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Enhancing Solubility of Carvedilol through Liquisolid Compact Technique: Formulation, Characterization and In Vitro Evaluation

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Ab**stract**

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. Liquisolid compacts were formulated by preparing a drug solution of Carvedilol in PEG with polysorbate 80 as the non-volatile solvent. Microcrystalline cellulose was selected as the carrier powder, while Aerosil served as the coating material. Various ratios of drug solution to carrier powder were investigated to optimize the formulation. The liquisolid compacts were compressed into tablets using a direct compression method. Characterization studies were performed to assess the physical properties and compatibility of the liquisolid compacts. Evaluation parameters included flow properties, compressibility, and compatibility studies using Fourier-transform infrared spectroscopy (FTIR). In vitro dissolution studies were conducted to determine the drug release profile for compact and tablet dosage forms. The results indicated that the liquisolid compacts exhibited good flow properties and compressibility, facilitating tablet formation. FTIR analysis revealed no significant interactions between Carvedilol and the excipients used. The enhanced solubility and dissolution rate of Carvedilol achieved through the liquisolid compact technique can potentially lead to improved bioavailability and therapeutic effectiveness. The increased surface area and improved wetting properties of the liquisolid compacts contributed to enhanced drug dissolution. These findings highlight the potential of the liquisolid compact technique as a promising approach for enhancing the solubility of poorly water-soluble drugs like Carvedilol.

Keywords Liquisolid compacts, Carvedilol, Solubility enhancement, formulation, Dissolution

1. Introduction

Enhancing the solubility of poorly aqueous-soluble drugs is imperative in pharmaceutical research and development. Such drugs often exhibit limited bioavailability, hindering their therapeutic effectiveness [1]. Poorly aqueous-soluble drugs face significant challenges in terms of bioavailability. When a drug has low solubility in water, it tends to form large and poorly dispersible drug particles when administered orally or intravenously. These particles have a limited surface area available for dissolution, resulting in slow and incomplete dissolution in the gastrointestinal fluids or plasma [2]. This poor dissolution directly impacts

the drug's bioavailability, which is the fraction of the administered dose that reaches the systemic circulation. Insufficient dissolution leads to inadequate drug absorption across biological barriers, such as the intestinal wall or blood vessels, resulting in lower systemic exposure. Consequently, the therapeutic concentration required for desired pharmacological effects may not be achieved, leading to reduced efficacy of the drug. Solubility enhancement techniques aim to improve drug dissolution, absorption, and systemic delivery. This is crucial for achieving optimal drug concentrations at target sites, ensuring desired therapeutic outcomes.[3] Various approaches are employed, including, particle size reduction, complexation, salt formation, Prodrug development, solid dispersion techniques, liquisolid compact formation and nanotechnology etc. These strategies enhance drug solubility, dissolution rate, and overall bioavailability. By overcoming solubility challenges, scientists can unlock the full potential of poorly soluble drugs, expanding treatment options and improving patient outcomes in numerous disease areas.

Liquisolid technology, also known as liquid-liquid dispersion technology, is a formulation approach used to enhance the solubility and dissolution of poorly water-soluble drugs. It involves converting a liquid drug or a drug dissolved in a non-volatile liquid solvent into a dry, free-flowing powder form by adsorbing it onto suitable carrier particles called "carrier particles" or "carrier powder" [4]. This process typically involves blending the drug solution with a powder mixture consisting of a selected adsorbent and a coating material. Liquisolid technology offers several advantages, including improved drug solubility, enhanced dissolution rate, increased drug load, and better flexibility in formulation design, making it a promising approach for addressing the solubility challenges of poorly water-soluble drugs [5].

Carvedilol is a beta-blockers and is used to treat various cardiovascular conditions, including hypertension (high blood pressure), congestive heart failure and left ventricular dysfunction following a heart attack. Carvedilol works by blocking the effects of certain neurotransmitters called beta-adrenergic receptors in the body. It acts as a non-selective beta-blocker, meaning it blocks both beta-1 and beta-2 adrenergic receptors. It also possesses alpha-1 blocking activity. By blocking these receptors, Carvedilol reduces the workload on the heart, decreases heart rate, and relaxes blood vessels, leading to lowered blood pressure and improved cardiac function. Carvedilol is well-absorbed from the gastrointestinal tract, with approximately 25-35% bioavailability. It undergoes extensive first-pass metabolism in the liver, resulting in a lower systemic availability. The drug is highly protein-bound, primarily to albumin. The solubility of Carvedilol is relatively low. It is sparingly soluble in water, with a reported solubility of approximately 2.9 mg/mL at 25°C [6]. The low solubility of Carvedilol presents challenges in formulating suitable dosage forms for administration. The dose of Carvedilol can vary (6.25mg to 50mg per day) depending on the specific condition being treated and individual patient factors. The present study is designed to enhance the solubility of carvedilol by the development of liquisolid compact formulation which will be finally compressed in tablet dosage form and evaluated for the quality parameters.

2. Materials and Methods

2.1 Materials

Drug Carvedilol was obtained as a gift sample from Intas Pharmaceuticals Limited, Ahmedebad. Polyethylene glycol 400 (PEG 400), Propylene glycol, Polysorbate 80 and other reagents were purchased from SD fine Chem Ltd. Microcrystalline Cellulose (MCC), Aerosil, Sodium starch glycolate (SSG) were purchased from Ankit Traders, Delhi.

2.2 Preformulation studies

The process of Drug Identification and Melting Point determination was conducted and compared with the standard parameters outlined in the monograph.[7] 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.

2.3 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 242 nm to determine the drug concentration [8].

2.4 Liquid load factor calculation

The liquid load factor (LLF) is a crucial parameter used to measure the capacity of liquid medication incorporation in liquisolid compacts. Its calculation involves the following equation:

$$LLF = (Q/MR) \times (1 / \Phi c)$$

In this equation, LLF represents the liquid load factor, Q denotes the quantity of liquid medication (in grams) needed to attain the desired drug dose, MR corresponds to the ratio of the powdered drug formulation's weight to the required amount of liquid medication (Q), and Φc represents the apparent porosity of the powdered drug formulation [9].

2.5 Liquisolid Compact preparation

Liquisolid compacts of Carvedilol were prepared by using Polyethylene Glycol (PEG) 400 and Polysorbate 80 with 5% concentration as nonvolatile solvent (liquid vehicle), Microcrystalline Cellulose (MCC) as carrier and Aerosil, as coating material along with Sodium starch glycolate (SSG) as disintegrant by trituration method [10]. The formulation matrix was designed for the preparation of different compact formulations with varying concentrations of additive as shown in table no. 1.

Formulation Variables	**FC1**	**FC2**	**FC3**	**FC4**	**FC5**	**FC6**
Carvedilol (mg)	06	06	06	06	06	06
(PEG 400) with Polysorbate 80 (5%) (gm)	10	15	20	25	30	35
Microcrystalline cellulose (MCC) (mg)	110	130	160	185	210	240
Aerosil (mg)	10	12	16	20	25	30
Sodium Starch Glycolate (SSG) (mg)	5	5	5	5	5	5

Table No. 1. Formulation Matrix of Carvedilol Liquisolid Compact

2.6 Flow behaviour Studies of compact

The flow characteristics of the developed compact were analyzed using standard methods, which involved determining the Angle of Repose, Carr's index and Hausner's Ratio. These parameters provide valuable insights into the flow behavior of the compact [11].

2.7 In Vitro dissolution studies of Compacts

The release pattern of the compact was evaluated through in vitro dissolution studies using the USP paddle apparatus II. The experiments were conducted in 900 mL of 0.1 N HCl (pH 1.2) at a controlled temperature of 37.5 ± 0.5∘C, with stirring maintained at a rate of 75 rpm [12]. Samples of 10 ml. were collected and filtered at specific time intervals (5, 10, 15, 20, 25 and 30 minutes). These samples were then analyzed using a UV-visible spectrophotometer at a wavelength of 242 nm. The drug release from each formulation was calculated based on the average of three determinations.

2.8 Preparation and Evaluation of Liquisolid Tablets

Tablets of Carvedilol Liquisolid compact were prepared by direct compression method using rotary tablet press, each containing 6 mg drug with sodium starch glycolate as a disintegrant in the compact. The liquisolid tablets that were prepared underwent various evaluations to assess their quality. These evaluations included weight variation, content uniformity, hardness, friability, and disintegration time. The hardness of the tablets was determined using a Pfizer hardness tester, while the friability was measured using a digital tablet friability tester. The disintegration time was determined using a USP disintegration apparatus [13]. Additionally, the flow properties of the tablets were evaluated based on the angle of repose. All of these evaluations were conducted in triplicate to ensure reliable and consistent results.

2.9 Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) thermograms are used to determine the compatibility between the drug and excipients and also used to evaluate the crystalline state of the drug. It helps in identifying potential interactions between the drug and excipients present in the liquisolid compact. By analyzing the thermogram, any shifts or changes in the characteristic peaks of the drug or excipients can be observed. Accurately weighed samples (5mg) were placed in non-hermetically aluminum pans and heated at the rate of 10 ºC/minute against an empty aluminum pan as a reference covering a temperature range of 40 ºC to 300 ºC in an automatic thermal analyzer system (Shimadzu, DSC– 60, Japan).

2.10 X-ray diffraction (XRD)

X-ray diffraction (XRD) is a valuable technique used to analyze the atomic and molecular structure of crystalline substances, including drugs and excipients. By examining the X-ray diffraction patterns, also known as diffractograms, it is possible to confirm the crystalline nature of a sample [14]. This information is crucial in determining whether the substances are in a crystalline or amorphous state [15]. In this study, diffractograms of the pure drug carvedilol and formulation FC3 were obtained using a Shimadzu diffractometer 6000 from Japan. The instrument was operated at an input voltage of 220V/50Hz, and the measurement conditions were set at a voltage of 40 kV and a current of 30 mA. The diffraction angles (2 theta) ranged from 5 to 50 degrees.

3. Result and Discussion

3.1 Preformulation studies

Carvedilol, obtained as a complimentary sample, underwent physical characterization according to the monograph, focusing on its organoleptic properties and melting point. The sample was determined to be in line with the specifications outlined in the monograph. Comparison of the FTIR spectra of Carvedilol with the standard spectra (Figure 1) revealed striking similarities, and all reference peaks were clearly discernible in the FTIR spectra of Carvedilol when combined with excipients, as depicted in Figure 2.

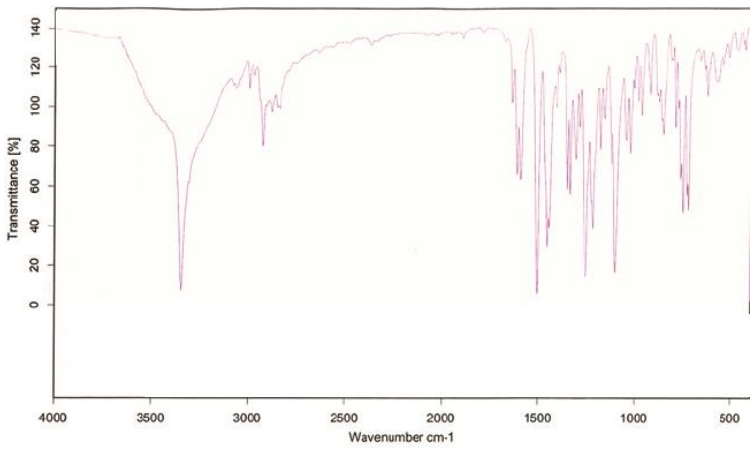


Figure No.1. FITR Spectra of Carvedilol

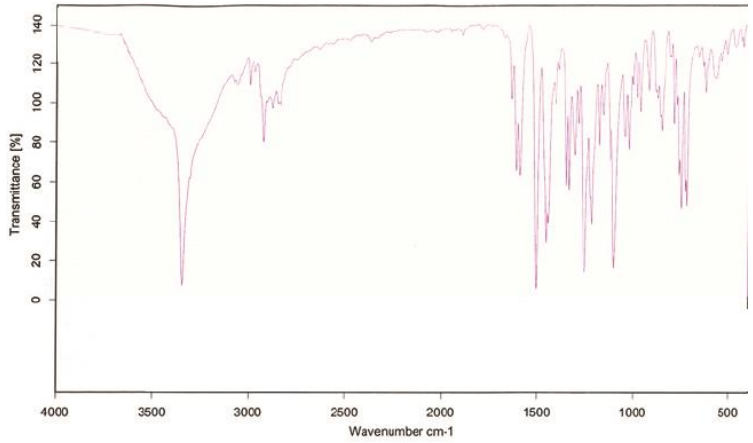


Figure No.2. FITR Spectra of Carvedilol with Excipients

3.2 Solubility studies

Solubility plays a critical role in the formulation development process as it significantly influences the selection of appropriate excipients, solvents, and manufacturing techniques required to create a stable and effective dosage form. In the case of Liquisolid compact development, evaluating the solubility of the drug candidate in various non-volatile solvents becomes crucial for selecting the suitable vehicle that would achieve a favorable bioavailability profile. The solubility of Carvedilol was assessed in Polyethylene glycol 400 (PEG 400), Propylene glycol (PG), Glycerol, and Polysorbate 80, resulting in solubility ranges of 4.7% to 2.4% w/w. Based on the solubility data, Polyethylene glycol 400 (PEG 400) combined with 5% Polysorbate 80 was chosen as the vehicle for formulation

development. This selection was made based on its solubility characteristics, ensuring optimal solubilization of the drug and facilitating the desired formulation properties.

3.3 Preparation of Liquisolid Compact

Carvedilol liquisolid compacts were formulated based on the matrix provided in Table no. 1. Polyethylene Glycol (PEG) 400 with 5 % of Polysorbate 80 was used as the liquid vehicle. Various ratios of Microcrystalline Cellulose (MCC) were employed in accordance with the liquid load factor, along with Aerosil and Sodium starch glycolate (SSG), using the trituration method. A total of six formulations (FC1 to FC6) were prepared following the matrix and subsequently subjected to optimization. The practical yield percentage ranged from 90.3% to 97.2%, while the drug content fell within the range of 94.2% to 98.5%, as illustrated in Table 2.

Formulation	**FC1**	**FC2**	**FC3**	**FC4**	**FC5**	**FC6**
% Production Yield	90.3	96.2	97.2	91.5	89.6	96.3
Drug Content	96.3	94.2	98.5	97.2	97.4	98.1

Table No. 2. Drug content & Percentage production yield of Carvedilol Liquisolid Compact

3.4 Flow behaviour Studies of compact

The flow properties of the developed compacts were assessed by measuring the Angle of Repose, Carr's index, and Hausner's Ratio, as presented in Table 3. The results indicate that the Carvedilol compacts exhibited favorable flow behavior, suggesting good flow properties.

Parameter	**FC1**	**FC2**	**FC3**	**FC4**	**FC5**	**FC6**
Carr's index (%)	19.1	15.9	15.3	19.6	17.5	19.3
Hausner's Ratio	1.4	1.3	1.2	1.3	1.2	1.6
Angle of repose	24.1	28.3	25.6	30.6	32.4	30.2

Table No. 3. Flow Behaviour Parameters of Carvedilol Liquisolid Compact

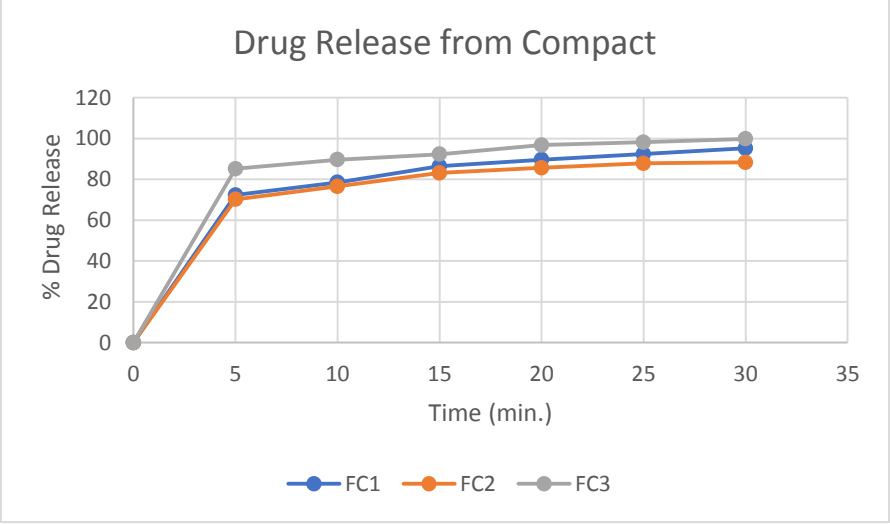
3.5 In Vitro dissolution studies of Liquisolid compact

In vitro dissolution studies were performed utilizing the USP paddle method in a medium consisting of 900 mL of 0.1 N HCl (pH 1.2) at a controlled temperature of 37.5 ± 0.5∘C. The findings demonstrate that the drug released from the compacts initiated within 5 minutes, with a range of 88.3% to 99.8% of the drug observed in the dissolution media within 30 minutes (refer to Table 4). The release profiles of all six formulations are illustrated in Figure 3.

Time (min)	FC1	FC2	FC3	FC4	FC5	FC6
0	0	0	0	0	0	0
5	72.3 ± 1.02	70.2 ± 1.60	85.2 ±1.04	79.1 ±2.32	62.2 ±1.93	58.8 ±2.74
10	78.5 ±1.65	76.5 ±3.00	89.6 ±2.56	82.1 ±1.25	70.5 ±3.18	71.2 ±2.99
15	86.4 ±2.06	83.1 ±3.31	92.3 ±2.58	89.2 ±1.54	76.8 ±1.63	78.4 ±3.32
20	89.6 ±2.99	85.6 ±1.85	96.8 ±1.68	94.2 ±2.47	79.1 ±1.62	86.4 ±2.10
25	92.4 ±1.47	87.8 ±1.58	98.2 ±1.25	96.8 ±1.62	84.6 ±1.87	94.4 ±1.84
30	95.2 ±2.82	88.3 ±1.47	99.8 ±1.49	97.3 ±1.26	87.3 ±1.52	97.6 ±1.68

n = 3 ± standard daviation

Table No. 4. In vitro Drug Release of Carvedilol Liquisolid Compacts



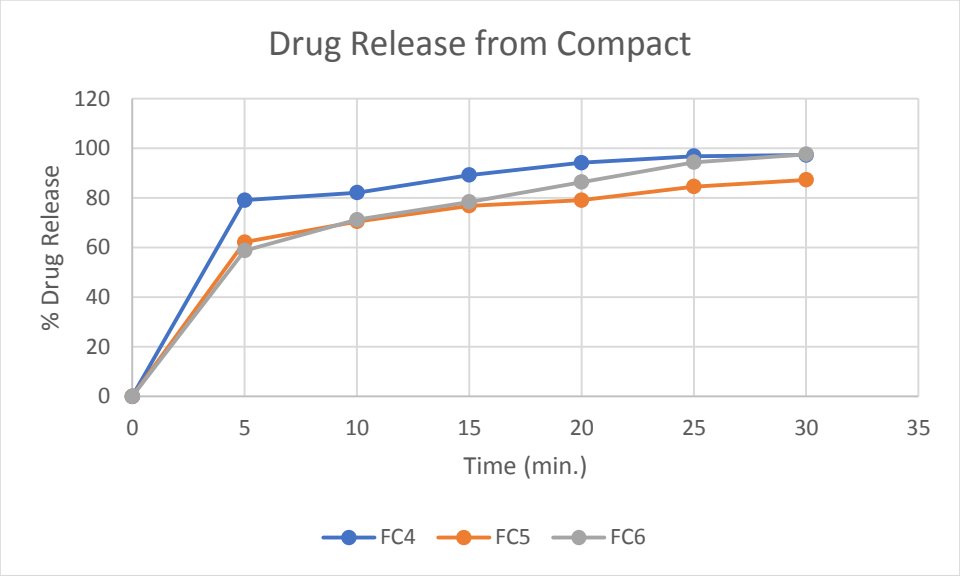


Figure No. 3. Drug Release of Carvedilol Compact

3.6 Preparation and Evaluation of Liquisolid Tablets

Tablets of different liquisoid compact formulations (FC 1 to FC 6) were prepared using the direct compression method. These tablets underwent various evaluation tests including thickness, uniformity of weight, drug content, hardness, friability, and in vitro dissolution, as presented in Tables 5 and 6. All formulations exhibited uniform thickness. In the weight variation test, the average percentage deviation of tablet formulations fell within the permissible limits defined by the IP standards, confirming uniformity of weight for all formulations. Remarkable uniformity in drug content was observed across different batches of tablets, with the drug content percentage 97.1% to 99.2% and drug release varying from 82.9% to 96.2 % among different tablet batch.

Parameter	**FC1**	**FC2**	**FC3**	**FC4**	**FC5**	**FC6**
Thickness (mm)	3.3 ±0.04	4.2 ±0.04	3.9 ±0.04	3.8 ±0.03	3.8 ±0.03	4.1 ±0.04
Hardness (Kg/cm^2)	4.4 ±0.17	5.3 ±0.21	5.2 ±0.12	4.9 ±0.28	4.9 ±0.26	3.8 ±0.24
Weight variation (g)	241.2 ±6.41	332.4 ±10.21	287.3 ±5.69	332.8 ±8.32	353.5 ±7.48	348.2 ±8.47

n = 3 ± Standard Deviation

Table No. 4. Carvedilol Liquisolid Compact Tablet Evaluation

Parameter	**FC1**	**FC2**	**FC3**	**FC4**	**FC5**	**FC6**
Friability (%)	0.84	0.52	0.63	0.54	0.87	0.82
Disintegration Time (Sec)	60 ±5.69	63 ±6.21	72 ±5.53	71 ±7.24	94 ±6.84	91 ±6.65
Drug Content (%)	99.2 ±1.22	98.4 ±1.91	98.9 ±1.32	97.1 ±1.58	98.2 ±1.43	97.5 ±1.27
% Drug Release (in 60 min.)	93.9 ±2.98	90.1 ±2.41	96.2 ±1.77	89.5 ±2.81	88.3 ±3.23	82.9 ±3.64

n = 3 ± Standard Deviation

Table No. 5. Carvedilol Liquisolid Compact Tablet Evaluation

3.7 Differential scanning calorimetry (DSC)

DSC thermograms play a crucial role in assessing the compatibility between the drug and excipients employed in liquisolid compact formulations. These thermograms provide valuable information about the melting points and enthalpy changes of individual components as well as the formulated mixture, allowing the identification of potential interactions or incompatibilities. Incompatible interactions can be detected through the appearance of new peaks, disappearance of existing peaks, or shifts in peak temperatures. The DSC thermogram of carvedilol, as depicted in Figure 4, exhibits a sharp peak at 116.72, which indicates no drug-excipient interaction, as it closely aligns with the melting point of Telmisartan (Figure 5).

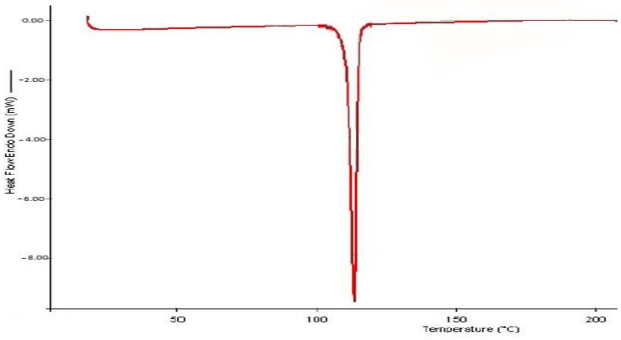


Figure No. 4. DSC Thermogram of Carvedilol

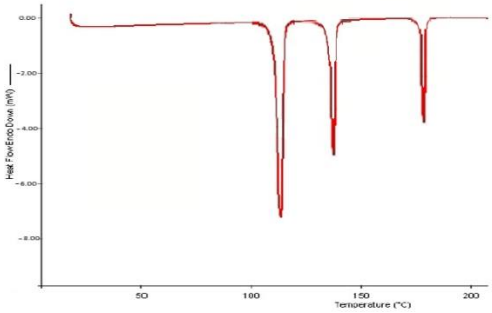


Figure No. 5. DSC Thermogram of Carvedilol Liquisolid Formulation FC3

3.8 X-ray diffraction (XRD)

XRD analysis is a valuable tool for evaluating the compatibility between the drug and excipients in liquisolid compact formulations. It enables the identification of drug-excipient interactions by detecting changes in the diffraction pattern or peak intensities, which may indicate solid-state reactions, crystalline transformations or the formation of new phases. Figure 6 illustrates the XRD spectra of the liquisolid compact, along with the pure Carvedilol revealing the conversion of Carvedilol from its crystalline structure to an amorphous form.

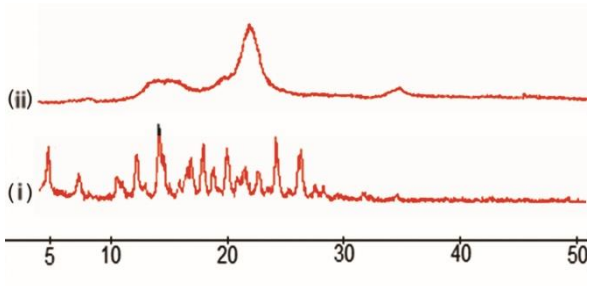


Figure No. 6. XRD Spectra of Carvedilol (i) and Formulation FC 3 (ii)

4. Conclusion

In conclusion, the application of the liquisolid compact technique proved to be a successful approach for enhancing the solubility and dissolution rate of Carvedilol, a poorly water-soluble drug used in the treatment of cardiovascular disorders. The formulated liquisolid compacts demonstrated favourable flow properties, compressibility and compatibility with Carvedilol, as confirmed by the characterization studies. The in vitro dissolution studies revealed a significant improvement in drug release from the liquisolid compacts compared to the conventional tablet. The enhanced drug dissolution observed in the liquisolid compacts can be attributed to the increased surface area and improved wetting properties achieved through the liquisolid formulation. This outcome has potential implications for improving the bioavailability and therapeutic efficacy of Carvedilol, enabling better patient outcomes in cardiovascular treatments.The findings of this study demonstrate the feasibility and effectiveness of the liquisolid compact technique as a viable strategy for enhancing the solubility of poorly water-soluble drugs like Carvedilol. Future investigations should focus on conducting stability studies and in vivo pharmacokinetic evaluations to further validate the suitability and performance of the liquisolid compact formulation.

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