

Research Article**SOLUBILITY ENHANCEMENT OF CARVEDILOL USING LIQUISOLID COMPACT TECHNIQUE****Tarique Ali Meer, Ajay Sav, Purnima Amin***Department of Pharmaceutical Sciences and Technology, Institute of Chemical Technology,
N. P. Marg, Matunga, Mumbai, 400019. India.**ABSTRACT**

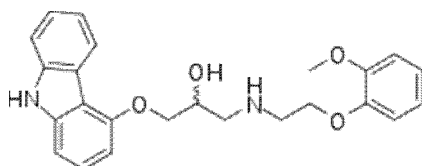
A novel liquisolid compact technique was used for solubility enhancement of poorly water soluble drug carvedilol (CAR). CAR was dissolved in water miscible non volatile solvent and then adsorbed on a solid carrier which was later compacted with other excipient into a tablet. The tablets were characterized with respect to hardness, friability, disintegration and *in-vitro* dissolution profile. Effect of storage conditions on dissolution profile was also studied. DSC and XRD studies were done to confirm the physical state of CAR in the formulation.

Keywords: Solubility Enhancement, Liquisolid Compacts, BCS Classification, Carvedilol

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About 40% of the drugs discovered falls into poorly water soluble or water insoluble categories [1]. For drugs belonging to biopharmaceutics classification system BCS class II (poor water solubility and high permeability) dissolution rate is rate determining step in drug absorption [2]. Therefore, the objective of the study was to enhance the aqueous solubility of CAR using liquisolid compaction approach. CAR (fig. 1) is an aryloethanolamine and has β adrenoceptor blocking activity and $\alpha 1$ blocking activity. It is indicated for hypertension. CAR being BCS class II (poor solubility, high permeability) has dissolution rate as a rate limiting factor. Solubility enhancement of CAR causes bioavailability improvement which has been reported in literature [3].

For dissolution rate enhancement various techniques have been reported. Namely, particle size reduction [4], surfactant incorporation [5], inclusion complex [6], micro-encapsulation [7], solid solutions [8] and prodrug formulations [9].

**Fig. 1:** Structure of Carvedilol

Liquisolid compact technique involves, a solid drug to be dissolved in water miscible non volatile liquid to prepare the 'liquid medication' which is then loaded onto a selected

solid carrier and coating materials to prepare dry, non adherent, free flowable and readily compactable powder admixture [10].

High solubility of CAR in PEG 400 and Tween 80 suggested their use in formulation of liquisolid compacts. Dissolution studies revealed strong dependence on Fm (fraction of drug dissolved completely in liquid), which could be attributed to the availability of drug in molecularly dispersed state.

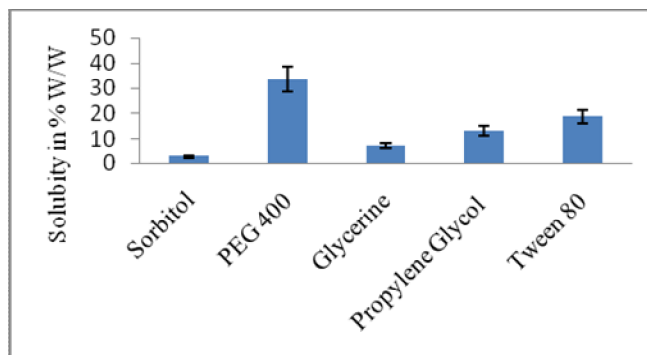


Fig. 2: Solubility of CAR in various liquid vehicles

Table 1: Hardness, friability and disintegration for liquisolid compact

LS	Crushing strength kg/cm ² ±SD	% Friability	Dt±SD
LS1	3.0±0.707	0.432	26±2.15
LS2	2.3±0.649	0.523	20±2.54
LS3	2.5±1.118	0.234	15±3.11
LS4	2.7±0.829	0.470	11±3.87
LS5	2.2±0.433	0.742	7±6.57

Dt: disintegration time; SD: standard deviation from mean

High viscosity of Tween 80 prolonged the disintegration time as it formed a hard mass. LS3 and LS4 were found to be suitable for carrying out their stability studies.

No significant change was observed in dissolution profile of LS4 as it had less load factor (amount of liquid medication per unit weight of solid carrier) compared to that of LS3.

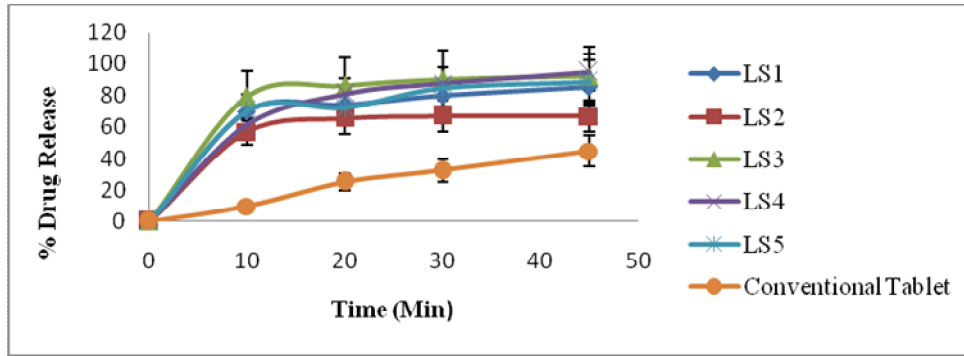


Fig. 3: Dissolution profiles of CAR from liquisolid and conventional tablets

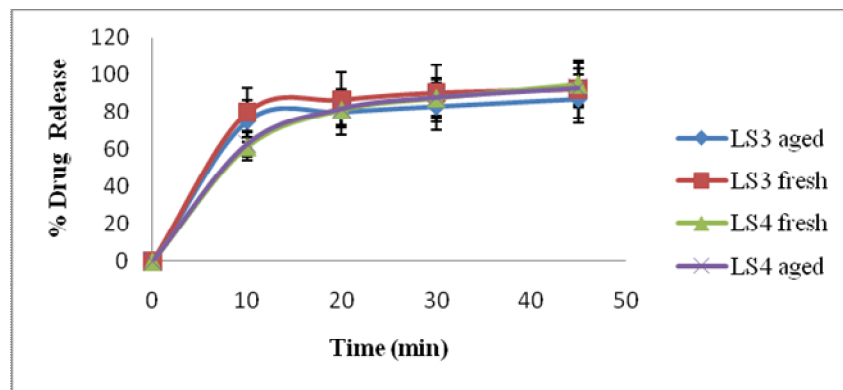


Fig. 4: Dissolution profiles of fresh vs. aged LS3 and LS4

In figure 5 sharp endothermic peak of the CAR was masked in the formulation, indicating absence of crystalline CAR in formulation.

Figure 6 revealed x ray diffraction pattern of CAR and LS4. The percent crystallinity for CAR and LS4 was found to be 34.4403 and 5.4110 respectively.

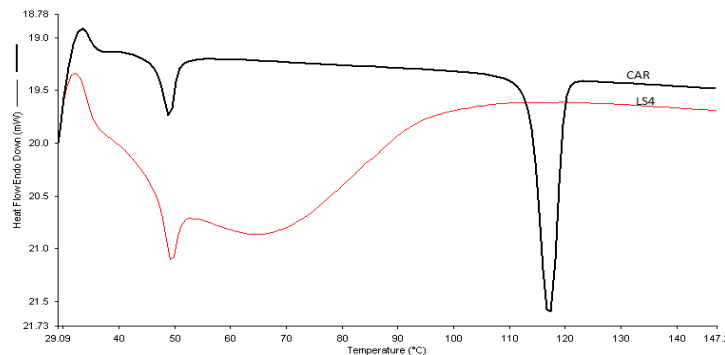


Fig. 5: DSC of CAR and LS4

In conclusion, this study showed that liquisolid compact technique could be a promising and cost effective strategy for improving dissolution of poorly water soluble drugs and formulating immediate release solid dosage forms.

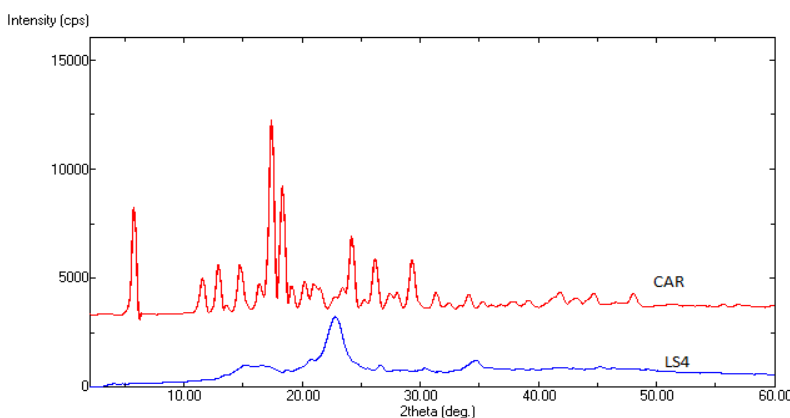


Fig.6: XRD of CAR and LS4

This technique enabled the drug CAR to be in a solution state (molecularly dispersed) thus improved the dissolution profile. Stability studies revealed that the dissolution was not significantly affected on storage.

Solubility of CAR (CTX Lifesciences, India) in various components was determined as follows: 500 mg of each of selected vehicle was added to each cap vial containing excess of drug (1 g). After sealing, mixture was heated at 40°C in water bath to facilitate solubilization. Mixing of system was done using a shaker, maintained at 25°C for 48 hours. After reaching equilibrium, each vial was centrifuged at 10000 rpm for 5 min and excess insoluble CAR was discarded by filtration using membrane filter (0.45 µm, 13 mm). The filtrate was then suitably diluted to quantify by UV-Spectrophotometric analysis.

CAR Liquisolid compacts denoted as LS1 to LS5 were prepared using Tween 80 and PEG 400. CAR (25 mg/tablet) was dissolved in liquid vehicle using a magnetic stirrer. All Liquisolid formulation contained Avicel PH 102 (FMC, USA) as a carrier and Aerosil P 200 (Degussa, Germany) as a coating material at a fixed ratio (R) of 30. The appropriate amount of carrier material Avicel PH102 was mixed with liquid medication. Aerosil P200 was then added to mixture under continuous mixing to make the powder admixture dry. Finally, 5% w/w sodium starch glycolate (SSG)(Roquette, France) was added as a distintegrant and mixed for 10 min. The final blend was compacted using 12 mm round standard concave punch and die set using a single punch tableting machine (Cadmach, India). Crushing strength of tablets were maintained 2 to 3 kg/cm².

Conventional tablet of CAR was also prepared in the same manner as of LS4 except addition of PEG400.

Each tablet contained 25 mg of CAR and 5% SSG of total tablet weight. Table 1 shows the composition of different liquisolid batches. *In vitro* dissolution test was carried out using USP type II dissolution test apparatus (with paddles); simulated gastric fluid without enzyme was used as dissolution media. The volume of dissolution medium was 900mL maintained at

37±1°C and stirred at a paddle speed of 50 rpm. Ten mL samples were collected at the time intervals of 10, 20, 30 and 45 min. The withdrawn samples were replaced by equal amounts of dissolution medium to maintain a constant volume.

Table 2: Formulation composition of liquisolid systems

LS	Liquid vehicle	Liquid medication mg	Carrier (Q) mg	Coating (q) mg	Disintegrant (SSG) mg	Molecular fraction (Fm)
LS1	Tween80	135.13	696.62	23.25	45	1.00
LS2	Tween80	100	516	17.65	33.35	0.74
LS3	PEG400	100	516	17.65	33.35	1.33
LS4	PEG400	75	387.5	12.5	25	1.00
LS5	PEG400	50	411	14	25	0.66

LS: liquisolid system; PEG400: polyethylene glycol 400; Fm = saturation solubility of CAR/actual concentration of CAR in liquid vehicle.

The samples extracted at the time intervals were analyzed after suitable dilutions, spectrophotometrically at λ_{\max} of 241 nm.

The friability of prepared tablets was measured as per procedure of USP27 [11].

Disintegration test was performed at 37±1°C in distilled water. The tablets were considered completely disintegrated when no residue remained on the screen or a residue consisting of a soft mass with no palpable firm or unmoistened core observed.

The tablets with significantly improved dissolution profiles were stored at 40°C/75%RH for 4 weeks. The stored tablets were evaluated for dissolution. The dissolution data of aged tablets were compared with freshly prepared tablets.

CAR and LS4 were also characterized by differential scanning calorimetry(DSC) and X-ray Diffraction (XRD).

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AUTHORS' STATEMENT

The authors declare no conflict of interest.

REFERENCES

1. Lipinski C. Poor aqueous solubility- an industry wide problem in drug discovery Am Pharm Rev. 2002; 5: 82-85
2. Lbenberg R, Amidon GL. Modern bioavailability, bioequivalence and biopharmaceutics classification system. New scientific approaches to international

- regulatory standards. *Eur J Pharm Biopharm.* 2000; 50: 3-12 doi: 10.1016/s0939-6411(00)00091-6
3. Wei L, Sun P, Nie S, Pan W. Preparation and evaluation of SEDDS and SMEDDS containing Carvedilol. *Drug Dev Ind Pharm.* 2005; 31: 785-794 doi: 10.1080/03639040500216428
 4. Dong Y, Kiong Ng W, Shen S, Kim S, Tan RBH. Preparation and characterization of spironolactone nanoparticles by antisolvent precipitation. *Int J Pharm.* 2009; 375: 84-88 doi: 10.1016/j.ijpharm.2009.03.013
 5. Balakrishnan A, Rege BD, Amidon GL, Polli JE. Surfactant-mediated dissolution: contributions of solubility enhancement and relatively low micelle diffusivity. *J Pharm Sci.* 2004; 93: 2064-2075 doi: 10.1002/jps.20118
 6. Jadhav GS, Vavia PR. Physicochemical, in silico and in-vivo evaluation of danazole- β cyclodextrin complex. *Int J Pharm.* 2008; 352: 5-16 doi: 10.1016/j.ijpharm.2007.10.005
 7. Ilić I, Dreu R, Burjak M, Homar M, Kerč J, Srčić J. Microparticle size control and glimepiride microencapsulation using spray congealing technology. *Int J Pharm.* 2009; 381: 176-183 doi: 10.1016/j.ijpharm.2009.05.011
 8. Moore MD, Wildfong PLD. Aqueous solubility enhancement through engineering of binary solid composites: pharmaceutical applications. *J Pharm Innov.* 2009; 4: 36-49 doi: 10.1007/s12247-009-9053-7
 9. Zhang P, Ye H, Min T, Zhang C. Water soluble poly(ethylene glycol) prodrug of silybin: Design, synthesis, and characterization. *J Appl Polym Sci.* 2008; 107: 3230-3235 doi: 10.1002/app.27450
 10. Nokhodchi A, Aliakber R, Desai S, Javadzadeh Y. Liquisolid compacts: The effect of cosolvent and HPMC on theophylline release. *Colloids Surf B Biointerfaces.* 2010; 79: 262-269 doi: 10.1016/j.colsurfb.2010.04.008
 11. Tablet Friability USP XXVII (Asian edition). 2004; 27: 2621-2622.