, 9th edition Mc Graw Hill, New York, 1193–1198.

Hong, J-Y., Kim, J-K., Song, Y. K., Park, J. S., & Kim, C. K. (2005). A new self-emulsifying formulation of itraconazole with improved dissolution and oral absorption. *J. Control. Release. 110*(2): 332–338.

Humberstone, W. N. (1997). Lipid based vehicles for the oral delivery of poorly water- soluble drugs. *Adv. Drug. Deliv. Rev*. *25*, 103–128.

Jose, S., & Kulkarni P. K. (2002). Self-emulsifying drug delivery systems (review). *Indian J. Pharm. Educ*., *36*(4), 184–190.

Kang, B. K., Lee, J. S., Cho, S. K., Jeong, S. Y., Yuk, S. H., Khang, G., Lee, H. B., & Cho, S. H. (2004). Development of self-microemulsifying drug delivery systems (SMEDDS) for bioavailability enhancement of Simvastatin in Begale dogs. *Int. J. Pharm.*, *274*, 65–73.

Kincl, F. A., & Rudel, H. W. (1986). Increasing intestinal absorption of drugs by formulation. *Arch. Pharm.319*, 615–624.

Patil, P., Praveen, S., Shobha Rani, R. H., & Paradkar, A. (2004). Bioavailability assessment of ketoprofen incorporated in gelled self-emulsifying formulation. *AAPS Pharm. Sci. Tech*., *06*(01): E9–E13.

Pouton, C. W. (1985). SMEDDS: Assessment of the efficiency of emulsification. *Int. J. Pharm*., *27*, 335–348.

Schwendener, R. A., Schott, H. (1996). Lipophillic 1- beta-D-arabino-Furanosyl cytosine derivatives in liposomal formulation for oral and parenteral antileukemic therapy in the murine L1210 Leukemia model. *J. Cancer Res. Clin. Oncol*., *122*, 723–726.

Shah, N. H., Carvajal, M. T., Patel, C. I., In Feld, M. H., & Mallack, A. W. (1994). SEDDS with polyglucoysed glycerides for improving in vitro dissolution oral absorption of lipophillic drugs. *Int. J. Pharm.*, *106*, 15–23.

Shengmiao C., Chunshun, Z., Dawei, C., & Zhonggui, H. (2005). Self-microemuslifying drug delivery systems (SMEDDS) for improving in vitro dissolution and oral absorption of pueraria lobata isoflavone. *Drug Dev. Indust. Pharm.*, *31*, 349–356.

Shicheng, Y. R., & Gursoy, N. (2004). Enhanced oral absorption paclitaxel in a novel self-microemulsifying drug delivery systems with or without concomitant use of P-glycoprotein inhibitors. *Pharm. Res.*, *21*(2), 261–270.

Wakerly, M. G., Pouton, C. W., Meakin, B., & Morton, F. (1986). Self-emulsification of veg oil—non-ionic surfactant mixtures. *ACS symp. Ser*., *311*, 242–255.

Wei, L., Sun, P., Nei, S., & Pan, W. (2005). Preparation and evaluation of SEDDS and SMEDDS containing carvedidolol. *Drug Dev. Ind. Pharm.*, *31*, 785–794.

Yamaoka, Y., Roberts, R. D., & Stella, V. J. (1983). Low melting phenytoin prodrugs as alternative oral delivery modes for phenytoin: a model for other high melting sparingly water-soluble drugs. *J. Pharm. Sci*., *72*, 400–405.