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ENHANCEMENT OF AQUEOUS SOLUBILITY OF CARVEDILOL BY LIQUISOLID TECHNIQUE.

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ABSTRACT

The aim of this study was to improve the solubility of the poorly soluble drug Carvedilol by delivering the drug as a liquisolid Pellets. There are several techniques to enhance the dissolution of poorly soluble drugs. Among them, the technique of liquisolid compact is most promising technique towards novel aim. Polyethylene glycol 400 (PEG400) used as solvent, Avicel pH 102 as carrier, and Kollidon VA 64 as the coating material. The liquisolid compact were prepared by Spheronization and extrusion to form liquisolid pellets. Further Pellets were evaluated for flow properties, disintegration time, drug content, and dissolution, DSC, SEM and XRD. The results for dissolution studies showed that liquisolid Pellets demonstrate significantly higher drug release rates than those of marketed ones. This was due to an increase in wetting properties and surface of drug available for dissolution. Increased wetting properties and dissolution rates leads to enhance solubility. The liquisolid technique appears to be a promising approach for improving the solubility of poorly soluble drugs.

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INTRODUCTION

The bio pharmaceutics classification system (BCS) categorizes drugs into four groups based on their aqueous solubility and intestinal membrane permeability, correlating in vitro drug dissolution and bioavailability. Solubility improvement can enhance oral bioavailability of BCSclass II and IV drugs. Such strategy is especially effective for class II compounds due to their dissolution-limited bioavailability, so even a small increase in .dissolution profile can result in a marked increase in bioavailability. One of the greatest challenges the pharmaceutical industry faces today is the application of technological strategies towards improving the dissolution performance of drugs, producing formulations with adequate bioavailability and therapeutic effectiveness. Several technologies have been studied to increase the solubility, dissolution performance and bioavailability of drugs, including micronization, complexation with cyclodextrins, solid dispersion, self-emulsifying systems and liquisolid systems. this work aimed to evaluate the feasibility of liquisolid pellets as an innovative drug delivery system combining the advantageous properties of the disintegrating pellets and the liquisolid formulations.

LIQUISOLID TECHNIQUES:

This technique includes conversion of liquid lipophilic drugs or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into “dry” (i.e., dry-looking), nonadherent, free flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

The term “liquisolid systems” refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into “dry” (i.e., dry-looking), nonadherent, free flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

Need for liquisolid Techniques:

Oral route is mainly preferred for administration of the drugs due to its patient compliance, convenience and low cost. Hence the drug should be sufficiently dissolved in gastric fluid for its maximum absorption. So improvement of solubility of poorly soluble drugs is the key factor for enhancing bioavailability of the drugs. In market there are about 40% of the drugs having poor water solubility and about 55% drugs undergoing problems during formulation. (Specially class II drugs).

Liquisolid technique is also one of the methods of solubility enhancement in which liquid drug or drug suspensions or drug solutions having poorly soluble drugs get converted in to freely flowing, dry, non adherent, readily compressible powder having less particle size.

Concept of liquisolid technique:

When the drug dissolved in the liquid vehicle is incorporated into a carrier material which has a porous surface and closely matted fibres in its interior as cellulose, both absorption and adsorption take place; i.e., the liquid initially absorbed in the interior of the particles is captured by its internal structure, and after the saturation of this process, adsorption of the liquid onto the internal and external surfaces of the porous carrier particles occur. Then, the coating material having high adsorptive properties and large specific surface area gives the liquisolid system the desirable flow characteristics.

In liquisolid systems the drug is already in solution in liquid vehicle, while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica).Thus, due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and consequently, improved oral bioavailability. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates. That is why soft gelatin elastic capsules containing solutions of such medications demonstrate higher bioavailability when compared to conventional oral solid dosage forms. A similar principle underlies the mechanism of drug delivery from liquisolid compacts and is chiefly responsible for the improved dissolution profiles exhibited by these preparations.

Advantages:

- Liquisolid technique is used mainly for converting liquid drugs or drug suspensions or solutions of poorly soluble drugs in to solid dosage form.
- It is used to formulate sustained release dosage forms.
- By using liquisolid technique controlled drug delivery systems can be formulated.
- Production cost of liquisolid system is also less as compared to soft gelatin capsules.
- This technique is also applied to convert liquid oily drugs in to solid dosage form.
- It enhances dissolution rate of poorly water soluble drugs by increasing their solubility.
- Liquisolid technique is also used for class II and class IV drugs for enhancing their bioavailability.
- Manufacturing of liquisolid tablets is simple as that of tablet formulation.

Applications

- It is used for enhancing rate of dissolution of the many poorly soluble drugs by enhancing their solubility.
- Bioavailability of many class II and class IV drugs get enhanced by using liquisolid technique.
- Release rates of many poorly water soluble drugs get increased by using liquisolid system.
- It is also used for designing controlled drug delivery system.
- Liquisolid technique is also successfully used for the formulation of many water insoluble or liquid lipophilic drugs.
- It is also used to formulate sustained release dosage forms.

Carvedilol is Antihypertensive drug. It ß-blocker (non selective).IUPAC NAME (±)-[3-(9*H*-carbazol-4-yloxy)-hydroxypropyl][2-(2-methoxyphenoxy)ethyl]amine

Structure

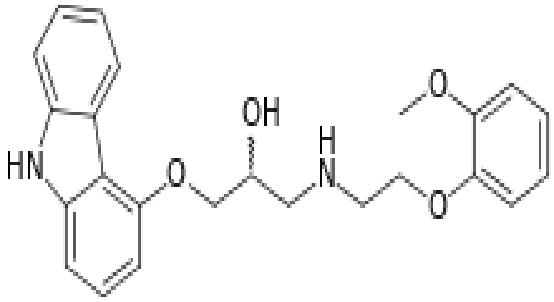

Fig.1: structure of Carvedilol.

Solid in state. Melting point ranges 114˚c-115˚c. Crystalline in nature. practically insoluble (0.00058mg/ml) in water. Bioavailability is 25-35%, Protien binding is 98%, Biological half life: 7-10hrs Metabolism in liver. Excreation: urine(16%) faeces(60%)Mechanism of action: Carvedilol is both a non-selective beta adrenergic receptor blocker (β1, β2) and an alpha adrenergic receptor blocker (α1). The S(-) enantiomer accounts for the beta blocking activity whereas the S(-) and R(+) enantiomer have alpha blocking activity. Carvedilol reversibly binds to beta adrenergic receptors on cardiac myocytes. Inhibition of these receptors prevents a response to the sympathetic nervous system, leading to decreased heart rate and contractility. This action is beneficial in heart failure patients where the sympathetic nervous system is activated as a compensatory mechanism. Carvedilol blockade of α1 receptors causes vasodilation of blood vessels. This inhibition leads to decreased peripheral vascular resistance and an antihypertensive effect. Adverse effect: The most common side effects includes Dizziness, fatigue, low blood pressure, diarrhoea, weakness, slowed heart rate, weight gain, dysfunction. Contraindication: Carvedilol should not be used in people with bronchial asthma or bronchospastic conditions. It should not be used in people with second- or third-degree AV block, sick sinus syndrome, severe bradycardia (unless a permanent pacemaker is in place), or a decompensate heart condition.

Pellets as multiparticulate system:

Multiple-unit dosage forms, including pellets, have been receiving great attention as more effective therapeutic alternatives for oral drug delivery, especially in the context of modified-drug release, even though single-unit dosage forms have been widely used for decades. The benefits of multiparticulate systems over single-unit dosage forms include better distribution along the gastrointestinal tract, resulting in increased drug bioavailability, lower local drug concentration, minimized side-effects and reduced inter- and intra-individual variations in bioavailability. Other advantages of multiple-unit systems are the easy adjustment in the dosage unit strength, the administration of incompatible drugs in a single dosage form by separating them into different multiparticulate, and the combination of units with different drug release rates to obtain the desired overall release profile. The multiparticulate systems are intended as intermediate products to facilitate the later manufacture of capsules or tablets. In this sense, they are much more suitable intermediate products when compared to the powder itself due to higher and more homogeneous particle size, leading to improved flowability, and reduced total surface area, diminishing the exposure to environmental conditions (*e.g.*, moisture and light). Pellet disintegration is undesired for sustained-release formulations, but it is an important issue when immediate drug release is required. The widely used microcrystalline cellulose (MCC) pellets, obtained by extrusion–spheronization, generally do not disintegrate and approaches have been proposed for overcoming this limitation. Recently, Chamsai and Sriamornsak (2013) developed fast disintegrating MCC-pellets, using a hydroethanolic solution of polyethylene glycol 400 (PEG 400) or polysorbate 80 as granulating liquid and croscarmellose sodium as a superdisintegrant. Their results suggest that the disintegrating pellets can enhance drug dissolution of poorly water-soluble drugs. Therefore, this work aimed to evaluate the feasibility of liquisolid pellets as an innovative drug delivery system combining the advantageous properties of the disintegrating pellets and the liquisolid formulations. The use of pellets as carriers to liquisolid systems is a suitable alternative due to the inherent technological advantages pellets have over the liquisolid powder form. In this way, liquisolid pellets were obtained by extrusion–Spheronization, using Carvedilol (BCS class II) as a model drug and microcrystalline cellulose 101 as the carrier material.

The effects of the concentration of Crosspovidone as a coating and disintegrant material and the type of non-volatile solvent, PEG 400, on the drug dissolution profile were assessed. Even though the colloidal silicon dioxide and other silica are the most commonly used coating materials in liquisolid systems, hereby the use of Crosspovidone as a new coating material was explored due to its disintegrating properties. The literature did not describe so far the development of liquisolid pellets and the use of Crosspovidone as coating material in liquisolid formulations. Therefore, this study consists of an innovation and expansion of the current liquisolid technology for application in pellets as multiparticulate systems.

MATERIALS AND METHODS

Carvedilol was gifted from Glenmark pharmaceuticals, Goa. Microcel® MC-101 (microcrystalline cellulose 101), Kollidon® CL-SF (Crosspovidone), Kollidon® VA 64 (Copovidone) and Lutrol® E 400 (polyethylene glycol; PEG 400) were gifted by BASF Chemicals Company, Mumbai. All other reagents and solvents were of analytical grade.

Preformulation studies:

Solubility

The solubility of Carvedilol was checked in PG, PEG400, Water, Glycerine, Methanol, and Ethanol.

Infrared spectroscopy:

IR absorption spectrum of Carvedilol was recorded using Attenuated Total Reflectance Spectrophotometer. The resultant spectrum of the drug was compared with reference Spectrum of Carvedilol.

Preparation of standard curve of Carvedilol (Methanol)

10 mg of drug was accurately weighed and transferred to 100 ml volumetric flask and sonicated. Drug was dissolved in 100 ml methanol. Thus, a stock solution of carvedilol of 100 µg/ml was prepared in Methanol .The solution were futher serially diluted with methanol produce solutions of concentrations 1-5 µg/ml. The UV spectrum was recorded in range of 200-400 nm. The maximum absorption wavelength (max) was found out from scan and then further preparation of calibration (standard) curve was carried out at the detected wavelength of maximum absorption (max).

Saturated solubility (selection of non volatile solvent)

To select the best non-volatile solvent for preparation of liquid medication, saturation solubility studies were carried out in non volatile solvents, i.e. PG, PEG 400 by preparing saturated solutions of the drug in those solvents and analyzing their drug content spectrophotometrically. Carvedilol was mixed with each of the above solvents in order to produce system containing excess of drug. The mixtures were sonicated for 24 hrs. After 24 hrs solutions were centrifuged to get clear supernatant. These supernatant solutions were further diluted with methanol and analyzed spectrophotometrically at 242 nm for their drug content. Three determinations were carried out for each sample to calculate the solubility of Carvedilol.

Method of Preparation of Liquisolid Pellets:

The liquisolid pellets formulations were obtained by the extrusion–Spheronization method the liquid medication was prepared by dispersing the model drug Carvedilol in the different concentration of the non-volatile solvent PEG 400 using mortar and pestle. The concentration of Carvedilol was based on the minimum amount of non-volatile solvent necessary to obtain the drug dispersion since the effect of the amount of PEG 400 in the extrusion–Spheronization process was unknown. Microcrystalline cellulose 101 was added to the dispersion as the carrier material. After complete incorporation of the liquid medication to the carrier particles, Crosspovidone was added to act as coating material and disintegrating agent F1 to F9 batches were prepared using factorial design. The liquisolid powder obtained was slowly wetted with a Copovidone in water solution (1% w/v). The wet mass was transferred into a rotating granulator and immediately extruded through a perforated screen (2.0 mm) at 60 rpm. The extrudates were transferred into an Spheroniser equipped with a cross-hatched friction plate and Spheroniser for 2 min at 500 rpm. The liquisolid pellets were dried in a oven for 10 min at 60 ◦C. The dried pellets were sieved and the usable fractions were separated for all the subsequent analyzes

Table 1: Levels of optimization.

Level	Crosspovidone	PEG 400
+ (high)	250	150
0 (Intermediate)	175	100
- (Low)	100	50

Table 2: optimization of batches.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carvedilol	250	250	250	250	250	250	250	250	250
Crosspovidone	100	100	100	175	175	175	250	250	250
PEG 400	50	100	150	50	100	150	50	100	150
Copovidone	100	100	100	100	100	100	100	100	100
Microcrystalline cellulose	4500	4450	4400	4450	4375	4350	4350	4300	4250

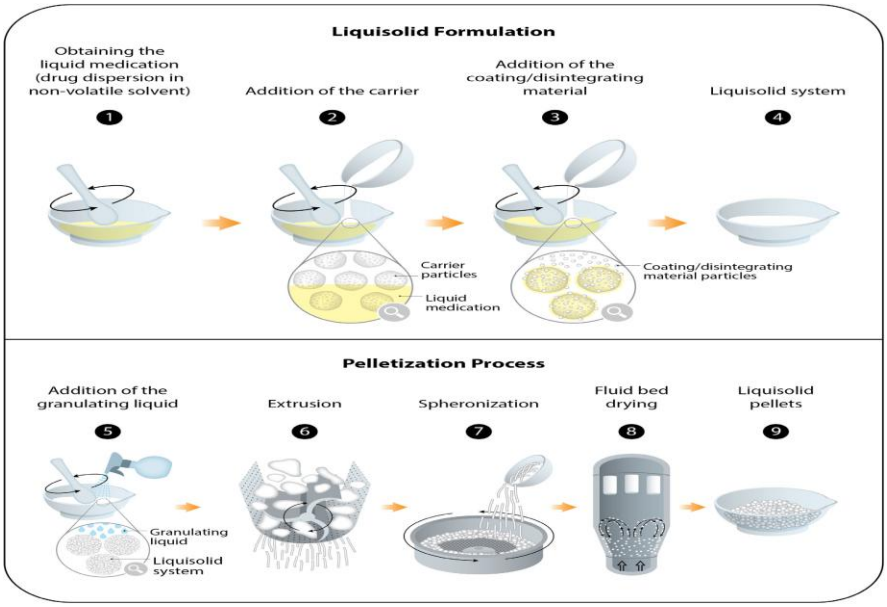

Fig 2: Liquisolid pellets formulation.

Evaluation of liquisolid pellets:

Flow Properties

Determination of angle of repose, Carr's index and Hausner's ratio were used to characterize flow properties of the liquisolid powder systems. The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of tablet dies, otherwise, high dose variations will occur.

Angle of Repose

Angle of repose for blend of each formulation was determined by fixed funnel method. The funnel is secured with its tip with height 'h' above a plane of paper kept on a flat horizontal surface. The powders were 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 below.

$$\mathbf{Tan}\theta = \mathbf{h/r}$$

% Compressibility (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 is calculated according to the equation given below.

$$\% \text{ Compressibility (Carr's index)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner found that the ratio tapped density/bulk density was related to inter particle friction as such, 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 less free flowing powders have Hausner's ratio greater than 1.6. Hausner's ratio less than 1.25 indicate good flow.

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

Content uniformity

Drug content uniformity was determined as per IP 2007 using following procedure.

Procedure:

100mg pellets were weighed and powered. Quantity of powder equivalent to 10 mg of drug was weighed and transferred to 100 ml volumetric flask containing Phosphate buffer 6.8. The flask was shaken to dissolve the drug and adjusted to volume with phosphate buffer 6.8 1ml of this solution was diluted to 10 ml with Phosphate buffer and absorbance of resulting solution was measured at maximum absorption wavelength of 242 nm.

Disintegration test

Disintegration test was carried out as described under procedure for pellets. The assembly was suspended in the liquid medium in the suitable vessel, preferably in 1000 ml beaker. The volume of the liquid such that the wire mesh at its highest point is at least 25 mm below the surface of liquid and its lower point is at least 25 mm above the bottom of the beaker. A thermostatic arrangement was made for heating the liquid and maintaining the temperature at 37 ± 2 ^{o}C. Assembly was suspended in beaker containing 900 ml of distilled water and the apparatus was operated for specified time. The assembly was removed from liquid. Disintegration time was noted.

In-vitro drug release

Dissolution Studies

In vitro dissolution studies of fast dissolving tablets were performed by using USP type-I apparatus

Test Parameters:

Volume of Dissolution medium - 900 ml, RPM- 50 rpm, temperature of dissolution medium- 37.0 ± 0.5 ^{o} C, Apparatus type - USP Apparatus I, Dissolution media – Phosphate buffer 6.8 .For all batches of Carvedilol the same media were used.

Procedure:

The tablets from each formulation batch were placed in dissolution medium and apparatus was run maintaining above stated test conditions. 10ml aliquots were withdrawn at time intervals of 0, 5, 10, 15, 20, 30, 45 and 60 minutes. Every time the equal volume of fresh dissolution medium was added to the bulk of the solution and temperature was maintained. Samples were filtered through Whattman filter paper no. 41, dilutions were carried out as per calibration curve and the absorbance was recorded at 242 nm. Percentage of labeled amount of drug released at each time point was calculated. The study was carried out in triplicate.

Scanning Electron Microscopy (SEM):

Scanning electron microscopy shows that there is presence or absence of crystal form of the drug or excipients in the formulation. If SEM shows that there is absence of crystal form of the drug then it shows that now the drug is completely solubilized in to carrier system.

X ray diffraction (XRD):

XRD pattern is checked generally for the drugs, excipients or for physical mixture of drugs and excipients. It is used mainly for determining that drug or excipient in the formulation is in crystalline form or in a solubilized form in a solvent. Appearance of specific constructive peak in the diffractogram shows that drug is in the crystalline form. If that peak is get disappeared in the diffractogram then it shows that drug is get converted in to amorphous form or in to its solubilized form. This solubilized form of the drug should be there for the liquisolid system which shows that drug is completely solubilized in to the carrier system which helps to improve its solubility and hence enhances its dissolution rate

Stability Testing of the Best Formulation5

Temperature dependent stability studies were carried out on the optimized batch. They were packed in Aluminium pouches and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 30 + 1˚Cand RH 65 % + 5%

(ii) 40 + 2 ˚C and RH 75 % + 5%

The pellets were withdrawn after a period of 7, 14 days, 1, 2 and 3 month and analyzed for physical characterization (Visual defects, , Disintegration, Dissolution etc.) and drug content

RESULT AND DISCUSSION

Preformulation studies:

Solubility:

Saturated solution was prepared and allowed to stand for 24hrs then it was filtered and filtrate was scanned under UV spectrophotometer at 242nm.

Table 3: solubility of Carvedilol in different solvent.

Solvents	Solubility (mg/ml)
Methanol	33.8
Ethanol	10
Water	Practically insoluble. (theoretical =0.000588)

IR Spectroscopy:

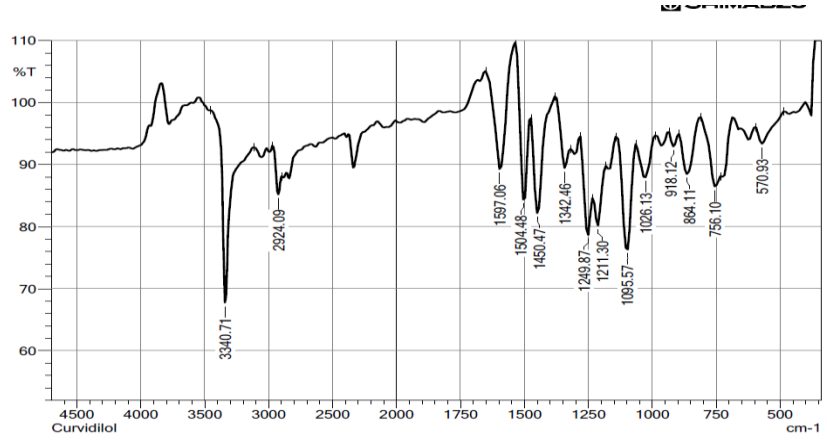

Fig 3 : IR spectra of Carvedilol.

Caliberation curve in Methanol:

10 mg of drug was accurately weighed and transferred to 100 ml volumetric flask and sonicated. Drug was dissolved in 100 ml methanol. Thus, a stock solution of Carvedilol of 100 µg/ml was prepared in Methanol .The solution were further serially diluted with methanol produce solutions of concentrations 1-5 µg/ml. The UV spectrum was recorded in range of 200-400 nm. The maximum absorption wavelength (max) was found out from scan and then further preparation of calibration (standard) curve was carried out at the detected wavelength of maximum absorption (max).

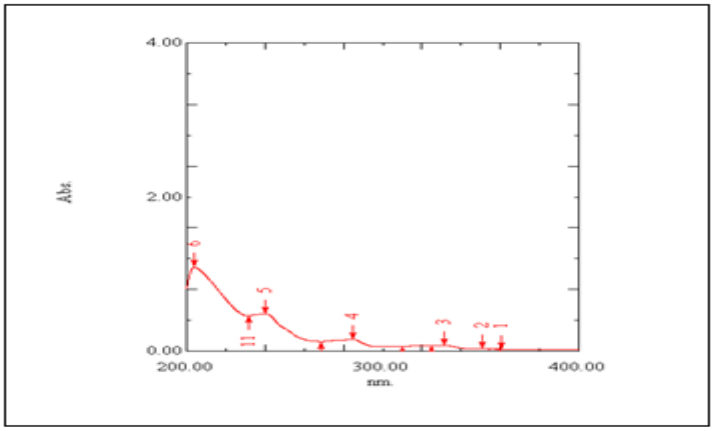

Fig 4 : caliberation curve in methanol.

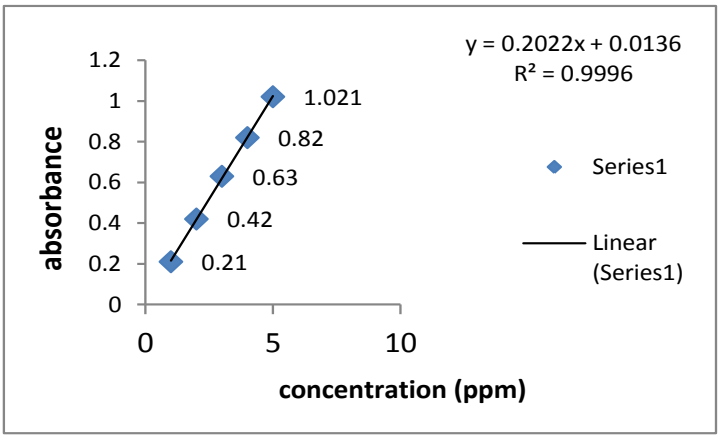

Fig 5: beer's Lambert plot in methanol.

Drug-Excipients compatibility study:

No Colour change was observed hence Carvedilol is compatible with the excipients used. Excipients used are Crosspovidone, Copovidone, and Microcrystalline cellulose. Further interpreted with DSC studies.

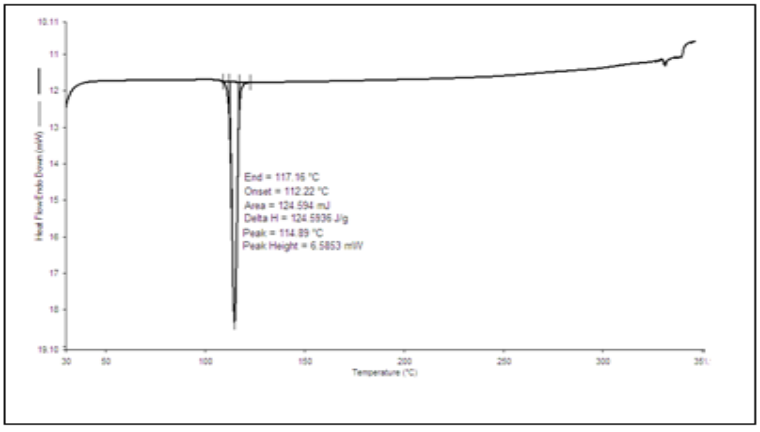

Fig 6: DSC thermogram of pure drug Carvedilol.

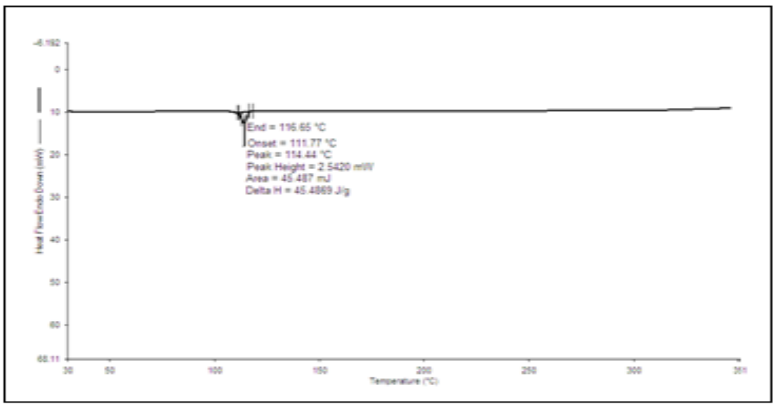

Fig 7 : DSC thermogram of mixture.

The DSC Thermograms of pure Carvedilol and DSC Thermograms of mixture (Carvedilol liquisolid powder) show no significant difference from their obtained Thermograms. It indicate minor shift of endothermic peak from 114.99 to 114.44. These obtained results indicate that there was no positive evidence for the interaction between Carvedilol and Excipients material. So, excipients used in Carvedilol liquisolid compact can be used for preparation of tablet of Carvedilol.

Selection of solvents:

Poor aqueous solubility of Carvedilol can be enhanced by addition of non solvents.Non solvents used are PEG 400, Propylene glycol, glycerine.

Table 4: solubility of Carvedilol in non volatile solvents.

Non solvents	Solubility(ug/ml)
PEG 400	1.22
propylene glycol	0.52
Glycerin	0.45

It was found that the drug was most soluble in PEG 400 hence PEG 400 was chosen as appropriate non solvent.

Evaluation of Pellets

Flow properties

Flow properties includes angle of repose, Carr's index, Hausner's ratio as it may affect compressibility, tablet porosity and dissolution. The effect of liquid load factor (Lf), which is a ratio of mass of liquid (PEG) added to the mass of carrier, Avicel PH 102 on flowability and compressibility of the final admixture of the powder is shown in table. As a general guide angle of repose greater than 40o has unsatisfactory flow properties whereas minimum angle close to 25o correspond to very good flow property. Powders showing Carr's index up to 21 are considered of acceptable flow property.

Table 5: Flow properties.

Formulation	Bulk density gm/cm^3	Tapped density gm/cm^3	Carr's Index %	Hausner's ratio	Angle of repose(ɵ)
F1	0.72	0.74	2.70	1.02	28.79
F2	0.68	0.75	10.29	1.10	24.57
F3	0.74	0.76	2.63	1.02	26.96
F4	0.76	0.78	2.56	1.02	27.10
F5	0.70	0.75	6.66	1.07	25.22
F6	0.74	0.76	5.12	1.05	26.49
F7	0.75	0.77	2.59	1.02	24.12
F8	0.81	0.87	6.89	1.07	27.32
F9	0.77	0.80	3.75	1.03	25.31

Flow properties of all batches were found to be in the range according to specification mentioned.

Drug content:

A fundamental quality attribute for all pharmaceutical preparations is the requirement for a Constant dose of drug . Uniform drug content was observed for the formulation which is as per the IP specification (90%-110%).

Table.6: Drug content.

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Content (%)	94	90.85	94.4	95.6	94.2	93.71	95	94.2	94.4

Solubility of liquisolid pellets in water:

Table 7: solubility in water.

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solubility (mg/ml)	0.024	0.026	0.051	0.032	0.031	0.029	0.043	0.049	0.053

From above study it was observed that F9 has shown higher aqueous solubility.

Disintegration time:

The disintegration time test revealed that the liquisolid pellet formula disintegrated within 3 min which is as per specifications given and result of the test are shown in table. Microcrystalline cellulose has disintegration property which could facilitate disintegration of tablets and dissolution of drug. Because of the presence of a non-volatile solvent acting as a binding agent in the liquisolid formulation, delayed disintegration time is expected. However, in the liquisolid pellets containing microcrystalline cellulose, a fast disintegration of tablet occurred which can be explained by the disintegrating property of microcrystalline cellulose. In addition, use of Crosspovidone accelerates the disintegration of pellets by virtue of its ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of pellets and therefore faster disintegration.

Table 8: Disintegration time.

Batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
DT (min)	2	2.1	2	2.4	2.3	2.0	2.5	2.4	2.5

Scanning electron microscopy:

Scanning electron microscopy of pellets carried out. The Scanning electron microscopy study of the prepared Pellets showed that the particles are in spherical in shape, with smooth surface and formation of few agglomerates of pellets.

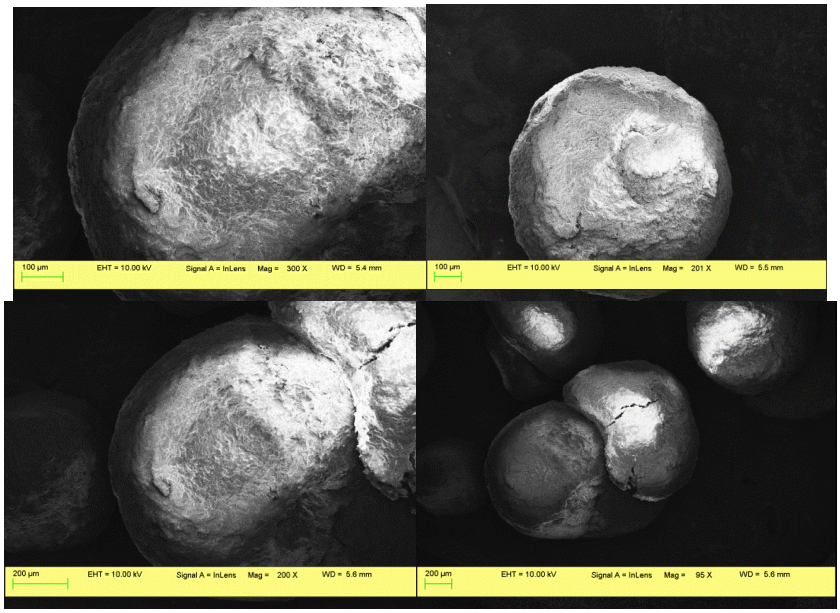

Fig 8: images of pellets in SEM.

XRD studies

XRD studies were carried out and it shows that the X-ray diffractogram of pure Carvedilol showed that the drug was in crystalline in nature as shown in the XRD graph. The XRD of Liquisolid pellets of Carvedilol prepared showed that some peaks of the pure drug were absent and or intensity of the peaks was reduced. Thus the result of powder XRD indicates that the drug in Pellets is in amorphous form than the pure Carvedilol. Thus the increased dissolution of the drug was observed.

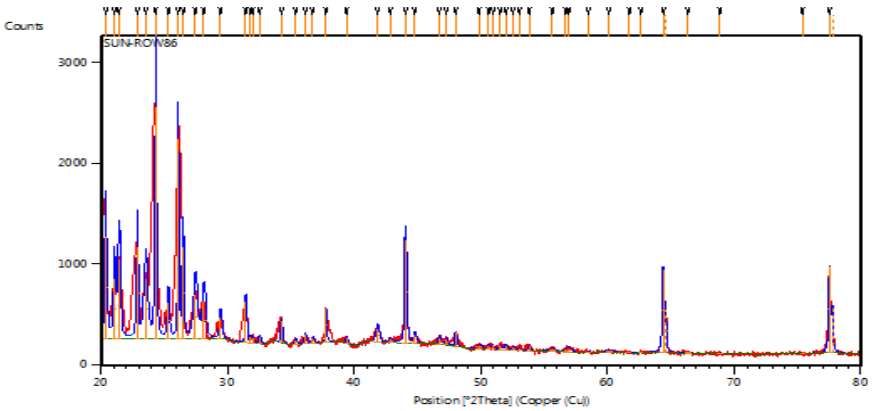

Fig 9: XRD for pure drug.

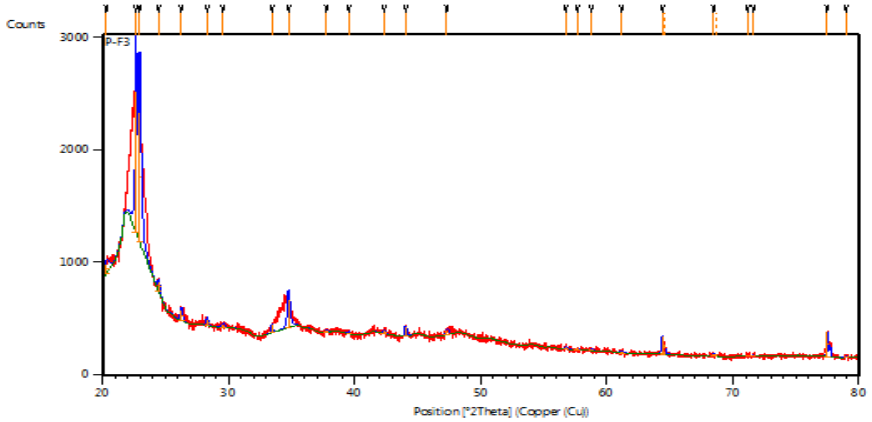

Fig 10: XRD for pellets.

Particle size determination:

The particle size of pellets was found in between 100-1000 d.nm. The average particle size was found was 1612 d.nm. it was done by using Malvern zetasizer.

In-vitro drug release

The results of in vitro percentage amount of drug released at different time intervals plotted against time to obtain the release profiles. The liquisolid compacts showed higher drug release than marketed tablet formulation. The enhanced dissolution rates of liquisolid compact compared to marketed tablet formulation may be attributed to the fact that, the drug is already in solution in PEG while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica). Thus, its release is accelerated due to its markedly increased wettability and surface availability to the dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compact. PEG facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. The dissolution profiles of the selected Carvedilol liquisolid Pellets formulation together with the dissolution profile of marketed tablet formulation tablets (MT) are presented.

***In-Vitro* dissolution study of Carvedilol liquisolid pellets in Phosphate buffer 6.8:**

Apparatus : USP type 1(basket type)
Media : phosphate buffer 6.8
Volume of media: 900 mL
Paddle RPM : 50
Temperature : 37±0.5 ^{o}C
Λmax : 242 nm

Table 9: Percent drug release.

Formulation	% Drug release in 10 mins	%Drug release in 1 Hr.
F1	31.51	91.72
F2	26.98	87.19
F3	35.10	92.09
F4	34.53	88.32
F5	34.68	90.95
F6	35.10	91.15
F7	34.19	88.32
F8	35.45	89.90
F9	34.50	96.51
Marketed tablet	20.77	79.36

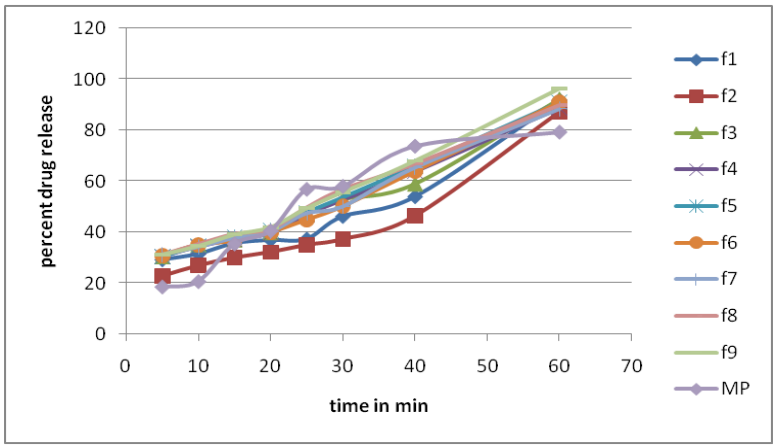

Fig 12: Drug release profile for F1 to F9 batch and marketed preparation.

Stability study:

Storage condition: 40 ^{0}C ±0.5^{0}C & relative humidity 75% ±0.2%.

No significant changes were observed during stability study hence formulation was found to be stable in mention temperature and humidity conditions.

CONCLUSION

The objective of present work was to enhance the solubility of poorly soluble drug Carvedilol. Polyethylene glycol 400 was used as non-volatile vehicle for enhancing the solubility of Carvedilol since the solubility studies revealed that the drug is soluble in it. For the formulation of the liquisolid pellets a number of excipients are available. The selection of the optimum carrier and coating material was done by formulating the liquisolid powder system of the drug with each carrier and coating material and then determining the solubility of Carvedilol in water by carrying out the saturation solubility studies for 24 hours. From this study it was found that the highest solubility enhancement yielding formulation containing Avicel PH 102 as a carrier material and Copovidone as a coating material. Then the various liquisolid powder systems were made from the two obtained optimum carrier and coating material. Again the solubility enhancement of each formulation was studied by saturation solubility studies for 24 hours. The optimized formulation was selected and evaluations were done.

Carvedilol: Polyethylene Glycol 400 liquisolid pellets:

From the findings of the study, the results can be summarized as follows -

The UV absorption spectrum of Carvedilol showed maximum absorption at 241 nm in Phosphate buffer pH 6.8. The melting point of Carvedilol by open capillary method was found to be 114-115 o C.

The saturation solubility of Carvedilol in Phosphate buffer 6.8 was 0.0392mg/ml DSC analysis data concludes that compacts of Carvedilol showed enhancement of dissolution due to the conversion of Carvedilol to a less crystalline and/or amorphous form.XRD studies were also carried out and it was found that Carvedilol was converted to amorphous form when compared. Kinetic treatment of drug release data revealed that the korsmeyer-peppas model is most appropriately fits the *in-vitro* dissolution data and gives an insight in to the possible drug release mechanisms invariably predominant by diffusion mechanism of liquisolid compact in distilled water. Liquisolid compact with batch F9 shows better drug solubility in distilled water. The in-vitro release profile of liquisolid compact of Carvedilol prepared in PEG was compared separately with marketed tablet formulation. The result shows that liquisolid Pellets of Carvedilol made in PEG shows better dissolution rate. Drug release profiles on model fitting follows first order model as best fit model. Such a way Carvedilol is BCS class II drug having low solubility and high permeability. Due to this formulation with liquisolid technique Carvedilol get shifted to BCS class I with high solubility and high permeability.

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Conflict of Interest:

We have no conflict of Interest.

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