Introduction

The poor dissolution rates of water insoluble drugs are still a substantial problem confronting the pharmaceutical industry. A great number of new and, possibly, beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution.

Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success. The technique of ‘liquisolid compacts’ is a new and promising addition towards such a novel aim. Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term ‘liquid medication’ implies oily liquid drugs and solutions or suspensions of water insoluble solid drugs carried in suitable nonvolatile solvent systems termed the liquid vehicles. Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free flowing and readily compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials. Various grades of cellulose, starch, lactose, etc., may be used as the carriers, whereas very fine particle size silica powders maybe used as the coating (or covering) materials. The industrial application of liquisolid compacts, however, can be hampered by the poor and erratic flow and compaction properties of the final liquid/powder admixtures. In previous work (Spireas et al., 1992) only the flowability of these systems, which were then termed ‘powdered solutions’ had been addressed. In later studies (Spireas, 1993), however, the flowability and compressibility of liquisolid compacts were addressed simultaneously resulting in the new formulation mathematical model of liquisolid systems, which enables one to calculate the appropriate quantities of excipients required to produce acceptably flowing and compressible powders. 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(Nelson, 1962). That is why soft gelatin elastic capsules containing solutions of such medications demonstrate higher bioavailability when compared to conventional oral solid dosage forms(Ebert, 1977). 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. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties.

In the present work, carvedilol, USP, a very slightly water soluble antihypertensive agent, was formulated into 25-mg liquisolid tablets consisting of similar powder excipients and different liquid vehicles and drug concentrations in their liquid medications. The in-vitro drug dissolution rates of such preparations were compared to those of conventionally prepared, directly compressed, tablets using a USP dissolution test apparatus II.

**Theoretical aspects**

In previous studies (Spireas, 1993), fundamental flow and compression issues have been addressed with the introduction of the new formulation mathematical model of liquisolid systems, which is based on the flowable ($\phi$-value) and compressible ($\Psi$-number) liquid retention potentials of the constituent powders. According to the new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties.

Depending on the excipient ratio ($R$) of the powder substrate, where:

$$R = \frac{Q}{q}$$

which is the fraction of the weights of the carrier ($Q$) and coating ($q$) materials present in the formulation, an acceptably flowing and compressible liquisolid system can be prepared only if a maximum liquid load on the carrier material is not exceeded. Such a characteristic amount of liquid is termed the liquid load factor ($L_f$) and defined as the weight ratio of the liquid medication ($W$) and carrier powder ($Q$) in the system, i.e.:

$$L_f = \frac{W}{Q}$$

It should be emphasized that the terms ‘acceptably flowing’ and ‘acceptably compressible’ imply preselected and desirable levels of flow and compaction which must be possessed by the final liquid: powder admixtures. Essentially, the acceptable flow and compaction characteristics of liquisolid systems are ensured and, in a way, built in during their manufacturing process via the $\phi$-value and $\Psi$-number concepts, respectively. These are recently introduced (Spireas et al., 1992;
Spireas, 1993) fundamental properties of powders and are referred to as their flowable and compressible liquid-retention potentials, respectively. The $\phi$-value of a powder represents the maximum amount of a given non-volatile liquid (e.g. polyethylene glycol) that can be retained inside its bulk (w/w) while maintaining acceptable flowability. The $\Psi$-number of a powder is defined as the maximum amount of liquid that a powder can retain inside its bulk (w/w) while maintaining acceptable compactability, namely, producing cylindrical compacts of adequate crushing strengths and acceptable levels of friability without presenting any ‘liquid-squeezing-out’ phenomena during compression. The $\phi$-value of powders may be determined using a new procedure referred to as the liquisolid flowability (LSF) test, which employs recording powder flowmetry (Gold et al., 1966) for the flow characterization of the tested liquid: powder admixtures (Spireas, 1993). The limits of acceptable flow properties of the finished liquisolid systems may be adjusted during LSF testing according to the intended process and equipment requirements and are built in the magnitude of the determined $\phi$-values of the carrier ($\phi$) and coating ($\varphi$) powder materials. The $\Psi$-number of powders may be determined using a new method.
termed the liquisolid compressibility (LSC) test or ‘pactisity testing’, which employs the recently proposed ‘pactisity theories’ (Spireas, 1993; Grover, 1998) to evaluate the compaction properties of the liquid: powder admixtures.

Accordingly, the pactisity (Ω) or maximum crushing strength of the liquisolid compacts consisting of certain liquid and powder, is inversely proportional to the liquid: solid weight ratio (Cw) of the preparations. The desired compression properties of the finished liquisolid systems maybe adjusted during pactisity testing according to the requirements of the individual target product and are, in essence, built in the magnitude of the determined Ψ-numbers of the carrier (Ψ) and coating (ψ) powders. It has been established (Spireas, 1993) that, for a given powder substrate consisting of a certain carrier and coating powders mixed at various powder excipient ratios (R), there are specific maximum liquid load factors (Lf) which must be employed in order to produce acceptably flowing liquisolid systems. Such flow able Lf values, denoted as ĆLf, are related to the R-values of their powder blends by:

\[ ĆLf = \phi + \varphi*(1/R) \]  \hspace{1cm} (4.3)

where, as mentioned earlier, \( \phi \) and \( \varphi \) are the \( \phi \)-values of the carrier and coating powder materials, respectively.

Similarly, the compressible liquid load factors, \( \Psi Lf \), required to produce liquisolid compacts with acceptable compaction properties, are related to the excipient ratios (R) of their powder substrates as follows:

\[ \Psi Lf = \Psi + \psi*(1/R) \]  \hspace{1cm} (4.4)

Where \( \Psi \) and \( \psi \) are the \( \Psi \)-numbers of the carrier and coating powders, respectively. Therefore, for any liquid medication incorporated onto a given powder substrate consisting of certain carrier and coating materials (e.g. microcrystalline cellulose and silica) blended at a specific excipient ratio (R), there exists an optimum liquid load factor, \( L_O \), required to produce acceptably flowing and, simultaneously, acceptably compressible liquisolid preparations. In essence, the \( L_O \) value required at a given powder excipient ratio for any system is equal to either its \( ĆLf \) or \( \Psi Lf \) value, whichever is less; thus:

\[ L_O = ĆLf \text{ when: } ĆLf < \Psi Lf \]  \hspace{1cm} (4.5)

or

\[ L_O = \Psi Lf \text{ when: } ĆLf > \Psi Lf \]  \hspace{1cm} (4.6)
Based on Equations. (4.1) and (4.2), as soon as the optimum liquid load factor of a given excipient ratio system is established, the appropriate quantities of carrier \( Q_0 \) and coating \( q_0 \) powder materials required to convert a given amount of liquid medication \( W \) into an acceptably flowing and compressible liquisolid system, may be calculated as follows:

\[
Q_0 = \frac{W}{L_0} \tag{4.7}
\]

and

\[
q_0 = \frac{Q_0}{R} \tag{4.8}
\]

The validity of the preceding principles has been repeatedly tested and verified by producing liquisolid compacts possessing acceptable (or anticipated at a desired level) flow and compaction properties. Several lab-scale and pilot batches of commercial and experimental drugs have been prepared by Spireas and coworkers yielding tablets of acceptable crushing strength, friability, weight variation and content uniformity, even for liquisolid compacts of a very low dose.

**Introduction to carvedilol**

Carvedilol \( (C_{24}H_{26}N_{2}O_{4}) \) is a non-selective beta blocker indicated in the treatment of mild to moderate congestive heart failure (CHF). It blocks beta-1 and beta-2 adrenergic receptors as well as the alpha-1 adrenergic receptors. (www.brugbank.ca, 2010)

![Molecular structure of carvedilol](Fig 4.2)

**Pharmacodynamics of carvedilol**

Carvedilol is a nonselective beta-adrenergic blocking agent with alphal-blocking activity and is indicated for the treatment of hypertension and mild or moderate (NYHA class II or III) heart failure of ischemic or cardiomyopathic origin. Carvedilol is a racemic mixture in which nonselective b-adrenoreceptor blocking activity is present in the S(-) enantiomer and a-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency.
Carvedilol has no intrinsic sympathomimetic activity. The effect of carvedilol's β-adrenoceptor blocking activity has been demonstrated in animal and human studies showing that carvedilol (1) reduces cardiac output in normal subjects; (2) reduces exercise-and/or isoproterenol-induced tachycardia and (3) reduces reflex orthostatic tachycardia.

**Mechanism of action**

Carvedilol is a racemic mixture in which nonselective β-adrenoceptor blocking activity is present in the S(−) enantiomer and α-adrenergic blocking activity is present in both R(+) and S(−) enantiomers at equal potency. Carvedilol's β-adrenergic receptor blocking ability decreases the heart rate, myocardial contractility, and myocardial oxygen demand. Carvedilol also decreases systemic vascular resistance via its α-adrenergic receptor blocking properties. Carvedilol and its metabolite BM-910228 (a less potent β blocker, but more potent antioxidant) have been shown to restore the inotropic responsiveness to Ca^{2+} in OH− free radical-treated myocardium. Carvedilol and its metabolites also prevent OH− radical-induced decrease in sarcoplasmic reticulum Ca^{2+}-ATPase activity. Therefore, carvedilol and its metabolites may be beneficial in chronic heart failure by preventing free radical damage.

**Table 4.1. Physical and pharmacokinetic profile of carvedilol**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>Soluble in DMSO, methanol, and methylene chloride</td>
</tr>
<tr>
<td>Melting point/boiling point</td>
<td>112-118°C</td>
</tr>
<tr>
<td>Polymorphism</td>
<td>Form I, II, and Amorphous</td>
</tr>
<tr>
<td>pKa/ pKb</td>
<td>8.74</td>
</tr>
<tr>
<td>Purity/ Assay</td>
<td>99.8% (as per COA)</td>
</tr>
<tr>
<td>Partition Coefficient</td>
<td>3.42</td>
</tr>
<tr>
<td>DSC study</td>
<td>Shows a sharp endotherm at 117°C</td>
</tr>
<tr>
<td>UV Absorption</td>
<td>Shows $\lambda_{max}$ of 242 nm in methanolic solution</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>406.5</td>
</tr>
<tr>
<td>Half life</td>
<td>7-10 h</td>
</tr>
<tr>
<td>Protein binding</td>
<td>98%</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>115 L</td>
</tr>
<tr>
<td>Clearance</td>
<td>500-700 mL/min</td>
</tr>
</tbody>
</table>
Absorption

Carvedilol is rapidly and extensively absorbed following oral administration, with an absolute bioavailability of approximately 25% to 35% due to a significant degree of first-pass metabolism.

Metabolism

Carvedilol is mainly metabolized through hepatic route. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. Demethylation and hydroxylation at the phenol ring produce three active metabolites with b-receptor blocking activity. The 4'-hydroxyphenyl metabolite is approximately 13 times more potent than carvedilol for b-blockade.

Route of elimination

Carvedilol is extensively metabolized. Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. The oxidative metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces.
The objective of the study was to enhance the aqueous solubility of carvedilol using liquisolid formulation approach. Carvedilol being BCS class II (poor solubility, high permeability) has dissolution rate as a rate limiting factor. Solubility enhancement of carvedilol causes bioavailability improvement which has been reported in literature (Wei et al., 2005). To overcome the solubility issues related with carvedilol researchers reported various methodologies namely solid dispersion preparation using Gelucire (Potluri et al., 2011), porous silica (Planinsek et al., 2011), and PVP K30 (Sharma et al., 2010). Another approach involved is complexation of carvedilol with cyclodextrin (Lofftsson et al., 2008), hydroxylpropyl β cyclodextrin (Shewale et al., 2008) and β cyclodextrin (Wen et al., 2004) SMEDDS (Wei et al., 2005) and nanoemulsifying tablets (Mahmoud et al., 2009) were also formulated successfully for the solubility enhancement of carvedilol. However, liquisolid tablet formulation strategy has not been employed to improve dissolution profile of carvedilol. To the best of our knowledge, there is no product available in the market which is formulated using liquisolid technology. This study and similar research would contribute in some way to use liquisolid technology for commercial production of formulations.
A. STANDARDIZATION OF DRUG

Carvedilol

Following tests were conducted for the standardization of the drug. Tests were performed as per the specifications laid down in literature and certificate of analysis.

Description

The drug sample was observed for color and appearance.

Solubility

Solubility of the drug in dimethyl sulphoxide (DMSO), methanol, methylene chloride and water was determined. Excess quantity of carvedilol was added to a 100 mL conical flask containing 50 mL of individual media. The flasks were kept on a mechanical shaker for a period of 24 hours. The suspensions were centrifuged, supernatant filtered and appropriately diluted. Absorbance of the solution was measured at 240 nm using UV spectrophotometer.

Melting point

Drug in finely powdered and dried state was filled in a glass capillary tube, which was sealed at one end. Range of temperature from start of melting to the end was recorded. This range was compared with the reported value.

Spectral specifications

UV Spectroscopy

Absorption of a 10 μg/ml methanolic solution was recorded on a UV spectrophotometer using a 1 cm path length quartz cuvette. The solution was scanned from 200 to 800 nm and $\lambda_{\text{max}}$ was recorded.

Infrared Spectroscopy

IR spectrum of carvedilol was recorded on a Perkin Elmer IR spectrophotometer using the KBr disc method. The spectrum obtained thus was then compared with the reference spectrum.
Differential Scanning Calorimetry

Thermogram of carvedilol was recorded on Perkin Elmer DSC instrument. The sample was scanned at 10°C/min with a 20mL/min nitrogen purge, using an identical empty pan as a reference. Thermogram obtained thus was then compared to reference thermogram through a Pyris™ software and a resultant heat difference was plotted against temperature.

X- Ray Diffraction

X-ray diffraction (XRD) pattern was recorded on a Rigaku X-ray diffractometer with a Cu Kα radiations source, voltage 40KV, current 30mA, and a scanning rate of 2 degree/min.

Particle size analysis

Particle size analysis was carried out using Malvern Mastersizer equipped with 2000 Hydro MU (range 0.02µm-2000µm). The particle size distribution analysis was carried out using a laser diffraction principle. All measurements were reported as average of triplicate readings.

Loss on Drying (LOD)

Drug (1 gm) was accurately weighed and subjected to controlled heating (100°C) for 5 min using Citizen Moisture analyzer and LOD was calculated.

B. DEVELOPMENT OF ANALYTICAL METHODS

UV Spectroscopy

Calibration curves of carvedilol were prepared in distilled water, methanol and 1% SLS solution. An accurately weighed amount of carvedilol (10 mg) was transferred to 100 mL volumetric flask. The drug was dissolved in respective media and volume was made up with the same solvent. This stock solution was diluted to give concentrations in linear range. Absorbance of these solutions was measured against respective media as blank. A series of such calibration curves were constructed and the linearity range was
determined. The above experiments were repeated in triplicate. This UV-Spectrophotometric method was used for drug content analysis and *in vitro* drug release studies.

**High Performance Liquid Chromatography (HPLC)**

A stability indicating HPLC method was developed and validated for the determination of drug content during stability studies. The chromatographic conditions followed were as follows:

<table>
<thead>
<tr>
<th>HPLC unit</th>
<th>Jasco Intelligent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pump</td>
<td>Jasco PU 980 Intelligent HPLC pump</td>
</tr>
<tr>
<td>Detector</td>
<td>Jasco MD-2015 plus UV detector</td>
</tr>
<tr>
<td>Column</td>
<td>C-18 Waters Spherisorb -5µm, ODS 4.6mm X250 mm</td>
</tr>
<tr>
<td>Mobile phase</td>
<td>Acetonitrile: water (40: 60 %v/v)</td>
</tr>
<tr>
<td>Flow rate</td>
<td>1 ml/min</td>
</tr>
<tr>
<td>Detection</td>
<td>270nm</td>
</tr>
<tr>
<td>Loop size</td>
<td>20 µL</td>
</tr>
</tbody>
</table>

**Degradation studies**

The drug was subjected to forced degradation under acidic conditions (1N HCl), basic conditions (1N NaOH) and oxidation (30% H₂O₂) by heating at 90°C for 4 hrs. A 100 µg/ml aqueous solution was prepared and accordingly treated. These solutions were further neutralized, diluted to final concentrations of 5µg/ml with the mobile phase and injected.

**Method validation**

The developed HPLC method was validated for linearity, precision, recovery, limit of detection, limit of quantification and stability of analyte.

**Linearity**

It is a measure of how well a calibration plot of response versus concentration approximates a straight line.
Carvedilol (50 mg) was accurately weighed and transferred to a 50 ml volumetric flask. Volume was made up with methanol to obtain the primary stock. This stock was suitably diluted with same solvent to obtain concentrations in the range of 1µg/ml to 5µg/ml. These individual solutions were then injected into the HPLC system. The peak areas were calculated and plotted against respective concentrations. A series of such calibration curves were constructed and the linearity range was determined. The coefficient of correlation was also computed. The above experiments were repeated in triplicate.

**Precision**

*Instrumental precision (repeatability)*

Sequential, repetitive injections (n=3) of the same sample of 5 µg/ml carvedilol concentration was carried out followed by averaging the peak areas and determination of % C.V. of all injections.

*Intra assay precision*

Solutions with 5 µg/ml concentrations from 3 different weighing were injected. Relative standard deviation of the data gave a measure of accuracy of the method.

*Inter day precision*

Duplicate analysis of 5 µg/ml samples on 2 different days was carried out and %C.V. was determined.

**Ruggedness**

A solution of 5 µg/ml was analyzed at intervals of 0, 8, and 24 hours, storing the samples at room temperature. The samples were checked for, whether there is any peak corresponding to the degradation products.

**Limit of detection (LOD)**

It is defined as the smallest amount of analyte that gives a measurable response. It was determined by first examining the noise of the instrument by injecting the mobile
phase in triplicates and finding values with the highest and lowest peak areas at a range covering the retention time of the drug. The difference in the areas gave the noise of the instrument. Peak area having three times the noise gave an estimate of the LOD.

**Limit of quantification (LOQ)**

It is the smallest concentration of analyte, which gives a response that can be accurately quantified. Noise of the instrument was determined as given above and the peak area having ten times the value of noise gave an estimate of the LOQ.

**Assay**

To determine the content of carvedilol from the tablets, 20 tablets were weighed and crushed. The mix powder equivalent to 10 mg of carvedilol was weighed accurately and transferred to a 100 ml of volumetric flask. Methanol was used for extraction. To ensure complete extraction of drug, solution was sonicated to 20 minutes and the volume was made up to 100ml. The resulting solution was centrifuged and the supernatant was diluted with the mobile phase and injected. The analysis was repeated in triplicate. The assay was reported under results and discussion of stability studies.

C. PRELIMINARY STUDIES

**Equilibrium solubility study**

Excess amount of drug (1gm) was added to 25ml of distilled water in a stoppered conical flask and the suspension was mechanically shaken for 48 hours at 25°C. The same study was repeated using aqueous solutions of different pH. The resulting suspension was filtered and analyzed using UV spectrophotometer. The absorbance was then used to calculate the equilibrium solubility of carvedilol. Similar study was carried out in various media to evaluate the effect of media change on the solubility.

**Dose number calculation**

Dose number is the critical parameter to be considered for selecting drug for solubility enhancement. Dose number is the correlation value that gives an estimate of the
“dissolution rate limiting bioavailability”. The value obtained from equilibrium solubility study was used to calculate the dose number of carvedilol using following formula:

\[
\text{Dose number} = \frac{\text{Maximum dose}}{\text{(solubility of drug X 250)}} \]

(D.3)

**Dissolution rate studies**

Carvedilol (25 mg) was accurately weighed and passed through sieve (mesh no. 60) without abrasion. The powdered drug was then subjected to dissolution studies to find out the drug release parameters. Dissolution study was carried out as per official method available on FDA dissolution methods database website, using USP type 2 apparatus in 900 mL of simulated gastric fluid without enzyme (dissolution medium) the paddles were rotated at 50 rpm. Aliquots were taken at 10, 20, 30 and 60 mins and analyzed using UV spectrophotometry at 242 nm.

**D. SELECTION OF COMPONENTS**

**Compatibility study**

Carvedilol was analyzed for compatibility with all the possible excipients to be used in formulation. Carvedilol and solid excipient were sifted through ASTM #40 and mixed in equal amounts. The liquids were mixed with the drug in equal amounts. The resultant mixtures were stored in glass vial and kept at 40ºC for 2 weeks and observed for the physical appearance of the mixture.

**Table 4.2.** List of various excipients used for compatibility study

<table>
<thead>
<tr>
<th>Solids</th>
<th>Liquids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>Polyethylene glycol 400</td>
</tr>
<tr>
<td>HPMC E5</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Microcrystalline cellulose (102)</td>
<td>Sorbitol</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Polysorbate 80</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>Oleic acid</td>
</tr>
<tr>
<td>Colloidal silicon dioxide (Aerosil 200)</td>
<td></td>
</tr>
</tbody>
</table>
Screening of liquids

Solvent to be used in the formulation was screened based on its capacity to solubilize the given amount of carvedilol. Different hydrophilic water miscible nonvolatile liquids were used for the studies. These liquids include PEG400, propylene glycol, sorbitol and polysorbate 80. Solubility of carvedilol in various components was determined as per the standard protocol (Higuchi et al., 1965) briefly, 500 mg of each of selected vehicle was added to each cap vial containing excess of drug (1 g). After sealing, mixture was heated at 40°C in water bath to facilitate solubilization. Mixing of system was done using a shaker maintained at 25°C for 48 hours. After reaching equilibrium, each vial was centrifuged at 10000 rpm for 5 min and excess insoluble carvedilol was discarded by filtration using membrane filter (0.45 µm, 13 mm). The filtrate was then suitably diluted to quantify by UV-Spectrophotometric analysis.

E. GENERAL PROCEDURES AND OPTIMIZATION

Determination of angle of repose

Standard procedure reported in the literature was followed (Parikh, 2009). Briefly 10 g or Aerosil 200 was weighed and placed in funnel which was vertically mounted at a distance of 5 cm from a horizontal plate. The material was allowed to flow to form a conical heap on plate. The height of heap (h) was determined by measuring the distance between the plate and tip of the heap. The diameter of heap (d) is determined at its base. The angle of repose (θ) was calculated as:

\[ \theta = \tan^{-1} \left( \frac{2h}{d} \right) \]  

Angle of repose corresponding to 40° corresponds to optimal flow properties (USP, 2007).

Determination of Φ value for Aerosil 200

To the 10 g of aerosil 200, increasing amounts of polyethylene glycol (PEG400) was added and mixed using mortar and pestle. The resultant blend is then subjected to determination of angle of repose. At each concentration of PEG400 the angle of repose was redetermined and the Φ value determined as:

\[ \Phi = \frac{\text{amount of liquid in g}}{\text{amount of solid in g}} \]
Φ value is then plotted against corresponding to angle of repose values. Φ value corresponding to 35° signifies the flowable liquid retention potential of Aerosil 200. Φ for the Avicel PH 102 was reported to be 0.15 (Spireas et al., 1992)

**Preparation of liquisolid blend**

Carvedilol liquisolid compacts were prepared using different water soluble nonvolatile liquids. Carvedilol was dissolved in liquid vehicle using a magnetic stirrer. All liquisolid formulation contained Avicel PH 102 (FMC, USA) as a carrier and Aerosil 200 (Degussa, Germany) as a coating material at a fixed ratio (R) of 20. The appropriate amount of carrier material Avicel PH102 (Q) was mixed with liquid medication. Defined quantity of Aerosil 200 (q) was then added to mixture under continuous mixing to make the powder admixture dry. The blend is then sifted through 40# mesh. Finally, sodium starch glycolate (SSG) (Roquette, France) was added as a disintegrant and mixed. Table 4.3 shows the composition of different liquisolid batches.

**Determination of compressibility index**

Compressibility index (C_i) is often used as a measure of flow property. Smaller values of C_i indicates good flow properties of the powder bed (Leiberman et al., 1986). C_i was determined (Brittain et al., 1995) as 20 g of blend is weighed and placed in 50 mL volumetric cylinder. Initial Volume (V_i) of the powder was noted down. The cylinder was then tapped by lifting to a height of 12 to 14 mm and allowing it to fall under its own weight, till the blend within cylinder achieves a constant volume (V_b). Compressibility index is given by following equation:

\[ C_i = \frac{(V_i - V_b)\times 100}{V_i} \]  

\[ \text{…………………(4.11)} \]

**Compression of blend into tablets**

The final blend was compressed into tablets using 13 mm round standard concave punch and die set using a single punch tabletting machine (Cadmach, India). Crushing strength of tablets were maintained 7 to 9 kg/cm².
Directly compressible conventional tablet (conventional tablet) of carvedilol was also prepared in the same manner as of liquisolid formulation except addition of liquid vehicle. Each tablet contained 25 mg of carvedilol.

**Effect of liquid vehicle**

Different water soluble no volatile liquids were used in the formulation as shown in the table along with the composition.

**Table 4.3.** Formulation composition of liquisolid systems

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>R</th>
<th>Lf</th>
<th>Cd (%w/w)</th>
<th>Liquid(mg)</th>
<th>Q (mg)</th>
<th>q (mg)</th>
<th>SSG (mg)</th>
<th>Total (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG</td>
<td>20</td>
<td>0.18</td>
<td>33.33</td>
<td>50</td>
<td>400</td>
<td>20</td>
<td>26.05</td>
<td>521.05</td>
</tr>
<tr>
<td>PG</td>
<td>20</td>
<td>0.18</td>
<td>33.33</td>
<td>50</td>
<td>400</td>
<td>20</td>
<td>26.05</td>
<td>521.05</td>
</tr>
<tr>
<td>Tween 80</td>
<td>20</td>
<td>0.18</td>
<td>33.33</td>
<td>50</td>
<td>400</td>
<td>20</td>
<td>26.05</td>
<td>521.05</td>
</tr>
<tr>
<td>Conventional Tablet</td>
<td>20</td>
<td>--</td>
<td>--</td>
<td>0.0</td>
<td>400</td>
<td>20</td>
<td>26.05</td>
<td>471.05</td>
</tr>
</tbody>
</table>

PEG: polyethylen glycol 400 and PG: Propylene glycol.

**Effect of excipient ratio**

To check the effect of different quantities of Avicel PH102, Aerosil 200 and load factor on the formulation and release behavior of carvedilol, the composition of the formulation is shown in table 4.4.

**Table 4.4.** Formulation composition with different R values for liquisolid systems

<table>
<thead>
<tr>
<th>Batch code</th>
<th>R</th>
<th>Lf</th>
<th>Cd (%w/w)</th>
<th>Liquid(mg)</th>
<th>Q (mg)</th>
<th>q (mg)</th>
<th>SSG (mg)</th>
<th>Total (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>11</td>
<td>0.26</td>
<td>30</td>
<td>58.33</td>
<td>319</td>
<td>29</td>
<td>22.7</td>
<td>454.03</td>
</tr>
<tr>
<td>R2</td>
<td>5</td>
<td>0.23</td>
<td>40</td>
<td>37.5</td>
<td>266</td>
<td>53</td>
<td>20.07</td>
<td>401.57</td>
</tr>
<tr>
<td>R3</td>
<td>8</td>
<td>0.23</td>
<td>40</td>
<td>37.5</td>
<td>266</td>
<td>33.25</td>
<td>19.04</td>
<td>380.78</td>
</tr>
<tr>
<td>R4</td>
<td>20</td>
<td>0.18</td>
<td>33.33</td>
<td>50</td>
<td>400</td>
<td>20</td>
<td>26.05</td>
<td>521.05</td>
</tr>
<tr>
<td>R5</td>
<td>20</td>
<td>0.125</td>
<td>50</td>
<td>25</td>
<td>400</td>
<td>20</td>
<td>24.74</td>
<td>494.74</td>
</tr>
</tbody>
</table>

**F. EVALUATION OF DEVELOPED FORMULATION**

**Appearance**

The general appearance of tablets, its visual identity and overall ‘elegance’ is essential for consumer acceptance, control of lot-to-lot uniformity and general tablet-to-
tablet uniformity and for monitoring the production process. The control of general appearance involves measurement of attributes such as a tablet’s size, shape, color, presence or absence of odor, taste, surface textures, physical flaws and consistency. Thus, the tablets were evaluated for above mentioned parameters by visual observation.

**Friability**

The friability of prepared tablets was measured using a friability tester (Electrolab, India). The drum was rotated at 25 rpm to complete 100 revolutions. The mass loss was determined, and % friability was calculated using following equation:

\[
\% \text{ friability} = \left( \frac{\text{loss of mass}}{\text{initial mass}} \right) \times 100 \quad \text{(4.12)}
\]

**Disintegration**

Disintegration test was performed at 37±1°C in distilled water for six tablets from each formulation using tablet disintegration unit (Electrolab, India). The tablets were considered completely disintegrated when there is no residue remains on the screen or a residue consists of a soft mass with no palpably firm or unmoistened core.

Disintegration test was performed at 37±1°C in distilled water. The tablets were considered absolutely disintegrated when no residue remained on the screen or a residue consisting of a soft mass with no palpable firm or unmoistened core observed.

**Hardness**

The hardness or crushing strength of the tablets was determined using Monsanto type hardness tester. The Monsanto hardness tester is handy for taking quick readings. The tablet was placed within the jaws of hardness tester and the scale was adjusted to zero before application of force and then force was applied till the tablet got crushed. The reading was noted down in kg/cm².

**Weight variation test**

In order to maintain dose of the active ingredient within the permissible limits, it is essential to keep weight of the tablet within specified range. Tablets (20 no.) taken randomly from the batch were weighed individually and the mean of the weight was
determined. Weight variation was found out by comparing the percent variation of the weight of individual tablet from the average weight.

<table>
<thead>
<tr>
<th>Average weight of tablet (mg)</th>
<th>Percent difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>130 or less</td>
<td>10</td>
</tr>
<tr>
<td>130 to 324</td>
<td>7.5</td>
</tr>
<tr>
<td>More than 324</td>
<td>5</td>
</tr>
</tbody>
</table>

**Content uniformity test**

The test for uniformity of content of single-dose preparations is based on the assay of the individual contents of active substance(s) of a number of single-dose units to determine whether the individual contents are within limits set with reference to the average content of the sample. Individual contents of active substance(s) of 10 dosage units were taken at random. The test was performed as per European Pharmacopoeia which states “The preparation complies with the test if each individual content is between 85 per cent and 115 per cent of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75 per cent to 125 per cent of the average content. If one individual content is outside the limits of 85 per cent to 115 per cent but within the limits of 75 per cent to 125 per cent determine the individual contents of another 20 dosage units taken at random. The preparation complies with the test if not more than one of the individual contents of the 30 units is outside 85 per cent to 115 per cent of the average content and none is outside the limits of 75 per cent to 125 per cent of the average content.”

**In vitro dissolution kinetics study**

The *In vitro* dissolution test was carried out using USP type II dissolution test apparatus (with paddles); simulated gastric fluid without enzyme was used as dissolution media. The volume of dissolution medium was 900mL maintained at 37±1°C and stirred at a paddle speed of 50 rpm (USFDA dissolution methods database).
Ten mL samples were collected at the time intervals of 10, 20, 30 and 45 min. The withdrawn samples were replaced by equal amounts of dissolution medium to maintain a sink condition and constant volume. The amount of drug release from each of the liquisolid and conventional tablets was compared with that of marketed Cardivas®.

**In vitro multimedia dissolution**

In vitro multimedia dissolution studies were done for the final optimized batch, as the carvedilol exhibited a pH dependent solubility profile. All the dissolution conditions were kept same except the dissolution medium composition. The dissolution media used for the study were pH 1.2 HCl, pH 4.5 acetate and pH 6.8 Phosphate buffer.

**Thermal analysis**

DSC measurements were carried out using an instrument Pyris 6 DSC (Perkin Elmer). Sample equivalent to 5 mg of carvedilol were accurately weighed and sealed in an aluminium pan. The measurements were performed under a nitrogen purge flow rate of 20 mL/min at 20 to 150 °C at a heating rate of 10 °C/min. An empty pan was used as reference and for calibration prior to each experiment.

**Powder X-ray diffraction analysis**

The XRPD patterns of carvedilol and liquisolid formulation were recorded in a Rigaku powder X-ray diffraction system (Miniflex, Japan) with Cu-Ka radiation. The samples were run over the most informative range from 0° to 60° of 2θ. The step scan mode was performed with a step size of 0.02° at a rate of 2°/min.

**G. STABILITY STUDIES**

The purpose of stability studies is to provide evidence on how the quality of a drug substance varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and enables recommended storage conditions and shelf life to be established.

To carry out these studies, the formulation was subjected to 25°C/60% relative humidity (R.H), 30°C/65% R.H and 40°C/75% R.H as per the stability protocol (Table 4.6). Samples were charged in stability chambers (Thermolab, India) with humidity and
temperature control. They were drawn at specified intervals for analysis over a period of 6 months. Drug content of the tablets was analyzed using previously developed and validated stability indicating HPLC method.

**Table 4.6.** Stability Protocol for carvedilol tablets

<table>
<thead>
<tr>
<th>PRODUCT NAME:</th>
<th>CARVEDILOL TABLETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BATCH NO.</td>
<td>R4</td>
</tr>
<tr>
<td>APPEARANCE</td>
<td>White tablets</td>
</tr>
<tr>
<td>TOTAL NO.</td>
<td>400 tablets</td>
</tr>
<tr>
<td>FOR SAMPLE</td>
<td>90 tablets</td>
</tr>
<tr>
<td>QUANTITY</td>
<td>6 months (stability testing as per ICH guidelines)</td>
</tr>
</tbody>
</table>
A. STANDARDIZATION OF DRUG

Carvedilol

Description

The drug was white to off white powder with a fluffy texture.

Solubility

Carvedilol was soluble to different extent in various solvents. The corresponding solubility of carvedilol is shown in following table.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility of carvedilol (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>40.22</td>
</tr>
<tr>
<td>Methanol</td>
<td>33.8</td>
</tr>
<tr>
<td>Methylene chloride</td>
<td>10.13</td>
</tr>
</tbody>
</table>

Melting point

The drug started to melt at 114°C and complete melting was observed around 116°C. Beyond 116°C a pale yellowish liquid was formed which subsequently converted into black liquid and fumes indicating its degradation.

Spectral specifications

UV spectroscopy

The prepared solution upon UV scanning in the range of 200 to 800 nm showed a \( \lambda_{\text{max}} \) of 242 nm.

![Absorption spectrum of methanolic solution of carvedilol](image)
Infrared Spectroscopy

The IR spectrum of carvedilol is shown in figure 4.4. The observed corresponding values for the presence of functional groups within the molecule are given in table 4.8.

![FTIR spectrum of carvedilol](image)

**Fig 4.4.** FTIR spectrum of carvedilol

<table>
<thead>
<tr>
<th>Values (cm(^{-1}))</th>
<th>Functional group</th>
</tr>
</thead>
<tbody>
<tr>
<td>748</td>
<td>N-H wag (secondary amine)</td>
</tr>
<tr>
<td>3345</td>
<td>O-H (broad) and N-H stretching (secondary amine)</td>
</tr>
<tr>
<td>2923</td>
<td>C-H stretching alkyl</td>
</tr>
<tr>
<td>1041 and 1256</td>
<td>C-O stretching band (ether)</td>
</tr>
<tr>
<td>1591</td>
<td>N-H bending</td>
</tr>
</tbody>
</table>

Differential Scanning Calorimetry

Thermal behavior of carvedilol is shown in fig 4.5. A subtle transition was observed at around 50°C followed by a complete melting exhibited by the presence of sharp endotherm at 116°C.
Chapter IV: Liquisolid tablets of carvedilol

Results and discussion

Fig 4.5. DSC thermogram of carvedilol

**X- Ray Diffraction**

Fig 4.6. X-ray diffraction pattern of carvedilol

Important peaks for carvedilol were found at 2θ values of 5.817, 11.64, 17.5, 18.43 and 24.24. The molecules exhibits itself into a crystalline form which usually remain less water soluble (as they contains least possible free energy and high stability) as compared to their amorphous counterpart.

**Particle size analysis**

A bimodal distribution curve was observed for the given drug sample. The particle size distribution was found to be of D_{10} (11.17µ), D_{50} (63.19µ) and D_{90} (142.11µ) with span value of 2.07. Increased particle size often results into a decreased surface area which again plays a role...
for decreased solubility/dissolution of the drug in aqueous media. This phenomenon often explained in a detailed manner using Noyes Whitney’s equation:

\[
\frac{dW}{dt} = DA(C_s - C)/L 
\]  

(4.13)

Where, 

dW/dt is rate of dissolution, 

A is the surface area of the solid, 

C is the concentration of the solid in the bulk dissolution medium, 

C_s is the concentration of the solid in the diffusion layer surrounding the solid, 

D is the diffusion coefficient, 

L is the diffusion layer thickness.

**Loss on Drying (LOD)**

Loss on drying for carvedilol was found to be 0.28% w/w. Higher values for LOD have to be taken into consideration when initial quantities of the drug calculated for the formulation development.

**B. DEVELOPMENT OF ANALYTICAL METHODS**
UVSpectroscopy

For routine analysis UV spectroscopic method was developed in various media. The developed method was found to obey Beer Lambert’s law for absorption of UV spectra in dilute solutions.

**Table 4.9.** Analytical parameters for carvedilol analysis using UV spectrophotometry

<table>
<thead>
<tr>
<th>Medium</th>
<th>Distilled water</th>
<th>SGFWE$^5$</th>
<th>pH 1.2</th>
<th>pH 4.5</th>
<th>pH 6.8</th>
<th>Methanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linearity (µg/mL)</td>
<td>1 to 7</td>
<td>1 to 8</td>
<td>1 to 5</td>
<td>1 to 4</td>
<td>1 to 10</td>
<td>1 to 5</td>
</tr>
<tr>
<td>Wavelength (nm)</td>
<td>241</td>
<td>242</td>
<td>241</td>
<td>241</td>
<td>242</td>
<td>242</td>
</tr>
<tr>
<td>Slope</td>
<td>0.139</td>
<td>0.124</td>
<td>0.181</td>
<td>0.245</td>
<td>0.113</td>
<td>0.124</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.999</td>
<td>0.999</td>
<td>0.999</td>
<td>0.999</td>
<td>0.999</td>
<td>0.999</td>
</tr>
<tr>
<td>$y$ - Intercept</td>
<td>-0.006</td>
<td>0.004</td>
<td>0.166</td>
<td>0.002</td>
<td>-0.160</td>
<td>0.330</td>
</tr>
</tbody>
</table>

$^5$ Simulated gastric fluid without enzyme

**High Performance Liquid Chromatography (HPLC)**

**Degradation studies**

The chromatographic conditions were optimized in order to obtain a good separation between drug and its degradation products. The chromatograms confirmed that carvedilol degrades in extreme conditions of pH, oxidation and heat.
Chapter IV: Liquisolid tablets of carvedilol

Results and discussion

(b)

(c)

(d)

(e)
The carvedilol was found to be degraded in acid with multiple degradations as evident from the number of peaks in the chromatogram. Carvedilol almost degraded completely during the oxidation, whereas a subtle effect of light on the stability of carvedilol in solution state was observed. Therefore, it is recommended to store the carvedilol solution in cool and dark place to avoid the light and heat degradation.

**Method validation**

The developed HPLC method was validated with respect to linearity, precision, limit of detection, limit of quantification and stability of analyte as shown in table 4.10.

<table>
<thead>
<tr>
<th>Validation Parameters for HPLC analysis of Carvedilol</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linearity</strong></td>
<td>Linearity range: 1 to 10 ppm</td>
</tr>
<tr>
<td></td>
<td>Line equation: y = 13804x - 672.5</td>
</tr>
<tr>
<td></td>
<td>Correlation Coefficient: =0.9996</td>
</tr>
<tr>
<td><strong>Instrumental precision</strong></td>
<td>Mean AUC±SD: 68095±328.852</td>
</tr>
<tr>
<td>(Repeatability)</td>
<td>%RSD: 0.482</td>
</tr>
<tr>
<td><strong>Intraday precision</strong></td>
<td>Mean AUC±SD: 68341.33±609.519</td>
</tr>
<tr>
<td></td>
<td>%RSD: 0.892</td>
</tr>
<tr>
<td><strong>Inter-day precision</strong></td>
<td>Mean AUC±SD: 68249.83±526.178</td>
</tr>
<tr>
<td></td>
<td>%RSD: 0.771</td>
</tr>
<tr>
<td><strong>Ruggedness</strong></td>
<td>0 hour Mean AUC±SD: 68095±328.852</td>
</tr>
</tbody>
</table>
C. PRELIMINARY STUDIES

Equilibrium solubility study

Solubility of the drug was also determined in water and different pH (aqueous media). Since carvedilol has ionizable groups therefore it is expected to show pH dependant solubility. The obtained solubility data is shown in figure 4.10.

Dose number calculation

Higher dose number indicates that dissolution is rate limiting step for the bioavailability of the drug in systemic circulation.

Dose number for carvedilol = 25/ (0.3*250) = 0.333

Dissolution rate studies

Fig. 4.9. pH dependant solubility of carvedilol
Carvedilol (25 mg) being an insoluble class of compound showed reluctant dissolution behavior. Most of drug particles were found to remain afloat thereby minimizing the surface area available for the dissolution and hence the poor dissolution. The dissolution needs to be performed till either 85% of drug released observed or a constant release is observed till three consecutive readings. The dissolution rate can be improved through decreasing the particle size, improving wettability and decreasing the crystallinity of API. All these features can be attained in just one technique by simply dissolving the particles in water soluble liquid.

![Dissolution profile of neat carvedilol](image-url)

**Fig 4.10.** Dissolution profile of neat carvedilol

### D. SELECTION OF COMPONENTS

**Compatibility study**

In order to be certain whether the formulation would remain stable after the product development during stability study, it is safe strategy to keep data handy about the compatibility of individual excipient with the drug in accelerated condition. Following observations were made during the compatibility studies. The study revealed incompatibility of the drug with lactose, HPMC, magnesium stearate, polysorbate 80 and oleic acid. Carvedilol is a basic compound (Guarve and Gupta, 2010) contains two nitrogen atoms which might be participating in reaction with lactose through Maillard’s reaction. Since the carvedilol is basic in nature, has a tendency for neutralization with oleic acid and hence the incompatibility.
### Table 4.11. Observations during the compatibility study for carvedilol

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Initial</th>
<th>First week</th>
<th>Second week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Off white powder</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Lactose</td>
<td>White powder</td>
<td>No change</td>
<td>Little brown particles</td>
</tr>
<tr>
<td>HPMC E5</td>
<td>White powder</td>
<td>No change</td>
<td>Brown mixture</td>
</tr>
<tr>
<td>Microcrystalline cellulose (102)</td>
<td>White powder</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>White powder</td>
<td>Slightly brown in color</td>
<td>Brown powder</td>
</tr>
<tr>
<td>Sodium starch glycolate</td>
<td>White powder</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Colloidal silicon dioxide (Aerosil 200)</td>
<td>White powder</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Polyethylene glycol 400</td>
<td>Clear liquid with some settled particle</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Clear liquid with settled particles</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>Clear liquid with settled particles</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>Pale Yellowish liquid with particles</td>
<td>Color change to light brown</td>
<td>Brown color liquid</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>Yellowish liquid</td>
<td>Pale yellow liquid</td>
<td>Pale yellow liquid</td>
</tr>
</tbody>
</table>

### Screening of liquids

In order to screen a suitable liquid vehicle for carvedilol in liquisolid formulation solubility studies were carried out. Solubility of carvedilol in various water miscible nonvolatile liquids is shown in the fig. 4.2. Highest solubility of carvedilol was found to be in PEG 400 therefore, PEG 400 was used as a liquid vehicle for liquisolid tablet formulation.
E. GENERAL PROCEDURES AND OPTIMIZATION

**Determination of $\Phi$ value for Aerosil 200**

Angle of repose for neat Aerosil 200 and Aerosil 200 loaded with various quantities of PEG400 was determined. The relationship between the two is shown in fig 4.12. Angle of repose having value of 33º was considered as cutoff (USP <1174>, 2007). The corresponding $\Phi$ value was found to be 0.7.

Therefore the load factor $L_f$ for the system can be calculated as:

$$L_f = \Phi + \varphi(1/R) \quad \ldots \ldots \ldots \ldots \ldots \ldots \ldots (4.14)$$

where, $\Phi$ and $\varphi$ are the flowable liquid retentions potentials of carrier and coating materials respectively.

From the literature the $\Phi$ value for Avicel PH 102 was taken as 0.15.

$$L_f = 0.15 + 0.7 \times (1/20) = 0.185$$

For the present liquisolid formulation the $L_f = 0.1875$ is used which is close to the calculated value.
F. EVALUATION OF DEVELOPED FORMULATION

Appearance

The tablets were white to off white in color and round biconvex in shape. The tablets were uncoated and exhibited plain surface on both sides.

Weight variation test

Twenty tablets were taken randomly. Individual weight of 20 tablets was found to be within 5.0% of the average weight. Therefore these liquisolid tablets passed the weight variation test.

Content uniformity test

The test was performed for the optimized formulation and the average assay (initial) was found to be 101%. The every individual tablet has an assay within the range of 94 to 105% (as per guidelines criterion is range within 85 to 115% of the mean value).

Friability, hardness and disintegration of tablets

Hardness, friability and disintegration time of the formulated tablet is shown in table 3. The tablets were found to have passed the acceptable hardness, friability and disintegration time. The tablets showed uniformity in weight, drug content, thickness and diameter.
Table 4.12. Hardness, friability and disintegration for liquisolid tablets and conventional tablets

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Crushing strength kg/cm²</th>
<th>% Friability</th>
<th>Disintegration time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG</td>
<td>7.0</td>
<td>0.112</td>
<td>80</td>
</tr>
<tr>
<td>PG</td>
<td>6.5</td>
<td>0.198</td>
<td>70</td>
</tr>
<tr>
<td>Tween 80</td>
<td>6.0</td>
<td>0.214</td>
<td>75</td>
</tr>
<tr>
<td>Cardivas</td>
<td>7.5</td>
<td>0.010</td>
<td>70</td>
</tr>
<tr>
<td>Conventional Tablet</td>
<td>7.5</td>
<td>0.240</td>
<td>60</td>
</tr>
<tr>
<td>R1</td>
<td>5.0</td>
<td>0.872</td>
<td>90</td>
</tr>
<tr>
<td>R2</td>
<td>6.5</td>
<td>0.215</td>
<td>76</td>
</tr>
<tr>
<td>R3</td>
<td>7.0</td>
<td>0.219</td>
<td>60</td>
</tr>
<tr>
<td>R4</td>
<td>7.0</td>
<td>0.115</td>
<td>84</td>
</tr>
<tr>
<td>R5</td>
<td>6.5</td>
<td>0.129</td>
<td>62</td>
</tr>
</tbody>
</table>

**In vitro Dissolution kinetics Study**

Liquisolid tablets containing PEG400 showed a relatively better release profile as compared to Cardivas. Liquisolid tablets release carvedilol more than 75% within the first 10 min of the dissolution. The comparative dissolution profile of carvedilol in various formulations is shown in fig. 4.13. The higher release of carvedilol from the PEG based tablets may be due to presence of drug in molecularly dispersed state (solubilized) in carvedilol. This may be due to the presence of major fraction of the drug in molecularly dispersed state in PEG.
In order to understand the effect of excipient ratio on dissolution profile of carvedilol these batches were planned. The blend used for compression into tablets was also evaluated for Carr’s index. The corresponding values of Ci are shown in Table 4.15.

Table 4.13. Ci values for different liquisolid blends

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>R5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ci (%)</td>
<td>31.81</td>
<td>35.33</td>
<td>21.43</td>
<td>25</td>
<td>20</td>
</tr>
</tbody>
</table>

R1 being highest amount of PEG containing tablet showed high dissolution of carvedilol however as expected the corresponding blend showed poor flow as exhibited by higher values of Ci. Therefore it is a prerequisite to understand that the tablet should contain higher quantity of liquid (PEG) while maintaining decent flow of blend, to avoid weight variation and content non uniformity. On the contrary R4 showed almost similar kind of dissolution profile with acceptable Ci value. Thus there will be minimal chances of weigh variation and content non uniformity. Therefore R4 was finalized as a final optimized formulation. The same formulation was subjected to further evaluation and stability studies.
In vitro multimedia dissolution

The formulation is expected to face different pH and environmental conditions. Therefore, dissolution studies were planned in dissolution media having different pH. Since the carvedilol has pH dependant solubility it is expected to have a different release profile as shown in fig 4.16. Through these studies it clear to understand that the developed formulation has improved dissolution as compared to conventional and marketed one at all pH conditions.
Fig 4.15. Carvedilol release profiles in pH a: 1.2, b: 4.5 and c: 6.8

In any of the case the drug release from the liquisolid formulation (R4) was found to be at least 80% within first 10 minutes thus complying for immediate release formulation specification.

**Thermal analysis**

Often, solubility of a substance is dependent on melting point via latent heat of fusion. Latent heat of fusion is the heat released by the substance during melting or fusion. In general, crystals having weak bonds have a low melting point and low heat of fusion, and crystals having strong bonds give high melting point and high latent heat of fusion. The structure of drug crystal had to be broken to solubilize it in a solvent. Accordingly high melting point usually reflects low solubility (Wells, 2002).
Fig. 4.16. DSC of a: neat carvedilol and b: liquisolid formulation

DSC study as shown in fig. 4.17, was used to predict the physicochemical interaction between the formulation components. The thermogram of pure carvedilol showed sharp endothermic peak at 118°C due to drug melting. Thus, indicating crystalline anhydrous state. Liquisolid formulation’s DSC thermogram masked the characteristic melting peak of carvedilol indicating complete solubilization of carvedilol and interaction between carvedilol and excipients (Mura et. al., 2005)

**Powdered X-ray diffraction studies**

Figure 4.17 revealed x-ray diffraction pattern of neat carvedilol and liquisolid formulation. There were some differences between the two samples in relative integrated intensities of each peak, which could be attribute to the interaction of carvedilol with PEG 400. The percent crystallinity for carvedilol and liquisolid formulation (R4) was found to be 34.4 and 5.4 respectively.

Fig. 4.17. XRD of a: neat carvedilol and b: liquisolid tablet
G. SABILITY STUDIES

Stability studies were performed on the optimized formulation R4. The assay, friability hardness, disintegration and dissolution pattern was found to be acceptable. With respect to these parameters a successful stability studies was done and the formulation was found to be stable upon storage. Since the formulation was found to be stable in accelerated conditions thus an assumption for the stability and subsequently shelf life of formulation can be made for a period of two years in real time.

Table 4.14. Stability data of carvedilol liquisolid tablets (R4)

<table>
<thead>
<tr>
<th>Storage condition</th>
<th>Time (months)</th>
<th>Assay (%)</th>
<th>Friability (%)</th>
<th>Disintegration (seconds)</th>
<th>Hardness (kg/cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 °C/60% RH</td>
<td>0</td>
<td>101</td>
<td>0.111</td>
<td>80</td>
<td>7.0</td>
</tr>
<tr>
<td>25 °C/60% RH</td>
<td>1</td>
<td>100</td>
<td>0.183</td>
<td>60</td>
<td>7.5</td>
</tr>
<tr>
<td>25 °C/60% RH</td>
<td>2</td>
<td>101</td>
<td>0.165</td>
<td>90</td>
<td>8.0</td>
</tr>
<tr>
<td>25 °C/60% RH</td>
<td>3</td>
<td>99.5</td>
<td>0.176</td>
<td>95</td>
<td>6.5</td>
</tr>
<tr>
<td>25 °C/60% RH</td>
<td>6</td>
<td>101.2</td>
<td>0.125</td>
<td>97</td>
<td>7.5</td>
</tr>
<tr>
<td>30 °C/65% RH</td>
<td>1</td>
<td>100</td>
<td>0.190</td>
<td>89</td>
<td>7.5</td>
</tr>
<tr>
<td>30 °C/65% RH</td>
<td>2</td>
<td>99.9</td>
<td>0.272</td>
<td>83</td>
<td>6.0</td>
</tr>
<tr>
<td>30 °C/65% RH</td>
<td>3</td>
<td>99.3</td>
<td>0.369</td>
<td>98</td>
<td>8.5</td>
</tr>
<tr>
<td>30 °C/65% RH</td>
<td>6</td>
<td>102</td>
<td>0.128</td>
<td>96</td>
<td>7.0</td>
</tr>
<tr>
<td>40 °C/75% RH</td>
<td>1</td>
<td>99</td>
<td>0.210</td>
<td>87</td>
<td>6.5</td>
</tr>
<tr>
<td>40 °C/75% RH</td>
<td>2</td>
<td>103</td>
<td>0.309</td>
<td>69</td>
<td>7.0</td>
</tr>
<tr>
<td>40 °C/75% RH</td>
<td>3</td>
<td>99.9</td>
<td>0.343</td>
<td>95</td>
<td>6.5</td>
</tr>
<tr>
<td>40 °C/75% RH</td>
<td>6</td>
<td>101</td>
<td>0.323</td>
<td>98</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Table 4.16 showed the stability data. The tablets were found to be stable upon storage as per ICH guidelines. There was no significant change in drug content of the formulation and the dissolution profile was found to remain unaltered.
Chapter IV: Liquisolid tablets of carvedilol  

Results and discussion

Fig. 4.18. Dissolution profile of carvedilol liquisolid formulation upon storage at a: 25°C/60%RH, b: 30°C/65%RH and c: 40°C/75%RH
Conclusion

This study showed that liquisolid tablet technique could be a promising and cost effective strategy for improving dissolution of poorly water soluble drugs and formulating immediate release solid dosage forms. PEG400 is a suitable nonvolatile water miscible liquid for the formulation of carvedilol liquisolid tablets containing Avicel PH 102 and Aerosil 200 at the excipient ratio \( R = 20 \) and \( L_f = 0.1875 \) without showing any squeezing out phenomena. The prepared tablets showed acceptable values with respect to disintegration, hardness and friability. Also liquisolid tablet exhibit improved dissolution profile compared to marketed formulation Cardivas®. This technique enabled the drug carvedilol to get good wettability thus improved the dissolution profile.
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References


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References


U. S. Food and Drug Administration, Dissolution Methods, Carvedilol, FDA, Silver Spring (MD), Dec 15 2005; http://www.accessdata.fda.(MD)gov/


