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Research Article

# FORMULATION AND EVALUATION OF LIQUISOLID COMPACTS OF AMLODIPINE BESYLATE

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**ABSTRACT**
Amlodipine is a long-acting calcium channel blocker used as an antihypertensive and in the treatment of angina pectoris. Like other calcium channel blockers, amlodipine acts by relaxing the smooth muscle in the arterial wall, decreasing total peripheral resistance and hence reducing blood pressure; in angina, it increases blood flow to the heart muscle. Liquisolid compacts of poorly water soluble drug Amlodipine Besylate were prepared to enhance its dissolution rate and bioavailability. Liquisolid tablets were prepared using Propylene Glycol (PG) as a non-volatile organic solvent with Avicel PH-101 as carrier and Aerosil as coating material. The prepared liquisolid systems were evaluated for flow properties such as Bulk Density, Tapped Density, Angle of Repose, Hausner's Ratio and Carr's Index. The physicochemical properties of liquisolid systems were evaluated by Infrared Spectra (IR), Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD). DSC studies revealed that there were no interactions between the drug and carrier; XRD studies demonstrated that there was a significant decrease in crystallanity of pure drug present in liquisolid system.
**Keywords**: Liquisolid, Amlodipine, Carrier Material, Coating Material, Poor Water Solubility, Powdered Solution Technology

## INTRODUCTION

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure. [1]

It has poor water solubility, thus exhibiting the problem of variable bioavailability.[2]

Formation of liquisolid compacts is the most promising method for enhancing solubility, thus promoting dissolution. Liquid formulations such as solutions or suspensions of poorly soluble drugs in a non-volatile liquid vehicle are converted into acceptably flowing and compressible powders with Liquisolid technique as described by Spireas by simple physical blending with selected excipients named the carrier and the coating material.[3-5] The liquid portion can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles. Once the carrier is saturated with liquid vehicle, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Hence, an apparently dry, free flowing, and compressible powder is obtained. Generally, various grades of microcrystalline cellulose (MCC) are used as carrier material and various grades of amorphous silicon dioxide (colloidal silica) as coating material.[6-7]

The liquid medication is to be mixed with the excipients and then compressed to tablets. It is known that more rapid release rates are achieved with smaller drug concentration in the liquid medication, since drugs in a high concentration tend to precipitate within the silica pores.[8]

### Theory of liquisolid systems

Only limited amounts of liquid can be retained by a powder while maintaining acceptable flow and compression properties. A mathematical approach for the formulation of liquisolid systems has been developed by Spireas to calculate the required amounts of powder excipients (carrier and coating materials). This approach is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potential for each powder/liquid combination.[9-10]

The Φ-value of a powder is defined as the maximum amount of a non-volatile solvent that can be retained inside its bulk while maintaining an acceptable flowability. The flowability of powder may be determined by measurement of the angle of repose or angle of slide.[11]

The Ψ-number of a powder is defined as the maximum amount of non-volatile solvent that can be retained inside its bulk while maintaining acceptable compactability resulting in compacts of sufficient hardness with no liquid leaking out during compression. The compactability may be determined by the maximum crushing strength of a one-gram tablet compacted at sufficiently high compression forces. [12]

For calculating the appropriate quantites of carrier and coating material to be used in the liquisolid system, first, liquid load factor (*Lf*) has to be determined.

$$Lf = \Phi + \varphi.(1/R)$$

where Φ and φ are the Φ-values of the carrier and coating material, respectively.

$$R = Q/q$$

*R*=represents the ratio between the weights of the carrier (*Q*) and the coating (*q*) material present in the formulation

As soon as the optimum liquid load factor is determined, the quantities of carrier (*Qo*) and coating (*qo*) material required to convert a given amount of liquid formulation (*W*) into an acceptably flowing and compressible liquisolid system may be calculated as follows:

$$Qo = W/Lo \text{ and } qo = Qo/R$$ [13-17]

## MATERIALS AND METHODS

### Materials

Amlodipine besylate was obtained as a gift sample from **Aurobindo Pharma Limited**, **Hyderabad**. Avicel PH-101 and Crospovidone were provided by Yarrow Chemical Products. Mumbai. Sodium starch glycolate and Propylene Glycol were provided by Loba Chemicals Pvt. Ltd. Mumbai. Aerosil was provided by Ipzah Pharmaceuticals. Patiala. Methanol was provided by Changshu yanyuan Chemicals. China.

### Methodology

Saturated Solubility Studies

Solubility studies of Amlodipine Besylate were carried out in Phosphate Buffer pH 6.8, Polyethylene glycol – 400, Polyethylene glycol – 600, Proplylene Glycol, Tween 80 and Span 80 to determine the best non-volatile solvent. Saturated solutions were prepared by adding excess drug to the vehicle

kept on orbital shaker for 48hrs at 25 ºC. The solutions were then centrifuged at 500 rpm for 1 hr to separate out un-dissolved drug. The solutions so obtained were diluted with methanol and the concentration of drug was analysed by UV Spectrophotometer at 366nm. [18]

Determination of angle of slide

Angle of slide is used as a measure of flow properties of powders. Determination of angle of slide is done by weighing the required amount of carrier material and placing it at one end of the metal plate having a polished surface. The end is gradually raised till the plate becomes angular to the horizontal at which powder is about to slide. This angle is known as the angle of slide. Angle of 33º is regarded as optimum.

Determination of Flowable Liquid Retention Potential (Φ value)

The term "Flowable Liquid Retention Potential" (Φ value) of a powder material describes its ability to retain a specific amount of liquid while maintaining good flow properties. The Φ value is defined as maximum weight of liquid that can be retained per unit weight of powder material in order to produce an acceptably flowing liquid / powder admixture.

$$\Phi \text{ value} = \frac{\text{weight of liquid}}{\text{weight of solid}}$$

Calculation of Liquid Load Factor ($L_f$)

Liquid Load Factor is used to calculate the amount of carrier and coating materials required in the formulation.

$$L_f = \Phi + \varphi.(1/R)$$

Where, Φ and φ are the Φ-values of the carrier and coating material, respectively.[19-20]

**Coprocessing of Superdisintegrants**

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and sodium starch glycolate (in the ratio of 1:1, 1:2 & 1:3) was added to 10ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through #44-mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through #44-mesh sieve and stored in airtight container till further use. [21]

**Preparation of Liquisolid System**

Calculated quantities of Amlodipine Besylate and proplylene glycol were accurately weighed and mixed at 25 ºC for 1 min at 60 rpm. Calculated quantities of carrier (Avicel PH-101) was incorporated to the admixture of drug + vehicle and blended thoroughly. The coat material (Aerosil 200) was added and mixed. The powder is left standing for 10 min and then it is scraped off from the walls of mortar with the help of aluminium spatula. The optimum concentration of coprocessed superdisintegrants (1:1) is then added. The formulated powder is passed through a sieve to obtain the particles of same size. Then the powder is compressed using a rotary press.

**Precompression Studies of Prepared Liquisolid Powders**

Flow properties

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.

a) Angle of repose (θ)

It was measured according to the fixed funnel method by using

$$\theta = \tan^{-1}(h/r)$$

where, h = height of the heap, r = radius of the heap

b) Bulk and tapped Density

A fixed weight of each of the liquisolid powder formulae prepared were placed in a graduated cylinder & the volume occupied was measured and the **Initial Bulk Density (ρB)**.

The cylindrical graduate was then tapped at a constant velocity till a constant volume is obtained when the powder is considered to reach the most stable arrangement; the volume of the powder was then recorded as the **Final Tapped Density (ρT)**.

c) Carr's Compressibility index (C)

$$C = [1-(\rho B/\rho T)] \times 100$$

Where, ρB = Bulk Density, ρT = Tapped Density

d) Hausner ratio (H)

$$H = \rho T/\rho B$$

Where, ρB = Bulk Density, ρT = Tapped Density [22]

Drug-Excipient Interactions

It is very important to check for any drug-excipient interactions in the dosage forms as the drug can produce toxic metabolites or total suppression of drug activity may take place due to interactions.

a) X-Ray Diffratrometry (XRD)

Polymorphic changes in the drug are important since they might affect the dissolution rate and bioavailability. Therefore, it was necessary to study these changes of Amlodipine Besylate in Liquisolid Compacts. XRD spectra of samples were recorded using a high power X-Ray Diffractrometer with Cu as target.

b) Differential Scanning Calorimetry (DSC)

The possible interactions of drug and excipients in liquisolid compact were determined by DSC. Thermograms of drug and liquisolid mixture were recorded using a differential scanning calorimeter. Accurately weighed (2-5mg) sample was heated in pierced aluminium pan from 30 ºC to 300 ºC at heating rate of 10ºC/min under stream of nitrogen at flow rate of 50ml/min. [23]

**Evaluation of Prepared Liquisolid Tablets**

Weight Variation Test

Twenty tablets were individually weighed and the average was calculated. Each tablet was observed of the deviation from the average weight.

Hardness

Tablet Hardness was measured by *Monosanto Hardness Tester*. Optimum hardness values should be 2-5 kg/cm$^2$

Friability

5 tablets were accurately weighed and placed in the drum of *Roche Friabilator*. The drum was rotated at 25rpm for 4 min. Then tablets were removed, dedusted and re-weighed.

$$F = [1-(W/W_0)] \times 100$$

Where, W = Final Weight of Tablets, $W_0$ = Initial Weight of Tablets

Optimum values of friability should be < 1 %

Disintegration Time (DT)

The DT was measured for LS tablets in distilled water at 37ºC $\pm$ 2ºC using disintegration apparatus.

Dissolution Studies

Dissolution studies of LS tablets were carried out in USP Apparatus II (Paddle Type). Tablets were placed in dissolution vessels containing 900ml of phosphate buffer (pH 6.8) maintained at 37 $\pm$ 0.5ºC at 50rpm. Sink conditions were maintained.

Wetting Time

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 6 ml of water. The tablet was placed on the paper and the time required for the complete wetting was measured.

$$\text{Water absorption ratio (R)} = \frac{W_a - W_b \times 100}{W_b}$$

Where, $W_b$ = weight of the tablet before water absorption, $W_a$ = weight of the tablet after water absorption [24]

## RESULTS AND DISCUSSION

### Saturated Solubility Studies

Saturation Solubility Studies were carried out to select the best solvent for liquisolid system. Following table gives the results of solubility studies. Amlodipine Besylate showed maximum solubility in **Propylene Glycol**, hence the same was selected as non-volatile solvent. Figure 1 shows the results of solubility studies.

### Angle of slide

Angle of slide study was performed on carrier and coat material. Table 1 shows the angle of slide of carrier and coat material.

**Table 1: Angle of Slide**

| Excipients | Angle of Slide |
|---|---|
| Avicel PH 101 | 37° (± 0.5) |
| Aerosil 200 | 29° (± 0.5) |

Each value represents mean + SD (n=3)

### Flowable Liquid Retention Potential (Φ value)

Φ value of Carrier and Coat Materials in Propylene Glycol were cited in the literature & found to be **0.164** and **1.5** respectively.

### Liquid Load Factor ($L_f$)

According to mathematical model proposed by Spireas et. al. equation for Avicel PH-101 and Aerosil 200 in Porpylene Glycol was calculated by using R values as

$$L_f = 0.164 + 1.5\ (1/R)$$

Liquisolid powder systems were prepared with different excipient ratios like 10, 15 and 20 and powder system with best flow properties was selected.

### Coprocessed Superdisintegrants

According to the trails optimum concentration was found out to be 1:1 as this concentration of sodium starch glycolate and crospovidone exhibit quick disintegration and improved drug dissolution.

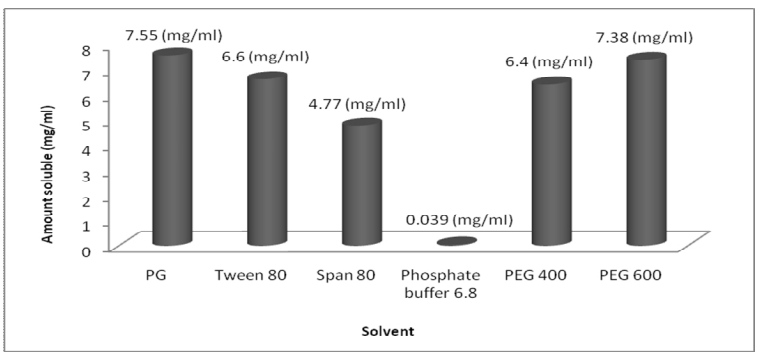


**Figure 1: Solubility Studies of Amlodpine Besylate**

### Preparation of Liquisolid System

**Table 2 : Composition of different Amlodipine liquisolid formulae prepared using PG as a liquid vehicle according to the mathematical model**

| Formulation | Amlodipine conc. in PG | R | $L_f$ | Avicel 101 Q = W/$L_f$ | Aerosil q = Q/R | Super-disintegrant 4% | Unit Weight (mg) |
|---|---|---|---|---|---|---|---|
| **F1** | 10% | 10 | 0.314 | 175.15 | 17.5 | 10 | 257.65 |
| **F2** | | 15 | 0.264 | 208.33 | 13.88 | 10 | 287.22 |
| **F3** | | 20 | 0.239 | 230.12 | 11.50 | 12 | 308.63 |
| **F4** | 20% | 10 | 0.314 | 95.54 | 9.55 | 6.4 | 141.49 |
| **F5** | | 15 | 0.264 | 113.63 | 7.57 | 6.6 | 157.81 |
| **F6** | | 20 | 0.239 | 125.52 | 6.27 | 6.8 | 168.59 |
| **F7** | 30% | 10 | 0.314 | 68.98 | 6.89 | 4 | 101.54 |
| **F8** | | 15 | 0.264 | 82.04 | 5.47 | 4.5 | 113.67 |
| **F9** | | 20 | 0.239 | 90.62 | 4.53 | 4.8 | 121.62 |

**Precompression Studies of Prepared Liquisolid Powders**

Flow Properties

**Table 3 : Flow properties of prepared liquisolid powders of respective formulae**

| Formulation | Angle of Repose (θ) | Bulk Density (g/ml) | Tapped Density (g/ml) | Carr's Index (%) | Hausner's Ratio |
|---|---|---|---|---|---|
| **F1** | 35° (± 0.5) | 0.355 (± 0.04) | 0.581 (± 0.004) | 38.888 (± 0.02) | 1.636 (± 0.012) |
| **F2** | 19.5° (± 0.5) | 0.38 (± 0.01) | 0.5541 (± 0.01) | 31.428 (± 0.08) | 1.458 (± 0.015) |
| **F3** | 15° (± 0.5) | 0.366 (± 0.02) | 0.513 (± 0.015) | 28.571 (± 0.02) | 1.4 (± 0.012) |
| **F4** | 36° (± 0.5) | 0.387 (± 0.04) | 0.688 (± 0.006) | 43.75 (± 0.01) | 1.777 (± 0.017) |
| **F5** | 35° (± 0.5) | 0.385 (± 0.05) | 0.623 (± 0.003) | 38.095 (± 0.04) | 1.615 (± 0.021) |
| **F6** | 26° (± 0.5) | 0.318 (± 0.03) | 0.716 (± 0.016) | 55.555 (± 0.06) | 2.25 (± 0.004) |
| **F7** | 30° (± 0.5) | 0.45 (± 0.04) | 0.771 (± 0.012) | 41.666 (± 0.03) | 1.714 (± 0.007) |
| **F8** | 25° (± 0.5) | 0.414 (± 0.01) | 0.725 (± 0.007) | 42.857 (± 0.02) | 1.75 (± 0.022) |
| **F9** | 36° (± 0.5) | 0.342 (± 0.04) | 0.65 (± 0.007) | 47.368 (± 0.03) | 1.9 (± 0.015) |

Drug-Excipient Interactions

X-Ray Diffratrometry (XRD)

The absence of characteristic peaks of Amlodipine in the Liquisolid system showed that the drug is entirely converted into amorphous or solublized form. The absence of crystallinity of the drug in the liquisolid system might be due to result in solublization in liquid vehicle which was absorbed into carrier material and adsorbed onto coating material.

Differential Scanning Calorimetry (DSC)

There were no interactions between drug and excipients due to absence of characteristic peak of amlidipine in Liquisolid system that is a result of complete solbilization or amorphization of drug in the non-volatile liquid vehicle.

**Evaluation of Liquisolid Tablet**

Liquisolid powder formula F8 was selected as optimized on the basis of flow properties, compressibility, hardness and drug content.

**Table 4 : Evaluation of Selected Formulation F8**

| Drug Content (%) | Disintegration Time (sec) | Hardness ($kg/cm^2$) | Friability (%) | Wetting Time (sec) | Water Absorption Ratio |
|---|---|---|---|---|---|
| 99.86 | 19.66 | 1.866 | 0.395 | 20.66 | 76.946 |

Each value represents mean (n=3)

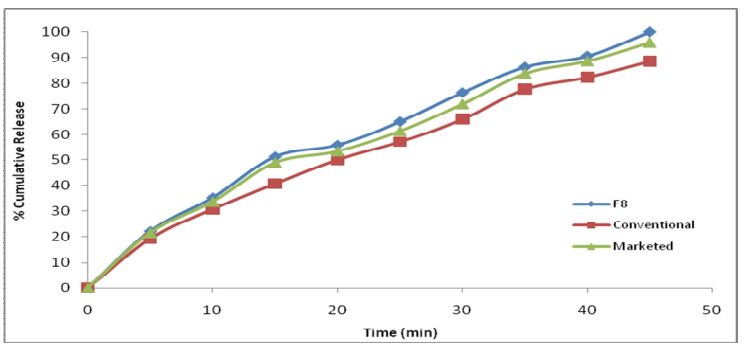


**Fig. 2 : Comparison of *in-vitro* Release Study of Optimized Liquisolid Formula F8, Conventional tablet and Marketed Formulation Of Amlodipine**

The Optimized formulation F8 showed 99.86 % release in 45 min, Conventional tablet showed 88.60% release and Marketed Formulation showed 95.78 % release. F8 exhibited higher dissolution rate as compared to Marketed Formulation and conventional tablet.

## CONCLUSION

From the above results it was possible to conclude that the wettability of Amlodipine was improved by making a suspension in Propylene Glycol as non-volatile organic solvent. Amlodpine liquisolid tablets produced a powder of optimal flow properties and readily compressible into tablets without any liquid oozing out phenomenon. The prepared tablets showed good wettability, rapid disintegration, and acceptable dissolution rate comparable to the generic product.

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