Section A-Research paper
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FORMULATION AND EVALUATION OF SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM OF CARVEDILOL

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ABSTRACT

The current work involves preparation and evaluation of self-micro emulsifying drug delivery system of carvedilol, a nonselective beta blocker and alpha-1 blocker. Oral self-micro-emulsifying drug delivery system of Carvedilol were prepared by studying the solubility in different oils, surfactants and co-surfactants and formulations were prepared using mixtures of oils, surfactants, and cosurfactants in various proportions. Based on the solubility study, the optimized self-micro-emulsifying drug delivery system of carvedilol was prepared using Acrysol El 135 as oil phase and tween 20 and transcutol P as surfactant and co-surfactant, respectively. SMEDDS of Carvidilol were prepared with good self-emulsification efficiency and having globule size in nanometric range which may be physiologically stable. The optimized formulation consisting of Carvidilol (20mg), Capmul MCM (14.40%w/w), Tween 80 (27.20% w/w) and Propylene glycol (54.40% w/w) exhibited faster release profiles with a rapid rate of emulsification. The optimized SMEDDS formulation of Carvidilol showed a significant increase in oral absorption compared to the marketed product. The exposure (Cmax and AUClast) of developed SMEDDS was found to be comparatively higher (1.54 fold) than reference marketed product indicating better rate and extent of absorption than reference formulation.

Keywords: Carvidilol, Formulation, Release profiles, Emulsification

INTRODUCTION

Amongst the available various dosage forms, oral delivery systems are preferred for chronic treatment. The potent lipophilic molecules which are used in the chronic oral treatment, exhibits low bioavailability owing to their poor aqueous solubility. Nearly 40 % of new drug candidates

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exhibit low solubility in water due to the lipophilic nature, which leads to poor oral bioavailability, high intra and inter-subject variability and lack of dose proportionality. The dissolution of these molecules in the gastrointestinal fluids is the rate limiting step for the absorption [1]. Self-Emulsifying Drug Delivery System (SEDDS) gained great importance in last two decades as promising lipid-based drug delivery approach for poorly water soluble and low bioavailable drugs, as an alternative strategy to the conventional drug delivery system [2-4]. SEDDS are isotropic systems comprising of oil, surfactant, co-surfactant/co-solvent. Upon oral administrations of SEDDS, the digestive motility of the stomach and intestine provide the agitation necessary for self-emulsification into a fine oil-in-water emulsion which are thermodynamically stable and homogenous systems [4]. This leads to in situ solubilization of drug that can subsequently be absorbed by lymphatic pathways, bypassing the hepatic first-pass effect resulting in increasing the bioavailability.

Carvedilol (CVD), a non-selective beta blocker with selective alpha-1 blocking activity, is Biopharmaceutical Classification System Class II drug which is widely use for the treatment of high blood pressure, Congestive Heart Failure (CHF), and left ventricular dysfunction in people who are otherwise stable [5]. After oral administration CVD is absorbed rapidly from the gastrointestinal tract but due extensive first-pass metabolism by Cytochrome P450 it exerts low bioavailability (about 25 %) with a short elimination half-life of about 2-6 h [6,7]. The CVD shows a pH dependent aqueous solubility in physiological pH range of the gastro-intestine from 1.2 to 7.8. The solubility in water is only about 30 µg/ml, whereas the high solubility (500 to 2500 µg/ml) is observed in pH age of 1.2 to 5.0 and this solubility decreased with increasing the pH which explain its low availability at the absorptive site [8,9]. Thus, the aim of this investigation is to enhance the oral bioavailability of CVD by preparation and characterization of a SEDDS formulation of CVD which will increase the solubility and avoid the extensive hepatic first-pass metabolism by lymphatic absorption, thus resulting in increased bioavailability.

MATERIALS AND METHODS [10-38]

Carvidilol is purchased from carbino, Hyderabad Capmul® MCM Acconon® C-80, Captex® 200 Captex® 355 Transcutol® Plurol Oleique® labrafil® M 2125CS ,Lauroglycol® 90 ,Acrysol® K 140 ,Acrysol® El 135,Tween® 80,Tween® 60,Propylene glycol, sunflower oil Castor oil Signet chemicals pvt,ltd ,Mumbai

Preparation of standard curve for Carvidilol:

Standard Solution of Carvidilol

25mg of OLM pure drug was accurately weighed & transferred into a 25ml volumetric flask, dissolved in little quantities of methanol, then made up to 25ml with methanol (1000µg/ml). From this solution, 10ml of solution was withdrawn into a 100ml volumetric flask & made up to 100ml with 6.8 phosphate buffer to get a concentration of 100µg/ml. From this, again pipetted

out 10ml of solution & diluted to 100ml with 6.8 phosphate buffer to get a concentration of 10µg/ml.

Preparation of various concentrations:

From the above stock solution pipetted out 10ml of solution & diluted to 100ml with 6.8 phosphate buffer to get a concentration of 10µg/ml. Then from that prepared 2,4,6,8 & 10 ml of solutions using 6.8 pH phosphate buffer.

Determination of wavelength of maximum absorption

A standard stock solution of carvedilol phosphate(100µg/mL) was prepared using diluents to further obtain 10µg/mL. An UV spectroscopic scanning (200-400 nm) was carried out with final diluted solution to determine λmax for the detection of carvedilol phosphate using diluents as a blank.

Drug-Excipients Compatibility Studies

FTIR studies

An FTIR-8400S spectrophotometer (Shimadzu, Japan) equipped with attenuated total reflectance (ATR) accessory was used to obtain the infra-red spectra of drug in the isotropic mixtures of excipients, Analysis of pure drug, Acrysol® EL135, Transcutol® P, Tween® 80, physical admixtures of the drug with the excipients (1:2 ratio) and their co- melt (1:2 ratio) were carried out using diffuse reflectance spectroscopy (DRS)-FTIR with KBr disc. All the samples were dried under vacuum prior to obtaining any spectra in order to remove the influence of residual moisture. For each the spectrum, 8 scans were obtained at a resolution of 4 cm-1 from a frequency range of 4000-600 cm-1.

Pseudo-Ternary Phase Diagram for SMEDDS Formulation

Surfactant (Tween® 80) and co-surfactant (Transcutol® P) were mixed (S mix) in different volume ratios (1:1, 1.5:1, 2:1). For each phase diagram, oil (Acrysol® EL 135) and specific surfactant/co-surfactant (S mix) ratio were mixed thoroughly in different volume 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 glass vials. Pseudo ternary phase diagrams were developed using the aqueous titration method. Slow titration with the aqueous phase was performed for each combination of oil and S mix separately. The amount of aqueous phase added was varied to produce a water concentration in the range of 5% to 95% of total volume at around 5% time intervals. The calculation for the addition of aqueous phase was done by calculating the percentage of each component of the micro emulsion present at each 5% addition. The beauty of this system is that the scale- up of the proportions is easy, as the system is thermod ynamically stable. After each 5% addition of the aqueous phase to the oil: S mix mixture, visual observation was made and recorded. Through visual observation the following

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categories were assigned: (1) transparent and easily Flowable: oil/water Micro emulsions. (2) Transparent gel: Micro emulsion gel. (3) Milky or cloudy: Emulsion. (4) Milky gel: Emulgel.

In a similar manner, calculations for the other ratios of oil and S mix were also done. For each Smix ratio, a separate phase diagram was constructed, and for each phase diagram visual observations were recorded.

Preparation of Self-Micro Emulsified Formulations

OLM (20 mg) was added in accurately weighed amount of oil into a screw-capped glass vial and heated in a water bath at 40°C. The surfactant and co-surfactant were added to the oily mix using positive displacement pipette and stirred with magnetic bar. The formulation was further sonicated (Ultrasonic cleaner EN-30-US, Electro quip, India) for 15 min and stored at room temperature until their use in subsequent studies. Eight SMEDDS formulations were prepared and compared their self-emulsifying performance. The composition of four formulations is shown in table 1.

Table 1: Selected Formulations at a different % Vol. /Vol. of Oil, Surfactant and Co-surfactant

Formulation code	Composition (% vol. /vol.)		
	Acrysol El 135	Tween 80	Transcutol P
S1	30	35	35
S2	34	33	33
S3	36	32	32
S4	40	30	30
S5	33	30	37
S6	35	32	33
S7	38	30	32
S8	37	31	32

In vitro dissolution studies

The *in vitro* drug release of OLM from the optimized SMEDDS was performed using USP dissolution Apparatus II (TDT-08L, Electro lab, Mumbai, India). Hard gelatin capsules, size "00" filled with preconcentrate (equivalent to 20mg OLM) and pure drug (20mg) separately were put into each of 900ml phosphate buffer pH 6.8, at 37 ± 0.5°C with a 50 rpm rotating

Speed. Samples (10ml) were withdrawn at regular time intervals (5, 10, 15, 30, 45, and 60 min) and filtered using a 0.45 µ m filter. An equal volume of the dissolution medium was added to maintain the volume constant. The drug content of the samples was assayed using UV visible spectrophotometric method. All measurements were done in triplicate.

Determination of drug content

OLM from S MEDDS formulation was extracted in methanol using sonication technique. The solutions were filtered, using whatman filter paper. The methanolic extract was analyzed for the OLM content spectrophotometrically (UV–1800, Shimadzu, Japan) at 257 nm using standard curve.

Optical clarity

Each formulation (1 ml) was diluted with 100 ml of water in glass beaker. Absorbance of each dispersion was measured at 400 nm using a UV spectrophotometer immediately after micro emulsions formation, and after 0hrs, 6hrs, and 24 hrs. respectively.

RESULT AND DISCUSSIONS

Method development of Carvedilol

Carvedilol is almost insoluble in aqueous medium and freely soluble in organic solvents like methanol and 0.1N HCL. During the development phase, the use of methanol with 0.1N HCL as the diluent resulted in preferable outcome in UV analysis. The pre-determined wavelength of maximum absorption (λmax) was 246nm. (Fig. 1)

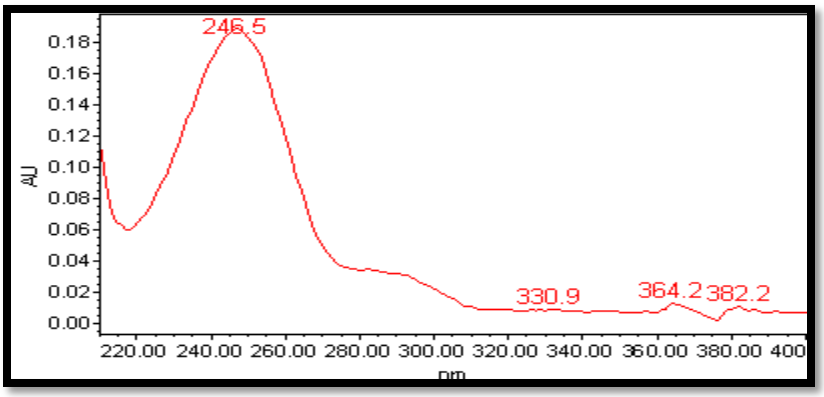

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Figure 1: Uv spectrum of Carvedilol

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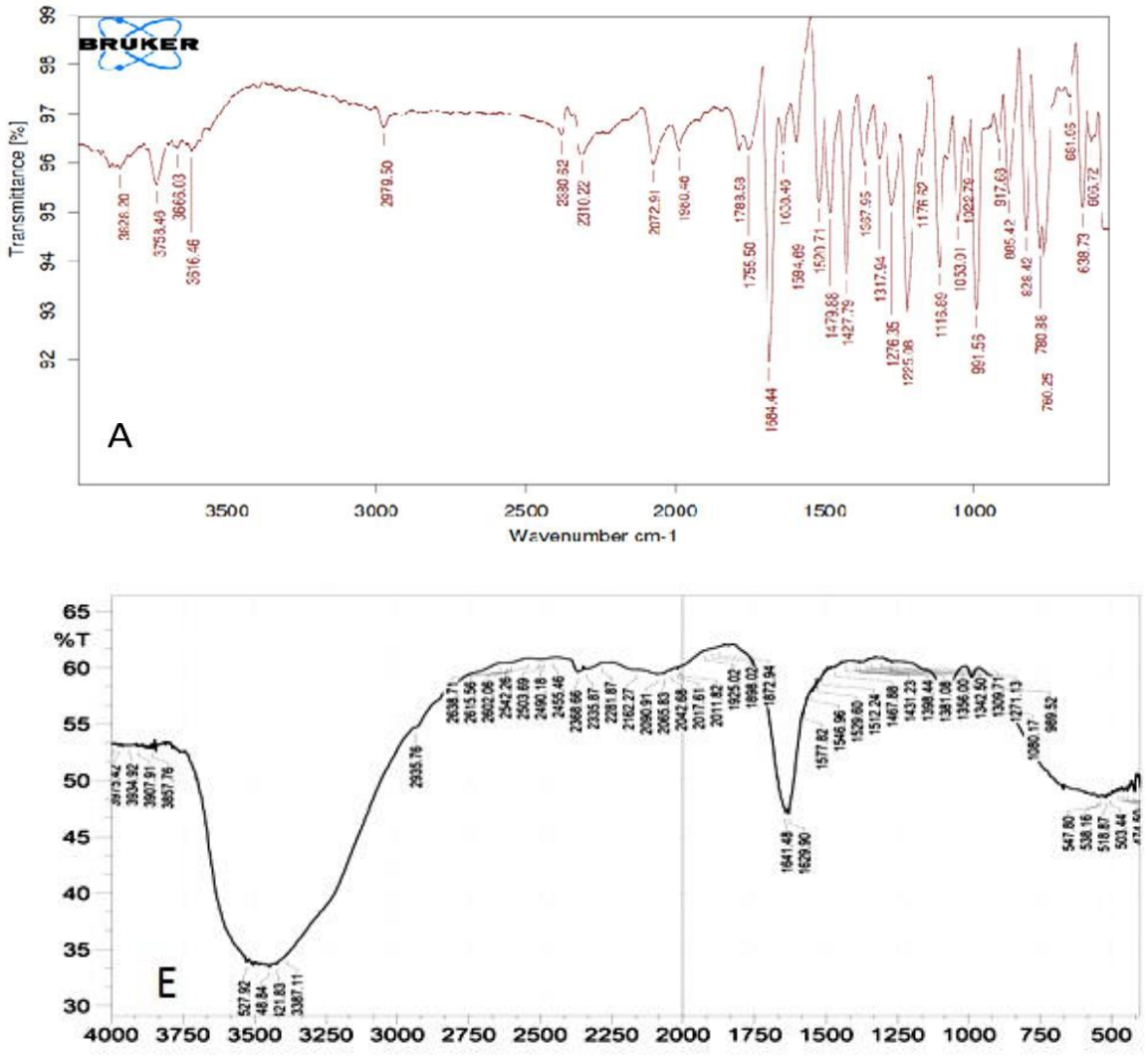
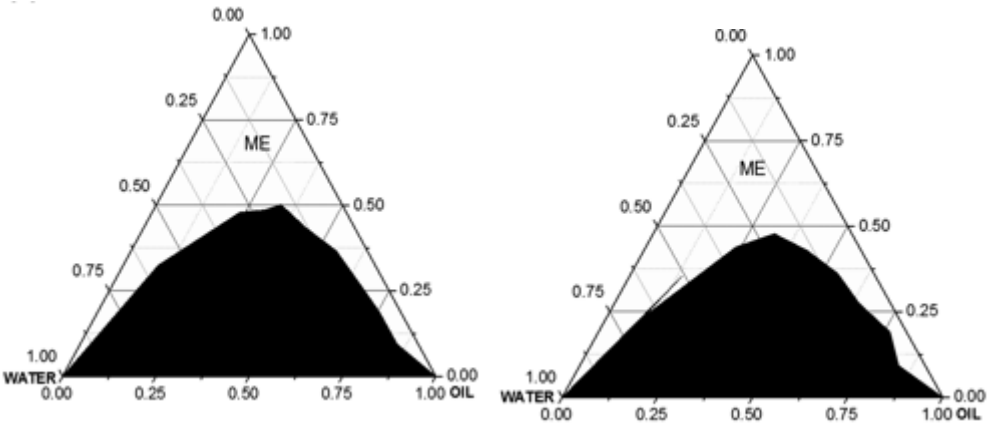


Figure 2: FTIR Spectra of Carvidilol and Formulation

Construction of Pseudo Ternary Phase Diagrams

Pseudo ternary phase diagrams were constructed in the absence of OLM to identify the self-emulsifying regions and to optimize the concentration of oil, surfactant, and co-surfactant in the SMEDDS formulations. A series of the SMEDDS were prepared and their self- emulsifying properties were observed visually. The phase diagrams were constructed at surfactant/co-surfactant ratios of 1:1, 1.5:1, and 2:1(v/v). The gel-like region was found to become large with the increasing concentration of Tween®80, while the self-micro emulsifying region decreased. The maximum self- micro emulsifying region had to be at a ratio of 1:1. However, the drug precipitation was observed after several hours at ratios of 1.5:1 and 2:1. Co-surfactants are beneficial to form a micro emulsion at a proper concentration range. However, an excessive amount of the co-surfactant will cause the system to become less stable for its intrinsic high aqueous solubility and lead to the droplet size increasing as a result of the expanding interfacial film[21]. Hence, the optimal ratio of surfactant to co-surfactant was selected to be 1:1 as shown in Figure 3.



ISSN 2063-5346

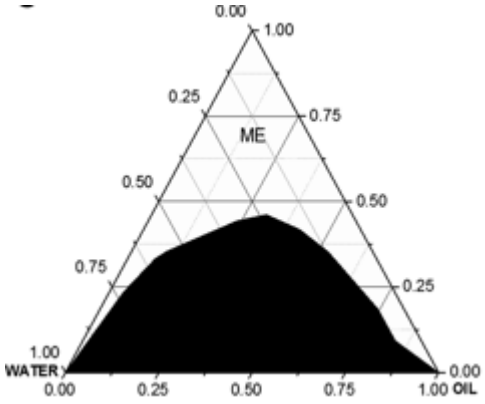


Figure 3: (A)surfactant/co-surfactant1:1 (B)surfactant/co-surfactant 1.5 :1& (C)surfactant/co-surfactant 2 :1 Pseudo ternary phase diagram of the system, Acrysol EL 135, Tween 80: Transcutol®P and water

In vitro drug release

Dissolution studies were performed for the SMEDDS formulations in phosphate buffer pH 6.8 and the results were compared with the pure drug (Figure 3). There is no any significant difference in dissolution of four SMEDDS formulation. As the emulsification time is below 35 s, about 100% percentage of the drug is released within 15 min in case of SMEDDS, while plain drug showed only 14.1% dissolution at the end of 15 min. The dissolution studies were conducted for 1 hrs to observe the variation or occurrence of precipitation over a time. The in vitro dissolution studies indicates that formulation of O LM in the form of SMEDDS formulation enhance the dissolution properties.

Drug content

Irrespective of difference in composition the drug content of formulations S1 to S8 was found in range of 99.35 – 101.79 %

Optical clarity

Optical clarity measured by directly taking the absorbance of the diluted SMEDDS is a measure of droplet stability. The result indicates that formulation S2 and S3 were well stable till 24 hrs. as their absorbance values did not changed at the end of 24 hrs. Moderate changes in absorbance values were observed for formulations S1 at the end of 24 hrs. For formulations S4 to S8 a drastic change in absorbance values were observed indicating instability of droplets with time

Stability Studies:

On the basis of results of all characterization points it was found that formulation S3 was the optimized formulation therefore its stability study was performed. The stability study was

performed as per ICH guidelines; conditions can be decided based on that particular zone. An accelerated stability (40±2˚C / 75 ± 5 %) and real time stability study (25±2˚C / 60 ± 5 %) was performed on the formulation S3 for a period of three months. Formulation S3 shows decreased in the assay content at the accelerated condition which indicates instability of formulation at this condition.

The values clearly prove that after the stability study, formulation S3 doesn't show significant difference for particle size, zeta potential and PDI. After 3 months' stability study the particle size of S3 was found to be 10.87 nm in water and the initial particle size was 9.15 nm, so no significant difference was found. The PDI was found to be 0.221 initially and 0.186 after stability study. The zeta potential was initially found to be -23.2 mV and after stability study it was found to be -22.2 mV.

This result indicates that all the excipients used are compatible and hence form stable micro emulsion with almost same particle size. Since, zeta potential governs the stability of micro emulsion, it is important to measure its value for stability samples. The high value of zeta potential indicates electrostatic repulsion between two droplets. DLVO theory states that electric double layer repulsion will stabilize micro emulsion where electrolyte concentration in the continuous phase is less than a certain value. A negative force means a negative potential between the droplets.

Conclusion

A SMEDDS formulation of a poorly water soluble drug, CVD was formulated as direct filled hard gelatin capsules, which are convenient for oral administration. The formulation S3 was found to be the optimized formulation on the basis of results of pseudo ternary phase diagram, droplet size and physicochemical stability. The optimized formulation showed rapid self-emulsification in an aqueous media. The results from the study show the effectiveness of SMEDDS formulation to enhance solubility and dissolution characteristics of sparingly soluble compounds like CVD.

Conflict of interest:

The authors declared no conflict of interest.

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