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Research Article

Preparation and characterization of self-microemulsifying drug delivery system of carvedilol

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ABSTRACT

Carvedilol is a non-selective beta blocker and belongs to the third generation of beta blockers antihypertensive agent which is administered orally that has absolute bioavailability of only 25% to 35% due to the poor aqueous solubility (0.583 mg/L & log P 4.115). The aim of the present investigation was to develop a self-microemulsifying drug delivery system (SMEDDS) to enhance the oral absorption of Carvedilol. The solubility of Carvedilol in various oils, surfactants, and cosurfactants was determined. Pseudoternary phase diagrams was plotted to identify the efficient self-emulsification regions using Oleic acid, Tween 80, PEG-400 to identify the efficient self-micro emulsification region. Prepared SMEDDS was further evaluated for its visual assessment and emulsification time, effect of pH, robustness, dispersibility, transmittance test, cloud point measurement, optical clarity, drug content and *in vitro* dissolution study. All the prepared formulation exhibited self-emulsification properties. The optimized formulation F3 contains Carvedilol (6.25 mg), Oleic acid (20%), Tween 80(68.5%) and PEG-400 (11.4%). From the study, it was concluded that formulation F3 has good emulsification property with uniform globule size, satisfactory *in vitro* drug diffusion profile which identify future opportunities for Carvedilol delivery.

Keywords: Carvedilol; co-surfactant; phase diagram; SMEDDS; Tween 80.

INTRODUCTION

Poor bioavailability is a trouble, frequently faced in the drug development process. Enhancement of bioavailability of poorly water soluble drugs becomes farthest challenge for pharmaceutical scientist. Most of new drug candidates reveal low solubility in water, which leads to poor oral bioavailability, high intra- and inter-subject variability and lack of dose proportionality. Various approaches should use to improve the dissolution rate of the drug (Agarwal V et al, 2009; Akhter S, Hossain Md. I 2012; Bhagwat D. A., D'Souza J. I 2012; Durgacharan Arun Bhagwat, John Intru D'Souza 2012). The fundamental step in the solubilisation of drug compounds is the selection of an appropriate salt form, or for liquid dosage forms, adjustment of pH of the solution. This is an especially important selection process for polar compounds as the majority of newer solubilisation techniques such as nanosuspensions and microemulsions utilize co-solvents when applied to a polar compound. These technologies include both traditional methods of solubility enhancement, such as particle size reduction via comminution, spray drying, addition of surfactants, inclusion in cyclodextrin-drug complexes, and the use of more novel mechanisms such as self-emulsifying systems, micronisation via nanoparticles, pH adjustment and salting-in processes (Pouton CW 1985; Singh A et al., 2008; Robinson J.R 1996; Divyakumar Bora eet al., 2012). Among them, Self micro emulsifying drug delivery systems (SMEDDS) have shown great pledge for enhancing bioavailability of poorly soluble compounds.

SMEDDSs are isotropic and thermodynamically stable solutions consisting of an oil, surfactant, cosurfactant (CoS; or solubilizer), and drug mixtures that spontaneously form oil-in-water (o/w) microemulsions when mixed with water under gentle stirring. The motility of stomach and intestine provides the agitation required for self-emulsification *in vivo* (Shah N. H et al., 1994). SMEDDS spreads readily in the GI tract, and the digestive motility of the stomach and the intestine provides the agitation necessary for self-emulsificati on. This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption (Charman S. A et al., 1992). Apart from solubilization, the presence of lipid in the formulation further helps improve bioavailability by affecting the drug absorption. Selection of a suitable self-emulsifying formulation depends upon the assessment of (1) the solubility of the drug in various components, (2) the efficient self-emulsifying region as obtained in the phase dia-

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gram, and (3) the droplet size distribution of the resultant emulsion following self-emulsification (Kommuru T. R et al., 2001).

Carvedilol is a non-selective beta blocker. It has been used extensively in patients with hypertension and has also been used in patients with angina and congestive cardiac failure. Oral bioavailability of Carvedilol is very law (25-35%), due to its poor water solubility (log P 4.115) (Darji Sweta V, 2014). Thus, improving solubility and dissolution rate of Carvedilol can increase clinical efficacy or reduce the oral dosage required to achieve the same effect. Therefore, we use SMEDDS formulation with Oleic acid, Tween 80, PEG-400 with the aim to enhance the solubility and dissolution velocity of Carvedilol. The formulation was characterized for its ability to form microemulsions based on various physical characterization and drug dissolution characteristics.

METHODS AND MATERIALS

Carvedilol was obtained as a gift sample from Dr Reddy's laboratory limited Oleic acid, Tween 80, and propylene glycol were purchased from Merck Specialities Pvt. Ltd., Mumbai, India. PEG 400 was purchased from SD Fine chemicals, Mumbai, India. All other chemicals were of analytical reagent grade.

Preparation method of SMEDDS

A series of SMEDDS formulation were prepared with varying ratios of oil (20-30%), surfactant (45-69%), and co-surfactant (10-27%) as shown in Table 1. The surfac- tant and co-surfactant (S/co S) tested were in ratio of 2:1, 4:1and 6:1. A single dose of Carvedilol (6.25mg) was incorporated in all formulations. The formulations were prepared by dissolving the drug in surfactant fol- lowed by addition of co surfactant and oil in a glass vials. The resultant mixtures were stirred continuously by vortex mixing and heated at 40^0c to obtain a ho- mogenous isotropic mixture (Surender Reddy U et al., 2011; Gupta A.K et al., 2012). The SMEDDS formula- tions were stored at ambient temperature until further use.

Construction of phase diagram

A visual observation was made immediately for spontaneity of emulsification, clarity, phase separation and precipitation of drug and excipients. A formulation 0.2 ml was introduced into 300ml of distilled water in a glass beaker at 37^0C, and the contents were mixed gently with a magnetic stirrer at 100 rpm. The resultant emulsions were stored for 48h at ambient temperature and observed for clarity, phase separation, drug precipitation and coalescence of droplets. Emulsions showing phase separation, cracking and coalescence of oil droplets were judged as unstable emulsions (Pradeep Patil, Vandana Patil, 2007). All the studies were repeated thrice with and without drug with similar observations made between repeats. Phase diagram was constructed identifying the self emulsifying region.

Charcterization of SMEDDS

Visual assessment and Emulsification Time

The emulsification time for a (pre concentrate to form a homogeneous mixture upon dilution) was monitored by visually observing the disappearance of SMEDDS and the final appearance of the micro emulsion in triplicate. A visual test to assess the self-emulsification properties of SMEDDS formulation was performed by visual assessment. In this method, a predetermined volume of formulation (1ml) was introduced into 300ml of water in a glass beaker that was maintained at 37^0c, and the contents mixed gently using a magnetic stirrer (P. S. Rajinikanth et al., 2012). The time to emulsify spontaneously and progress of emulsion droplets were observed as per standards mentioned in table 2.

Effect of pH and robustness to dilution

Formulations were subjected to 50, 100, 1000 fold dilution with enzyme free simulated gastric fluid (pH 1.2), enzyme free simulated intestinal fluid (pH 6.8). The resultant diluted emulsions were monitored for any physical changes such as coalescence of droplets, precipitation or phase separation after 24 h storage (Surender Reddy U et al., 2011).

Dispersibility Test

The efficiency of self-emulsification of oral nano or micro emulsion is assessed by using a standard USP XXII dissolution apparatus 2 for dispersibility test. One millilitre of each formulation was added in 500 ml of water at 37 ± 10C. A standard stainless steel dissolution paddle is used with rotating speed of 50 rpm provided gentle agitation (Suresh Preeti K, Sharma Sudhanshu, 2011).

The *in-vitro* performance of the formulations is visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 min

Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulations falling in Grade C coul d be recommend for SEDDS formulations.

Transmittance test

Stability of the Self micro emulsifying drug delivery systems with respect to dilution was checked by meas-

uring transmittance through UV spectrophotometer (UV- 1700, Shimadzu). Transmittance of samples was measured at 650 nm and for each sample three replicate assays were performed (Maulik J. Patela 2010).

Cloud point measurement

The cloud point measurement was carried out for the SMEDDS formulation. The formulation was diluted up to 100 folds with distilled water and kept in a water bath which was maintained at a temperature of 25^0C with gradual increase in the temperature at a rate of 5^0C/min and the corresponding cloud point temperature's were read at the first sign of turbidity by visual observation (Ashok R Patel, Pradeep R Vavia, 2007).

Optical clarity

Each formulation (1ml) was diluted with 100ml of water in glass beaker. Absorbance of each dispersion was measured at suitable nanometer using UV spectrophotometer immediately after microemulsions formulation, and after zero hours, six hours and 24 hours (Urvashi Goyal, Ritika Arora, 2012).

Drug content

Drug from pre-weighed SMEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug. A1ml quantity of each batch of the SMEDDS was placed in a 100 ml volumetric flask. The flask was made up to volume with the appropriate solvent in each case, and allowed to equilibrate for 24h at room temperature and there after cooled to 0^0 C, in a refrigerator, filtered through a filter paper and analysed spectrophotometrically at an appropriate wavelength (Sundhanshu Sharma, Preeti K Suresh, 2010).

***In vitro* Dissolution studies**

The *in vitro* drug release of Atenolol from the optimized SMEDDS was performed using USP dissolution Apparatus II. Soft gelatin capsules, size 00 filled with preconcentrate (equivalent to 6.25 mg of Carvedilol) and pure drug separately, were put into each 500 ml acid buffer pH1.2, at 37°C.With a 50 rpm rotating speed. Each samples (5ml) were withdrawn at regular time intervals (0, 10, 20, 30, 40, 50, 60, 70, 80, 90,100, 110 and 120min.) and filtered using a 0.45µm filter. An equal volume of the dissolution medium was added to maintain the volume constant. The drug content of the samples was measured by using UV spectrophotometric method (Yogeshwar G Bachav, Vandana B, 2009; Pradeep Patil, Vandana Patil, 2007).

EXPERIMENTAL RESULTS

Solubility studies

Solubility studies indicated that Carvedilol does not display good solubility profile. It was found to be insoluble in water, soluble in many solvent such as Ethanol and methanol. Solubility studies of drug in oil indicated that it was more soluble in oleic acid, Tween 80, Propylene glycol 400. Thus these excipients were used for the preparation of SMEDDS. All the oils used were able to emulsify and could be used for preparation of self micro emulsifying formulation. Oleic acid is a medium chain mono glyceride is selected as oil components which promote water penetration. Tween 80 a hydrophilic non ionic surfactant (HLB 15) was found to have maximum solubilising capacity which is much superior at providing fine, uniform emulsion droplets which are more likely to empty from stomach. PEG 400 was selected as co surfactant which helps in further lowering of interfacial tension. Based on the solubility studies the SMEDDS formulations were developed employing varying concentrations of Oleic acid (20-50%), Tween 80 (33-68%), PEG 400 (7-27%).

Ternary phase diagram

Formation of emulsion systems was observed at ambient temperature. Ternary phase behaviour investigations help to choose the proper concentration of excipients i.e., oil proportion and optimum S/Co S ratio in the formulation to produce emulsions with good stability. All the emulsions were stable at zero time and this may be due to higher HLB value of Tween (R) 80 (HLB15), higher solubilising capacity of PEG 400. Since the free energy required to form an emulsion is very low, due to surfactant which reduces the interfacial tension, the formation is thermodynamically spontaneous. Surfactants also provide a mechanical barrier to coalescence. After observing clarity, stability after 48 h, it was noted that formulations with S/Co S ratio of 6:1 that is F3 produced stable emulsions. The obtained ternary phase diagram is shown in figure 1.

Characterisation of SMEDDS

Visual assessment

The efficiency of self emulsification could be estimated primarily by determining the rate of emulsification which is an important index for the assessment of the efficiency of emulsification, that is SMEDDS should disperse completely and quickly when subjected to aqueous dilution under mild agitation. Formulation F1 and F2 was slightly less clear emulsion, F3 and F6 was clear, slightly bluish appearance with good stability, F4, F5, were bright white emulsion like milk.

These visual observations indicated that higher the proportion of surfactant system, greater the spontaneity of emulsification, this may be due to excess penetration of aqueous phase into the oil phase causing massive interfacial disruption and ejection of droplets into the bulk aqueous phase. The visual assessment of SMEDDS is shown in table 3.

Emulsification time

Emulsification time is the most important parameter for SMEDDS and microemulsion formulation. The results suggest that the formulations up to 30% oil con

Table 1: Composition of SMEDDS Formulations of Atenolol

FORMULATION CODE	INGREDIENTS IN %W/W		
	OLEIC ACID	TWEEN-80	PEG-400
F-1	20	53.3	26.6
F-2	20	64	16
F-3	20	68.5	11.4
F-4	30	46.6	23.3
F-5	30	56	14
F-6	30	60	10

Carvedilol - 6.25mg

Table 2: Visual assessment criteria for self microemulsification (Maulik J. Patela 2010)

Grade	Appearance	Time of self-micro emulsification
I	Rapid forming micro emulsion which is clear or slightly bluish in appearance	<1 min
II	Rapid forming, slightly less clear emulsion, which has a bluish white appearance.	<2 min
III	Bright white emulsion	< 3min
IV	Dull, grayish white emulsion with a slightly oily appearance that is slow to emulsify.	>3min
V	Exhibit poor or minimal emulsification with large oil droplets present on the surface	>3min

Table 3: Visual assessment, Robustness and Dispersibility test of various formulations of SMEDDS

Formulation	Visual assessment		Robustness				Grade of Dispersibility test
			Phase separation		Drug precipitation		
	Grade	Time required for micro emulsion formation	0.1N HCL	Phosphate buffer pH 6.8	0.1N HCL	Phosphate buffer pH 6.8	
F-1	III	<3min	-	-	--	--	B
F-2	II	<2min	-	-	--	--	B
F-3	I	<1 min	-	-	--	--	A
F-4	II	<2min	-	-	--	--	B
F-5	III	<3min	-	-	--	--	C
F-6	I	<1min	-	-	--	--	A

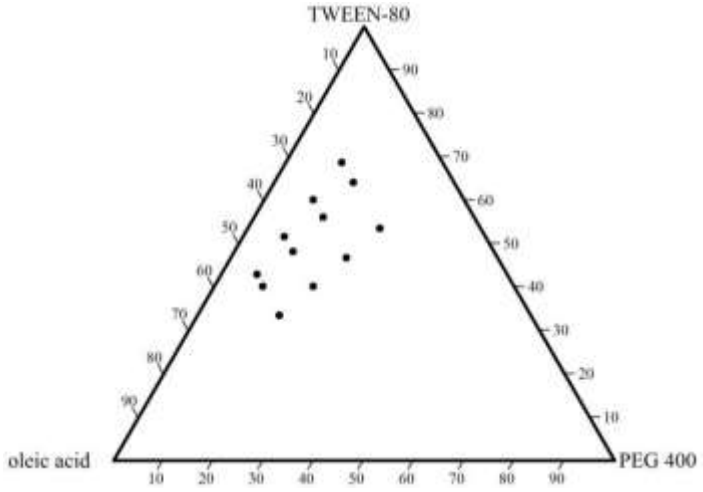

Figure 1: Ternary phase diagram

Table 4: Percentage transmittance results of various SMEDDS

Formulation code	Transmittance (% mean ± SD)			
	Dilution with water		Dilution with 0.1M HCl	
	50 times dilution with water	100 times dilution with water	50 times dilution with 0.1 mol/HCL	100 times dilution with 0.1 mol/ HCL
F1	14.09 ±0.01	15.14 ±0.03	16.61 ±0.021	16.66 ±0.011
F2	75.46 ±0.02	77.97 ±0.01	78.77 ±0.025	79.82 ±0.012
F3	92.14 ±0.04	92.18 ±0.01	93.03 ±0.028	93.11 ±0.021
F4	16.96 ±0.02	18.97 ±0.01	19.91 ±0.011	20.97 ±0.015
F5	75.77 ±0.02	77.76 ±0.02	77.93 ±0.015	79.52 ±0.018
F6	95.35 ±0.02	95.40 ±0.01	95.2 ±0.017	95.36 ±0.013

Table 5: Cloud point, Optical clarity and Drug content measurements of SMEDDS

Formulation Code	Cloud point (°C±SD)	Optical clarity absorbance at			% DRUG CONTENT
		0hrs	6hrs	24hrs	
F1	50±0.023	0.369	0.432	0.450	85.5
F2	62±0.023	0.246	0.482	0.491	87.5
F3	70±0.0173	0.284	0.540	0.541	90.5
F4	65±0.0173	0.219	0.222	0.221	89.5
F5	69±0.023	0.405	0.677	0.675	94.5
F6	75±0.024	0.509	0.230	0.231	97.5

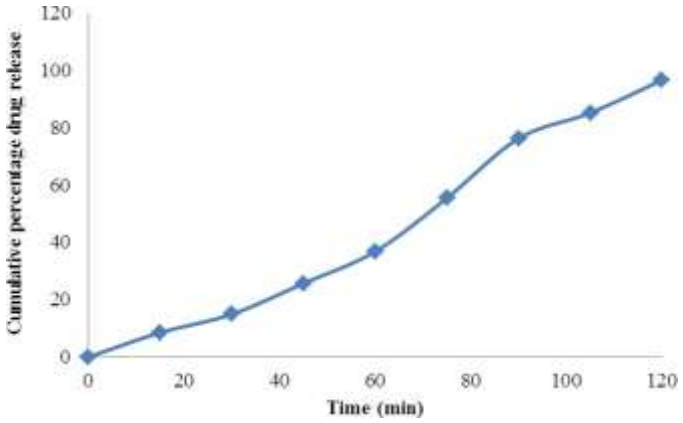

Figure 2: Invitro drug release of F3

tent showed the emulsification time of less than 2minutes, with increase of oil proportion the emulsification time was increase to more than 3 minutes. Emulsification times of various SMEDDS were shown in table 3.

Effect of pH and robustness to dilution

Robustness to dilution was studied by diluting the system with 50, 100, and 1000 times with various dissolution media such as 0.1N HCL and Phosphate buffer Ph (6.8). The diluted micro emulsions were stored for 12 h and it does not indicate any signs of phase separation or drug precipitation. Effect of pH of various SMEDDS is mentioned in table 3.

Dispersibility test

The efficiency of self-emulsification of oral micro emulsion was assessed using a standard USP XXII dissolution apparatus 2. The in-vitro performance of the formulations was assessed visually using the Dispersibility test. Formulation F1, F2-Grade B, F3, F6, showed Grade A, F4-Grade B, F5-Grade C. Various grades of formulations were shown in table 3.

Transmission test

Transmittance of light of the SMEDDS formulation as well as its 50 times dilution, 100 times dilution with water and 0.1mol/ HCL was checked at 650nm. The results showed the formulation F3, F6 are clear and transparent and does not effect even diluted with with 0.1 mol/ HCL. Various percentage transmission of SMEDDS were shown in table 4.

Cloud point measurement

The cloud point measurement is the temperature above which the clarity of formulation turns to cloudiness. This is due to drug precipitation and phase separation of emulsion. Since both the drug solubilisation and stability of emulsion decreases with phase separation, cloud point should be preferably above 37°C. The cloud point temperatures of different formulations were determined in the range of 50-77°C. The reason

for higher cloud point temperature may be attributed to solubility of drug in oil and surfactant system. This infers good stability of all the tested formulations. Above 78°C phase separation and precipitation was observed, this is due to dehydration of poly oxy ethylene moiety of Tween 80 and alkyl chains of PEG-400.Cloud point measurements of various SMEDDS were shown in table 5.

Drug Content

The Drug content test is used to ensure that every capsule contains the amount of drug substance intended with little variation among formulations within a batch. The results of the drug content were mentioned in table 5.

Optical clarity

Optical clarity measured by directly taking the absorbance of the diluted SMEDDS is a measure of droplet stability. The stability of SMEDDS formulation were mentioned in table 5.

***In-Vitro* Drug release studies**

After oral administration when SMEDDS encounter aqueous medium, drug may present in free molecular state or in emulsion form or in solubilised micellar solution. In order to release from emulsion drug should undergo interfacial transport across surfactant layer coated around droplet, which further enters into surrounding aqueous medium by diffusion and convective transport. It indicates when those fine oil droplets are dispersed in the medium and it will not lead to drug diffusion from oil droplet instantaneously. Under these circumstances, it is necessary to separate free drug molecules from those entrapped in the emulsion droplets or micelles to assess the real drug release pattern.

The drug release pattern of various stable SMEDDS were shown in Figure 2 reveals that the highest was observed with F3 formulation within 120 min that could be due to proper compromise between proportions of oil, surfactant and co surfactant in the system.

CONCLUSION

Based on the aforementioned results of spontaneity of emulsification, visual appearance, dispersibility test, percentage transmittance, optical clarity, cloud point measurement, effect of pH and robustness to dilution, drug content, particle size analysis, in vitro drug release studies, the formulation F3 is considered to be the optimised formulation among the formulations studied.

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