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Der Pharmacia Lettre, 2010, 2(5): 412-427
(http://scholarsresearchlibrary.com/archive.html)

Der Pharmacia Lettre
Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Liquisolid Technique for Enhancement of Dissolution Properties of Carvedilol

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ABSTRACT

The in vitro dissolution property of slightly water soluble Carvedilol was improved by exploring the potential of Liquisolid system (LS). The in vitro release pattern of Liquisolid compacts and directly compressed tablets were studied using USP-II apparatus. Different Liquisolid compacts were prepared using a mathematical model to calculate the required quantities of powder and liquid ingredients to produce acceptably flowable and compressible admixture. Avicel PH 102, Aerosil 200 and Sodium starch glycolate were employed as carrier, coating material and disintegrant respectively for preparing Liquisolid compacts. The prepared Liquisolid compacts were evaluated for their flow properties such as bulk density, tapped density, angle of repose, Carr's compressibility index and Hausner's ratio. The interaction between drug and excipients in prepared Liquisolid compacts were studied by differential scanning calorimetry (DSC) and X-ray diffraction (XRD). The drug release rates of Liquisolid compacts were distinctly higher as compared to directly compressed tablets, which show significant benefit of Liquisolid compact in increasing wetting properties and surface area of drug available for dissolution. The LS-1 of Liquisolid powder system showed acceptable flowability, Carr's compressibility index and Hausner's ratio. The DSC and XRD studies conforms the no significant interaction between the drug and excipients used in Liquisolid compacts. From this study it concludes that the Liquisolid technique is a promising alternative for improvement of dissolution property of water-insoluble drugs.

Keywords: Carvedilol; Dissolution rate; Liquisolid compacts

INTRODUCTION

For poorly soluble, highly permeable (class II) drug Carvedilol, the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal tract.[1] Therefore together with the permeability, the solubility and dissolution behaviour of a drug are key determinants of its oral bioavailability. The poor dissolution rate of such water-insoluble drugs shows a major obstacle in development of pharmaceutical dosage forms. The oral absorption of these drugs is often controlled by dissolution in GI tract. Thus dissolution of drug is of prime importance in

absorption. The different techniques used to enhance the dissolution of water insoluble drugs, some of them are particle size reduction, surfactant as solublizing agent, drug complex with hydrophilic carrier, pro-drug approach, and formulation of drug as solid solution to improve the dissolution rate by decreasing the crystallinity. [2] Among these the most promising method for promoting dissolution is the use of Liquisolid compacts. [3]

The term 'liquisolid systems' (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems, into dry looking, nonadherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials. Various grades of cellulose, starch, lactose, etc. are used as the carriers, whereas very fine silica powder is used as the coating (or covering) material. [4] The good flow and compression properties of Liquisolid may be attributed due to large surface area of silica and fine particle size of avicel. Hence Liquisolid compacts containing water-insoluble drugs expected to display enhanced dissolution characteristics and consequently improved oral bioavailability. In the present investigation, Carvedilol a very slightly water soluble drug was formulated into Liquisolid compacts consisting of similar powder excipients with different liquid vehicles concentration. The *in vitro* drug dissolution rates of such preparations were compared to those of conventionally prepared directly compressed tablets using a USP-II apparatus. DSC and XRD technique were used to ascertain any interaction and crystallinity changes of drug in Liquisolid compacts due to interaction between drug and other excipients. [5]

MATERIALS AND METHODS

2.1 Materials:

Carvedilol was obtained as a gift sample from Sun Pharmaceuticals Pvt. Ltd. Mumbai and Torrent Pharmaceuticals Pvt. Ltd. Ahmedabad. Avicel PH 102 was obtained as a gift sample from Alkem Labs Pvt. Ltd. Mumbai. Aerosil 200 was purchased from Himedia, Mumbai. PEG 200 and PEG 400 were purchased from Loba, Mumbai.

2.2 Spectrophotometric analysis:

Spectrophotometric analysis of all Carvedilol samples in 0.1N HCl was performed at 240 nm (UV/Visible spectrophotometer, Shimadzu, Japan). Standard curves were constructed by serially diluting stock solution of drug in 0.1N HCl to obtain concentrations in the range of 2-20 µg/ml. Each sample was analyzed in triplicate.

2.3 Solubility Studies:

Saturated solubility study of drug was carried out in three different non volatile solvents, i.e. PEG 200, PEG 400 and PG by preparing saturated solutions of the drug in these solvents and analyzing their drug content spectrophotometrically. Saturated solutions of Carvedilol were prepared in vehicles and kept in orbital shaker for 48 h at 25°C. After this period, the solutions were filtered, diluted and analysed by UVspectrophotometer at 240 nm. Three determinations were carried out for each sample to calculate the solubility of Carvedilol. The results were extrapolated to determine the percent w/w of Carvedilol in its saturated solution with the solvent under investigation.

Table 1: Solubility carvedilol in various solvents

Sr. No.	Solvent	Solubility (%w/w)
1	PEG 400	3.99
2	PEG 200	3.13
3	PG	2.91

2.4 Application of the mathematical model for designing the liquisolid systems

In the following study, polyethylene glycol (PEG 400) was used as liquid vehicle; Avicel PH 102 and Aerosil 200 were used as the carrier and coating materials, respectively. In order to attain optimal Carvedilol solubility in the liquisolid formulations, several factors were varied like the concentration of the liquid vehicle PEG 400 (10, 20 and 30 %), concentration of carrier and coating materials. The outline of the constituents of each of the formulae prepared is demonstrated in Table 2. In order to address the flowability and compressibility of liquisolid compacts, simultaneously, the ‘‘new formulation mathematical model of liquisolid systems” was employed as follows to calculate the appropriate quantities of excipients required to produce liquisolid systems of acceptable flowability and compressibility. This mathematical model was based on new fundamental powders properties (constants for each powder material with the liquid vehicle) called the flowable liquid retention potential (Φ-value) and compressible liquid retention potential ψ-number) of the constituent powders (carrier and coating materials). [4] According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties. Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used, where

$$R=Q/q \quad \text{... (1)}$$

As R represents the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation. An acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded; such a characteristic amount of liquid is termed the liquid load factor (Lf) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible liquisolid system. i.e.:

$$Lf=W/Q \quad \text{... (2)}$$

Flowable liquid retention potentials (Φ -values) of powder excipients used to calculate the required ingredient quantities, hence, the powder excipients ratios R and liquid load factors Lf of the formulations are related as follows [6]:

$$Lf = \Phi + \phi\,(1/R) \quad \text{... (3)}$$

Where, Φ and ϕ are flowable liquid retention potential of carrier and coating material respectively. So in order to calculate the required weights of the excipients used, first, from Eq. (3), Φ and ϕ are constants, therefore, according to the ratio of the carrier/ coat materials (R), Lf was calculated from the linear relationship of Lf versus 1/R. next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used. So, by knowing both Lf and W, the appropriate quantities of carrier (Q_o) and coating (q_o) powder materials required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system could be calculated from equation (1) and (2).

2.5 Preparation of Directly compressible tablet (DCT) and Liquisolid compact:

Directly compressible tablets (DCT) of Carvedilol were prepared by direct compression using multiple tablet punch machine, each containing 6 mg drug with Avicel PH 102, Aerosil 200 and sodium starch glycolate. Various Liquisolid compacts (LS-1 to LS-10) containing 6 mg of Carvedilol were prepared by dispersing in non-volatile vehicles such as propylene glycol and PEG 400. Then a binary mixture of carrier (Avicel PH 102) and coating material (Aerosil-200) was prepared at a ratio of 20:1. This binary mixture was added to the admixture of drug and vehicle. Depending upon the type of vehicle in the formulation, different liquid load factors were employed in Liquisolid preparations. Therefore, different concentrations of Avicel and silica were used to prepare different Liquisolid formulations. Finally sodium starch glycolate as disintegrant was added in above powder blend and mixed. The final powder blend was subjected to compression. Important formulation characteristics of Liquisolid compacts are shown in Table 2.

Table 2: Composition of different Carvedilol liquisolid formulation prepared using PEG 400 as a liquid vehicle according to mathematical model

FORMULA	DRUG CONC. IN PEG-400 (W) mg	Lf	AVICEL (Q=W/ Lf) mg	AEROSIL (q=Q/R) mg	SSG 5% mg	UNIT DOSE WEIGHT mg
LS1	50.0	0.230	237	10.85	14.6	313
LS2	40.0	0.232	179	8.6	11.61	239
LS3	33.3	0.235	146	7.0	9.47	195
LS4	28.5	0.238	117	5.8	7.96	159
LS5	25.0	0.240	116	5.2	7.06	154
LS6	22.0	0.243	106	4.5	6.15	139
LS7	20.0	0.245	90	4.0	5.52	119
LS8	16.0	0.250	68	3.2	4.37	92
LS9	12.5	0.250	50	2.4	3.31	68.5
LS10	10.0	0.250	40	2.0	2.30	54.8

** An appropriate amount of liquid medication containing 6 mg of drug was incorporated in each tablet.*

** Lf = Liquid load factor. Where, L_f = W/Q*

** Q = Weight of carrier material i.e. Avicel PH 102*

** W= Weight of liquid medication i.e Carvedilol and PEG 400*

2.6 Precompression studies of the prepared liquisolid powder systems

Prior to the compression of the formulations into tablets, in order to ensure the suitability of the selected excipients, various studies were performed including differential scanning calorimetry (DSC), X-ray diffraction (XRD) and scanning electron microscope (SEM). In addition, so as to select the optimal formulae for compression flowability studies were also carried out.

2.6.1 Differential scanning calorimetry (DSC)

DSC was performed using Shimadzu differential scanning calorimeter Mettler, in order to assess the thermotropic properties and thermal behaviour of the drug (Carvedilol) and the liquisolid compacts prepared. About 5 mg of the sample were sealed in the aluminium pans and heated at the rate of10 ^{o}C/min, covering a temperature range of 40^{o}C to 300^{o}C under nitrogen atmosphere of flow rate 100 ml/min.

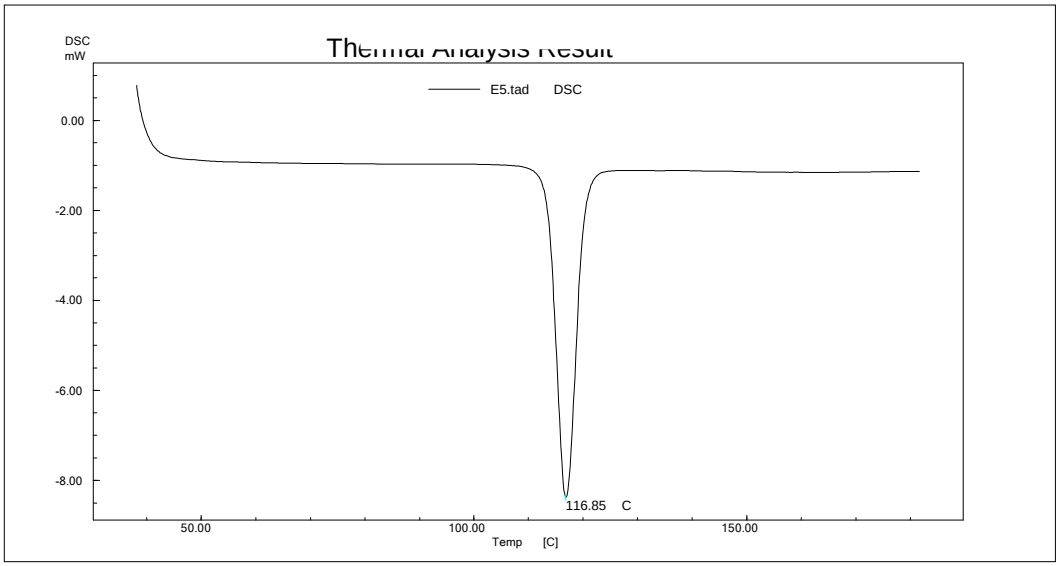

Fig. 1: DSC thermogram of Carvedilol

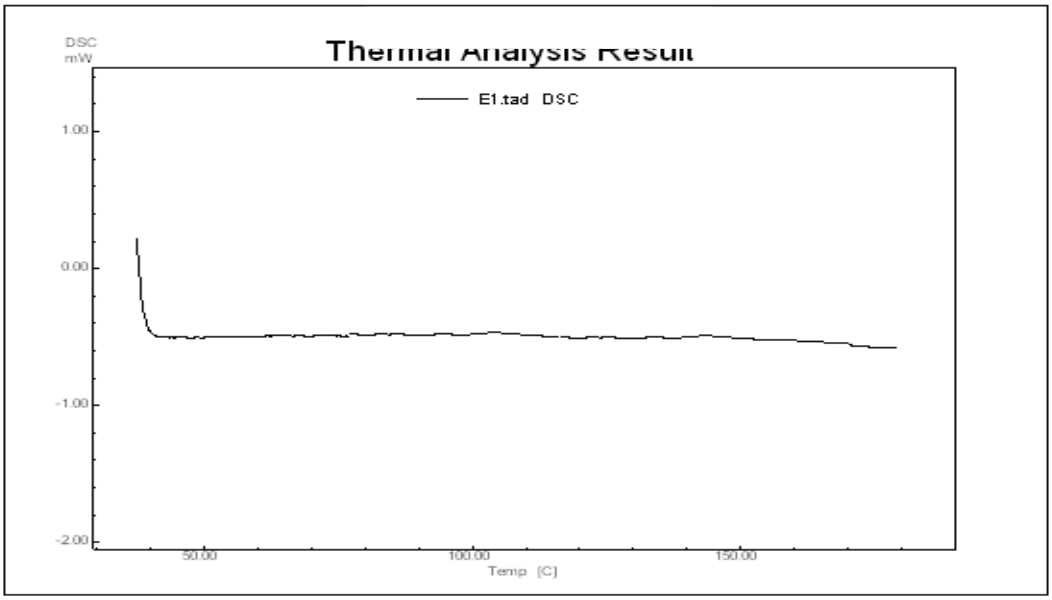

Fig. 2: DSC thermogram of Aerosil

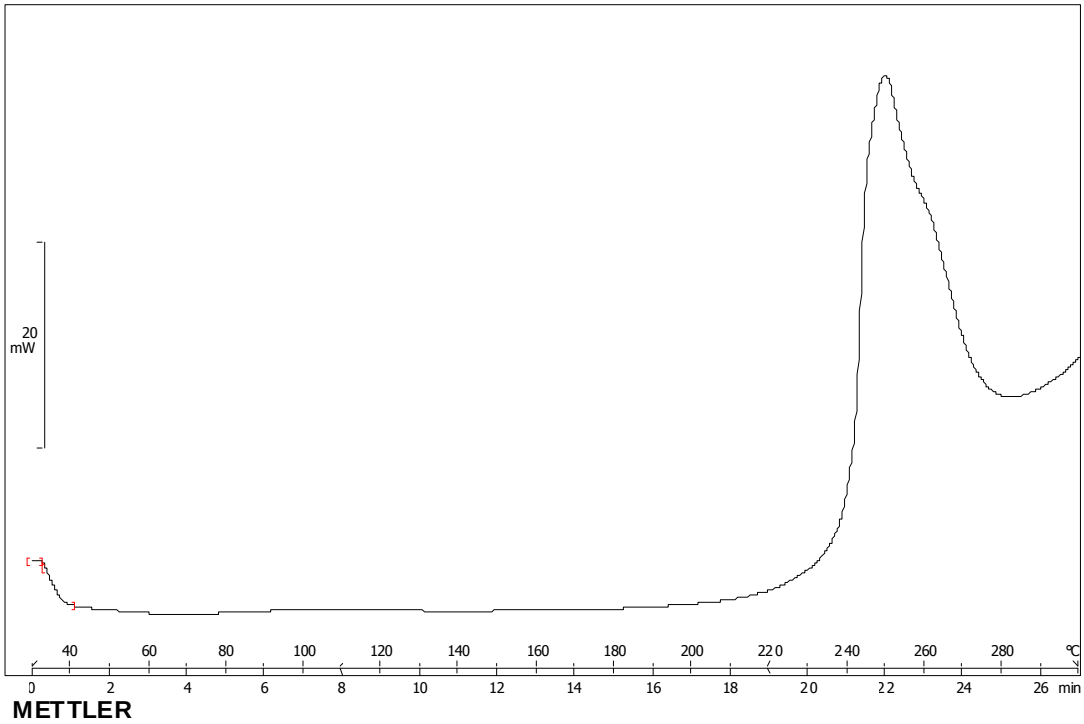

Fig. 3: DSC thermogram of liquisolid formulation

2.6.2 X-ray diffractometery (XRD)

It has been shown that polymorphic changes of the drug are important factors, which may affect the drug dissolution rate and bioavailability. [7] It is therefore important to study the polymorphic changes of the drug. For characterization of crystalline state, the X-ray diffraction (XRD) patterns for Carvedilol, physical mixture of Carvedilol: Avicel 102: Aerosil 200(1:1:1) and the liquisolid system prepared were determined using X-ray diffractometer with a copper target, at a voltage of 40 kV and current of 20MA. The rate of the scanning was 0.30°C /min.

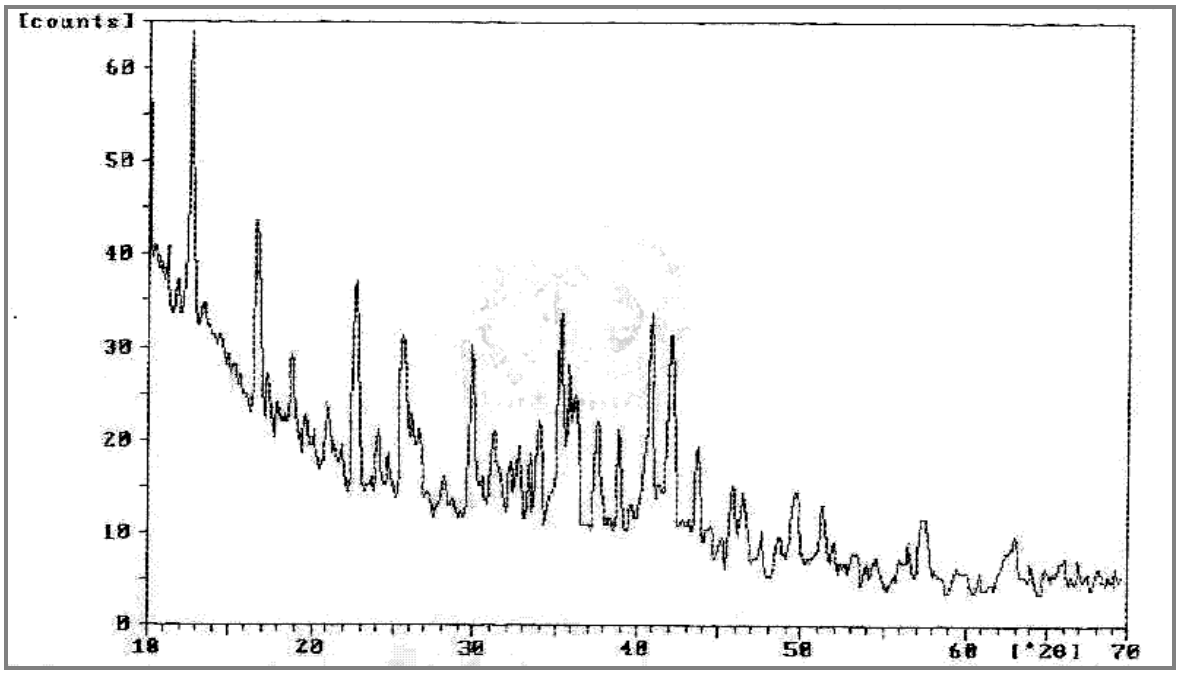

Fig. 4: X-ray diffractogram of Carvedilol

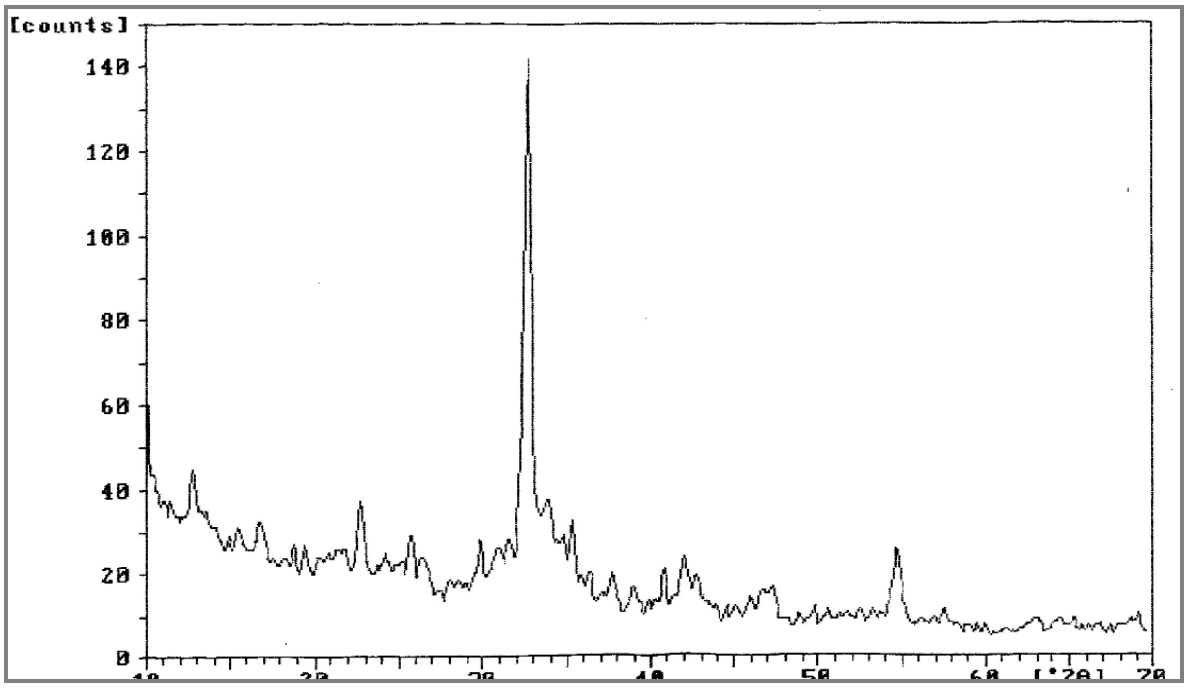

Fig. 5: X-ray diffractogram of Carvedilol: Avicel PH 102: Aerosil200 (1:1:1) physical mixture

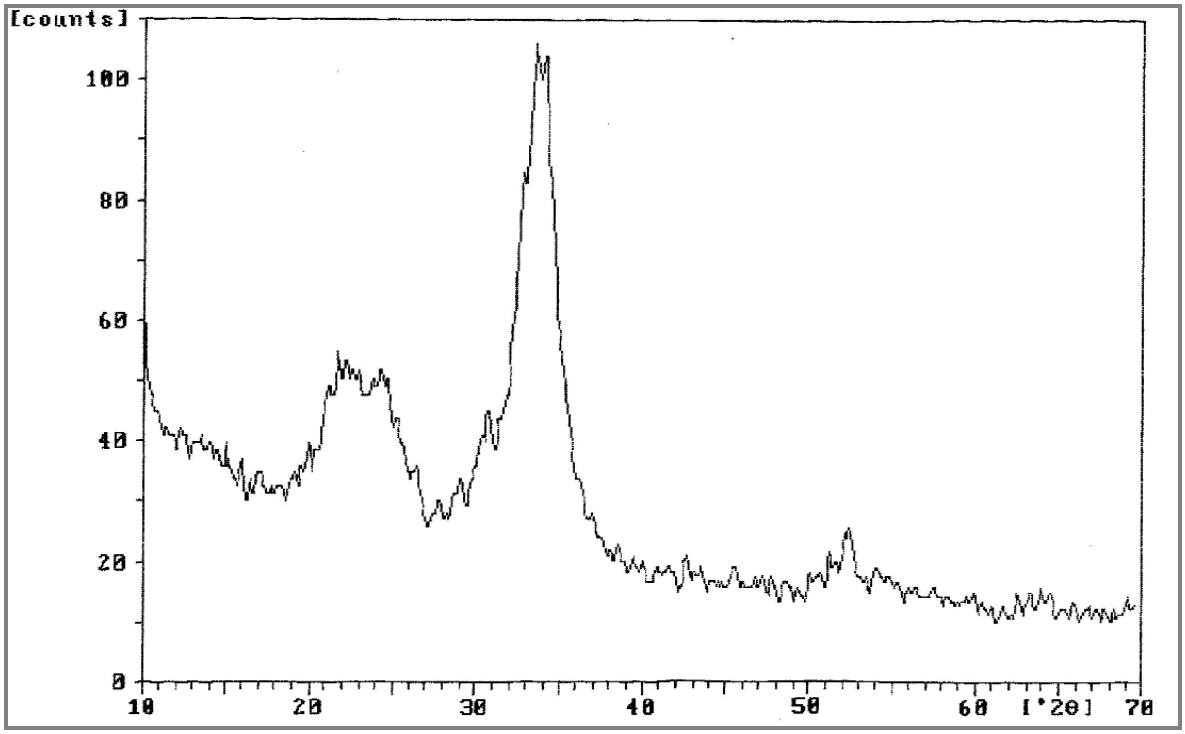

Fig. 6: X-ray diffractogram of liquisolid compact

2.6.3 Scanning electron microscopy (SEM)

SEM was utilized in order to assess the morphological characteristics of the drug-carrier systems and final liquisolid compact. The sample was mounted on double sided adhesive carbon tape on brass stubs and analyzed. The accelerating voltage was 15 kilo volts.

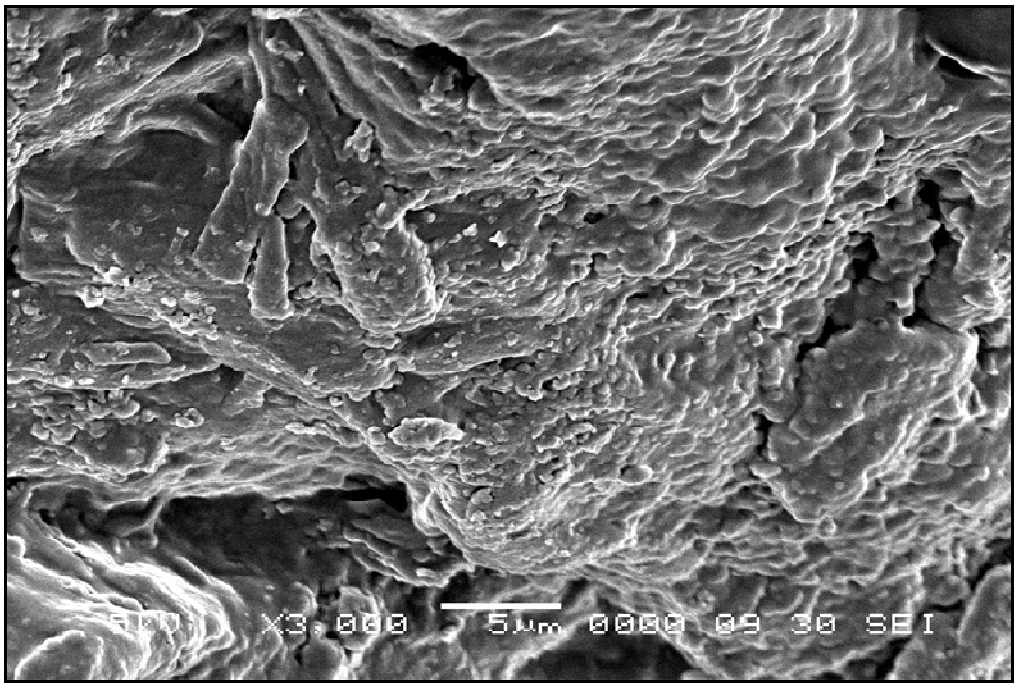

Fig. 7 a: SEM of Carvedilol liquisolid System

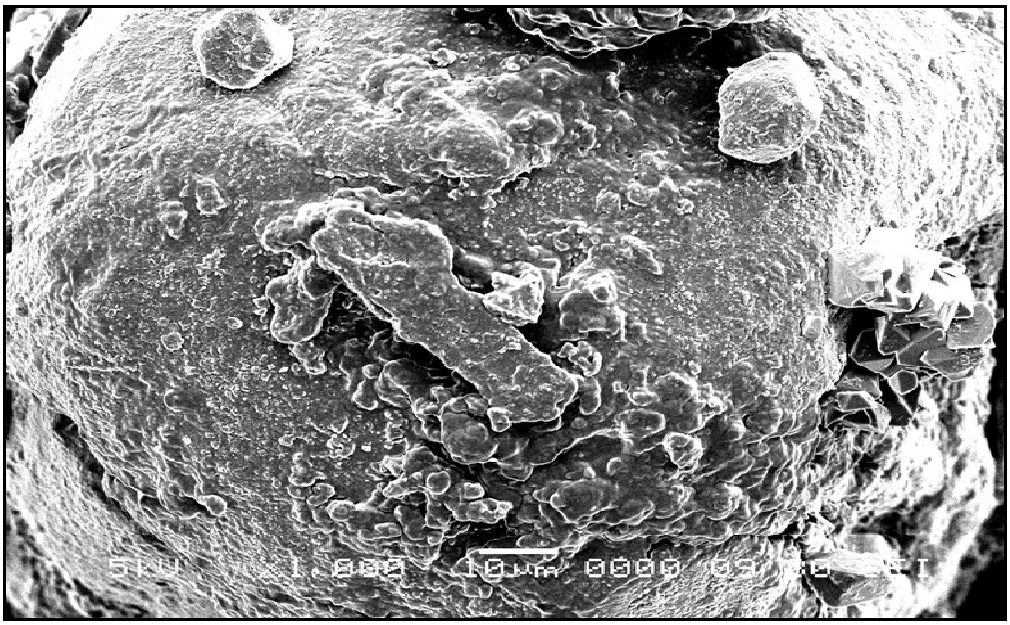

Fig. 7 b: SEM of Carvedilol liquisolid system

2.6.4 Flow properties of Liquisolid system [8]:

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies otherwise high dose variations will occur. Flow properties of the Liquisolid were estimated by tap density, bulk density, Angle of repose, Carr's compressibility index and Hausner's ratio. Angle of repose was measured according to the fixed funnel method. The tap density was determined using bulk density apparatus and calculated the Carr's compressibility index and Hausner's ratio.

Table 3: Flowability parameter of carvedilol liquisolid compact

Formulation No.	Average Angle of repose (θ)* ± SD	Average Carr's index	Average Hausner's ratio
LS1	25.25±1.12	13.67	1.20
LS2	30.58±0.65	15.39	1.21
LS3	30.76±0.82	18.52	1.23
LS4	31.56±1.05	18.91	1.25
LS5	32.33±1.1	20.00	1.33
LS6	35.93±1.6	21.25	1.35
LS7	37.63±0.77	22.17	1.38
LS8	40.54±0.51	25.54	1.41
LS9	40.58±0.69	26.71	1.47
LS10	41.03±1.4	28.89	1.50
DCT	28.12±0.94	20.12	1.24

* All values are expressed as mean ± SD (n=3)

2.6.5 Evaluation of Carvedilol liquisolid tables:

The prepared Carvedilol liquisolid tablets of the selected formulae were further evaluated. Carvedilol content in different liquisolid tablet formulations was determined by accurately weighing twenty tablets and powdered. The blend equivalent to 60 mg of Carvedilol was weighed and dissolved in sufficient quantity of 0.1N HCl. The solution was filtered through Whatman filter paper (no.45), suitably diluted with 0.1N HCl and assayed at 240 nm, using a UV-Visible double beam spectrophotometer. The friability of the prepared formulae was measured using tablet friability tester (Hicon, India) and the percentage loss in weights were calculated and taken as a measure of friability. The hardness of the liquisolid tablets prepared was evaluated using Pfizer hardness tester, Mumbai, the mean hardness of each formula was determined. The disintegration time was performed using disintegration apparatus (Hicon Ltd., India). Finally, the *in vitro* dissolution studies were carried out and the dissolution rate of Carvedilol from liquisolid tablets was determined using USP Dissolution Test Apparatus II (Labindia Disso 2000, India).

Table 4: Evaluation of carvedilol liquisolid tablet

Formulation No.	Thickness (mm)*	Hardness (kg/cm^2)*	Weight Variation (g)*
LS1	4.10 ± 0.057	4.7 ± 0.1	317.16 ± 10.16
LS2	3.91 ± 0.057	4.1 ± 0.057	245.16 ± 5.13
LS3	3.47 ± 0.057	3.8 ± 0.26	203 ± 6.40
LS4	3.15 ± 0.057	3.5 ± 0.10	160 ± 1
LS5	3.14 ± 0.057	3.6 ± 0.20	161.3± 15.27
LS6	2.70 ± 0.057	2.8 ± 0.30	145 ± 10.1
LS7	2.35 ± 0.057	2.6 ± 0.26	123 ± 5
LS8	2.28 ± 0.057	2.1 ± 0.20	101 ± 6.24
LS9	2.25 ± 0.057	1.9 ± 0.20	75.66 ± 12.58
LS10	2.20 ± 0.057	1.7 ± 0.15	60 ± 16

*All values are expressed as mean ± SD (n=3)

The USP paddle apparatus II was used to study drug release from the liquisolid tablets; 900 ml of 0.1N HCl was used as dissolution medium, at 37.0 ± 0.5° C. and rotation speed of 50 rpm was used. Aliquots were withdrawn at suitable time interval (5, 10, 15, 20, 25, 30, 45, 60 min.) and filtered through Whatman filter paper and diluted to 10 ml. Sink conditions were maintained throughout the study. The samples were then analyzed at λ_{max} of 240 nm by UV/visible spectrophotometer.

RESULTS AND DISCUSSION

Carvedilol was selected as the model drug for present study, since it is a very slightly water soluble drug and thus, it is an ideal candidate for testing the potential of rapid-release liquisolid compact. In addition, it can be easily assayed and quantitated in solution using spectrophotometric method. From the standard calibration curve of Carvedilol in 0.1 N HCl, it was observed that the Carvedilol obeys Beer-Lambert's Law in concentration range of 2-20 µg/ml in the medium. The results of solubility study of Carvedilol are given in Table 1, which shows higher solubility in polyethylene glycol PEG 400 as compared to others non-volatile solvent.

In order to calculate the required ingredient quantities, the flowable liquid retention potentials (Φ -values) of powder excipients were utilized. In polyethylene glycol 400, the Φ -value of Avicel PH 102 was found to be 0.005, while for Aerosil 200 the Φ -value used was equal to that of Cab-O-Sil M5 as they both possessed the same specific surface area and density thus, Aerosil 200 and Cab-O-Sil M5 are expected to have similar adsorptive power. [9] Therefore, the Φ -value used for Aerosil 200 in PEG 400 was 3.26. This relatively high Φ -value is advantageous as it results in smaller sizes of the formulated tablets.

Using ''the new formulation mathematical model", the straight line equation for Avicel PH 102 and Aerosil 200 in PEG 400 will be

$$Lf = 0.005+3.26(1/R)$$

For each R-value used, the corresponding Lf value can be calculated. As soon as the optimum liquid load factor Lf of a given excipients ratio is established for each formula and W is calculated according to Carvedilol concentration in PEG 400, the appropriate quantities of Avicel PH 102 (Q_o) and Aerosil 200 (q_o) required to convert a given amount of liquid medication (W) into an acceptably flowing and compressible liquisolid system, were calculated using equation (1) and (2). Table 2 represents the exact qualitative and quantitative composition for each formula.

3.1 Precompression studies of the prepared liquisolid powder systems:

One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation. DSC was performed in order to assess the thermotropic properties and thermal behaviour of the drug (Carvedilol) and the liquisolid compacts prepared. The DSC thermogram of the drug (fig. 1) depicts a sharp exothermic peak followed by an endothermic peak at 116.85°C corresponding to the melting transition temperature of Carvedilol. Such sharp endothermic peak signifies that Carvedilol used was in pure crystalline state. The DSC thermogram of the Aerosil 200 shows disappearance of the endothermic peak. On the other hand, the liquisolid system thermogram in fig. 3 displayed complete disappearance of both characteristic peaks of Carvedilol; a fact that agrees with the formation of drug solution in the liquisolid powdered system, i.e. the drug was molecularly

dispersed within the liquisolid matrix. Such disappearance of the drug peaks upon formulation of the liquisolid system was in agreement with McCauley and Brittain who declared that the complete suppression of all drug thermal features, undoubtedly indicate the formation of an amorphous solid solution. [10]

X-ray diffraction pattern in fig. 4 revealed that Carvedilol was clearly in crystalline state. The crystalline nature of the drug was demonstrated by the characteristic XRD pattern with peaks appearing at 6.38, 8.26, 14.90, 19.23, 20.74, 25.96, 26.82 and 27.70 2θ values. Carvedilol characteristic peaks were observed in the physical mixture (fig.5), demonstrating that its crystalline structure remained unchanged during the physical mixing, and that the loss of crystallinity was due to liquisolid system formation. On the other hand, the liquisolid powder X-ray diffraction pattern (fig.6) showed only one sharp diffraction peak at 2θ angle of 22.5 belonging to Avicel PH 102, indicating that only Avicel PH 102 maintained its crystalline state. Such absence of Carvedilol constructive reflections (specific peaks) in the liquisolid X-ray diffractogram indicates that drug has almost entirely converted from crystalline to amorphous or solubilized form, such lack of crystallinity in the liquisolid system indicates that Carvedilol solubilization in the liquid vehicle.
This amorphization or solubilization of Carvedilol in the liquisolid system may contribute to the consequent improvement in the apparent solubility and therefore the dissolution rate of Carvedilol.

The SEM outcomes presented in Fig. 7a and b further proved the results of both DSC and XRD. The scanning electron micrographs illustrate that pure Carvedilol has clearly crystalline nature as previously proved by the DSC and XRD, the photomicrograps of the final liquisolid system signify that complete disappearance of Carvedilol crystals. This fact indicates that the drug was totally solubilised in liquisolid system. It is also indicate that even though the drug is in solid dosage form, it is held within the powder substrate in solution or in solubilised, almost molecularly dispersed state as shown in fig. 7 which contributes to enhance drug dissolution property.

Powder flow is a complicated matter and is influenced by so many interrelated factors; the factor's list is long and includes physical, mechanical as well as environmental factors. [10] Therefore, in our study, because of the subjective nature of the individual types of measurements as indicators of powder flow, three flow measurement types were employed; the angle of repose, Carr's index (compressibility index), and Hausner's ratio and their results are presented in Table 3.

As the angle of repose (Θ) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive. As presented in Table 3 LS1, LS2, LS3, LS4, LS5, LS6 and DCT respectively, were chosen as liquisolid systems with acceptable flowability according to the angle of repose measurements, while those having higher angles of repose were considered as non-acceptable. Powders showing Carr's index up to 21 are considered of acceptable flow properties. In addition to Carr's index, Hausner ratio was related to the inter particle friction. Hausner showed that powders with low interparticle friction, had ratios of approximately 1.25 indicating good flow. [11] Therefore, formulae LS1, LS2, LS3 and LS4 were selected as acceptably flowing as they had average Carr's index of 13.67, 15.39, 18.52 and 18.91, respectively and average Hausner's ratios of 1.20, 1.21, 1.23 and 1.25, in the same order.

Finally, formulae LS1, LS2, LS3, LS4, LS5 and LS6 that were proved to be acceptably flowing according to either the angle of repose, Carr's index and Hausner's ratio. These formulae were compressed into tablets and subjected for further evaluation while the rest of formulae were nominated as having unacceptable flowability and therefore excluded from further investigation.

The effect of liquid load factor (L_f), which is a ratio of mass of liquid (PEG 400) added to the mass of Avicel PH 102 on flowability and compressibility of the final admixture of the powder is shown in Table 3. Increasing the L_f value in the range of 0.230 to 0.250 i.e. decreasing the amount of carrier material in the formulation resulted in decrease in the flowability of the final admixtures. This is evident from the increase in the angle of repose. With increase in L_f value flow property was found to be reduced. These decreasing flow properties may be due to decreasing amount of carrier and coating material which would be responsible for flowability and compressibility of the final liquisolid admixture. As L_f value increases the concentration of the carrier material decreases since, L_f=W/Q. As shown in formula load factor is inversely proportional to the weight of carrier material i.e. Avicel PH 102. All these results indicate that the granules possessed satisfactory flow properties.

3.2 Evaluation of Carvedilol liquisolid tablets

The tablets of different formulations were subjected to various evaluation tests such as thickness, uniformity of weight, drug content, hardness, friability and *in vitro* dissolution are presented in Table 4 and 5. All the formulations showed uniform thickness. In a weight variation test, the average percentage deviation of all tablet formulations was found to be within the IP limit and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets and the percentage of drug content was more than 95%. The formulation LS1 showed a comparatively high hardness value of 4.7 kg/cm^2. This could be due to the presence of high concentration of Aerosil 200 which is generally responsible for hardness of the tablet. As the level of Aerosil 200 in the granulation increased from 0.1% to 0.5%, the hardness of the tablet goes on increases. [12] The low hardness value observed with formulation LS7, LS8, LS9 and LS10 may be due to decreasing in the concentration of Aerosil 200 and Avicel PH 102. The hydrogen bonds between hydrogen groups on adjacent cellulose molecules in Avicel PH 102 may account almost exclusively for the strength and cohesiveness of compact. The high compressibility and compactness of Avicel PH 102 can be explained by nature of microcrystalline cellulose particles themselves which are held together by hydrogen bonds, when compressed. Tablet hardness is not an absolute indicator of strength. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the prescribed limits. The disintegration test revealed that the all liquisolid tablets disintegrate in less than 5 min. Liquisolid batches from LS1 to LS7 shows increase in disintegration time as concentration of sodium starch glycolate in formulation decreased.

The dissolution profiles of the Carvedilol liquisolid tablet formulations (LS1-LS10) together with the dissolution profile of Carvedilol directly compressed tablets (DCT) are presented in fig. 8. It was apparent that formula LS1 has the highest dissolution pattern in both the rate and the extent of drug dissolved. The percentage of Carvedilol dissolved from LS1 reached 97.55%, while the DCT had a maximum Carvedilol content 50.04 % dissolved after 60 min. The percent of drug dissolved from LS1 and DCT after 10 min (Q_{10}) and the drug release rate (D_R) were taken as a measure of the extent and the rate of drug dissolved from the prepared tablets respectively, as presented in Table 6. The results in the Table 6 clearly confirm that the liquisolid tablet formula LS1 had the highest percentage of drug dissolved in 10 minutes; it dissolved

99.64% of its Carvedilol content during the first 10 min. As well, it is clear from the table that LS1 had the highest Carvedilol dissolution rate of all the formulae.

Table 5: Evaluation of carvedilol liquisolid tablet

Formulation No.	Friability (%)	Disintegration Time (Sec)*	% Drug Content*	% Drug Release in 1 hr*
LS1	0.92	58.00±6.56	101.40±1.5	97.55±2.60
LS2	0.90	64.67±7.51	99.45±1.90	94.82±1.76
LS3	0.78	71.00±3.00	100.30±1.94	94.10±1.89
LS4	0.69	76.00±10.00	98.26±1.33	93.55±2.11
LS5	0.67	76.00±12.77	98.30±1.94	87.10±1.78
LS6	0.54	98.00±7.00	99.45±1.90	79.95±1.56
LS7	0.47	112.67±11.2	98.72±0.080	78.30±1.93
LS8	0.42	78.67±3.00	98.53±0.080	80.01±2.18
LS9	0.39	70.00±10.00	97.72±2.55	76.15±1.13
LS10	0.35	64.67±7.51	97.62±2.52	69.33±1.77
DCT	0.58	98.00±7.00	98.73±1.61	50.87±1.25

*All values are expressed as mean ± SD (n=3)

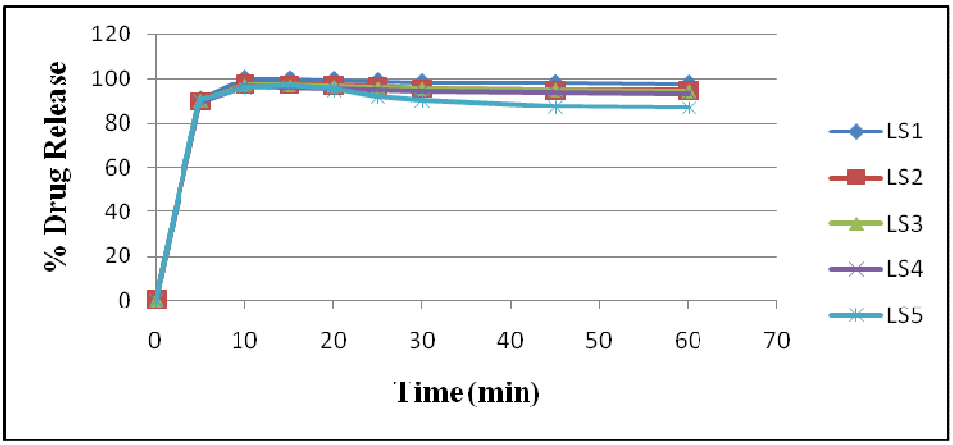

Fig. 8: Percentage drug release from Carvedilol liquisolid formulation (LS1-LS5)

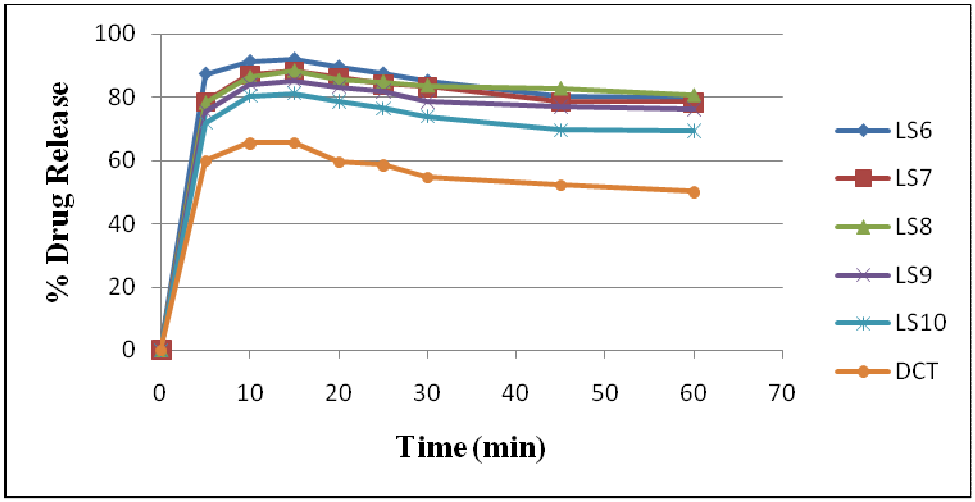

Fig. 9: Percentage drug release from Carvedilol liquisolid formulation (LS6-LS10) and DCT

Table 6, Fig. 8 and Fig. 9 signify that all the formulae had higher drug dissolution rates (D_R), and larger amounts of drug dissolved in the first 10 min (Q_{10}) than the conventional, directly compressed Carvedilol tablets. This could be explained according to the ‘‘Noyes–Whitney” equation [13] and the ‘‘diffusion layer model” dissolution theories, the dissolution rate of a drug (D_R) is equal to

$$D_R = \left(\frac{D}{h}\right) S (C_s - C)$$

Where,

D_R = Rate of dissolution
S = Surface area available for dissolution
D = Diffusion coefficient of the compound
Cs = Solubility of the compound in dissolution medium
C = Concentration of drug in the medium at time t
h = Thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

Since all of dissolution tests for formulations were done at a constant rotational paddle speed (50 rpm) and identical dissolution media, we can safely assume that the thickness of the stagnant diffusion layer (h) and the diffusion coefficient of the drug molecules remain almost identical. From the previous equation, the drug dissolution rate is directly proportional not only to the concentration gradient of the drug in the stagnant diffusion layer (Cs - C), but also to its surface area (S) available for dissolution. [14]

Table 6: Comparisons of dissolution rate (D_R)

Formulation	Q_{10}[a] %	D_R[b] (µg/ min)
LS1	99.64	498.2
DCT	65.34	326.7

a: Carvedilol dissolved after 10 min.
b: Ten-minute Carvedilol dissolution rate

Liquisolid tablets contain a solution of the drug in suitable solvent (Carvedilol in PEG 400), the drug surface available for dissolution is tremendously increased. In essence, after tablet disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a state of molecular dispersion, whereas the directly compressed tablets are merely exposing micronized drug particles. In other words, in the case of liquisolid tablets, the surface of drug available for dissolution is related to its specific molecular surface which by any means, is much greater than that of the Carvedilol particles delivered by the plain, directly compressed tablets. Significantly increased surface of the molecularly dispersed Carvedilol in the liquisolid tablets may be chiefly responsible for their observed higher and consistent drug dissolution rates. As shown in figure 8 Carvedilol liquisolid tablets LS1 displayed significantly improved dissolution properties compared to Carvedilol directly compressible tablet (DCT). Such enhanced drug dissolution rates may be mainly attributed to the fact that this practically water-insoluble drug is already in solution in polyethylene glycol 400, while at the same time it is carried by the powder particles of the liquisolid system. Since the drug is molecularly dispersed within its water-miscible liquid vehicle, its release is accelerated due to its markedly increased wettability and surface availability to the dissolving medium. Such higher drug dissolution rates displayed by liquisolid compact may also imply enhanced oral bioavailability.

Pair wise procedure such as similarity factor (f2) provides simple way to compare dissolution data. US FDA guidance proposes that f2 values of 50–100 indicate equivalence in dissolution profiles. Table 7 shows f2 values of all the batches. Batches showing f2 values >50; which indicates similarity in dissolution profile.

Table 7: similarity factor (f_2) values of liquisolid compact compared with marketed tablet.

Formulation Batch Code	f_2	Dissolution Profile.
LS 1 and MKT	51.82	Similar
LS 2 and MKT	54.66	Similar
LS 3 and MKT	56.89	Similar
LS 4 and MKT	57.60	Similar
LS 5 and MKT	57.06	Similar
LS 6 and MKT	53.09	Similar
LS 7 and MKT	52.31	Similar
LS 8 and MKT	57.52	Similar
LS 9 and MKT	48.24	Dissimilar
LS 10 and MKT	41.02	Dissimilar

The batch LS1 was subjected to stability study. Stability study was conducted at 45°C to investigate the effect of temperature on physical parameter of the formulation. Tablet was packed in glass bottle covered with aluminium foil and kept in an incubator maintain it at 45°C $\pm$ 0.5 for 2 month. Changes in parameter were investigated after 1 and 2 month. No major differences were found in evaluated parameter before and after storage at 45°C.

Acknowledgements
Authors are thankful to Principal Sharad Pawar College of Pharmacy, Nagpur for providing the necessary facilities for experimental work and Sun Pharmaceuticals Pvt. Ltd. Mumbai for providing gift samples of drug.

REFERENCES

[1] A. Nokhodchi, *J. Pharm .Sci.*, **2005**, 8(1), 18-25.
[2] S.G Kapsi, T.W Ayres, *Int. J. Pharm.*, **2001**, 229, 193-203.
[3] S. Spireas, S. Sadu, *Int. J. Pharm.*, **1998**, 166,177-88.
[4] Patents: S. Spireas ,United State Patent., 423,339B1, **2002**
[5] S.Gubbi, R. Jarag, *Res. J. Pharm and Tech*, **2009**, 2(2), 382-86.
[6] S. Spireas, T. Wang, R. Grover, *Drug Develop Ind Pharm*, **1999**, 25(2), 163-68.
[7] H.M. Abdou, In: H.M. Abdou (Ed.), Dissolution, bioavailability and bioequivalence. (Easton, Mack Pub. Co., PA, **1989**) 53–72.
[8] J. Staniforth, In: M. Aulton (Ed.), Pharmaceutics: the science of dosage form design. (Edinburgh: Churchill Livingstone, Longman group, **2002**) 197-210.
[9] S. Spiros, C. Jarowski, D, *Pharm Res*, **1992**, 9, 233-40.
[10] G.E. Amidon, In: H.G. Brittain (Ed.) Physical characterization of pharmaceutical solids, Drugs and pharmaceutical sciences. (Marcel Dekker, New York ,**1995**) 282-317.
[11] J. Wells, In: M. Aulton (Ed.) Pharmaceutics: The science of dosage form design. (Edinburgh: Churchill Livingstone, Longman group,**2002**) 114-38.
[12] L.I. Augshurger, R.F. Shangraw, *J. Pharm.Sci.*,1966, 55(4), 418-23.
[13] A.A Noyes , W.R. Whitney, *J Am. Chem. Soc.*,1897, 19, 930-34.

[14] Y. Javadzadeh, M.R. Siahi-Shadbad, M. Barzegar-Jalali, A. Nokhodchi, *Int. J. Pharm.* Il Farmaco,2005, 361-65.