Research Article

Formulation and evaluation of lipid based solid dispersions of Carvedilol

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Abstract

Background: Carvedilol is a non-selective beta blocker used in treatment of mild to moderate congestive heart failure. The drug has low bioavailability about 25% to 35%. Intestinal lymphatic route is the major uptake mechanism of carvedilol from gastrointestinal tract. **Objective:** Present work aimed to improve dissolution and bioavailability of drug through SMEDDS, solid dispersions and lipid based solid dispersions for therapeutic uses. **Material and Methods**: The solubility of carvedilol in various oils, surfactants and co-surfactants was determined, the excipients were screened and those showing maximum solubility were selected for the formulations of Self-microemulsifying Drug Delivery System (SMEDDS). SMEDDS were developed using different combinations of oils, surfactants and co-surfactants. Pseudo ternary phase diagrams were constructed using Triplot V 4.1.2 software and micro emulsification area was determined. Formulations were prepared based on phase diagrams using various proportions of oil, surfactant and co-surfactant. The SMEDDS formulations were selected by evaluating the drug release and self-micro emulsification ability when introduced into an aqueous medium under gentle agitation. **Results and conclusion:** Among different formulations, formulation containing oleic acid, tween80 and caproyl 90 were selected. The *in-vitro* drug release of SMEDDS in 0.1N HCl (S-mix ratio 1:3) showed higher drug release (83.98% for 1 hour). Solid dispersions were developed using gelucire 44/14 and gelucire 50/13 as inert carrier. Solid dispersions of carvedilol containing gelucire 50/13 in the drug: carrier ratio of 1:5 was selected as it exhibited higher drug release (85.54% for 1 hour). Lipid based solid dispersions of carvedilol were prepared using SMEDDS and solid dispersions. The drug release from lipid based solid dispersions was found to be higher (92.97% for 1 hour) than SMEDDS and solid dispersions.

Keywords: Carvedilol, SMEDDS, solid dispersions, lipid based solid dispersions

Introduction

Lipid based formulations enhance the oral bioavailability of highly lipophilic compounds. They combine the benefits of SMEDDS and solid dispersions and enhance the drug solubility within gastro intestinal tract (O'Driscoll and Griffin, 2008). SMEDDS may be defined as isotropic mixtures of oils, surfactants & cosolvents/cosurfactants. It consists of blend of lipids and surfactants which self-emulsify on dispersion in gastro intestinal tract to form fine o/w micro-emulsions (Gershanik and Benita, 2000). For poorly water-soluble drugs, which are dissolution-rate limited, SMEDDS approaches the advantage of avoiding drug dissolution as the drug is effectively solubilized throughout intestinal transit (Pouton and Porter, 2008). The choice of lipid excipients in the SMEDDS blend is therefore critical to maintain solubilization of the drug on dispersion in intestinal fluid, and avoid drug precipitation during GIT transit (Fei et al., 2013). SMEDDS formulations are characterized by in vitro lipid droplet sizes of 200nm–5mm and the dispersion has a turbid appearance (Stillhart et al., 2013).

Solid dispersions are formulations where the hydrophobic drug is dispersed in an inert hydrophilic carrier molecule by fusion method, solvent evaporation method or fusion solvent method.

SD formulation approaches include, fusion method, solvent Evaporation method, fusion solvent method (melt evaporation). The particle size reduces to a near molecular level and/or produces an amorphous form of the drug

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dispersed within the carrier, with the aim of increasing the dissolution rates relative to the pure crystalline form of the drug (Chiou and Riegelman, 1971).

Carvedilol is a BCS class II drug with low solubility and high permeability. The intestinal lymphatic route is the major uptake mechanism of carvedilol from the gastro intestinal tract (Faisal et al., 2010). Long chain triglycerides enhance the intestinal lymphatic transport of highly lipophilic drugs (Caliph et al., 2000). LCT-SMEDDS formulations were designed. Carvedilol may be formulated as SMEDDS, lipid based self-emulsifying drug delivery systems, self-emulsifying pellets (Khoo et al., 2003). Gelucire based solid dispersions were designed to enhance the dissolution characteristics of lipophilic drug, carvedilol (Aungst et al., 1997). Gelucire® are solid waxy materials of saturated poly-glycolyzed glycerides consisting of mono-, di-, and tri- glycerides, mono-, di- fatty acid esters of polyethylene glycol (Griffin and O'Driscoll, 2006).

Materials and Methods

Carvedilol was a kind gift sample from Aizant drug research solutions, India. Labrafac PG, caproyl 90, labrafil M 2125 CS, labrafac WL 1349, transcutol, gelucire 44/14 & gelucire 50/13 were gift samples from Gatteffose, Mumbai, India. Methanol, isopropyl alcohol, tween 80, oleic acid was obtained from S.D. Fine-Chem. Ltd, India.

Preformulation studies

A) Solubility studies

Solubility studies were conducted using a rotary shaker (Table orbital shaker. Eltek®) for 72 hours in order to choose the components of the formulation based on the solubility of the drug. An excess amount of drug was introduced into each excipient such as oil, surfactant and co-surfactant followed by sealing in vials. Each vial was centrifuged at 15,000 rpm for 10 min using centrifuge (REMI. Mumbai, India) followed by the removal of undissolved drug by filtering with a Whatman filter paper (0.45µm). Samples were suitably diluted and the drug solutions were analyzed. The experiment was repeated three times. Results were represented as mean values (Mean±SD).

B) Emulsification studies (for selection of Surfactant)

300 mg of surfactants was added to 300 mg of the selected oily phase. The mixtures were gently heated at 50°C for homogenization of the components. Each mixture 50 mg was diluted with distilled water to 50 ml in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversions required to yield a homogenous emulsion. Emulsions were allowed to stand for 2 hours, and their percent transmittance was evaluated at 560 nm double-beam UV spectrophotometer using distilled water as a blank.

C) Emulsification studies (for selection of Co-surfactant)

Mixtures of 100 mg of co-surfactant, 200 mg of selected surfactant, and 300 mg of selected oil were prepared. The mixtures were gently heated at 50°C for homogenization of the components. Each mixture 50 mg was diluted with distilled water to 50 ml in a stoppered conical flask. The ease of emulsification was made by the number of flask inversions to yield a homogenous emulsion. Emulsions were allowed to stand for 2 hours and their percent transmittance was evaluated at 560 nm by a double-beam UV spectrophotometer using distilled water as a blank.

Preparation of the drug loaded SMEDDS

Oleic acid was selected as oil, tween 80 was selected as surfactant and caproyl 90 was selected as co-surfactant, on basis of solubility and emulsification studies. To determine the concentration of components for the existing range of the micro-emulsion, a pseudo ternary phase diagram was constructed using water titration method at ambient temperature (25°C). The pseudo ternary plot was constructed using TRIPLOT V14 (4.1.0.2) software. In brief, oil was added to previously weighed carvedilol. The components were then kept in a sonicator at 37ºC until drug completely dissolved in oily phase. Surfactant and co-surfactant were then added to the prepared composition and were magnetically stirred until clear emulsion was formed. The prepared micro-emulsions were stored in the suitable container at ambient temperature for further studies.

Characterization of the drug loaded SMEDDS

Self-Emulsification time and Dispersibility tests

Self-emulsification ability and ease of dispersibility were assessed using USP type II dissolution apparatus. Each formulation was added to 900 ml distilled water maintained at 37±0.5ºC, with paddle rotating at 50rpm for gentle agitation. The in vitro performance of the formulations was visually assessed using the grading system as shown below.

- **Grade A:** Having a clear or bluish appearance, rapidly forming (within 1 min) emulsion.
- **Grade B:** Quickly forming, slightly less clear emulsion, having a bluish white appearance.
- **Grade C:** Fine milky emulsion that formed within 2 min.
- **Grade D:** Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).
- **Grade E:** Showing either poor or minimal emulsification with large oil globules present on the surface.

Thermodynamic stability tests

Selected formulations were subjected to different thermodynamic stability tests (Heating cooling cycle,

Centrifugation and Freeze thaw cycle), to overcome selecting metastable formulation.

a) Heating cooling cycle: Heating and cooling cycle was done in refrigerator, the temperature ranging between 4°C and 45°C for 48hrs. The formulations which were stable at these temperatures were subjected to centrifugation test.

b) Centrifugation: Centrifugation for selected formulations from phase diagrams was done at 3500 rpm for 30 min and observed for phase separation, creaming and cracking. Formulations that are stable were taken for freeze thaw cycle.

c) Freeze thaw cycle: Three freeze thaw cycles were carried out between -4°C and +40°C, where the formulation was stored for not less than 48 hours at each temperature. Those formulations, which passed these thermodynamic stress tests, were selected for further study.

d) Effect of pH and Robustness to dilution: Dilution and pH of the vehicle have considerable effect on the phase separation of the spontaneously emulsifying systems. Drug loaded SMEDDS were diluted with 10, 100 & 1000 times with 0.1N HCL. The resulting emulsions were stored for 24 hrs at room temperature and observed for any signs of phase separation or drug precipitation

e) Percent Transmittance: The percent transmittance of the system was measured using UV spectrophotometer (Lab India, Mumbai) keeping distilled water as blank at 560 nm.

In-vitro drug release studies

In-vitro dissolution studies of SMEDDS was done at 37 ± 0.5˚C using a USP type II apparatus (paddle) rotating at 50rpm in 900ml of 0.1N HCL. Dissolution samples of 5ml were collected at various time intervals. An equal volume of fresh dissolution medium was replaced immediately and maintained at same temperature to keep the volume of dissolution media constant and to maintain the sink conditions. Samples were analyzed by UV–visible spectrophotometer.

Preparation of the drug loaded solid dispersions

Solid dispersions of carvedilol with gelucire 44/14 and gelucire 50/13 as inert carriers were prepared by using solvent evaporation method at different molar ratios of 1:1, 1:5, 1:10. The carrier was taken in a glass vial and melted to form a uniform dispersion**.** The drug and isopropyl alcohol were added to the molten mixture to form a clear solution. The solvent was evaporated with constant agitation and kept on water bath and heated to 40˚C. Solid dispersion formed was stored in a desiccator overnight. Formulations were packed in vials with proper labeling and stored in desiccators until further study.

Evaluation of the drug loaded solid dispersions

In-vitro dissolution studies of solid dispersions was done at 37 ± 0.5˚C using a USP type II apparatus (paddle) rotating at 50rpm in 900ml of pH 6.8 phosphate buffer. Dissolution samples of 5ml were collected at various time intervals. An equal volume of fresh dissolution medium was replaced immediately and maintained at same temperature to keep the volume of dissolution media constant and to maintain the sink conditions. Samples were analyzed by UV–visible spectrophotometer.

Preparation of the drug loaded – lipid based solid dispersions (LBSD)

A combination of solid dispersions and SMEDDS were prepared. Solid dispersions were prepared by a solvent evaporation method. SMEDDS were prepared. After solvent removal, SMEDDS containing carvedilol was added to the dispersion and mixed well with spatula on water bath, cooled and finally stored at 8˚C.

Evaluation of the drug loaded – lipid based solid dispersions (LBSD)

In-vitro dissolution studies of LBSD was done at 37 ± 0.5˚C using a USP type II apparatus (paddle) rotating at 50rpm in 900ml of pH 6.8 phosphate buffer. Samples of 5ml were collected at various time intervals. An equal volume of fresh dissolution medium was replaced immediately and maintained at same temperature to keep the volume of dissolution media constant and to maintain the sink conditions. Samples were analyzed by UV–visible spectrophotometer.

Characterization of the drug loaded – lipid based solid dispersions (LBSD)

Powder X-ray diffraction (PXRD)

PXRD patterns were recorded using Philips PW 1729 X-ray generator, USA fitted with a copper target, a voltage of 40 kV, and a current of 30 mA. The scanning rate was 1°/min over a 2 θ range of 1-50°. PXRD patterns were traced for carvedilol, physical mixture and solid dispersions. The samples were slightly ground and packed into the aluminum sample container.

Results and discussion

Pre-formulation studies

Solubility Studies

Solubility of the drug in various oil, surfactants and co-surfactants was determined using shake flask method and indicated in figure 1.

The solubility of Carvedilol was found to be highest in Oleic acid as compared to other oils. Hence, Oleic acid was selected as oil phase. Oleic acid has HLB value of 4 and therefore has more strength to dissolve carvedilol then

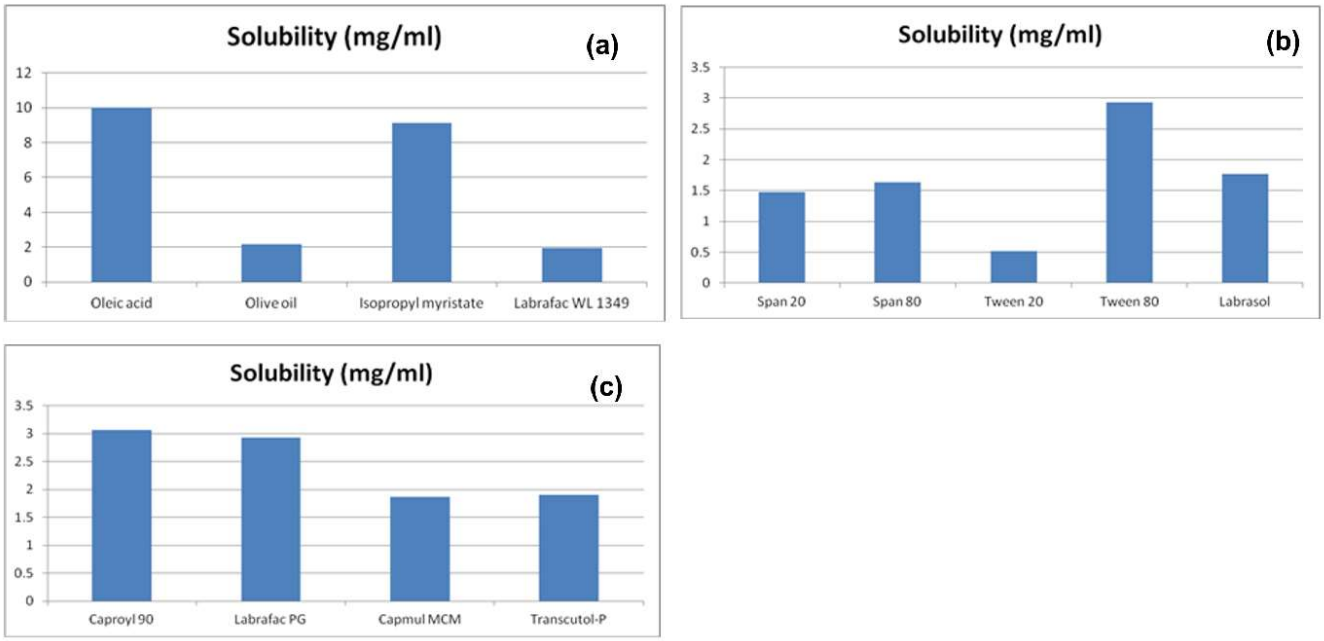

Figure 1. (a) Solubility of Carvedilol in different oils, **(b)** Solubility of Carvedilol in different surfactants, **(c)** Solubility of Carvedilol in different Cosurfactants

Table 1. Screening of surfactant based on emulsification using Oleic acid (300mg)

S. No.	Type of surfactant (300mg)	No. of flask inversions (Ease of emulsification)	% of transmittance at 560 nm
1.	Span 20	50+	8.1%
2.	Span 80	40+	56.3%
3.	Tween 20	09	87.2%
4.	Tween 80	06	96.2%
5.	Labrasol	40+	42.1%

Table 2. Screening of co-surfactants based on emulsification

S. No.	Oil	Surfactant	Cosurfactant	No of flask inversions	% transmittance at 560nm
1.	Oleic acid	Tween 80	Caproyl 90	03	97.4%
2.			Labrafac PG	05	93.2%
3.			Capmul MCM	14	84.5%
4.			Transcutol-P	12	92.2%

labrafac which has HLB value of 2. With the increasing HLB value of the oil phase the drug solubility increases.

The solubility of Carvedilol was found to be highest in Tween 80 when compared to the other surfactants. Hence Tween 80 was selected as surfactant as shown figure 2. The solubility of Carvedilol was determined in various co-surfactants and was found to be highest in Caproyl 90 as shown in figure 2. Hence Caproyl 90 was selected as co-surfactant.

Emulsification study: (Selection of Surfactants)

Surfactants were selected based on their ability of ease of emulsification by judging number of flask inversions of oil phase and percent transmittance. Oleic acid exhibited highest emulsification efficiency with Tween 80 (showed transmittance of 96.2% with 06 flask inversions) as shown in table 1.

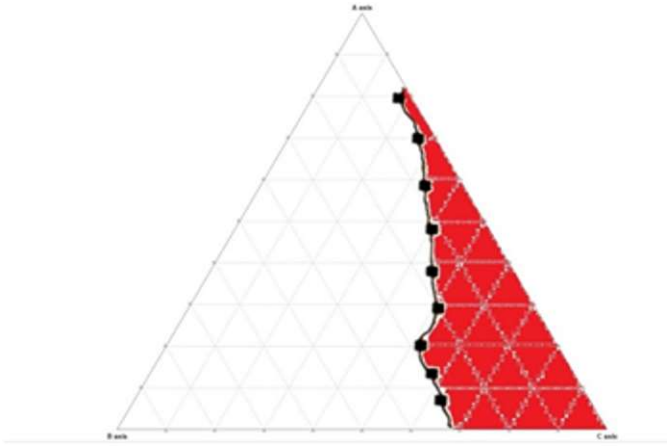

Figure 2. Construction of Pseudo Ternary phase diagram using Oil as Oleic acid, Surfactant as Tween 80, Co-surfactant as Caproyl 90 in 1:3 ratio

Emulsification study (selection of Co-surfactants)

Addition of a co-surfactant to the surfactant containing formulation was reported to improve dispersibility and drug permeation from the formulation. This can there by improve the absorption of the drug. As depicted in the table 2, Caproyl 90 was selected as co-surfactant, due to high solubility of drug.

Caproyl 90 was selected as co-surfactant as it exhibited high percentage transmittance with Tween 80 and oleic acid with less number of flask inversions (03 flask inversions) as shown in table 2.

Pseudo ternary phase diagram

Self-micro emulsifying systems form isotropic mixtures of oil and surfactants which are emulsified, upon their introduction into aqueous media. Surfactant and co-surfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy required for the emulsion formation consequently improves the thermodynamic stability of the micro-emulsion formulation. Therefore, the selection of oil and surfactant, and the mixing ratio of oil to S/Co-S, plays an important role in formulation of the micro-emulsion.

The aim of the construction of pseudo ternary phase diagrams was to determine the existence range of self-micro emulsifying region and to select suitable concentrations of oil, surfactant and co-surfactant. The ratio of surfactant to co-surfactant was very effective for a stable and an efficient micro emulsion formation. The phase diagrams were constructed at surfactant/ co-surfactant ratios of 4:1,3:1,2:1,1:1,1:2,1:3,1:4 (w/w). They were constructed using Oleic acid as oil, Tween 80 as surfactant and Caproyl 90 as co-surfactant in different ratios. The greater existence range of micro-emulsion region was found to be more for the formulation (1:3) i.e., 30% as shown in figure 2.

Characterization of SMEDDS

Thermodynamic stability studies

All the formulations were subjected to different thermodynamic stability by centrifugation, heating and cooling cycle and freeze thaw cycle tests. Thermodynamic stability of micro emulsion differentiates them from the macro emulsions as shown in table 3.

SMEDDS of Carvedilol

In-vitro dissolution studies were carried out by using USP type II apparatus (paddle type). *In-vitro* dissolution studies of solid dispersions were conducted in 0.1N HCl.

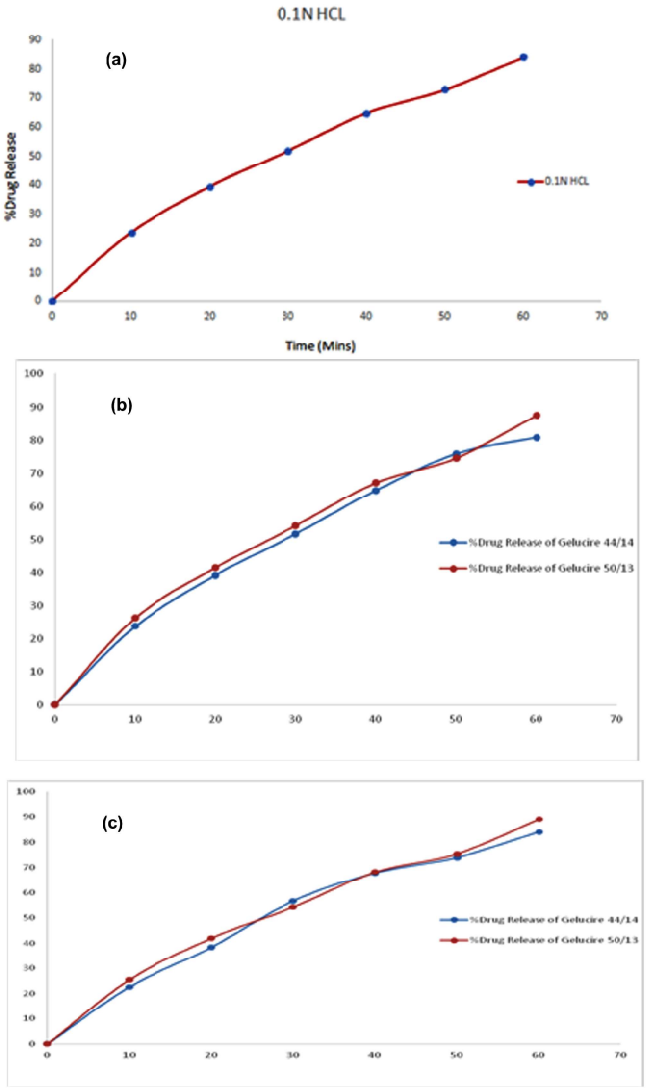

Figure 3. *In-vitro* Dissolution Studies of **(a)** SMEDDS of Carvedilol using 0.1N HCl in 1:3 ratio, **(b)** Solid dispersions of Carvedilol using pH 6.8 phosphate buffer in 1:5 ratio, **(c)** Lipid Based Solid Dispersions of Carvedilol using pH 6.8 phosphate buffer

Table 3. Characterization of SMEDDS and Thermodynamic evaluation parameters

Formulation (S-mix)	Self-emulsification and dispersibility tests	Effect of dilution	Percentage transmittance	Heating and cooling cycle	Centrifugation test ±SD	Freeze thaw method (-4°C for 2 days and +40°C for 2 days)
(1:2)	Grade A	Pass	95	Pass	Pass	Pass
(1:3)	Grade A	Pass	97	Pass	Pass	Pass

In-vitro dissolution studies of SMEDDS of carvedilol in 0.1N HCl in the Smix ratio of 1:3 ratio exhibited higher drug release (83.98%) in 1hr. *In-vitro* dissolution studies were conducted in 0.1N HCl and pH 6.8 phosphate buffer. But 0.1N HCl was more discriminating and hence it was selected as dissolution medium as shown in figure 3.

***In-vitro* dissolution studies of solid dispersions**

Solid dispersions of carvedilol were prepared using gelucire 44/14 and gelucire 50/13 as inert carrier by using solvent evaporation method. *In-vitro* dissolution studies were carried out by using USP type II apparatus (paddle type). *In-vitro* dissolution studies of solid dispersions were conducted in pH 6.8 phosphate buffer.

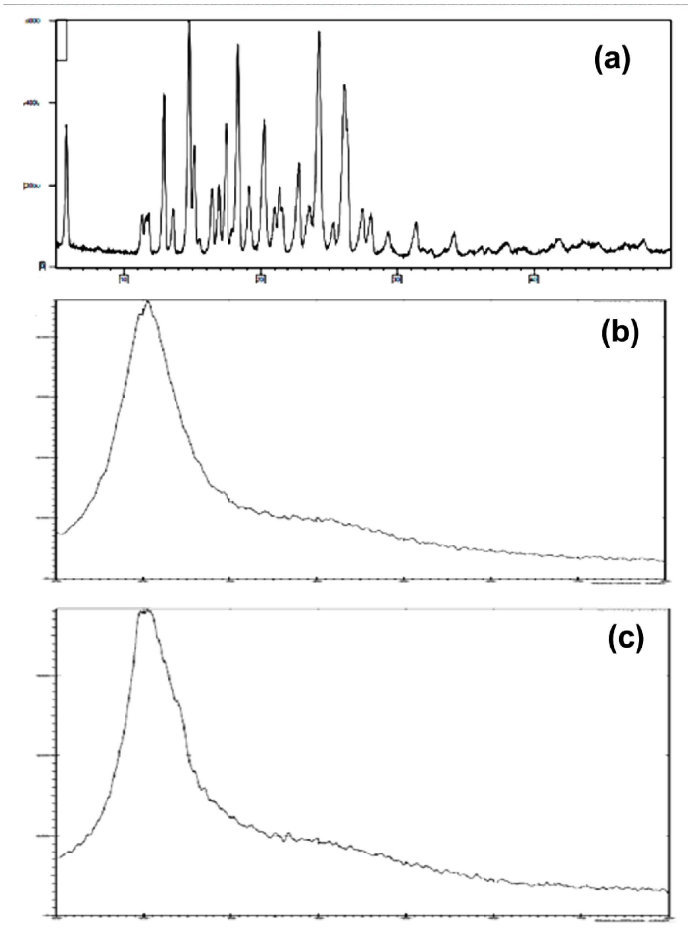

Figure 4. (a) XRD of pure drug of Carvedilol, **(b)** XRD of Carvedilol of LBSD using Gelucire 44/14, **(c)** XRD of Carvedilol of LBSD using Gelucire 50/13

Solid dispersions of carvedilol using Gelucire 50/13 exhibited greater drug release (87.53%) in 1hr, when compared to Gelucire 44/14 as shown in figure 3.

***In-vitro* dissolution studies of Lipid based solid dispersions**

Lipid based solid dispersions were prepared using SMEDDS and solid dispersions. *In-vitro* dissolution studies of these dispersions were carried out by using USP type II apparatus (paddle type in pH 6.8 phosphate buffer.

LBSD of Gelucire 50/13 exhibited greater drug release (92.97%) in 1hr, when compared to Gelucire 44/14 as shown in figure 3.

Characterization of LBSD

X-ray diffraction (XRD)

As seen in figure10 pure drug carvedilol has characteristic peak at 13.6˚, 15.5˚ and 18.2˚ at 2θ. On comparing the diffractograms of LBSD and carvedilol no obvious peaks representing crystals of carvedilol were seen in LBSD indicating that the drug is present in the amorphous state in LBSD. This accounts for enhancement of dissolution rate of carvedilol in LBSD (Figure 4).

Conclusions

Lipid based solid dispersions of carvedilol aimed to enhance the solubility and absorption of lipophilic drug carvedilol. Lipid based solid dispersions formulation combines the benefits of SMEDDS approach where the portion of drug is solubilized within the lipid excipients, and solid dispersions approach where the remaining portion of drug is dispersed within lipidic inert carrier phase to enhance dissolution characteristics. The blend of lipids and surfactants within LBSD can increase the drug absorption by increasing the uptake into intestinal cells and simulating lymphatic uptake.

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Conflict of interest

None

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