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FORMULATION AND CHARACTERIZATION OF POORLY WATER SOLUBLE LIQUISOLID DRUG CARVEDILOL VIA ADVANCED SOLUBILITY ENHANCEMENT TECHNIQUES

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Abstract

Carvedilol is a commonly prescribed medication for cardiovascular diseases, however it is not very water-soluble, which makes it difficult to have the best possible therapeutic effect. The purpose of this study was to determine whether the liquisolid compact technology could improve Carvedilol's solubility and rate of dissolution. To create the liquidsolid compacts, a Carvedilol medication solution was prepared in PEG 400 serving as the non-volatile solvent. The carrier powder was chosen to be microcrystalline cellulose, while the coating substance was Aerosil. The formulation was optimized by exploring different medication solution to carrier powder ratios. A direct compression approach was used to compress the liquisolid compacts into tablets. The compatibility and physical features of the liquisolid compacts were evaluated by characterization investigations. Compatibility tests employing Ultra violet(UV) Fourier-transform infrared spectroscopy (FTIR), Differential Scanning Calorimetry(DSC), flow characteristics, and compressibility were all included of the evaluation factors. The drug release profile for both compact and tablet dosage forms was determined by in vitro dissolution tests. The liquisolid compacts were found to have excellent compressibility and flow characteristics, which made it easier to manufacture tablets. There were no discernible interactions between Carvedilol and the excipients analyzed using FTIR. Carvedilol may have better bioavailability and therapeutic efficacy as a result of the liquisolid compact technique's increased solubility and dissolving rate. The liquisolid compacts' superior wetting capabilities and larger surface area led to better drug solubility. These results show that the liquisolid compact method could be a good way to make medications like Carvedilol that aren't very water-soluble more soluble.

Keywords: Liquisolidformlation, BSC Class, Polymorphism, Medication content ect.

Introduction

1.Improvement of Dissolvability

Water solubility Whether a chemical molecule or substance may dissolve in a solid, liquid, or gaseous solvent is referred to as its "solubility" quality [1,2]. This makes it easier for the solute and solvent to combine into a uniform solution. Solvency is largely influenced by solvent composition, temperature, pressure, and solute concentration. The saturation concentration or solubility is the most important aspect to consider when trying to determine how much of a solute can be dissolved in a given solvent to create a homogeneous solution.section[3]. Solubility can be influenced by the chemical reaction that occurs between the solute and the solvent.[4]

2. Solubility classification [5,6]

Table1:Classificationofsolubility parameters

S,No.	Typesofsolubility	Solventpartrequiredto onepartofsolute
01	Verysoluble	Lessthan1part
02	Freelysoluble	From1-10part
03	Soluble	From10-30part
04	Sparinglysoluble	From30-100part
05	Slightlysoluble	From100-1000part
06	Veryslightlysoluble	From1000-10,000part
07	Insoluble	Greaterthan10,000part

The classification system for biopharmaceuticals is as follows: Inadequate bioavailability is the result of BCS class II medications having a low rate of dissolution in the aqueous gastrointestinal fluid and having a low water solubility.[7] Class II medications are characterized by a lower water solubility and a higher permeability, as indicated by this classification system. There are a number of different approaches that can be utilized to enhance the solubility of these drugs absorptiondissolutionofdrugsandultimatelyrateandextentofdrugreachestosystemiccirculationwillimprove.[8].

BCSClassification

AsperBCSClassificationdrugsaredividedintofourcategoriesorgroupsasshowninTable 2:

Table2:BCSClassification ofDrugs [9]

S.No.	BCS Class	BasedonPermeability	Based onSolubility
01	ClassI	High	High
02	ClassII	High	Low
03	ClassIII	Low	High
04	ClassIV	Low	Low

3. The Solubilization Process in Motion [10]

Dissolving an insoluble substance begins with dissolving the intermolecular forces that bound the molecules together. Dissolved solvent molecules create an opening for solute molecules to be ensnared by the solvent. A homogeneous solution can only be produced when the solute molecule interacts with the solvent's surface.

This process involves the expulsion of solute molecules from the solution. The third step in making a solution involves completely mixing the solute molecule with the solvent molecule's cavity.

4. Factors Affecting Solubility [11]

Particle size of solute: Solute particle size affects solubility. Solubility is also depends on particle size, as we know smaller the particle size larger the surface area and escalate of dissolution and absorption of drug compound due to better involvement of solute and solvent particles. Solubility of any compound is effected by particle size of solute and report by given equation [11]

$$\log \frac{S}{S_0} = \frac{2\gamma V}{2.303\ R\ T\ r}$$

This shows,

S = solubility of infinitely large particles S0 = solubility of small particles

V =volume

γ = surface tension of the solid (n/m2) r = radius of the particle

T represents temperature (absolute)°K R denotes to gas constant (universal).

Temperature: is one of the most important factors that determines solubility. A decrease in solubility will occur in the event of an exothermic reaction during solubilization, while an increase will occur in the event of an endothermic reaction. The inability to mix the solute in the solvent to produce a homogenous solution is a direct result of the larger molecular size and reduced solubility of molecules with a higher molecular weight. Two sources: [10,11].

The amount of solvent and solute: When a specific amount of a solute dissolves in a specific amount of solvent under the appropriate atmospheric conditions, a solution is formed. For instance, when brought to room temperature, 100 grams of water dissolves only 1 gram of lead (II) chloride and 200 grams of zinc chloride.Two sources: [10,11]

Impact of Pressure: The impact of pressure is one of the properties that works for vapor solutes. The solubility of a substance is observed to increase with an increase in applied force and to decrease with a decrease in force. However, both solid and liquid solutes are unaffected by the applied force.Two sources: [10,11]

Because of its optical feature, divergence affects the solubility of the substance. Most drugs have a low solubility in water if they are not polar in nature. While polar solvents allow polar solutes to diffuse, nonpolar solvents are devoid of polar solutes.

Impact of Polymorphism: Polymorphism is the process through which a crystalline solid displays several crystalline forms; polymorphs, in turn, are solids or molecules that display polymorphism because of their crystalline structure [10,11].

5.Techniquestoovercomepoorsolubility [12]

Polymorphs are distinguished from one another, and eventually, polymorphs display variable degrees of solubility. melting points are also a characteristic of polymorphs.The numbers [10,11].

Table3:Advancement variousTechniquesforsolubility

I. PhysicalModeration	II. ChemicalModerations
1. ReductionofParticlesize a) Formalmethod b) Micromilling c) Nanonisation 2. Modificationofthecrystalhabit a) Polymorphs b) Pseudopolymorphs	1) Salt Formation 2) Co-crystallization 3) Co-solvency 4) Hydrotropy 5) Useofnovelsolubilizer 6) Nanotechnology

6. Liquisolid Technology[13,14]

To improve the solubility and dissolution of medications that are not very water-soluble, a formulation strategy called liquid-liquid dispersion technology or liquidsolid technology is employed. A process known as "carrier particles" or "carrier powder" is used to transform a medicine that is in a liquid or dissolved in a non-volatile liquid solvent into a dry, free-flowing powder. The medication solution is usually mixed with a powder mixture of an adsorbent and a coating material during this process. One potential answer to the problem of poorly water-soluble pharmaceuticals' solubility is liquidsolid technology, which has various benefits such as greater drug load, better formulation design flexibility, faster dissolution rate, and better drug solubility.

Patients with hypertension (high blood pressure), congestive heart failure (CHF), or left ventricular dysfunction (LVD) after a heart attack may find relief with the use of beta-blockers like carvedilol. The action of carvedilol is based on its ability to inhibit the action of specific neurotransmitters known as beta-adrenergic receptors. Because of its non-selective beta-blocking action, it inhibits the beta-1 and beta-2 adrenergic receptors. Additionally, it has the ability to inhibit alpha-1 receptors. Carvedilol improves cardiac function by lowering blood pressure and decreasing the burden on the heart by inhibiting these receptors, which in turn decreases heart rate and relaxes blood vessels. Carvedilol has a bioavailability of about 25–35% once it has been absorbed from the GI tract. Its reduced systemic availability is due to its substantial first-pass metabolism in the liver. The medicine binds well to proteins, especially albumin. It takes a lot of water to dissolve Carvedilol. Its solubility in water is low; at 25°C, it dissolves about 2.9 mg/mL, according to reports. The formulation of appropriate dosage forms for administration is hindered by Carvedilol's low solubility.

7.Material and Methods

I. Preperation of liquisolidblend[14]

A range of water-soluble nonvolatile liquids were used to create carvedilol-containing liquisolid compacts. Carvedilol was dissolved in a liquid media using a magnetic stirrer. Avicel PH 102 (FMC, USA) and Aerosil 200 (Degussa, Germany) were combined in liquisolid formulations with a constant ratio (R) of 20. Avicel PH102 (Q) carrier material was added to the liquid drug at the correct volume. After that, the powder component was dried by adding a certain amount of Aerosil 200 (q) to the mixture while it was being stirred constantly. After that, the mixture is sifted using a 40# mesh. Last but not least, add the disintegrant sodium starch glycolate (SSG) from Roquette, France, and stir everything well. Table 4 displays the composition of multiple batches of liquisolid.

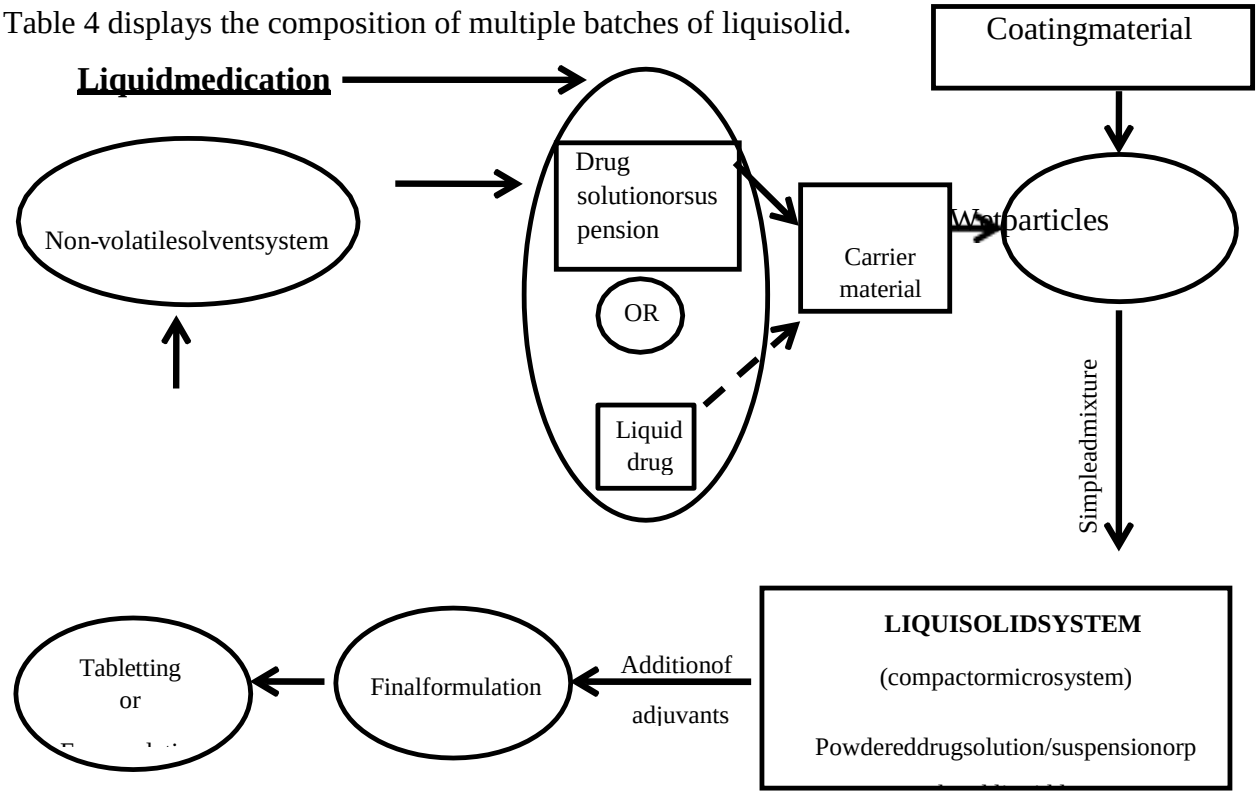


Fig1.Schematic diagram ofliquisolid formulations of Carvedilol

II. Compression of blend into tablets

The finished blend was compressed into tablets using a single punch tabletting machine (Cadmach, India) with a 13 mm round standard concave punch. Between 7 and 9 kg/cm2 were the crushing strengths of the pills maintained. Standard carvedilol tablets were made in the same way as the liquisolid formulation; the only difference was the addition of a liquid carrier. Each tablet contained 25 mg of carvedilol.

Table 4. Formulation composition of liquisolidsystems[15]

BatchCode	R	Lf	Cd(%w/w)	Liquid(mg)	Q(mg)	q(mg)	SSG(mg)	Total(mg)
PEG	20	0.18	33.33	50	400	20	26.05	521.05
PG	20	0.18	33.33	50	400	20	26.05	521.05
Tween80	20	0.18	33.33	50	400	20	26.05	521.05
Conventional Tablet	20	--	--	0.0	400	20	26.05	471.05

PEG:polyethylenglycol400andPG:Propyleneglycol.

III. Effectofexcipientratio

Here you can see how the release behavior of carvedilol is affected by varied quantities of AvicelPH102,Aerosil200,andload factor.

Table5. FormulationcompositionwithdifferentRvaluesforliquisolidsystems

Batchcode	R	Lf	Cd(%w/w)	Liquid(mg)	Q(mg)	q(mg)	SSG(mg)	Total(mg)
R1	10	0.29	40	59.43	329	30	25.7	460.03
R2	6	0.26	50	40.5	276	55	20.07	410.57
R3	9	0.26	50	40.5	276	35.25	20.04	390.78
R4	20	0.20	44.33	50	380	20	27.05	500.05
R5	20	0.135	50	30	380	20	27.74	500.74

8. EvaluationofdevelopedFormulation[16]

First impression

The round, biconvex tablets ranged in colour from white to off-white. The pills had a smooth, uncoated surface on both sides.

Variance analysis of weight

Twenty pills were chosen at random. Twenty pills' individual weights were determined to be within 5.0 percent of the mean. This means that the weight variation test was successful for these liquid-solid caps.

A test for content uniformity

The optimised formulation was tested, and the initial average assay yielded a value of 101%. Each tablet's assay falls somewhere between 94.5 and 105% (the recommended range is between 85.1 and 115% of the mean value).

Tablets' pliability, toughness, and disintegration

Table 6 displays the formulated tablet's hardness, friability, and disintegration time. All three tests (hardness, friability, and disintegration time) were successful for these pills. The weight, medication content, thickness, and diameter of the tablets were all consistently displayed.

Table6 Hardness,friabilityanddisintegrationforliquisolidtabletsandconventionaltablets

BatchCode	**Crushingstrength kg/cm^2**	**%Friability**	**Disintegrationtime(sec)**
PEG	7.0	0.112	80
PG	6.5	0.198	70
Tween80	6.0	0.214	75
Cardivas	7.5	0.010	70
ConventionalTablet	7.5	0.240	60
R1	5.0	0.872	90
R2	6.5	0.215	76
R3	7.0	0.219	60
R4	7.0	0.115	84
R5	6.5	0.129	62

9. InvitroDissolution kineticsStudy of liquisolidTablet[17]

Liquisolid tablets containing PEG400 had a release profile that was superior to Cardivas in an in vitro dissolution kinetics study. Upon dissolving, liquidsolid pills release around 75% of their carvedilol content in the first 10 minutes. Figure 6.13 shows the solubility profile of carvedilol in different formulations. One possible explanation for the increased carvedilol release from PEG-based tablets is that the medication is already present in a molecularly dispersed (solubilized) form.Reasons for this could include the medication's molecular dispersion in PEG, which contains a significant portion of the drug.

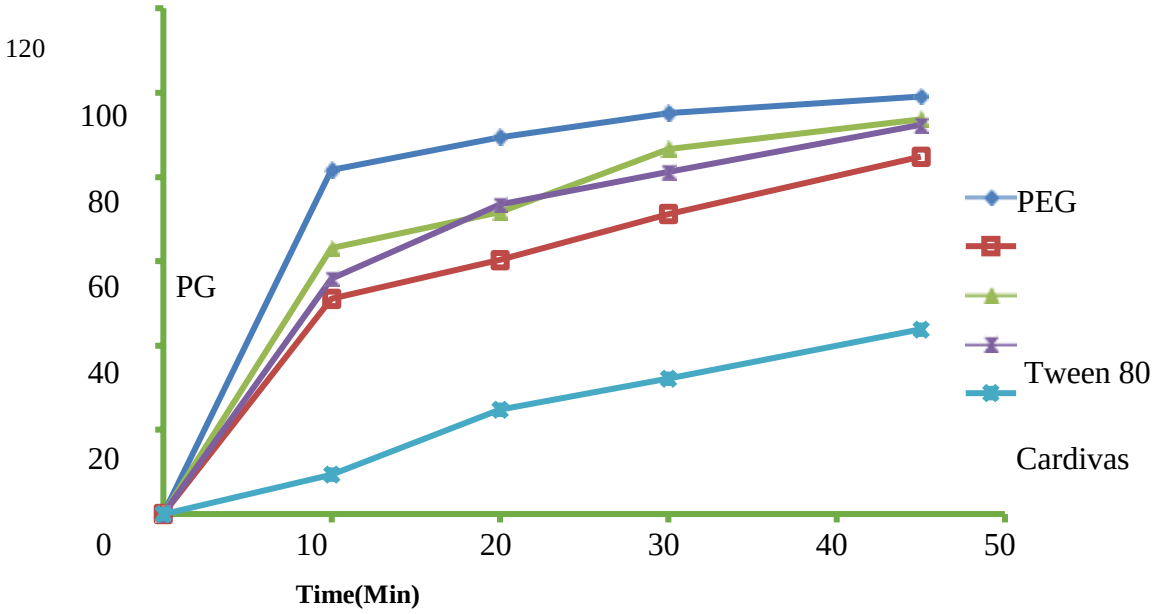
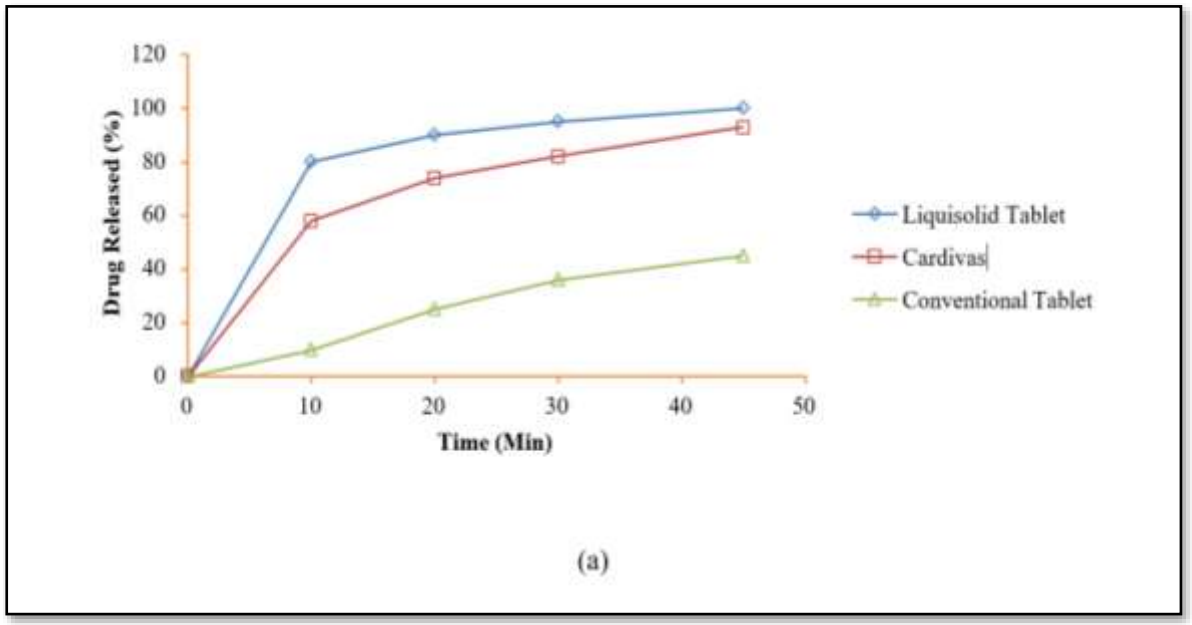


Fig.2. Invitrodissolutionprofileofcarvedilolliquisolidtabletscontaindiff.liquids

10. Dissolution of multimedia in vitro[18]

It is anticipated that the formulation may encounter varying pH and ambient conditions. Hence, experiments were intended to be conducted in dissolving media with varying pH levels. As illustrated in Fig.3, a distinct release profile is anticipated for carvedilol due to its pH-dependent solubility. It is evident from these investigations that the created formulation outperforms the conventional and commercially available ones in terms of solubility, regardless of the pH level.



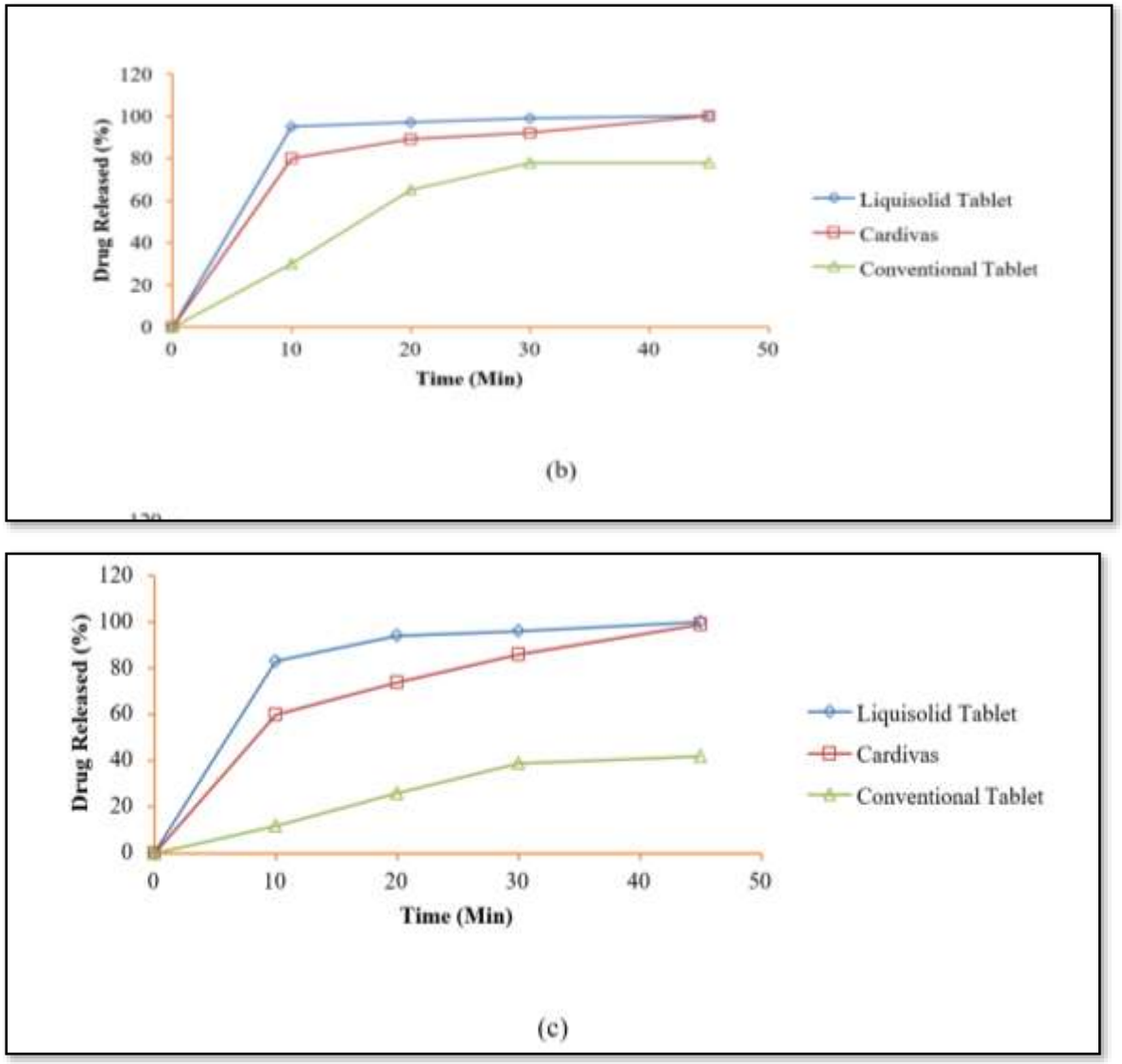


Fig.3 Carvedilolrelease profilesinpH a: 1.2,b: 4.5andc:6.8

11. Spectral specifications UV spectroscopy

The prepared solution uponUV scanning in the range of 200 to 800 nm showed a λ maxof290nm.

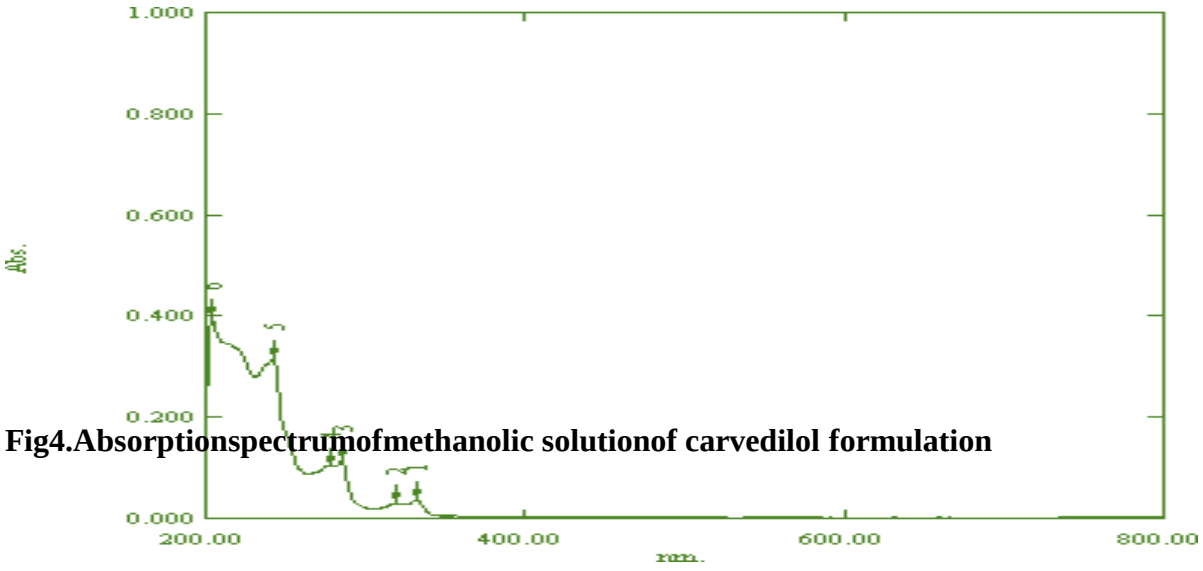


Fig4.Absorptionspectrumofmethanolic solutionof carvedilol formulation

12. InfraredSpectroscopy

Figure 5 displays the carvedilol infrared spectrum. Table 6.8 provides the observed matching values for the functional group presence inside the molecule.

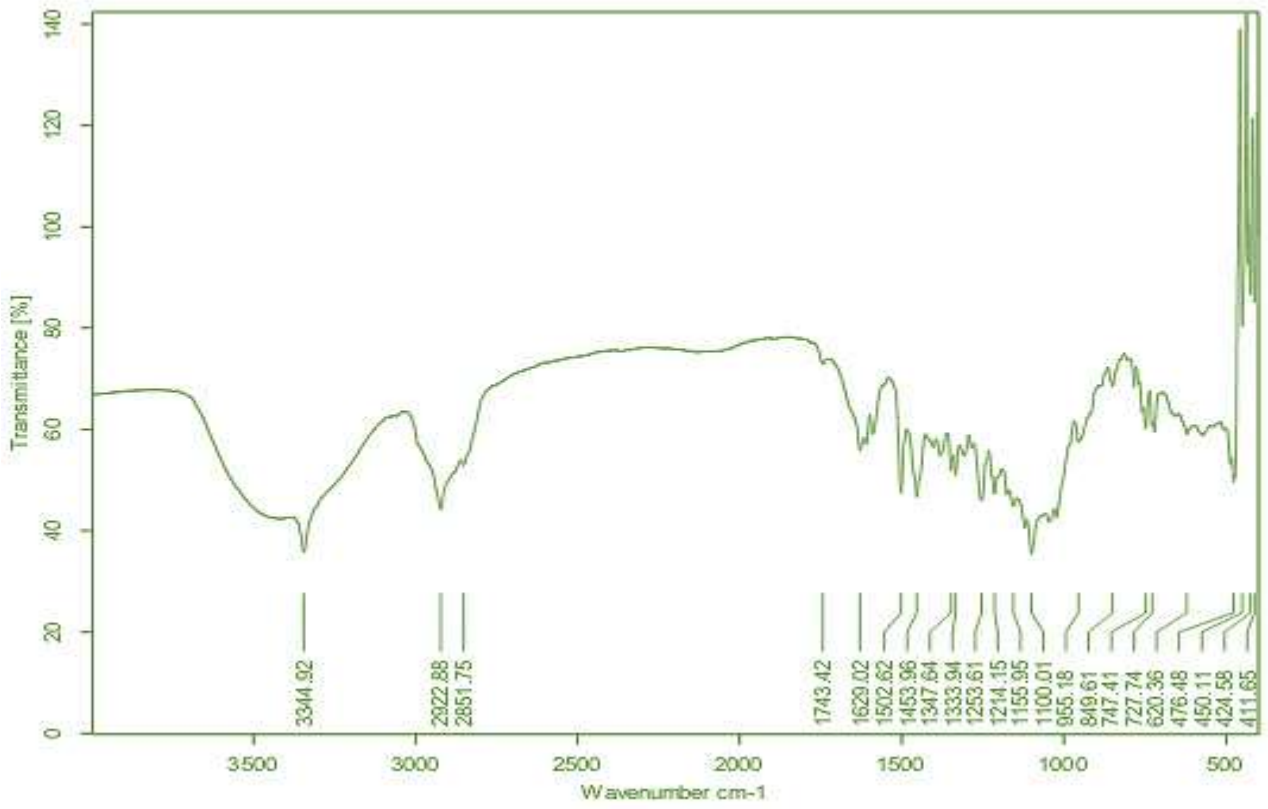


Fig5. FTIR spectrumofcarvedilol formulation

Table 7. Observed values with their corresponding functional groups for carvedilol formulation

Values(cm^{-1})	Functionalgroup
750	N-Hwag (secondaryamine)
3340	O-H(broad) andN-Hstretching(secondaryamine)
2900	C-Hstretchingalkyl
1040 and 1253	C-Ostretchingband (ether)
1590	N-Hbending

13.DifferentialScanningCalorimetry[19]

Thermal behavior of carvedilol is shown in Fig.6 A subtle transition was observed at around 50°C followed by a complete melting exhibited by the presence of sharp endotherm at 120°C.

Temperature(°C)

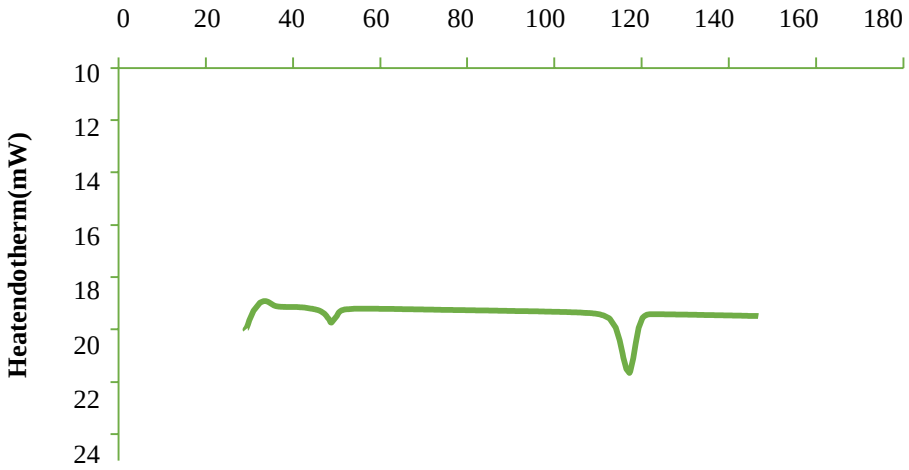


Fig6. DSCthermogramofcarvedilol formulation

14.Stability Studies of Carvedilol formulation

The improved formulation R4 was the subject of stability tests. All of the tests, including those for friability, hardness, disintegration, and dissolution pattern, came back positive. The formulation was determined to be stable following storage according to the results of the stability studies conducted using these parameters. It is reasonable to assume that the formulation will be stable for at least two years in real time, given that it was determined to be stable under accelerated settings.

15.Result and Discussion

Carvedilol with PEG400 has a superior hydrophilic environment to boost solubility of the medication, according to analysis of saturation solubility of drug polymer ratios in various solvents in aqueous, acidic, and basic media. The results of the saturation solubility test showed that, when compared to the pure drug, Carvedilol had the greatest solubility in water. Solubility, melting point, drug polymer compatibility, and calibration curve (UV) experiments were conducted on Carvedilol prior to formulation. No parameter has deviated from the norm. The FTIR spectra showed that the polymers and the medicines did not interact with each other. No drug-compatible polymers were employed in their production. A dosage form with increased solubility and dissolution can be determined by the amount of polymer utilised, which is shown by the saturation solubility. The solubility of solid dispersion is improved with the application of the fusion procedure during preparation. The concentration of Carvedilol in the pH 1.2 methanol is used to construct the calibration curves, which range from 10 to 60µg/ml. Values of the regression coefficients ranging from 0.999 to 1.0 validate the approach. Various excipients are used in varying proportions to prepare the formulation of liquidsolid for use in liquidsolid tablets by the compression process.

Carvedilol is a medication used to treat cardiovascular diseases; however, it is not very watersoluble. The liquisolid compact technology was an effective way to increase its solubility and dissolution rate. The characterisation studies indicated that the formulated liquisolid compacts had good compressibility, flow, and compatibility with Carvedilol. Studies on drug solubility in vitro showed that liquisolid compacts significantly outperformed the standard tablet in terms of medication release. The liquisolid formulation increases the surface area and improves the wetting qualities, which in turn enhances the drug solubility in the compacts. This finding may lead to better patient outcomes in cardiovascular therapy by increasing Carvedilol's bioavailability and therapeutic effectiveness.This study's results show that the liquisolid compact approach can be a good way to make medications like Carvedilol that aren't very water-soluble more soluble. Further validation of the appropriateness and performance of the liquisolid compact formulation should be achieved by the completion of stability tests and in vivo pharmacokinetic evaluations in future investigations.

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