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Development And Evaluation of Liquisolid Compacts of Anti-Hypertensive Drug.

Sachin Sanap, Research Scholar, SunRise University, Alwar, Rajasthan
Pramod Burakle, Professor, SunRise University, Alwar, Rajasthan, India.

Abstract

The solubility of Carvedilol, a poorly water-soluble drug widely used in cardiovascular disorders, presents a significant challenge in achieving optimal therapeutic efficacy. This research aimed to enhance the solubility and dissolution rate of Carvedilol through the application of the liquisolid compact technique. Different Liquisolid compacts were prepared using required quantities of powder and liquid ingredients to produce acceptably flowable and compressible admixture. Avicel PH 102, PEG, Crosspovidone 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 Fourier Transform Infrared spectroscopy (FT-IR)differential scanning calorimetry (DSC) and Xray 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 F3 of Liquisolid powder system showed acceptable flowability, Carr's compressibility index and Hausner's ratio. The FTIR, DSC and XRD studies conforms the no significant interaction between the drug and excipients used in Liquisolid compacts. Hence it concludes that the Liquisolid technique is a promising alternative for improvement of dissolution of Carvedilol.

Keywords: carvedilol, Liquisolid compacts, Dissolution, Solubility, disintegrants

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 compactss' 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] 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. .[6-7]

MATERIALS AND METHODS

Materials

Carvedilol was provided by Cipla Ltd. Mumbai, Polyethylene Glycol (PEG-400),Microcrystalline Cellulose 200 (Avicel® PH 200),) (Research Lab Fine Chem Industries Mumbai), SSG and CP (HPMC) (Loba Chemi Pvt. Ltd. Mumbai) were used.

Preformulation studies The process of Drug Identification and Melting Point determination was conducted and compared with the standard parameters outlined in the monograph.[8] Melting Point was measured using the capillary tube method. Fourier transform infrared spectroscopy (FT-IR) spectra were analysed to investigate the possibility of any interaction or complexation between Carvedilol and the excipients employed in the formulation of the liquisolid compact, as well as with the excipients used in the tablets. For this analysis, all the samples were finely ground and thoroughly mixed with potassium bromide in a weight ratio of 1:5 (sample: potassium bromide). The resulting spectra were recorded within the wave number range of 4000-400 /cm using an FT-IR Shimadzu 8300 from Japan.

Solubility studies To conduct solubility studies, a saturated solution of the drug was prepared in various solvents such as Poly ethylene glycol 400 (PEG 400), Propylene glycol (PG), Glycerol and Polysorbate 80 by adding an excess amount of the drug to each solvent. The mixtures were shaken using an orbital shaker for a specific duration and left undisturbed for 48 hours. Subsequently, the solutions were filtered using filter paper to eliminate any excess drug content. Next, the solution was appropriately diluted and analyzed using a UV spectrophotometer at a wavelength of 273 nm to determine the drug concentration.

Formulation of Liquisolid tablets:

A drug was initially dissolved in the suitable non volatile solvent system (Propylene glycol) having different drug solvent ratios. Then a suitable carrier material (microcrystalline Cellulose) was added in the above liquid preparation and triturated in the mortar. To the above blend suitable coating material (silica) was added to get fine absorptive particle.To the above mixture suitable superdisintegrants like sodium Starch Glycolate, crosspovidone, was added in the prepared mixture with continuous stirring in the mortar. The remaining additives like magnesium Stearate and talc was added and mix well.Then the dump mass was passed through the sieve no 20 to obtain Granules. These granules were dried at 60°C for 1 hour. After the drying of granules they were compressed by tablet punching machine.[9]

Evaluation of Liquisolid powder system:[10]

Precompressional evaluation

Bulk density:

Bulk density was determined by USP method. A quantity of powder blend from each formulation was introduced into 250 ml measuring cylinder. Then the volume of powder measured directly from the graduation marks on the measuring cylinder as ml. The volume measured was called as bulk volume and the bulk density was calculated by following formula:

Bulk density = weight of the powder / bulk volume

Tapped density

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume wasnoted as Va and again tapped for 750 times and the volume was noted as Vb. If the difference between Va and Vb not greater than 2% then Vb is considered as final tapped volume and the tapped density was calculated by following formula:

Tapped density = weight of the blend / final volume

Angle of Repose:

Angle of repose has been used as indirect method for quantifying powder flowability. Angle of repose for the blend of each liquisolid formulation was determined by fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The height and radius of the powder cone was measured at five different points and average was taken for calculating the angle of repose by using following formula. tan **θ = h/r**

θ = tan-1 h/r

Where = angle of repose, h = Height of the heap, r = Radius of the heap.

Carr's Index:

It is used to evaluate flowability of liquisolid powder by comparing the bulk density and tapped density of a liquisolid powder. The percentage compressibility of the Liquisolid powder was calculated by using following formula:

Carr's index = Tapped density-Bulk density/Tapped density X 100.

Postcompressional evaluation

Tablet dimensions:[11]

The thickness and diameter of prepared tablet from each liquisolid formulation were measured by using vernier caliper. Three tablets from each formulation were used and average values were calculated.

Tablet hardness:

Tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing. The hardness of the Liquisolid compacts prepared was evaluated using Monsanto hardness tester. It is expressed in Newton (N). The mean of the hardnessof each formulation was determined.

Weight variation test:

The weight of the liquisolid tablet was measured to ensure that the tablet contain proper amount ofthe drug. The test was performed as per Indian Pharmacopeia. Twenty liquisolid tablets of Carvedilol were selected randomly and weighed. Then average of the tablet was determined. The percentage weight variation of the individual tablet should fall within the specified limits. Not more than the two of the individual weights deviate from the average weight by more than5% percentage deviation.

Friability Test:

Tablet hardness is not an absolute indicator of tablet strength, since some formulations compressed into very hard tablets tend to capon attrition losing their crown portions. Therefore another measure of tablet strength is its friability which is often measured. Roche friabilitor was used for testing the friability using following procedure. Twenty tablets were selected and their aggregate weight was measured as initial weight. The tablets were kept in a drum in friabilitor apparatus and then rotated at 100 rpm and then tablets were removed. Any loose dust from the tablets was removed and accurate weight was taken. Finally the friability of each liquisolid formulation was calculated by following formula:

Drug Content Uniformity:

The amount of active pharmaceutical ingredient is determined by the method described in assay and it is calculated. Since active ingredient of present work is not official in any Pharmacopeia, the following method was used for determination of drug content. Ten tablets were weighed and finely powdered. The drug content was determined by dissolving powder equivalent to 10mg of Carvedilol in 10ml of methanol and filter it using 0.45 µm whatman filter paper, diluted with 1.2 PH HCL buffer and analyzed by UV Spectrophotometer at 264 nm against buffer as a blank.

Disintegration test:

For the tablets the first important step toward solution is the breakdown of the tablet into

smaller particles or granules known as disintegration. The Carvedilol compact tablet was kept in every tube of the basket in the assembly. Then the assembly was suspended in the liquid mediumin a suitable vessel preferably in 1000 ml beaker. The volume of the liquid medium was adjusted such that the wire mesh at its highest point is at least 25 mm below the surface of the liquid and it's lower point is at least 25 mm above the bottom of the beaker. A thermostatic arrangement was made for heating the liquid maintaining the temperature at37 ± 2°C. Assembly was suspended in beaker containing the 1000 ml of distilled water and the apparatus was operated for specified time. Then the assembly was removed from the liquid. The tablet passes the test if all of them have disintegrated. If1 or 2 tablets fail to disintegrate repeat the test for 12 additional tablets; not less than 16 of the total 18 tablets tested. Finally the disintegration time of tablets was observed.

In vitro drug release study:

The USP rotating paddle apparatus II was used for all the in vitro dissolution studies of liquisolid formulations. The dissolution medium consists of 900 ml of HCL buffer pH 1.2 with 5% SLS. The release was performed at,37 ± 2°Cat a rotation speed of 50 rpm. Sample (5ml) were withdrawn by using calibrated pipette at suitable time interval (5, 10, 15, 20, 25, 30, 45, 60, 90 and 120 minutes) and filtered through Whatman filter paper. Sink conditions were maintained throughout the study. The samples were analyzed at 273 nm by using UV visible spectrophotometer. The study was carriedout in triplicate.

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed using PerkinElmer 6000. Accurately weighed samples (about 2 mg) were placed in a sealed aluminium pans, under static air at a scan rate of 100C min-1 over a 25 to 2500 C temperature range. Indium oxide was placed in aluminium pans and used as a reference. The heat flows as a function of temperature is measured for the drug , carrier and liquisolid formulation.[12]

Powder X-ray diffraction spectroscopy (PXRD):

X-ray diffraction pattern of Valsartan and its various co-crystalsprepared with as coformer were obtained using the X-ray diffractometer (BRUKER D8 ADVANCE, Germany) at 40 kV, 30 mA and a scanning rate of 1^0 /min at the diffraction angle 2θ over the range of 10-60^0using Cu (as anode) radiation of wavelength 1.5406A^0[13]

Stability studies of Carvedilol Liquisolid compacts Tablet [16]

Short-term accelerated stability testing was carried out according to ICH guidelines considering 40±2 °C/75±5% relative humidity (RH) in a stability chamber for a period of 6 month. The Liquisolid compacts tablets of optimized formulation was subjected to stability chamber at a minimum of three-time points, including the initial, intermediate and final time points (e. g., 0, 3, and 6 month). At the end of 3rd and 6 month of the tablets exposed to stability chamber were again analyzed for their physical appearance, assay (%) and *in vitro* drug release profile.[14]

RESULT AND DISCUSSION:

Determination of melting point:

Melting point determination of the Carvedilol drug sample was done as it is the first indication of the purity of the sample and the result of melting point is as given in Table No1.

Table No. 1 : Melting point of Carvedilol.

Sr. No.	Melting point of	Observation/Result
1	Carvedilol	389°C
2	Carvedilol	390°C
3	Carvedilol	391°C
	Average	390°C

Solubility study of Carvedilol in different non volatile solvents:

The solubility of Carvedilol in propylene Glycol, PEG 400, Acetonitrile, PEG 200 is given in the table no. It is observed that, Carvedilol has the lowest solubility in PEG 400. Solubility was found to be increased when polar solvents such as PG were used. The solvent being employed, and consequently the intermolecular interactions between Carvedilol and the solvent, have a significant impact on the drug's solubility. As the polarity of solvents rises, so does the solubility of the medications. Solubility of the medications is therefore significantly influenced by the solvent's polarity. PG was chosen as a non-volatile solvent to prepare liquisolid compacts.

Table No. 6.2: Solubility data of Carvedilol.

Sr. No.	Solubility medium	Solubility (mg/ml)
1	Propylene Glycol	1.070 mg/ml
2	PEG 400	0.947 mg/ml
3	PEG 200	0.962 mg/ml
4	Tween 80	0.821 mg/ ml

Evaluation of Liquisolid tablets:

Precompressional evaluation:

The bulk powder's density, porosity, particle size, and shape all affect the flow property. An uneven powder flow from the hopper results in tablets with uneven weights. As a result, it is impossible to produce tablets with precise dose and content measurements. Therefore, prior to formulation, it is essential to determine the mass, tapped, angle of repose, Carr's index, and Hausner's ratio because they have an impact on compressibility, tablet porosity, and dissolving. In general, value of bulk density less than 1.2 g/cm^3 indicates good packing. The angleof repose greater than 40° has very poorflow properties whereas minimum angle close to 20° correspond to very excellent flow property. Powders showing Carr's index up to21 are considered of acceptable flow property and Hausner's ratio values less than 1.25indicate good flow properties. Formulation F3, F4, F8 and F9 were proven to be excellent flow properties according to angle of repose, Carr's index and Hausner's ratio. Formulation F1, F2 and F5 were proven to be acceptably flowing properties.

Table 2: Micromritic Properties of different liquisolid formulations.

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Carr's Index	Hausner's Ratio
F1	0.5980	0.7475	30.10	20.00	1.25
F2	0.5763	0.7044	30.18	18.18	1.22
F3	0.5215	0.5650	30.14	07.69	1.08
F4	0.6140	0.6822	30.31	10.00	1.11
F5	0.6420	0.8025	30.02	20.00	1.25
F6	0.5085	0.5933	30.14	14.28	1.16
F7	0.6977	0.7850	30.31	11.11	1.12
F8	0.4973	0.5738	29.98	13.33	1.15
F9	0.5178	0.6061	29.94	14.28	1.16

Post compressional evaluation:

6 Tablet dimensions:

The thickness of Carvedilol liquisolid tablet ranged from 2.11 to 2.31 mm anddiameter of all the Liquisolid tablets was found to be 8 mm. **Hardness:**

Ideally, tablet formulation should aim to maximize tablet hardness without using excessive compression force, while also ensuring quick tablet disintegration and medication dissolution. In other words, a tablet must be strong enough to not break when handled normally, yet soft enough to dissolve properly when swallowed. This

means the hardness of each liquisolid formulation was determined and presented in table 3.

Friability:

No tested formula showed a percentage loss in tablet weights that exceeded 1%, hence all liquid- solid compacts exhibited acceptable friability. (Table no.9.2.2) Friability below 1% is a sign of the tablets' strong mechanical resistance. As a result, tablets is ensured to be durable enough to endure pressure and shocks during handling, transit, and manufacturing operations.

Weight variation:

The tablets evaluated as under the range of Pharmacopoeial requirements based on weight variation. All formulas pass the test for weight variation.

Post compressional evaluation:

Tablet dimensions:

The thickness of Carvedilol liquisolid tablet ranged from 2.11 to 2.31 mm anddiameter of all the Liquisolid tablets was found to be 8 mm.

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6.5.3**Friability:**

No tested formula showed a percentage loss in tablet weights that exceeded 1%, hence all liquid- solid compacts exhibited acceptable friability. (Table no.9.2.2) Friability below 1% is a sign of the tablets' strong mechanical resistance. As a result, tablets is ensured to be durable enough to endure pressure and shocks during handling, transit, and manufacturing operations.

6.5.4 Weight variation:

The tablets evaluated as under the range of Pharmacopoeial requirements based on weight variation. All formulas pass the test for weight variation.

Table No. 3: Result of evaluation of liquisolid tablets.

Formulation Code	Tablet dimensions		Hardness	Friability (%)	Weight variation (g)
	Thickness (mm)	Diameter (mm)			
F1	2.11	7	7.33	0.4166	0.199
F2	2.22	7	7.63	0.3636	0.207
F3	1.94	7	6.89	0.3424	0.198
F4	1.84	7	8.35	0.7812	0.217
F5	1.83	7	8.56	0.3676	0.224
F6	2.27	7	5.34	0.3389	0.199
F7	2.15	7	8.23	0.3787	0.202
F8	2.31	7	9.22	0.6644	0.219
F9	2.33	7	7.50	0.5988	0.200

Drug content uniformity:

The necessity for a steady dosage of medicine between each tablet is a key need for all the pharmaceutical preparations. It was observed that formulae F3, F6, F5, F9 and F7 compiled with the test of Carvedilol content uniformity according to Indian Pharmacopeia specification (90% - 110%), having the average Carvedilol content of 92.97 %, 94.18 %, 92.31 %, 94.30 % and 95.94 % w/w respectively. In each of the

mentioned formula, no more than one tablet is outside this limit nor is one individual outside the limits of 90 – 110%.

Disintegration time:

The liquisolid tablet formulation disintegrated in 15 minutes, according to the Indian Pharmacopoeia's criteria for uncoated tablets, according to the results of the disintegration time test. The disintegration property of microcrystalline cellulose may aid in the breakdown of drugs and the disintegration of tablets. Delay in disintegration time is anticipated since the liquisolid formulation contains a non-volatile solvent serving as a binding agent. Because it can quickly absorb a lot of water when exposed to an aqueous environment, sodium starch glycolate is also used to speed up pill disintegration. Tablets break due to water absorption, hastening the disintegration process

In vitro dissolution study of carvedilol Liquisolid tablets:

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 tablets showed higher drug release than the marketed preparation. The enhanced dissolution rates of liquisolid tablets compared to marketed preparation

This occurs may be due to the drug is already in the PG solution, while at the same time it is carried by the powder particles (MCC and SiO2).Thus it's release is accelerated due to the addition of non volatile solvent. The dissolution rate enhance by PG by facilitating wetting of drug particles by decreasing interracial tension between dissolution medium and tablet surface.

FTIR Compatibility study: The drug, excipients and mixture of both were subjected to Fourier Transform Infrared (FTIR) studies to check drug- excipients interaction using FTIR (Shimadzu).The sample preparation involved mixing of sample with potassium bromide, triturating in mortar and finally placing in a sample holder. Figure no. 1 and 2 shows the Infrared spectra of Carvedilol, and Liquisolid compact of Carvedilol.

Fig. 1: IR spectrum of Carvedilol

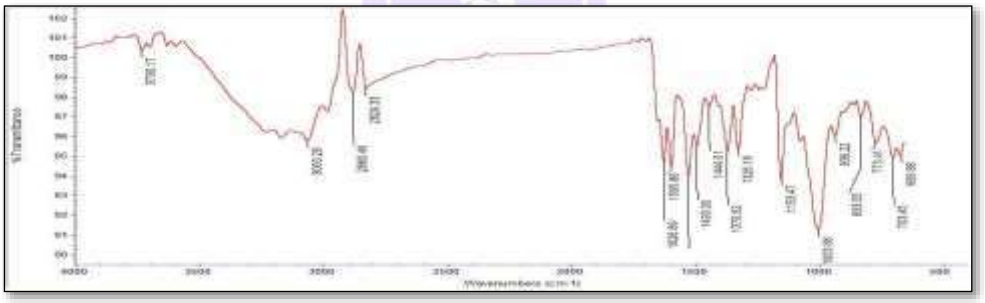
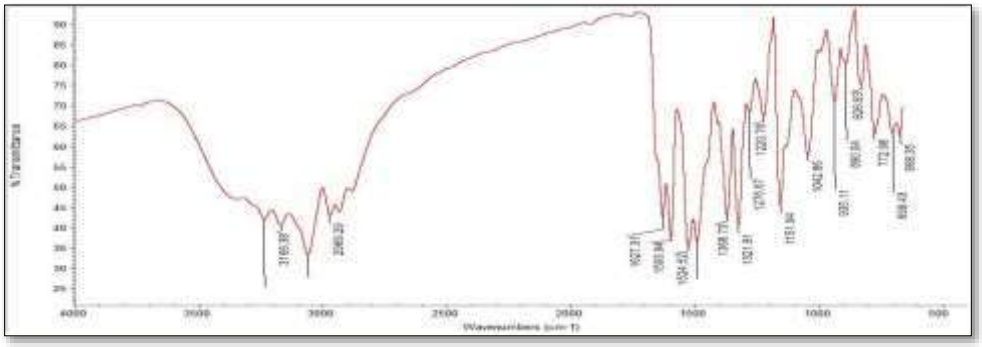


Fig. 2: FTIR Spectra of Liquisolid compact of Carvedilol



Differential Scanning Calorimetry:

The DSC studies were performed to understand the nature of drug in formulation. The thermo grams for pure Carvedilol were presented in figure 6.10. The pure drug showed a

melting endothermic peak at 95.5^{0}C, whereas thermo grams of optimized formulations did not show any significant shifts in endothermic peaks. The appearance of characteristics peaks of Carvedilo, correspond with formulation of drug solution in physical mixture due to the fact that drug is in a dissolved molecular state. Such appearance of drug peak upon the formulation of liquisolid system indicates that there is no interaction between the drug and excipients, The DSC graph F3 are shown in fig. 3 and 4.

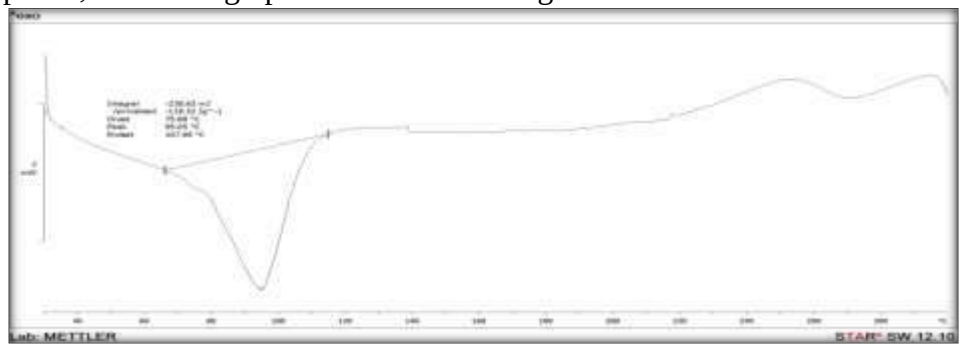


Fig. 3: DSC Spectra of Pure Carvedilol

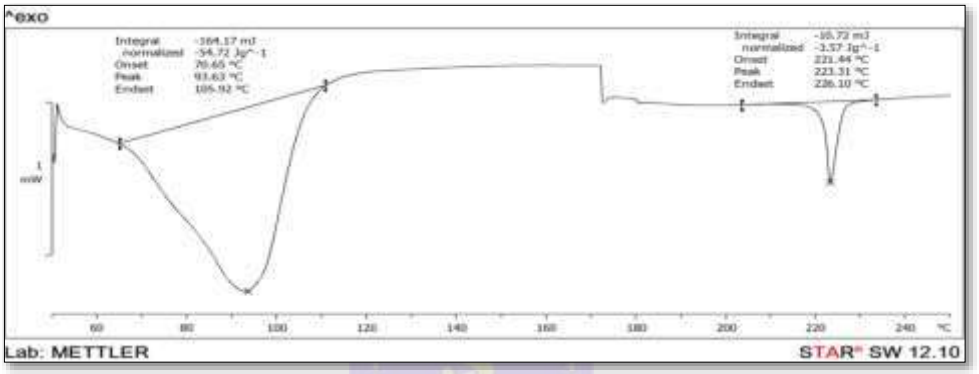


Fig. 4: DSC Spectra of Liquisolid compact of Carvedilol

X-ray powder diffraction:

X-ray diffractometry was conducted for the pure drug, mirtazapine, and for liquisolid compacts of mirtazapine. The diffractogram in Fig. 5 and 6 show some peaks that appeared at 9.54, 14.66, 20.24, 21.18, 22.38, 29.0, 30.52, 36.72, etc. The peaks supported the crystalline nature of the drug. The diffraction marks of the liquisolid compact showed less diffraction peak than that of pure carvedilol. That peak appeared to be due to the crystal state of Avicel PH 102, which was present in the liquisolid compacts. The X-ray diffractogram of liquisolid compact showed an absence of any specific peak. This confirmed the complete conversion of the drug from its crystal sate to an amorphous state. The drug was completely solubilized in liquid in the liquisolid compact, which caused no productive reflection in the diffractogram.

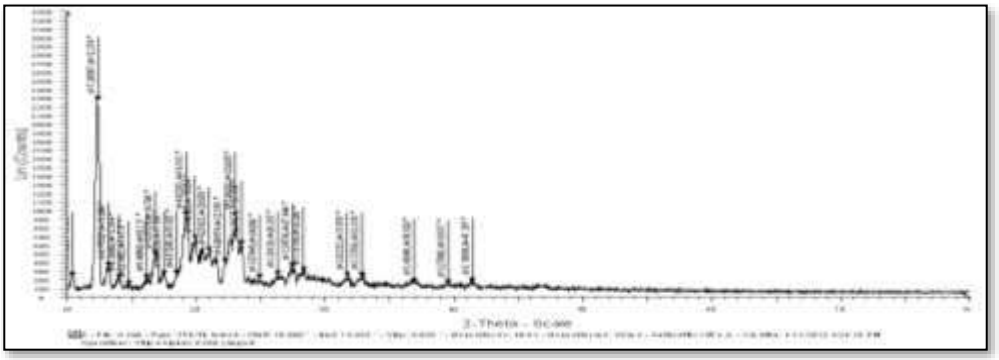


Fig. 5: XRD Spectra of Liquisolid compact of Carvedilol

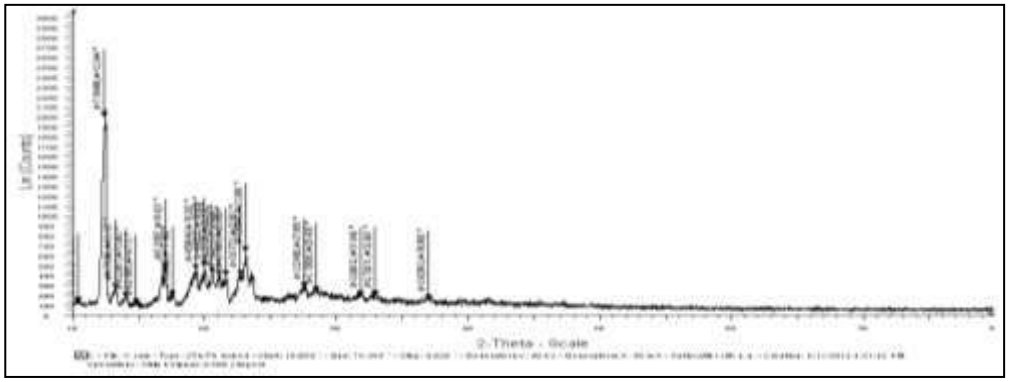


Fig. 6: XRD Spectra of Liquisolid compact of Carvedilol

Stability Study of Liquisolid compact of Carvedilol Tablet:

All the Tablets of Liquisolid compact of Carvedilol were screened for accelerated stability studies and showed slight physical changes during the study period. The drug content were observed (n=3) for Liquisolid compact (Table 6.10) which were quite stable at accelerated storage conditions. The stability of Cocrystals was proved by determining the percentage content under the above said accelerated storage condition. Values of all parameter slightly changes indicated that all the Liquisolid compact were stable without any alteration on the physical characters.

Table Accelerated stability Study for Carvediolol and Liquisolid compact of carvedilol Tablet

Evaluation Parameter	Before Stability Storage	After 3 month storage	After 6 month storage
Hardness (Kg/Cm^2)	6.89 ± 0.42	6.8±0.24	6.6±0.28
Friability (%)	0.34 ± 0.02	0.34±0.01	0.33±0.01
Drug Content (%)	93.57±0.70	93.10±0.50	93.00±0.60
Disintegration Time (Min.)	4.3	4.2	4.2
Drug Release (%)	93.93	92.00	90.00

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