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DESIGN AND DEVELOPMENT OF LIQUISOLID COMPACT OF CARVEDILOL

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Keywords:

Carvedilol; Dissolution rate; Liquisolid compacts; sustained release

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ABSTRACT

It is suggested here that liquisolid technique has the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems is possible . In the present study, carvedilol was dispersed in polyethylene glycol 400 as the liquid vehicle. Then a binary mixture of carrier–coating materials ((Avicel PH-102) as the carrier and silica200 as the coating material) was added to the liquid medication under continuous mixing in a mortar. The final mixture was compressed using the tablet compression machine. The effect of drug concentration, loading factor, thermal treating and on release profile of carvedilol from liquisolid compacts were investigated. The release rate of carvedilol from liquisolid compacts was compared to the release of carvedilol from matrix tablets. X-ray crystallography and DSC were used to investigate the formation of any complex between drug and excipients or any crystallinity changes during the manufacturing process. carvedilol tablets prepared by liquisolid technique showed greater retardation properties in comparison with matrixmatrix tablets. This investigation provided evidence that (HPMC)hydroxypropyl methylcellulose has important role in sustaining the release of drug from liquisolid tablets. The results also showed that wet granulation had remarkable impact on release rate of carvedilol from liquisolid compacts, reducing the release rate of drug from liquisolid compacts. The results showed that aging (liquisolid tablets were kept at 40^0C and 75 % relative humidity for 3 months) had no effect on hardness and dissolution profile of drug. The kinetics studies revealed that most of the liquisolid formulations followed the zero-order release pattern. Infrared spectroscopyand DSC ruled out any changes in crystallinity or complex formation during the manufacturing process of liquisolid formulations.

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 behavior 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 solubilizing 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, non adherent, 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. [4,6] by the help hydrophobic carriers such as of hydroxyl propyl methyl cellulose(HPMC) is used instead of hydrophilic carries in liquisolid systems, sustained release systems can be obtained [5]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 sustained releaseLiquisolid 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 matrixly 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. [5,6]

2. MATERIALS AND METHODS

2.1. Materials Carvedilol was provided by Ciplaltd.mumbai , Polyethylene Glycol (PEG-400),Microcrystalline Cellulose 200 (Avicel® PH 200), silica (Aerosil® PH 200) (Research

Lab Fine Chem Industries Mumbai), Hydroxypropyl Methylcellulose (HPMC) (LobaChemi Pvt. Ltd.mumbai) were used.

2.2 Application of the mathematical model for designing the liquisolid systems [10,13]

In the following study, polyethylene glycol (PEG 400) was used as liquid vehicle; Avicel PH 102and Aerosil 200 were used as the carrier and coating materials, respectively. In order to attainoptimal Carvedilol solubility in the liquisolid formulations, several factors were varied like theconcentration of the liquid vehicle PEG 400 (10, 20 and 30 %).To calculate the loading factor, 200 mg of Avicel® PH 200 and Aerosil® PH 200 in ratio 10, 15, 20 (w/w) ratio were added to the PEG 400 and blended for 10 min [8,910]. The outline of the constituents of each of the formulae prepared is demonstrated in Table 1. In order to address the flowability and compressibility of liquisolidcompacts, simultaneously, the ‘‘new formulation mathematical model of liquisolid systems” wasemployed as follows to calculate the appropriate quantities of excipients required to produceliquisolid systems of acceptable flowability and compressibility. This mathematical model wasbased on new fundamental powders properties (constants for each powder material with theliquid vehicle) called the flowable liquid retention potential (Φ-value) and compressible liquidretention 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 certainamounts of liquid while maintaining acceptable flow and compression properties. Depending onthe excipients ratio (R) or the carrier: coating ratio of the powder system used, where

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

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

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

Flowable liquid retention potentials (Φ -values) of powder excipients used to calculate therequired ingredient quantities, hence, the powder excipients ratios R and liquid load factors Lf ofthe formulations are related as follows [6,10]:

$$Lf = \Phi + \Phi (1/R) \quad ... (3)$$

Where, Φ and Φ are flowable liquid retention potential of carrier and coating materialrespectively. 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), Lfwas calculated from the linear relationship of Lf versus 1/R. next, according to the used liquidvehicle concentration, different weights of the liquid drug solution (W) will be used. So, byknowing both Lf and W, the appropriate quantities of carrier (Qo) and coating (qo) powdermaterials required to convert a given amount of liquid medication (W) into an acceptablyflowing and compressible liquisolid system could be calculated from equation (1) and (2)

2.3 Preparation of liquisolid tablets.[8,9]

Specific quantities of previously weighed solid drug were mixed with PEG 400 and constantly stirred until a homogeneous liquid medications were obtained for 10%, 20% and 30% respectively. According to a new mathematical model expression [6,9,13] calculated amounts of carrier (Avicel® PH 200) (Q) was added to the liquid medication and blended for 10 minutes. The resulting mixture was blended with the calculated amounts of coating material (Aerosil® PH 200) (q) and Hydroxypropyl Methylcellulose (HPMC). Crospovidone (5%) were added as a super disintegrant to the mixture of carrier and coating materials and blended thoroughly. The prepared liquisolid systems were compressed into tablets by using Rotary tablet minipress-I (Rimek, Karnavati Engineering Ltd)[2,6]

Table no.1Composition of Different Carvedilol Liquisolid Compacts

Formulation No.	Drug and PEG Conc.%	R value	Avicel PH 102(Q)(mg)	Aerosil 200 (q) (mg)	Lf Value	HPMC Mg	TOTAL Wt. Mg
F1	10%	10	200	20	0.031	45.25	284.81
F2	10%	15	200	30	0.031	47.25	297.67
F3	10%	20	200	40	0.031	49.25	310.27
F4	20%	10	200	20	0.031	45.25	284.81
F5	20%	15	200	30	0.031	47.25	297.67
F6	20%	20	200	40	0.031	49.25	310.27
F7	30%	10	200	20	0.031	45.25	284.81
F8	30%	15	200	30	0.031	47.25	297.67
F9	30%	20	200	40	0.031	49.25	310.27

R*= carrier and coating material ratio, Lf*= loading factor, formulations contain 5% crospovidone

2.4 Pre compression studies of the liquisolid powder systems [11,12]

Pre-compression studies may play a key role in dose variations, to get a uniform filling of tablet dies and acceptable flow properties are required for the proposed liquisolid powder systems. Angle of repose, Carr's Index and Hausner's Ratio were calculated. The fixed height cone method was used to determine the angle of repose in triplicate and the average value was calculated for each powder:

1) Angle of repose

Angle of repose has been used as indirect methods of quantifying powder flowability. Angle of repose for blend of each formulation was determined by fixed funnel method. The funnel was secured with its tip with height h, above a plane of paper kept on a flat horizontal surface. The powder was carefully poured through the funnel until the apex of the conical pile so formed just reaches the tip of funnel. Angle of repose was determined by substituting the values of the base radius 'r' and height of the pile 'h' in the given equation given below:

$$\tan\theta = h/r$$

Table No .2Angle of Repose as an Indication of Powder Flow Properties

Sr .No.	Angle of repose (degrees)	Type of flow
1	< 20	Excellent
2	20-30	Good
3	30-34	Passable
4	> 40	Very poor

2) Bulk density:

Bulk density was determined by pouring gently 10 gm of sample through a glass funnel in to a 100 mL graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated.

$$\text{Bulk density } (\rho_0) = \frac{M}{V_0}$$

Where, ρ_0 = Bulk density

M = Mass of powder taken

V_0 = Apparent unsettled volume

3) Tapped density:

10 gm sample (tablet blend) was poured gently through a glass funnel in to a 100mL graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping were recorded and tapped density was calculated (Lachman*et al*. 1991).

$$\textbf{Tapped density } (\rho_0) = \frac{M}{V_t}$$

Where, ρ_t = tapped density

M = weight of powder

V_t= tapped volume of powder in cm^3

4) Carr's index

It is used to evaluate flowability of powder by comparing the bulk density and tapped density of a powder. The percentage compressibility of a powder is direct measure of the potential of powder arch or bridge strength and it was calculated according to the given equation (Aulton 2002).

$$\textbf{\% Compressibility} = \frac{\textbf{Tapped density} - \textbf{Bulk density}}{\textbf{Bulk density}} \times 100$$

Table no.3 Carr's Index as an Indication of Powder Flow

Sr .No.	Carr's index (%)	Type of flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-35	Poor
5	33-38	Very poor
6	> 40	Extremely poor

5) Hausner's ratio

Hausner's found that the ratio tapped density/bulk density was related to inter particle friction and could be used to predict powder flow properties. He showed that the powder with low inter particle friction had ratio of approximately 1.2, whereas, more cohesive and less free flowing powders have Hausner's ratio greater than 1.6. Hausner's ratio less than 1.25 indicate good flow (Aulton 2002).

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

2.5 Differential scanning calorimetry (DSC)[6,9]

DSC was performed in order to assess the thermotropic properties and thermal behavior of the drug (Carvedilol) . The DSC study was carried out Shimadzu differential scanning calorimeter MettlerIndia Pvt. Ltd., Switzerland, by using aluminium crucible 40 mL at 10 ºC /min heating rate, under nitrogen environment. The temperature range used was 0–300ºC.

Differential scanning calorimetry (DSC) of physical mixture

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. Figure.2 illustrates DSC profiles of physical mixture (carvedilol and excipients.).

2.6 X-ray diffractometery (XRD)

It has been shown that polymorphic changes of the drug are important factors, which may affectthe drug dissolution rate and bioavailability. [7] It is therefore important to study thepolymorphic changes of the drug

2.7 IR spectroscopy[2,7,10]

IR study was carried out to check compatibility between drug and excipients.IR spectra of carvedilol, Avicel, Aerosil, PEG, crospovidone and final liquisolid formulation was determined by Fourier Transform Infrared spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. The method used was Diffused Reflectance Spectroscopy (DRS). Then the IR spectrum was taken by FT-IR spectrophotometer (Indian Pharmacopoeia, 2007).

2.8*In vitro* Drug Release[10,11]

Dissolution Study

In vitro drug release studies of the prepared matrix tablets were conducted for a period of 12 hours by using an USP Type II (Paddle) Dissolution apparatus (Electrolab TDT 08L, India) at 37± 0.5° C. The agitation speed was 50 rpm. The dissolution study was carried out in 900 ml 0.1 N hydrochloric acid at 37±0.5 ºC for first 2 hours and then in 900 ml of phosphate buffer (pH 6.8) up to 10 hours. 5 ml of the sample was withdrawn at regular intervals and the same volume of fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a whatmmam filter no.1 and the drug content in each sample was analyzed with UV spectrophotometer. The amount of drug present in the

samples were calculated with the help of calibration curve constructed from reference standard.

2.9Statistical analysis[5,6,8]

All the datawere statistically analyzed by analysis of variance or Tukey's multiple comparison test. Results are quoted as significant where $p < 0.05$.this analysis made bye the design expert 7.0 software.

3 RESULT AND DISCUSSION

Table no.4 Pre compression studies of the liquisolid powder systems

Formulation No.	Average Angle of repose (q) ± SD	Average Carr's index ± SD	Average Hausner's ratio ± SD	Friability
F1	28.81±0.887	7.69±0.809	1.08±0.0126	0.26
F2	31.38±0.886	4.21±1.452	1.04±0.0213	0.29
F3	28.94±0.069	1.92±1.602	1.01±0.0227	0.31
F4	28.81±0.11	8.1±0.639	1.08±0.008	0.21
F5	30.96±0.127	5.88±1.618	1.06±0.002	0.25
F6	31.42±0.184	8.1±0.344	1.07±0.004	0.29
F7	30.46±0.360	7.84±1.939	1.08±0.025	0.24
F8	31.86±0.207	5.21±1.136	1.10±0.014	0.36
F9	30.06±0.201	2.8±1.123	1.01±0.013	0.31

3.2 Differential scanning calorimetry (DSC) of drug carvedilol[6,9,10]

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 aluminiumpansby using aluminium crucible 40 mL at 10 ºC /min heating rate, under nitrogen environment. The temperature range used was 0–300ºC.

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. Figure.1 illustrates DSC.

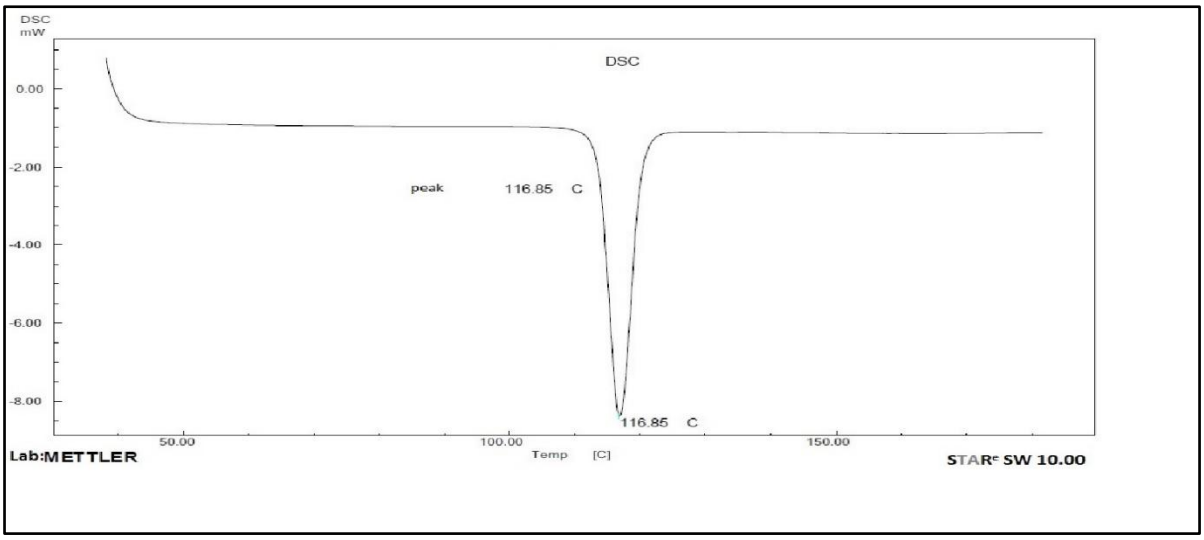

Fig no 1. Differential scanning calorimetry (DSC) of drug carvedilol

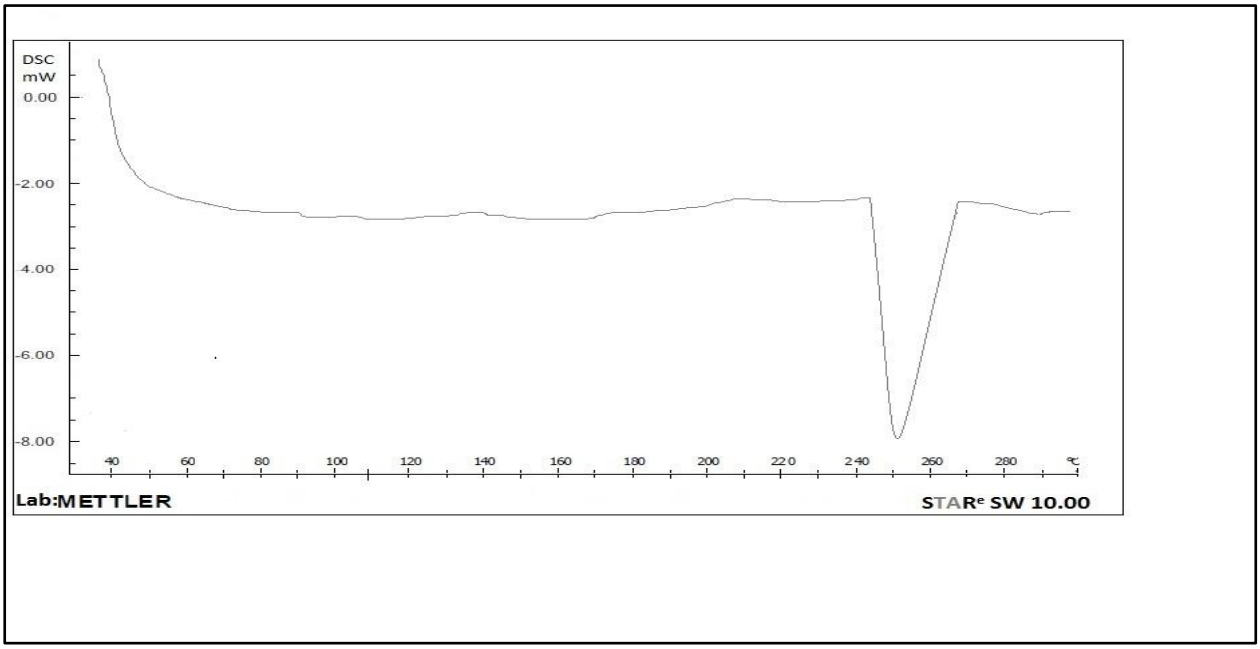

Fig no2.Differential scanning calorimetry (DSC) of physical mixture

3.3 X-ray diffractometery (XRD)

. For characterization of crystalline state, the X-ray diffraction(XRD) patterns for Carvedilol, physical mixture of Carvedilol.Avicel 102, Aerosil 200 and the liquisolid system prepared were determined using X-ray diffractometer with a coppertarget, at a voltage of 40 kV and current of 20MA. The rate of the scanning was 0.30°C /min.

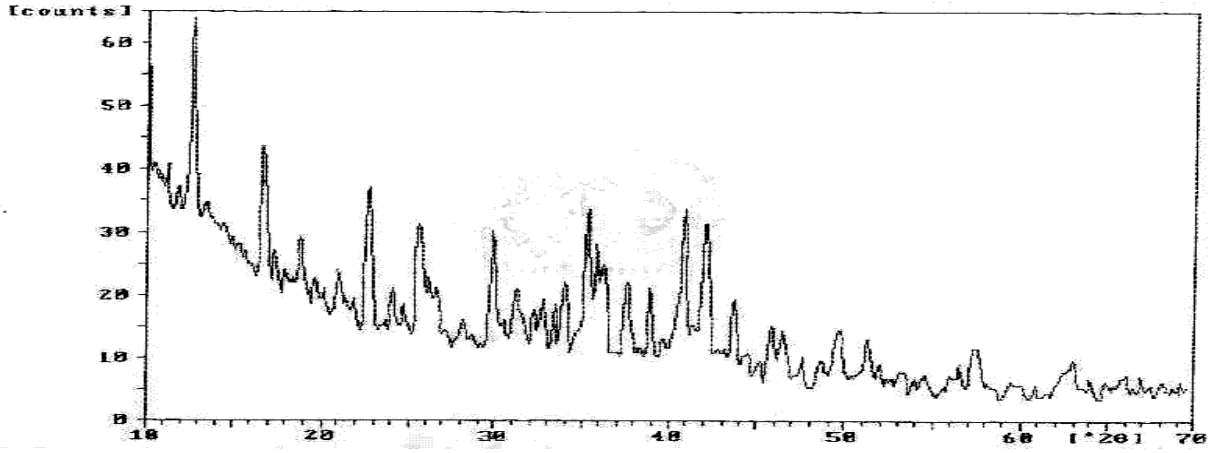

Fig no. 3: X-ray diffractogram of Carvedilol

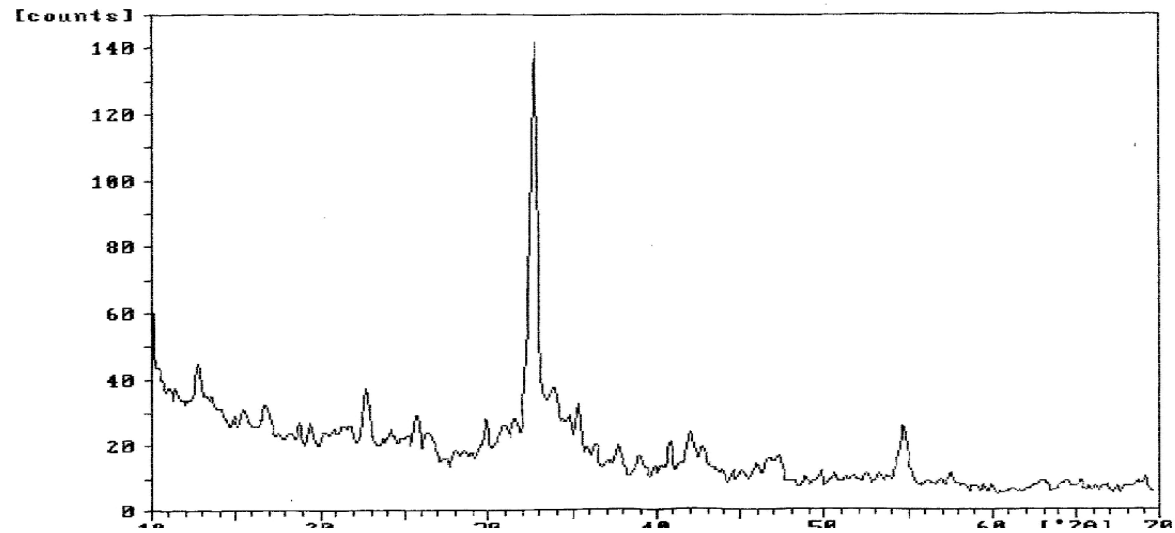

Fig no. 4 : X-ray diffractogram of Carvedilol, Avicel PH 102,Aerosil200(physical mixture)

3.4FT-IR Spectroscopy of Drug

Characterization of Carvedilol by FT-IR spectroscopy

Infra- red spectrum of Carvedilol shown in Fig.7. The major peaks observed and corresponding functional groups are given Table no. 5 Infra-red spectrum shows peak characteristic of structure of Carvedilol.

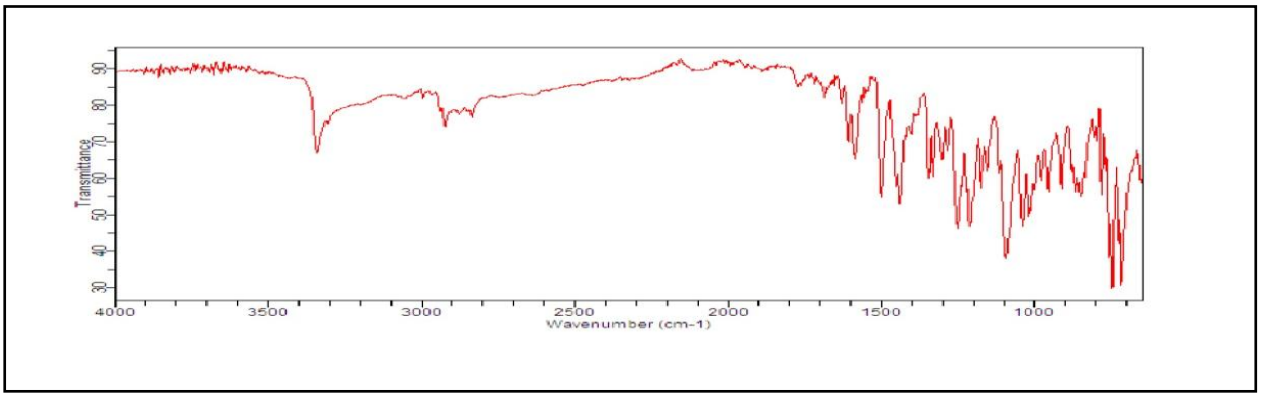

Fig.no 5FT-IR spectra of Carvedilol

Table no.5 Interpretation of FT-IR Spectra of Carvedilol

Sr. No	Functional Group	Standard frequency (cm-1)	Observed IR frequency (cm-1)
1	C-H aromatic	3100-3000	3057.49
2	C-C Stretch (in ring)	1600-1585	1586.38
3	N-H Bending	1650-1500	1500.38
4	C-O Stretch	1320-1000	1250.68
5	C-H Stretch of alkane	3000-2850	2923.28
6	C-H Stretch of aromatic	3100-3000	3057.49
7	-C=C- Stretch	1690-1640	1685.71
8	N-H stretch	3400-3250	3342.07

The IR spectra of carvedilol was recorded and analysed for the functional groups and the observed peaks comply with reported literature (Indian Pharmacopoeia, 2007).

IR Characterization of Polymers

Characterization of drug and polymer (FT-IR)

FTIR spectra of the samples were obtained in the range of 400 to 4000 cm^{-1} using FT-IR spectrophotometer by the KBr disc method. The FT-IR spectrum of polymer is shown in fig.4

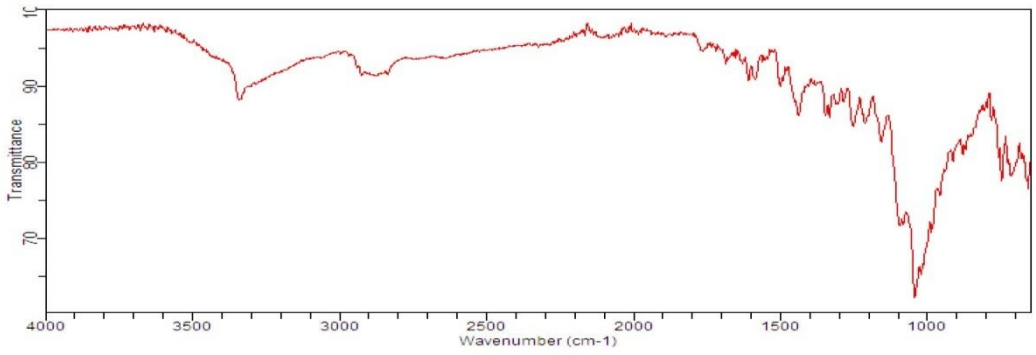

Fig no. 6 FT-IR spectra of mixture (drug and polymers)

Table no.6 Interpretation of FT-IR Spectra of (drug and polymers)

Sr. No	Functional Group	Standard frequency (cm-1)	Observed IR frequency (cm-1)
1	N-H stretch	3350-3310	3342.45
2	C=C Stretch (in ring)	2140-2100	2107.63
3	C=O stretch of carboxylic acid	1765-1755	1762.49
4	C-C Stretch aromatic	1500-1400	1500.47
5	C-C Stretch aromatic	1500-1400	1438.60
6	N-O stretch symm	1360-1290	1347.14
7	C-O- Stretch of carboxylic acid	1320-1000	1251.88
8	C-O stretch of ester	1150-1070	1094.05
9	C-H stretch out of plane	885-870	880.63
10	C-H stretch out of plane	885-870	715.70

Interpretation

The FT-IR spectra of mixture containing carvedilol, avicel, aerosol, Peg400,HPMC and crospovidone was recorded and analyzed for the observed peaks and the functional groups assigned to them.

3.5Preformulation Studies of Formulation

Powder flow is a complicated matter and was influenced by so many interrelated factors; the factors list is long and includes physical, mechanical as well as environmental factors. Therefore, determination of angle of repose, Carr's index, Hausener's ratio is important before formulation because it influenced compressibility, tablet porosity and dissolution.

The effect of liquid load factor (L_f), which is a ratio of mass of liquid (PEG400) added to the mass of Avicel PH 102 on flowability and compressibility of the final admixture of the powder is shown in table 19. Increasing the L_f value in the range of 0.031 to 0.032 i.e. increasing the volume of liquid vehicle 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. It also resulted in a decrease in the compressibility of final admixture.

3.6 Evaluation of liquisolid compacts[10,11]

3.6.1.Tablet dimensions

Thickness of liquisolid compacts ranged from 4.77 ±0.02 to 5.13 ±0.01 mm and diameter of all the liquisolid compacts was found to be 8.78 ± 0.0 to 8.80 ± 0.23 mm.

3.6.2.Hardness:

Formulation should be directed at optimizing tablet hardness without applying excessive pressure, while at the same time assuring rapid tablet disintegration.

Hardness was found to be in the range of 3.5±0.51 kg/cm^2 to 3.83±0.76 kg/cm^2. It is seen that as the amount of Avicel goes on increasing, hardness also increases.

3.6.3.Weight variation test

Weight variation test revealed that the tablets were within the range of Pharmacopoeial specifications. All the formulations passes weight variation test.

TableNo.7 Evaluation of liquisolid compacts

Formulation No.	Thickness (mm)	Hardness (kg/cm^2)	Weight Variation (mg)
F1	4.86±0.02	3.7±0.51	284.81±0.57
F2	4.96±0.04	3.5±0.57	297.67±1.52
F3	5.04±0.06	3.7±0.57	310.27±1.15
F4	4.79±0.02	3.7±0.50	284.81±1.15
F5	4.82±0.19	3.7±0.28	297.67±1.15
F6	5.13±0.11	3.8±0.50	310.27±2.08
F7	4.77±0.02	3.7±0.35	284.81±2.08
F8	4.85±0.20	3.6±0.76	297.67±3.60
F9	4.83±0.02	3.8±0.32	310.27±1.32

3.6.4. Friability

All the liquisolid compacts had acceptable friability as none of the tested formulae had percentage loss in tablet's weights that exceed 1%. Friability below 1% is an indication of good mechanical resistance of the tablets.This ensures that tablets could withstand to the pressure, shocks during handling, transportation and manufacturing processes.

Table No.8 Evaluation of liquisolid compacts

Formulation No.	Average Angle of repose (q) ± SD	Average Carr's index ± SD	Average Hausner's ratio ± SD	Friability
F1	28.81±0.887	7.69±0.809	1.08±0.0126	0.26
F2	31.38±0.886	4.21±1.452	1.04±0.0213	0.29
F3	28.94±0.069	1.92±1.602	1.01±0.0227	0.31
F4	28.81±0.11	8.1±0.639	1.08±0.008	0.21
F5	30.96±0.127	5.88±1.618	1.06±0.002	0.25
F6	31.42±0.184	8.1±0.344	1.07±0.004	0.29
F7	30.46±0.360	7.84±1.939	1.08±0.025	0.24
F8	31.86±0.207	5.21±1.136	1.10±0.014	0.36
F9	30.06±0.201	2.8±1.123	1.01±0.013	0.31

3.7 Drug content:[1,5]

A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual tablets. Uniform drug content was observed for all the formulations (87.15±0.48% to 97.69±0.68%), which is as per the IP specification (85%-110%).

Table No 9.Evaluation of Post Compression Parameter of Tablet

Formulation No.	Friability (%)	% Drug Content
F1	0.754±0.05	96.15±0.58
F2	0.641±0.17	88.4±0.64
F3	0.743±0.02	87.71±0.48
F4	0.667±0.03	88.22±0.44
F5	0.709±0.02	89.52±0.68
F6	0.742±0.02	97.69±0.54
F7	0.756±0.04	97.57 ±0.58
F8	0.763±0.09	94.02±0.62
F9	0.756±0.06	96.40±0.32

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

3.8*In-vitro* drug release[3,5,6]

The results of *In-vitro* percentage amount of drug released at different time intervals plotted against time to obtain the release profiles.

All the liquisolid compacts showed higher drug release than the pure drug. The result shows that there was significant difference ($P < 0.0001$) between the release profile of the pure drug and all the liquisolid compacts.

Table No.10The*In-vitro* Dissolution Data of Tablets for Formulations F1-F9

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	11.41 ±2.41	11.95 ±0.13	10.32 ±3.18	16.84 ±3.11	20.10 ±2.79	17.93 ±1.18	39.66 ±1.70	10.32 ±0.39	14.67 ±0.39
2	13.16 ±3.89	13.17 ±2.01	10.98 ±2.82	21.37 ±2.06	20.32 ±2.23	26.28 ±3.58	42.82 ±1.67	13.69 ±0.08	15.92 ±0.08
3	17.11 ±2.59	19.84 ±2.38	12.19 ±2.45	28.13 ±5.12	23.81 ±5.10	29.83 ±2.36	41.12 ±3.86	17.11 ±1.42	17.18 ±1.42
4	26.54 ±0.03	22.77 ±1.65	13.40 ±0.47	38.22 ±2.83	44.72 ±02.4	37.76 ±2.46	43.74 ±0.86	20.55 ±0.22	24.97 ±0.22
5	30.09 ±0.06	26.82 ±1.43	14.64 ±0.26	39.72 ±1.27	46.84 ±0.72	39.80 ±1.66	45.84 ±2.01	24.58 ±0.44	28.51 ±0.44
6	34.22 ±0.72	31.46 ±0.15	21.86 ±0.73	47.76 ±0.9	48.43 ±1.13	46.75 ±0.04	47.42 ±0.61	37.89 ±0.77	30.44 ±0.77
7	38.26 ±0.32	34.38 ±0.23	23.61 ±0.35	55.69 ±0.63	49.81 ±0.64	55.75 ±0.42	48.02 ±0.43	55.03 ±0.34	37.13 ±0.36
8	44.51 ±0.21	38.41 ±0.54	24.83 ±0.32	57.69 ±0.25	51.21 ±0.36	61.49 ±0.32	50.77 ±0.34	58.74 ±0.21	40.61 ±0.12
9	47.51 ±0.65	40.77 ±0.24	27.13 ±0.24	61.80 ±0.24	57.47 ±0.69	67.26 ±0.62	56.84 ±0.21	62.44 ±0.12	45.75 ±0.62
10	49.90 ±.23	43.68 ±0.43	28.91 ±0.26	63.67 ±.65	59.22 ±0.12	70.28 ±0.41	59.69 ±0.34	66.15 ±0.34	55.75 ±0.29
11	51.74 ±0.15	44.40 ±0.54	33.41 ±0.36	66.09 ±0.32	60.43 ±0.13	72.77 ±0.31	61.51 ±0.12	68.76 ±0.31	57.67 ±0.18
12	53.01 ±.25	50.51 ±0.32	42.77 ±0.64	67.91 ±0.35	61.63 ±0.41	74.68 ±0.42	63.25 ±0.63	70.72 ±0.23	66.13 ±0.27

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

3.9Effect of Carrier: Coat Ratio (R) on Dissolution:[2,7,8]

Release profile indicates the effect of carrier to coat concentration ratio (R) on the drug dissolution rate. As it can be seen, increase in the R-value shown improved dissolution.

According to "diffusion layer model" of dissolution, dissolution rate is in proportion to concentration gradient in stagnant diffusion layer. Drug dissolution is directly proportional to surface area available for dissolution i.e. effective surface area. The liquid medication was adsorbed and absorbed over the surface of hydrophilic carrier; effective surface available for mass transfer of drug molecules was tremendously increased. During the mass transfer process, as the drug was molecularly dispersed in the non-volatile solvent, the transfer of drug in the aqueous phase occurs as a separate molecular entity. Thus, the rate of drug dissolution is highly increased. If the carrier to coat ratio is increased, the surface area responsible for dissolution is also increased. Thus R-value imparted a positive effect on the dissolution rate of carvedilol.

Another mechanism thought for the positive effect of R-value on dissolution might be decreased amount of coat material. The coat material, Aerosil was used to enhance the flow characteristics of the blend. But due to the hydrophobic characteristics, it given a negative effect on the wettability of the formulation. Hence the contact area of liquid medication was decreased resulting in poor solubilization. Increased R-value resulted in decrease in the percentage of Aerosil used in the formulation, thus the wettability was minimally affected.

As formulation f_1 contains the minimum amount of aerosil 200 and constant amount of Avicel PH102 that was it have low R value due to which dissolution is retarded and f_6 formulation contain maximum amount of the Aerosil 200 and constant amount of Avicel PH102 that was it have high R value due to which dissolution is accelerated.

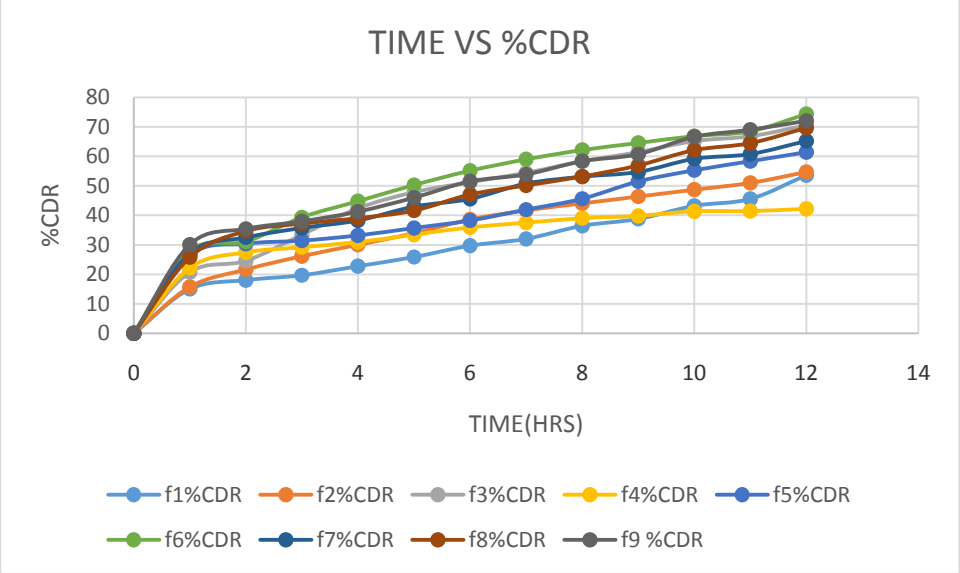

Fig no.7 % CDR Vs Time

3.10The *In-vitro* Dissolution Data of formulations F_6 and matrix tablet comparision

Table No 11. The *In-vitro* Dissolution Data of Tablets of formulations F_6 and matrix tablet

TIME (HRS)	(% Cumulative drug release)	
	F6	matrix tablet
0	0	0
1	17.93 ±1.18	22.20±0.21
2	26.28 ±3.58	26.75±0.34
3	29.83 ±2.36	30.63±0.25
4	37.76 ±2.46	35.98±0.21
5	39.80 ±1.66	39.95±0.11
6	46.75 ±0.04	42.53±0.32
7	55.75 ±0.42	44.17±0.33
8	61.49 ±0.32	45.77±0.41
9	67.26 ±0.62	48.79±0.62
10	70.28 ±0.41	53.22±0.63
11	72.77 ±0.31	56.93±0.34
12	74.68 ±0.42	59.23±0.31

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

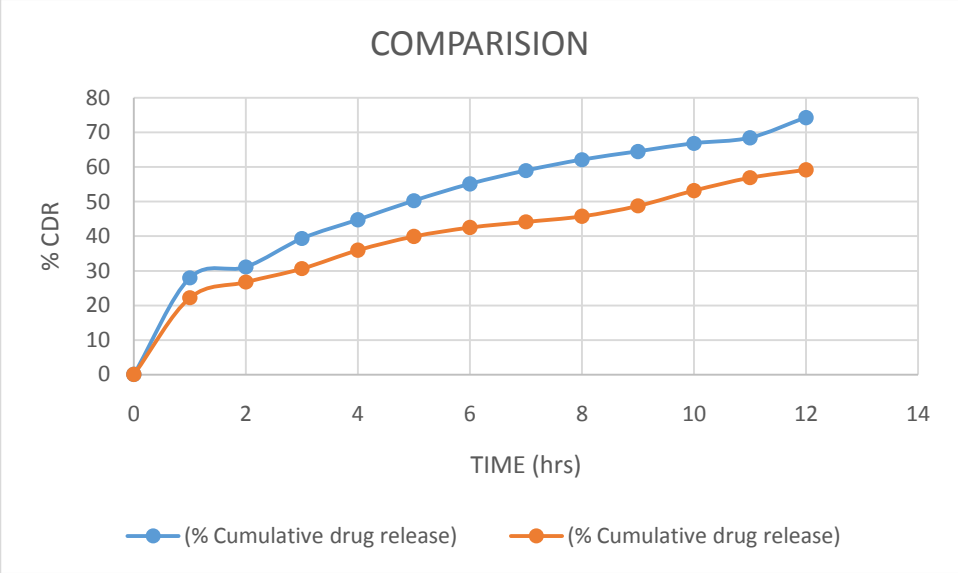

Fig no.8 The *In-vitro* Dissolution Data of Tablets of formulations F_6 and matrix tablet

3.11 Similarity Factor (*f*2) and Difference Factor (*f*1) study:[2,9,10]

Carvedilol Liquisolid formulations were compared with the Carvedilol matrix tablet formulation. FDA and the European Agency for the Evaluation of Medicinal Product, suggest that two dissolution profiles are declared similar if $f_2$valueis between 50 and 100 and f_1 value is between 0 to15. Results are shown in Table No.12.

Table No. 12: *f* 1 and *f* 2 values for all formulations

Sr. No.	Batch Code	Difference factor *f*1	Similarity factor *f*2
1	F1	24.67	74.63
2	F2	10.46	88.88
3	F3	18.01	77.73
4	F4	16.88	78.12
5	F5	0.68	94.36
6	F6	27.19	72.19
7	F7	11.92	87.16
8	F8	14.95	83.03
9	F9	23.05	75.75

From the above data it can concluded that liquisolid formulations F4 & F1show relatively similar result as that matrix tablet. They show same drug release as that of matrix tablet drug release. But other formulation also shows same drug release. It shows that similar release profile was found as compared to matrix tablet formulation

3.12 Model Assessment For The Dependent Variables[3,4]

The purpose of using 3^2 full factorial designs was to conduct comprehensive study of effect of process parameters like carrier: PEG 400 concentration (X_1) and coating material ratio i.e. R value (X_2) and their interactions using a suitable statistical tool (Design expert software version 7.1.5) by applying one way ANNOVA at 0.05 levels. Mathematical modelling was carried out. Polynomial equation was obtained depending on significant influences among 2 factors on their experimental design.

Table no 13: ANOVA for 2 hrs response

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	
Model	280.59	2	140.30	76.79	<0.0001	significant
A-PEG 400 conc	31.88	1	31.88	17.45	0.0058	
B-R value	248.71	1	248.71	136.14	<0.0001	
Residual	10.96	6	1.83			
Cor Total	291.55	8				

A) Model for Y_1:

After putting the data in Design Expert software (version 7.1.5), Fit summary applied to data in that, quadratic model had been suggested by the software so as per this model the equation is as follows: Model equation in coded term

$$Y_1 = +4.54+0.23050* A+1.2879* B+0.296* A * B$$

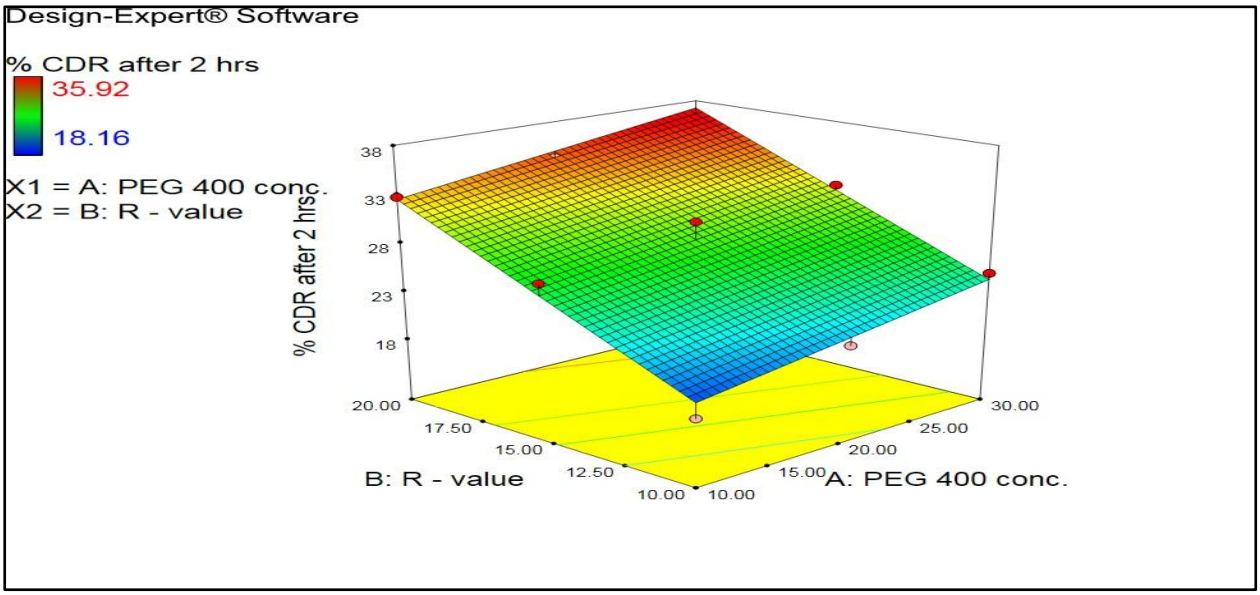

Fig no.9 Surface response plot showing effect of Carrier: PEG 400 conc. and Coating ratio (R value) on % CDR after 2hrs

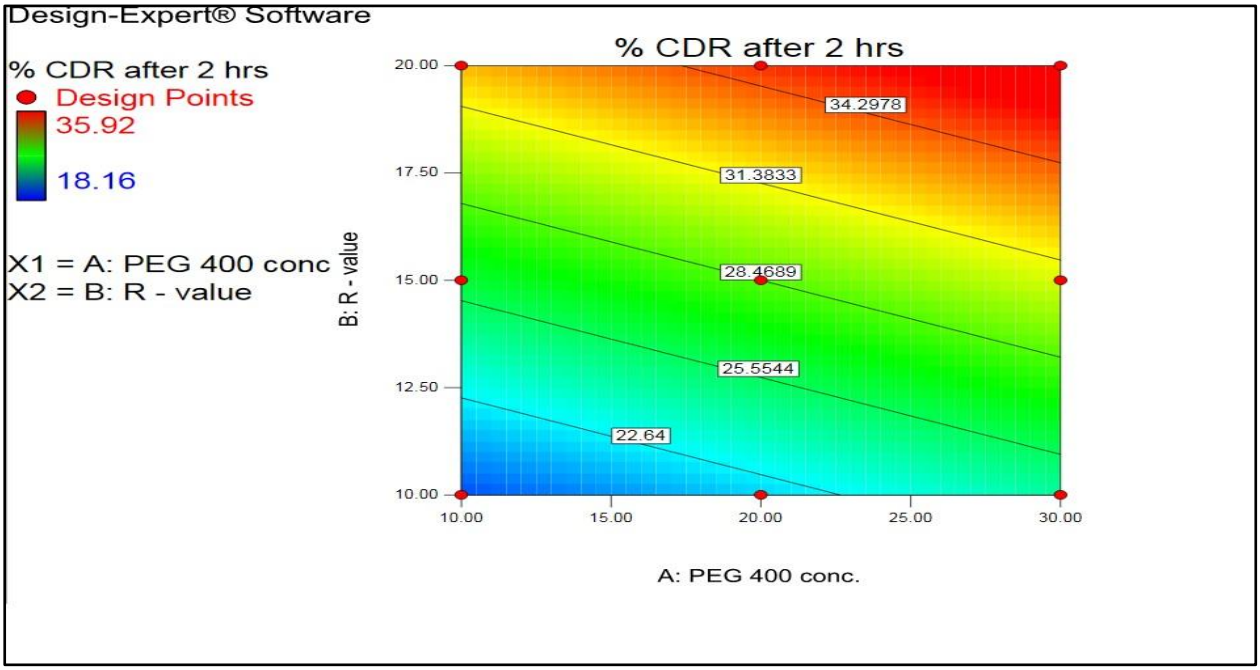

Fig no.10: counter plot showing effect of Carrier: PEG 400 conc. and Coating ratio (R value)on % CDR after 2hrs

Table no 14: ANOVA for 2 hrs response

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	
Model	588.82	2	294.41	6.61	0.0304	significant
A-PEG 400 conc	529.97	1	529.97	11.91	0.0136	
B-R value	58.84	1	58.84	1.32	0.2940	
Residual	267.5	6	44.51			
Cor Total	885.86	8				

B) Model for Y_2:

After putting the data in Design Expert software, Fit summary applied to data in that, Linear model had been suggested by the software so as per this model the equation is as follows.

Model equation in coded term,

Y_2=+33.42+0.93*A-0.63* B

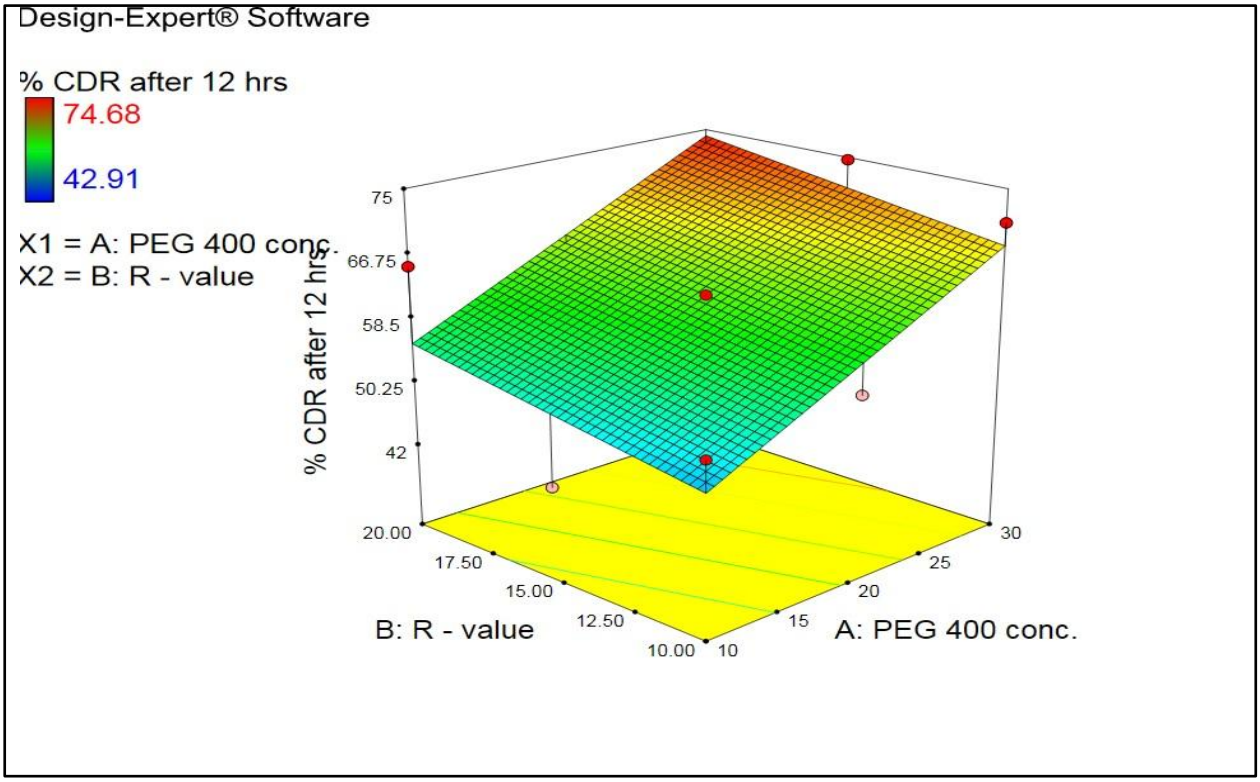

Fig no.11Surface response plot showing effect of Carrier: PEG 400 conc. and Coating ratio (R value) on % CDR after 12hrs

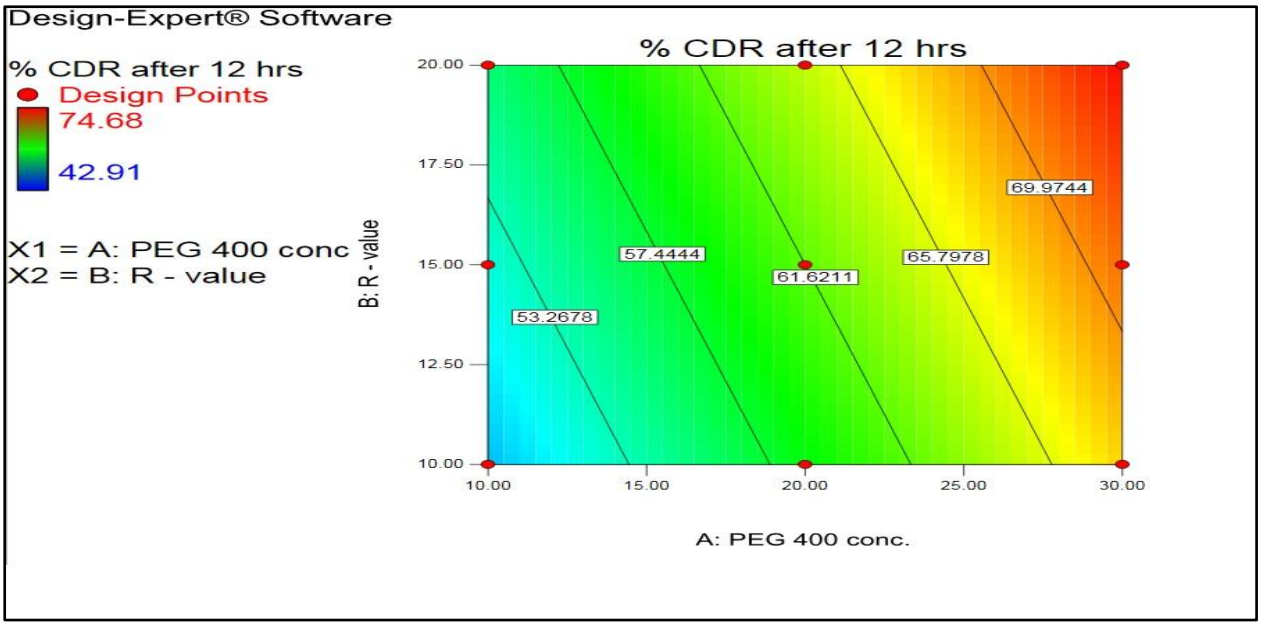

Fig no.12: counter plot showing effect of Carrier: PEG 400 conc. and Coating ratio (R value)on % CDR after 12hrs

3.13 Stability Study:[2,6]

Short term accelerated stability study was performed at 40^0C and 75 % RH for 3 months. After the period of 3 months the Liquisolid formulation was tested for its physical appearance, drug content and drug release. Results are shown in following table.

Table no.15Stability study of Liquisolid formulation

Formulation	Appearance	% drug content	% drug release
F8	White	97.69±0.85	74.33±0.56

From the study, it was observed that the stored tablet had good physical appearance. Also the percentage drug content and percentage drug release which was found 97.69 and 74.33% respectively. Suggesting that there was no significant difference before and after stability study. This confirmed the prepared tablets were stable for the stored period.

4. CONCLUSIONS

The present work showed that liquisolid compacts techniquecan be effectively used for preparation of sustained release(SR) matrix tablets of poorly water soluble drug carvedilol along with PEG 400 was used as liquid vehicle. Drug release profileson model fitting follow zero order model as the best fit model, which indicates carvediol released from this tablet follows sustained release profile. From the above study, we may also infer that microcrystalline cellulose (avicel), along with Aerosil as coating material provided better SR of carvedilol.

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