Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 3, 2013

ResearchArticle

ENHANCEMENT OF DISSOLUTION PROPERTIES OF AMLODIPINE BESYLATE USING LIQUISOLID TECHNIQUE

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Received: 30 May 2013, Revised and Accepted: 22 Jun 2013

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.

Objective: Liquisolid compacts of poorly water soluble drug Amlodipine Besylate were prepared to enhance its dissolution rate, hence bioavailability.

Methods: Liquisolid compacts were prepared by the mathematical model as defined by Spireas. Liquisolid tablets were prepared using Propylene Glycol (PG) as a non-volatile organic solvent with Avicel PH-102 as carrier and Aerosil as coating material.

Results: The optimized formulation showed increased dissolution rate as compared to the marketed formulation. The liquisolid tablet released 100% drug within 25 min of *in-vitro* dissolution studies.

Conclusion: The liquisolid technique is a promising alternative to enhance the absorption as well as dissolution rate thereby it may enhance the bioavailability of poorly soluble drugs, liquid drugs, insoluble or lipophilic drugs. Liquisolid tablets prepared were found to be superior in terms of Faster Disintegration Time, Dissolution Profile, Acceptable Tablet Properties and Stability.

Keywords: Liquisolid, Amlodipine, Carrier Material, Coating Material, Poor Water Solubility, Powdered Solution Technology

INTRODUCTION

Amlodipine being a peripheral arterial vasodilator acts directly on vascular smooth muscle to reduce peripheral vascular resistance and therefore reduction in blood pressure. It is known to have poor water solubility, thus exhibiting the problem of variable bioavailability.[1]

The most promising method for enhancing solubility, therefore promoting the rate of dissolution is the formation of liquisolid compacts.[2]With Liquisolid technique as described by Spireas 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, by simple physical blending with selected excipients named the carrier and the coating material. 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.[3-6]

The liquid medication is to be mixed with the excipients and then compressed to tablets. Since drugs in a high concentration tend to precipitate within the silica pores, it is known that more rapid release rates are achieved with smaller drug concentration in the liquid medication.[7]

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.

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.

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.

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.

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

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 and qo = Qo/R[8-9]

MATERIALS AND METHODS

Materials

Amlodipine besylate was obtained as a gift sample from *Aurobindo Pharma Limited, Hyderabad, India.* Avicel PH-102 and Crospovidone were provided by Yarrow Chemical Products. Mumbai; India. Sodium starch glycolate and Propylene Glycol were provided by Loba Chemicals Pvt. Ltd. Mumbai; India. 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 ^{0}C. 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 (Systronics, India) at 366nm.[10]

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 33^0 is regarded as optimum. [11]

Determination of Flowable Liquid Retention Potential (Φ value)& Liquid Load Factor (L_f)

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.

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

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

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

Where, Φ and φ are the Φ-values of the carrier and coating material, respectively.[12]

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. From the preliminary studies, ratio 1:1 of the prepared co-processed superdisintegrants was found out to be the optimum one.[13]

Preparation of Liquisolid System

Calculated quantities of Amlodipine Besylate and proplylene glycol were accurately weighed and mixed at 25 ^{0}C for 1 min at 60 rpm. Calculated quantities of carrier (Avicel PH-102) 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.[14]

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.Bulk Density and tapped Density play a crucial role in determining the various factors like Carr's Index and Hausner Ratio. 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)*.

Angle of repose (θ) is 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

Carr's Compressibility index (C)Hausner ratio (H)

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

Where, ρB = Bulk Density

ρT = Tapped Density[15]

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.X-Ray Diffratrometry (XRD)studies are performed to detect polymorphic changes in the drug 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.Differential Scanning Calorimetry (DSC)studies are performed todeterminethe possible interactions of drug and excipients in liquisolid compact. 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 ^{0}C to 300 ^{0}C at heating rate of 10^{0}C/min under stream of nitrogen at flow rate of 50ml/min. Fourier Transform Infrared Spectroscopy (FTIR) studies are also performed to determine the possible interactions of drug and excipients in liquisolid compact.[16-17]

Evaluation of Prepared Liquisolid Tablets

Weight Variation Test is done to determine drug content uniformity in tablets. The test is performed by weighing twenty tablets individually and the average was calculated. Each tablet was observed of the deviation from the average weight.Hardness is measured by Monosanto Hardness Tester. Optimum hardness values should be 2-5 kg/cm^2. Friability is measured with the help of Roche Friabilator. 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. Optimum values of friability should be < 1 %. Disintegration Time (DT) is measured for LS tablets in distilled water at 37^{0}C ± 2^{0}C using disintegration apparatus.

$\text{Friability} = [1-(W/W_0)] \times 100$

Where, W = Final Weight of Tablets

W_0 = Initial Weight of Tablets

***In-vitro* 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 ± 0.5^{0}C at 50rpm. Sink conditions were maintained.[18]

Application of Release Kinetics Model

Graphs of the optimized formulation were plotted. Different models like 0-order, 1st-order, Hixon Crowell, Higuchi and Korsmeyer peppas models were tested and the appropriate model which the

release follows is obtained according to the R^2. The highest value of R^2 is considered.

Accelerated Stability Studies

Tablets were kept in the Stability chamber at $40^0C \pm 5^0C$ and 75% ± 5% RH. Parameters like Hardness, Disintegration time and in-vitro Drug release were tested at time intervals of 15 days, 30 days and 60 days. The results obtained were compared with readings at 0 time interval. Ideally there should be minimum defections

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.

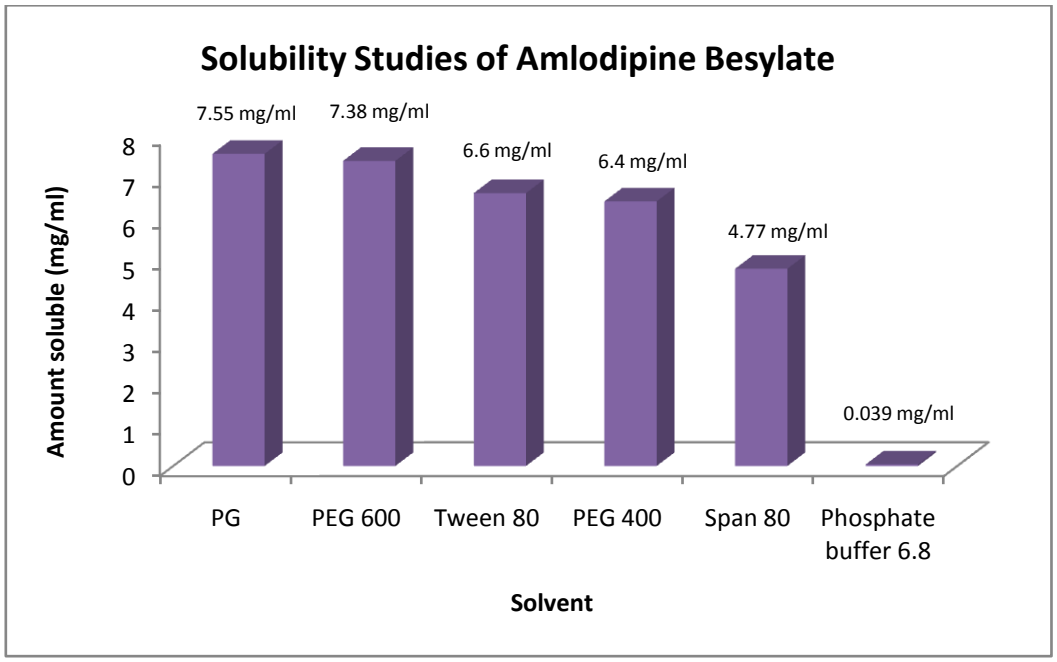


Fig. 1: It shows solubility studies of Amlodpine Besylate

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: It shows angle of slide of carriers and coat material

Excipients	Angle of Slide
Avicel PH 102	$31^0(\pm 0.5)$
Aerosil 200	$29^0(\pm 0.5)$

Each value represents mean ± SD (n=3)

Flowable Liquid Retention Potential (Φ value)& Liquid Load Factor (L_f)

Φ value of Carrier and Coat Materials in Propylene Glycol were cited in the literature & found to be **0.16** and **1.5** respectively. According to mathematical model proposed by Spireas et. al. equation for Avicel PH-102 and Aerosil 200 in Porpylene Glycol was calculated by using R values as

$$L_f = 0.16 \pm 1.5\ (1/R)$$

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 preliminary studies 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.

Preparation of Liquisolid System

Table 2: It shows 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 102 $Q = W/L_f$	Aerosil $q = Q/R$	Super-disintegrant 4%	Unit Weight (mg)
F1	10%	10	0.31	177.42	17.74	10.4	260.56
F2		15	0.26	211.54	14.11	11.6	292.24
F3		20	0.235	234.04	11.70	12.5	313.24
F4	20%	10	0.31	96.77	9.68	5.6	142.05
F5		15	0.26	115.38	7.69	6.3	159.37
F6		20	0.235	127.66	6.38	6.8	170.84
F7	30%	10	0.31	69.87	6.98	4	102.52
F8		15	0.26	83.31	5.55	4.6	115.12
F9		20	0.235	92.17	4.61	4.9	123.34

Formulation	Amlodipine conc. in PG	L_f	Neusilin US2	Super-disintegrant 4%	Unit Weight (mg)
FN	20%	1.55	19.35	2.05	51.40

Precompression Studies of Prepared Liquisolid Powders

Flow Properties

Table 3: It shows 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 Ratio
F1	40^0(± 0.5)	0.348 (± 0.04)	0.42 (± 0.004)	17.073 (± 0.02)	1.205 (± 0.012)
F2	22^0(± 0.5)	0.321 (± 0.01)	0.544 (± 0.01)	40.909 (± 0.08)	1.692 (± 0.015)
F3	38^0(± 0.5)	0.309 (± 0.02)	0.503 (± 0.015)	30.461 (± 0.02)	1.625 (± 0.012)
F4	42^0(± 0.5)	0.314 (± 0.04)	0.523 (± 0.006)	40 (± 0.01)	1.666 (± 0.017)
F5	42^0(± 0.5)	0.296 (± 0.05)	0.485 (± 0.003)	38.888 (± 0.04)	1.636 (± 0.021)
F6	23^0(± 0.5)	0.361 (± 0.03)	0.509 (± 0.016)	29.166 (± 0.06)	1.411 (± 0.004)
F7	42^0(± 0.5)	0.351 (± 0.04)	0.527 (± 0.012)	33.333 (± 0.03)	1.5 (± 0.007)
F8	32^0(± 0.5)	0.347 (± 0.01)	0.607 (± 0.007)	42.857 (± 0.02)	1.75 (± 0.022)
F9	37 (± 0.5)	0.351 (± 0.04)	0.527 (± 0.007)	33.333 (± 0.03)	1.5 (± 0.015)

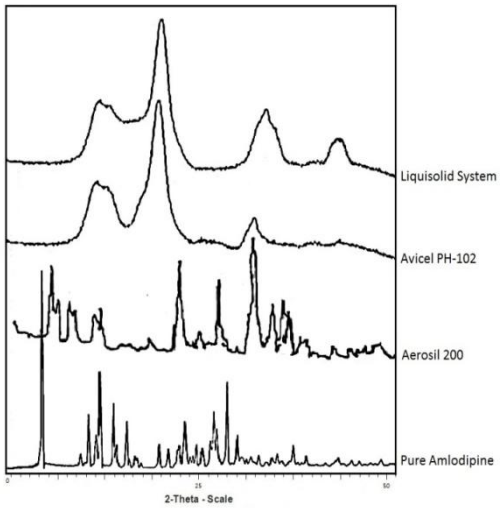
Drug-Excipient Interactions

X-Ray Diffratrometry (XRD)

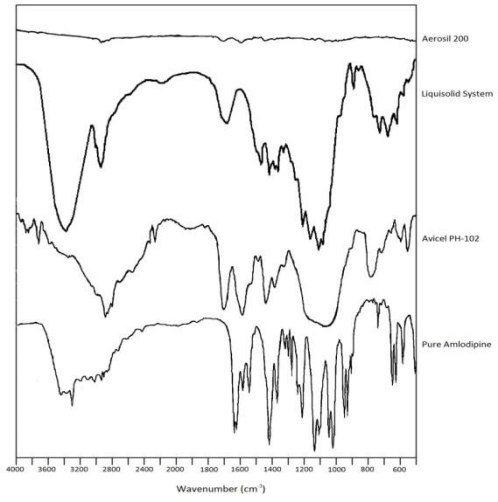
The absence of characteristic peaks of Amlodipine in the Liquisolid system showed that the drug is entirely converted into amorphous or solublized form. The absence of crystallinity of the drug in the liquisolid system might be due to result in solublization in liquid vehicle which was absorbed into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

Differential Scanning Calorimetry (DSC) & Fourier Transform Infrared Spectroscopy (FTIR)

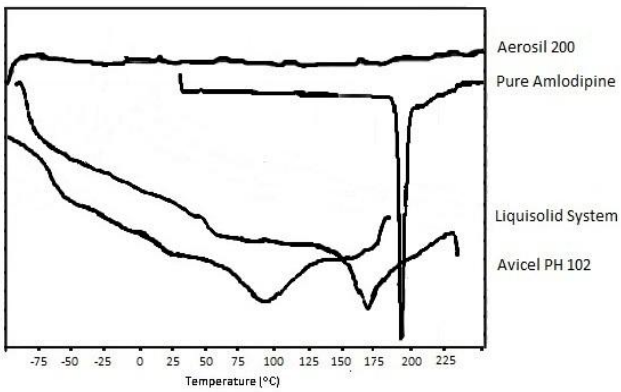
There were no interactions between drug and excipients due to absence of characteristic peak of amlidipine in Liquisolid system that is a result of complete solubilization or amorphization of drug in the non-volatile liquid vehicle.



Overlay plot of X-ray Diffraction



Overlay Plot of Fourier Transform Infrared Spectroscopy



Overlay Plot of Differential Scanning Calorimetry

Evaluation of Liquisolid Tablet

Table 4: It shows evaluation of prepared liquisolid tablets of respective formulae

Formulation	Drug Content (%)	Disintegration Time (sec)	Hardness (kg/cm^2)	Friability (%)
F1	96.26	25	2.1	0.563
F2	98.69	23	2.5	0.154
F3	95.39	20	2	0.279
F4	99.03	23	18	0.693
F5	97.38	19	2.3	0.516
F6	99.63	21	2.1	0.674
F7	95.47	25	2.4	0.464
F8	91.22	29	2.2	0.651
F9	93.61	35	1.9	1.104
FN	94.42	28	2.3	0.383

Each value represents mean (n=3)

From the above given evaluation data F6 was chosen as the optimized formulation based on drug content, hardness, disintegration time and in-vitro dissolution studies.

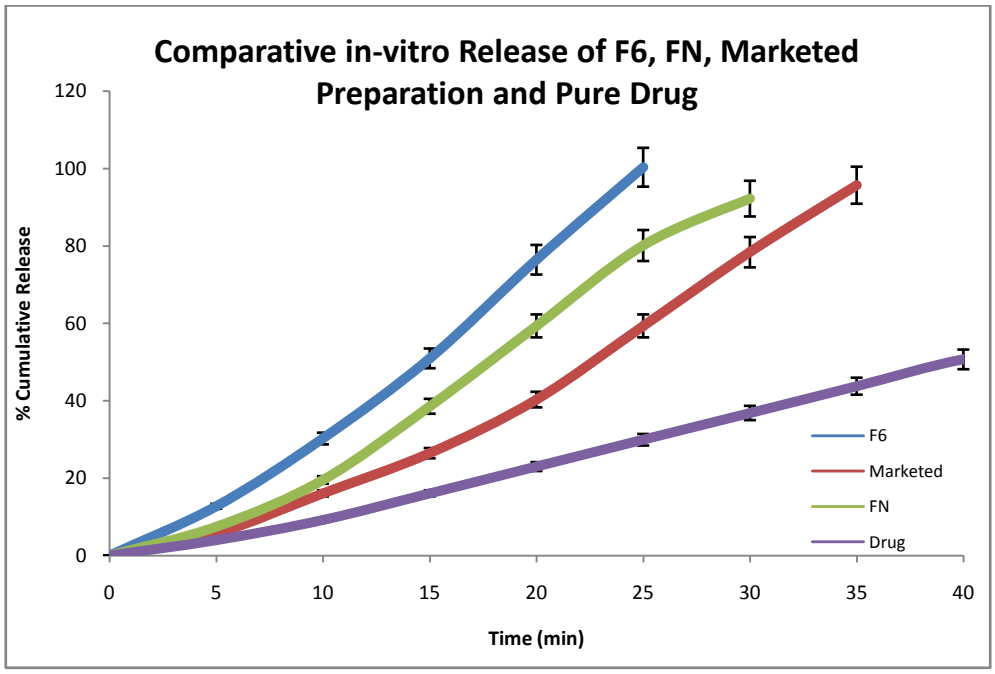


Fig. 2: It shows comparison of *in-vitro* release study of optimized liquisolid formula F6, formulation with neusilin FN,marketed formulation of amlodipine and pure drug

The Optimized formulation F6 showed 100.354 % release in 25 min, Marketed Formulation 95.78 % in 35 min, Formulation with Neusilin 92.25% in 30 min and Pure drug 54.17% in 45 min. F6 exhibited higher dissolution rate as compared to Marketed Formulation, formulation with Neusilin US2 and Pure Drug.

Application of Release Kinetics Model

Table 5: It shows R^2 values with respect to the different models

Models	R^2
0-Order	0.9871
1st-Order	0.8812
Hixon-Crowell	0.9181
Higuchi	0.9559
Korsmeyer Peppas	0.9962

The studies revealed that the release follows Korsmeyer-Peppas Model.

$M_t / M_\infty = Kt_n$

Where, M_t / M_∞ is a fraction of drug released at time t

k is the release rate constant

n is the release exponent.

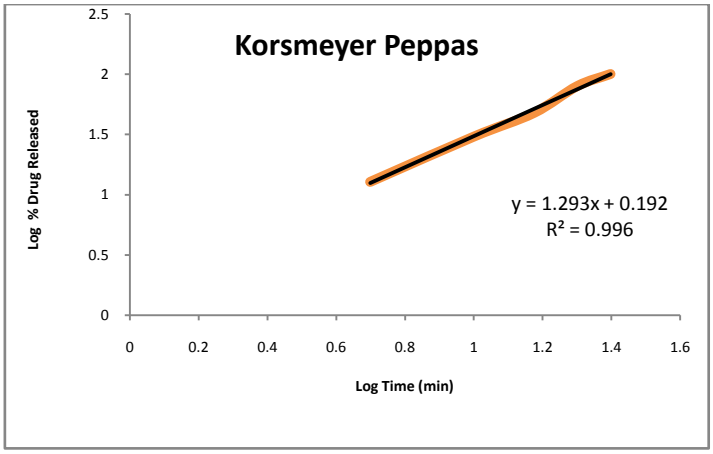


Fig. 3: It shows graph depicting the Korsmeyer Peppas model

Accelerated Stability Studies

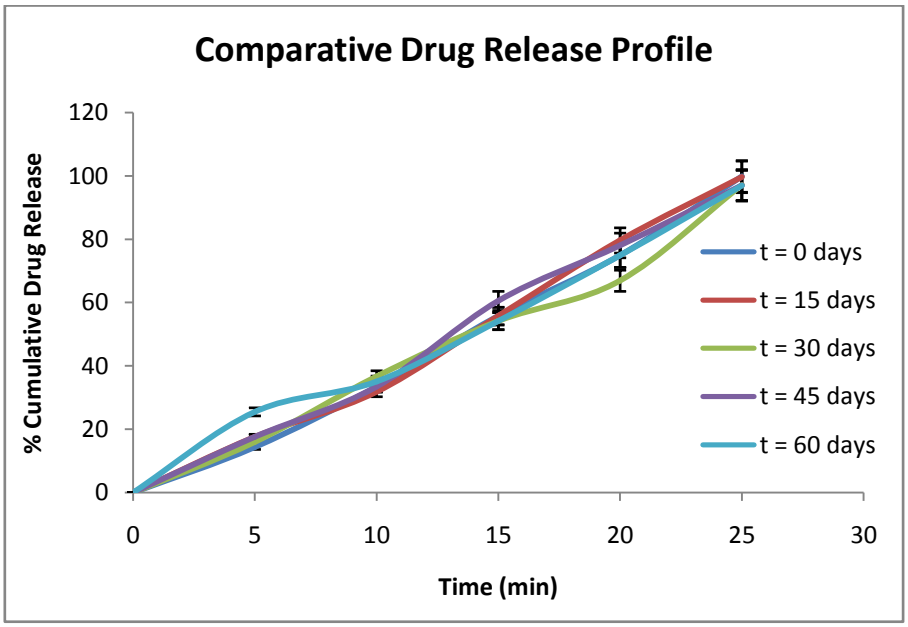


Fig. 4: It shows comparative drug release profile at different time intervals.

Table 6: It shows different calculated parameters at different time intervals

Other Parameters		
Time Period (days)	**Hardness (kg/cm²)**	**Disintegration Time (sec)**
0	2.15	22
15	2.15	23.5
30	1.95	22.5
45	1.9	24
60	2.05	23.5

The 60 day study revealed negligible change in the final release of drug, hardness and disintegration time; therefore it indicates the success of stability studies on the tablets. The graph given above shows the comparative drug release during the stability studies, hardness and disintegration time.

CONCLUSION

The liquisolid technique is a promising alternative to enhance the absorption as well as dissolution rate thereby it may enhance the bioavailability of poorly soluble drugs, liquid drugs, insoluble or lipophilic drugs.Liquisolid tablets prepared were found to be superior in terms of Faster Disintegration Time, Dissolution Profile, Acceptable Tablet Properties, Stability.The batches with more effective excipients like Neusilin caused reduction in tablet weight.The stability studies came out to be a success due to minimal deflections in the tested parameters. The technique is also used to design immediate release or sustained release systems. Therefore, this technique has potential as safe and efficacious method.

ACKNOWLEDGEMENT

We are very thankful to *Aurobindo Pharma Limited, Hyderabad. India,* for providing the gift sample of drug Amlodipine Besylate.

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