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Research Article

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Enhancement of solubility and dissolution of lercanidipine by liquisolid technique

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ABSTRACT

Lercanidipine is a BCS Class II drug having poor aqueous solubility and good permeability through the plasma membranes. Absolute bioavailability of the drug is only 10% and the main reason attributed for such a low bioavailability is poor aqueous solubility of the drug. Different methods have been tried to enhance the solubility of the drug but most of them have not been found satisfactory due to either less enhancement of solubility or limited industrial application. Liquisolid technology is one of the most promising techniques to enhance the aqueous solubility. In the present study the drug was screened with three non-volatile liquid vehicles namely PEG 400, Polysorbate 80 (Tween 80) and Propylene glycol (PG). The best result was obtained with PEG 400 because of the highest solubility of the drug in PEG 400 amongst the non-volatile liquid vehicles. Hence optimization of the formula was done taking PEG 400 to achieve 100% drug release. Avicel PH 102 and Aerosil 200 were used as carrier and coating material correspondingly. The In-vitro dissolution test was carried out with USP Type II (paddle) apparatus taking phosphate buffer (pH 6.8) as dissolution medium. The compatibility of the formulation was checked by FT-IR study. The improved wetting property and increased surface area (molecular dispersion) are believed mechanisms for enhancement of the solubility of lercanidipine. The method of production of liquisolid compact is very easy and there is no use of highly developed equipment, which makes this technology industrially applicable.

Keywords: Poorly soluble drugs, coating material, carrier material, hydrophilic solvent, liquisolid compacts, Propylene glycol (PG).

INTRODUCTION

Since the implementation of combinatorial chemistry and high throughput screening for the investigation of new chemical entities, the molecular weight and lipophilicity of drugs increase and this in turn decreases water solubility[1]. Especially poorly soluble, highly permeable active pharmaceutical ingredients (BCS Class II drugs) represent a technological difficulties, as their poor bioavailability is mainly caused by poor water solubility resulting in low drug absorption[2]. Therefore new technologies increasing the solubility. Release enhancement of poorly soluble drugs may be achieved by an increase in the drug solubility, the drug surface area, or by formulating the drug in its dissolved state: Several methodologies such as micronization[3], co-grinding[4,5], formulation of inclusion complexes[6], solid dispersions[7,8], and lipid based formulations [9] such as self-emulsifying drug delivery systems (SEDDS) have been introduced with different success.

The liquisolid systems are generally considered as acceptably flowing and compressible powdered forms of liquid medications (that implies liquid lipophilic (oily) drugs, or water-insoluble solid drugs dissolved in suitable water-miscible nonvolatile solvent systems). Such liquid medicament may be converted into a dry looking, non-sticky, acceptably flowing, and easily compressible powders by a simple admixture with selected powder excipients referred to as the carrier and coating materials. However, despite the fact that in the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder surface on which an organism is

attached in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-immiscible drug may be expected to display enhanced drug release, and consequently enhanced bioavailability [10, 11].

EXPERIMENTAL SECTION

2.1 Materials

Lercanidipine was kindly gifted by Glenmark Generics Limited (Colvale) Goa. PEG 400, Polysorbate 80 and Propylene glycol were obtained from CDH Delhi. Avicel PH 102 was obtained from Ozone International Mumbai. Aerosil 200 was obtained from Cadila Pharmaceuticals Limited, Ahmedabad.

2.2 Determination of saturation solubility

Solubility study was performed using agitation method and saturated solution of lercanidipine was prepared in respective solvent media and stirred for 24 hours. The solution was then centrifuged for 15 min over 10,000 rpm and filtered through whatmann filter paper (#44). The concentration of lercanidipine was determined using UV-visible spectrophotometer (UV-1800, Shimadzu corporation) against respective solvent as blank [12].

2.3. Preparation of liquisolid compact

First the liquid vehicle was taken into motor and the drug was added to it. The mixture was stirred well to dissolved the drug or disperse into the liquid vehicle. Then the stated amount of carrier material was added to the liquid blend and stirred well until all the liquid gets absorbed into the carrier material. Then coating material was added and further stirred for 10 minutes until the powder blend gets dry look [13, 14].

2.3.1. Screening Design

The screening design was aimed to select the best liquid vehicle from amongst PEG 400, PG and Polysorbate 80 for lercanidipine liquisolid compacts [15, 16].

Table 5.3 Formulations of liquisolid compact

Batch Code	Liq. Vehicle	Drug Conc (mg)	Lf= W/Q	Vehicle (mg)	Q (mg) Avicel PH 102	q (mg) Aerosil 200	Unit Wt (mg)
F-1	PEG400	10	0.168	50	357.14	17.86	435.00
F-2		10	0.168	25	208.33	10.42	253.75
F-3	PG	10	0.240	50	250.00	12.50	322.50
F-4		10	0.240	25	145.83	7.29	188.12
F-5	POLYSORBATE 80 (Tween 80)	10	0.210	50	285.71	14.29	360.00
F-6		10	0.210	25	166.67	8.33	210.00

2.4. Solid state characterization by instrumental analysis (FT-IR, DSC and SEM)

2.4.1. Fourier Transform Infrared Spectroscopy (FTIR)

FT-IR spectrum of the pure drug sample was recorded with Shimadzu 8400S. The interference study was carried out using FTIR analysis. The infrared absorption spectra of pure drug, polymer and physical mixture of polymer and drug were performed for polymer drug interaction studies between 4000 $cm^{-1}$to 400 cm^{-1}.

2.4.2. Differential scanning calorimetric analysis (DSC)

The possibility of any interaction between the drugs and the carriers during different approaches was assessed by carrying out thermal analysis of drug as well as the optimized formulation, using DSC. DSC analysis was performed using Shimadzu-Thermal Analyzer DSC 60 (Japan) on 1 to 5 mg samples. Samples were heated in an open aluminium pan at a rate of 10°C/min conducted over a temperature range of 50 to 300°C under a nitrogen atmosphere.

2.4.3. Scanning electron microscopy (SEM)

Morphology of prepared solid dispersion were examined by scanning electron microscope (JSM-5610, Tokyo, Japan) operating at 20.0 kV accelerating voltage. For conventional imaging in the SEM, specimens must be electrically conductive, at least at the surface, and electrically grounded to prevent the accumulation of electrostatic charge at the surface. Therefore the optimized solid dispersions were carbon coated before being subject to electron scanning. The energy of electron beam was set at 20 kV.

2.5. *In-vitro* drug release/dissolution studies

Drug release studies were carried out using paddle type dissolution test apparatus (50 rpm, 37 °C) in phosphate buffer pH 6.8. At the end of the each sampling time period 05 ml of the samples were taken and analyzed for drug

content. A 05 ml Volume of fresh dissolution medium was added to make the volume after each sample withdrawal. Sample was analyzed by UV method.

2.6 Drug content uniformity

50 mg of Liquisolid formulation was taken for content uniformity analysis. Liquisolid formulation was dissolved in 150ml of methanol and the solution was stirred for 1.5hr then it was filtered through Whatmann filter paper. Amount of drug was detected by UV spectroscopic method.

2.7 Statistical analysis [17]

All the results were expressed as mean value ± standard deviation (SD). One way analysis of variance (ANOVA) was used to test for significance, at a 5% significance level. Statistical difference dealing ($P < 0.05$) was considered significant.

RESULTS AND DISCUSSION

3.1 Saturation solubility

Saturation solubility of lercanidipine was determined in various aqueous media (PEG 400, PG, Polysorbate 80, DD water, 0.1 N HCL, phosphate buffer pH 6.8 and methanol). From the solubility profile it can be judged that the drug was very soluble in all the non-polar liquid vehicles and very slightly soluble in water and other aqueous solutions. And amongst the non-polar liquid vehicles the drug has highest solubility in PEG 400.

Table 3: Solubility study data

Liquid Vehicle	Solubility (mg/ml)
PEG 400	9.989659
PG	9.553540
Polysorbate 80 (Tween 80)	8.535761
Methanol	3.953110
Distil water	0.000871
0.1N HCl	0.000721
6.8 pH Phosphate buffer	0.000902

3.3 Fourier Transform Infrared Spectroscopy (FTIR) analysis

Fig. 3 shows the FTIR spectrum of Lercanidipine and its optimized liquisolid system. Characteristic peaks of lercanidipine at 3028.03 cm^{-1}(Ar-H), 2842.88 cm^{-1}(C-O-CH_3), 1693.38 cm^{-1}(C=O aryl aldehyde), 1649.02 cm^{-1}(nitro compound –O-N=O), 1452.30 cm^{-1}(aromatic compound C=C) were observed.

Optimized liquisolid system showed characteristic peaks of lercanidipine drug and carriers. These results indicated that there is no chemical interaction between drug and carrier when formed as liquisolid system.

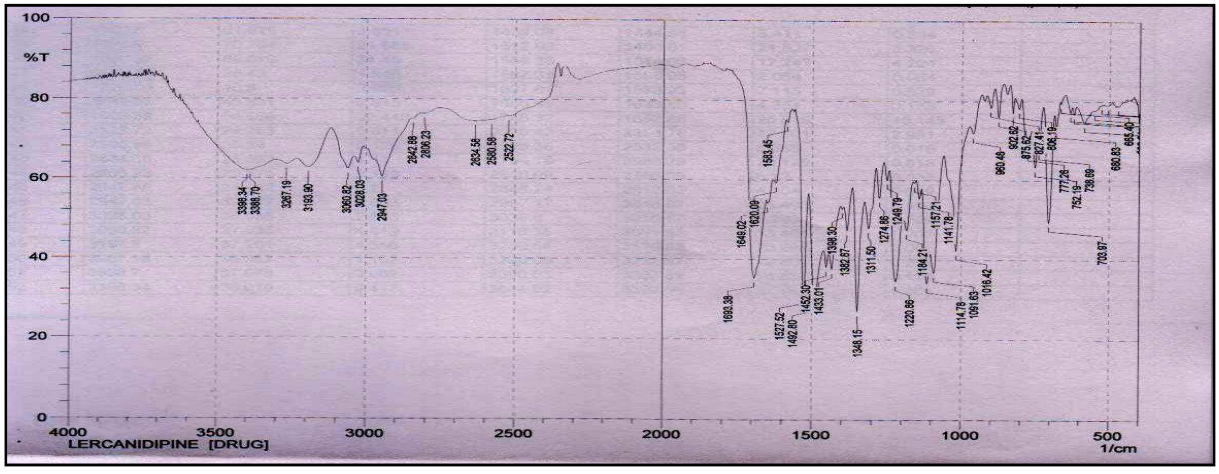


Fig. 2: FT-IR spectra of Lercanidipine

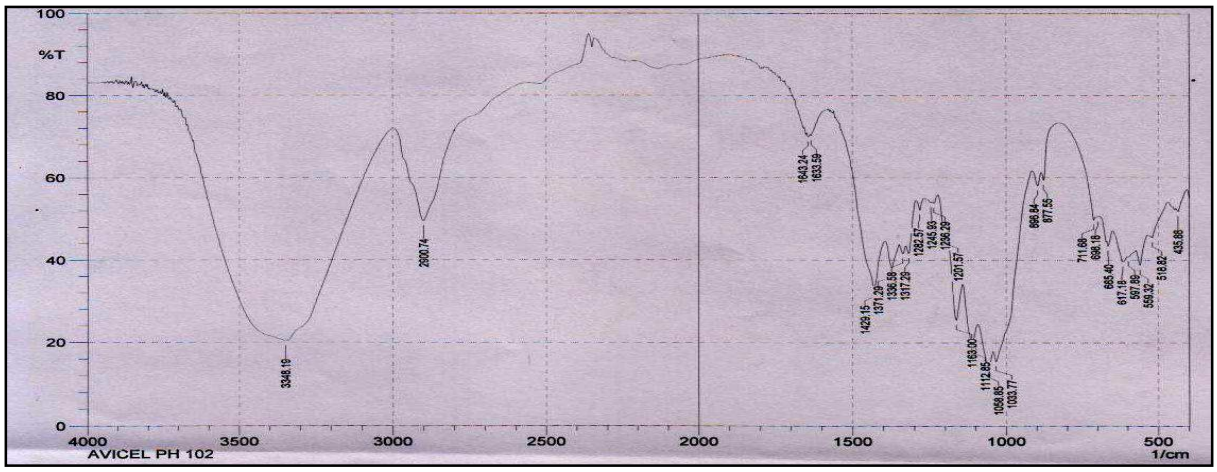


Fig. 3: FT-IR spectra Avicel PH 102

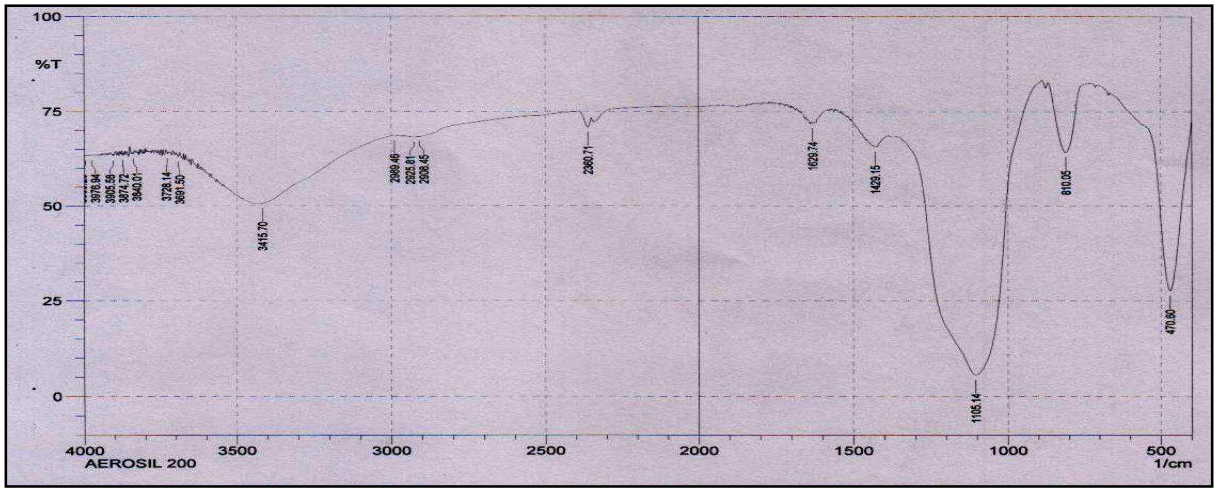


Fig. 4: FT-IR spectra of Aerosil 200

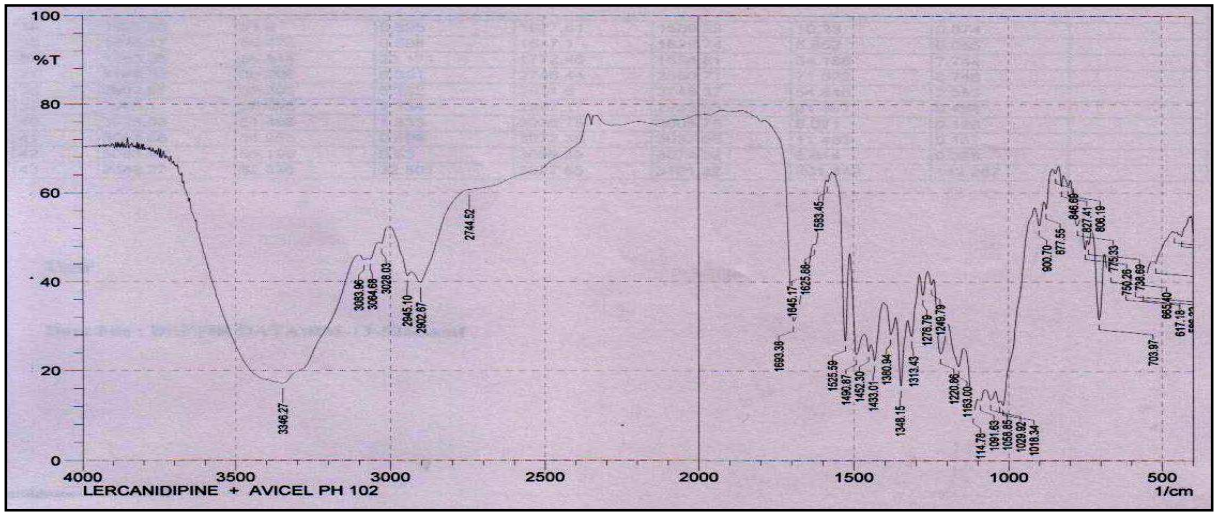


Fig. 5: FT-IR spectra of Lercanidipine and Avicel PH 102

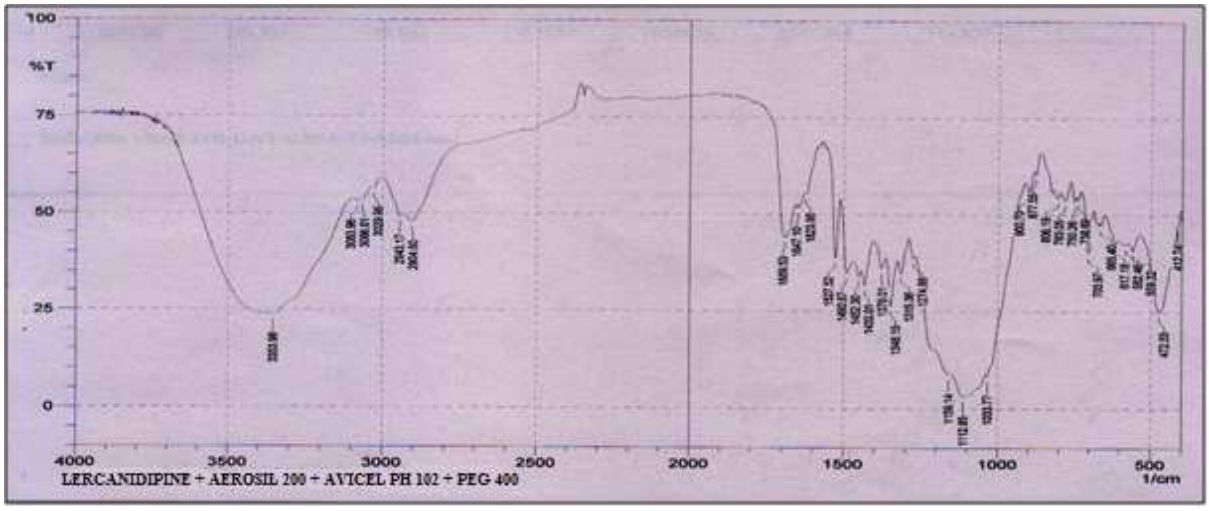


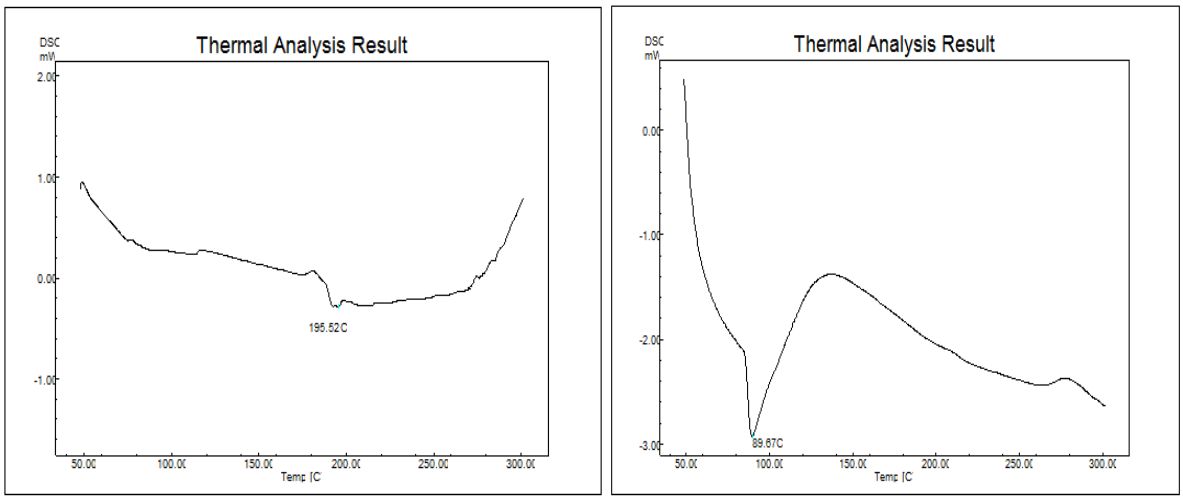
Fig. 6: FT-IR spectra of liquisolid system

3.4 Differential scanning calorimetric analysis (DSC)

Thermal behavior of pure drug and corresponding drug-carrier system is depicted in (Fig. 4) The DSC curve of lercanidipine profiles a sharp endothermic peak at 195.52ºC corresponding to its melting, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug melting was altered in the optimized liquisolid system.

A complete disappearance of the drug melting peak was observed in optimized liquisolid system (Fig. 4). It should also be noted that the incorporation of lercanidipine into PEG 400 resulted in a change in the peak temperature of the endotherms displayed by the carrier, indicating that the presence of carrier material and coatimg material. Uniform distribution of drug in the crust of liquisolid system, resulted in complete miscibility of molten drug in carrier and coating material.

Apart from this, no polymorphic changes were observed in any of the optimized formulations.



(A) **(B)**

Fig. 7: (A) DSC of lercanidipine (B) DSC of liquisol compact

3.5 Scanning electron microscopy (SEM)

For conventional imaging in the SEM, specimens must be electrically conductive, at least at the surface, and electrically grounded to prevent the accumulation of electrostatic charge at the surface. Therefore the optimized liquisolid formulation were carbon coated before being subject to electron scanning. The energy of electron beam was set at 20 kV.

The SEM results again proved the result of DSC. Scanning electron micrograph of pure Lercanidipine shows needle shaped crystals indicating the crystalline nature of the drug (Fig. 2A). The SEM images of optimized liquisolid

system are shown in Fig. 2B. SEM photomicrograph of optimized system shows that the drug particles are entrapped within the carrier matrix, confirming FTIR and DSC data analyses. This surface modification ensures the decrease in crystallinity of the drug particle. These images indicate the change in surface morphology of drug particle due to entrapment into the respective carrier and coating material.

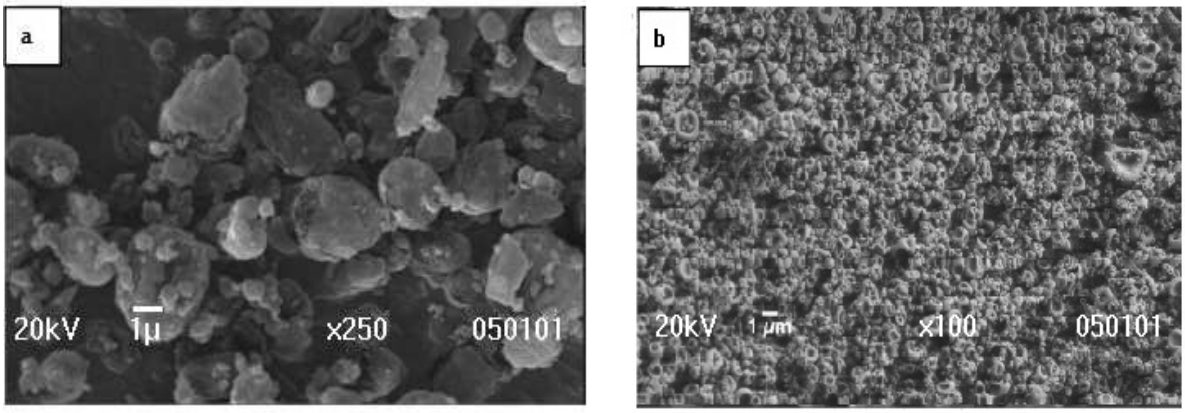


Fig. 8: Scanning electron micrograph of (A) Pure Lercanidipine (B) liquisolid system

3.6 *In-vitro* drug release/dissolution studies

To carry out *In-vitro* drug release study in phosphate buffer pH 6.8. From the results of the test for screening design. F2 shows highest amount of drug release i.e. the formulation with the PEG-400 as the liquid vehicle has the higher %drug release than PG. This was because of the higher solubility of the drug in PEG [18].

From the result of drug release it is concluded that the drug release in following order F2>F3>F1>F4>F5>F6.

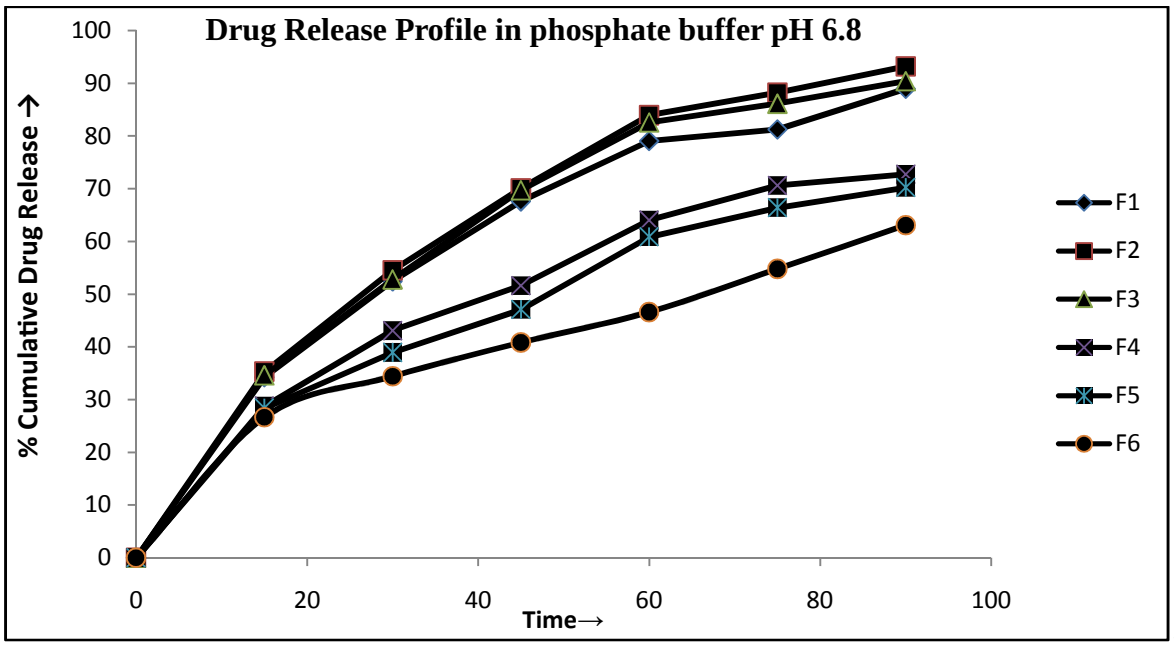


Fig. 6.1 %Drug release in phosphate buffer pH 6.8 for Screening Design

From these results, PEG-400 can be screened out as the best liquid vehicle for lercanidipine amongst the two selected liquid vehicles. Dissolution study was carried out in phosphate buffer pH 6.8 for the optimization formulations. In dissolution media, observing the %CDR profiles, it was confirmed that drug shows highest solubility from the F2 formulation. Then going from F3, F1, F4 and F5, the %CDR of the drug gets reduced gradually and the F6 formulation shows the least %CDR. The sole reason attributed for this decrease was the Molecular Fraction of the drug in the liquid vehicle. Molecular Fraction was the amount of drug in the solution/dissolved form in the liquid vehicle. As we go from the formulation F2 to F6 the amount of the liquid vehicle in the formulation gets reduced but the amount of drug remains same, that means molecular fraction of the

drug will be decreased and more amount of the drug would remain in the suspended form which will not get dissolved in the dissolution media resulting in the decreasing %CDR.

3.7 Drug content uniformity

From the result of drug content of liquisol compacts maximum amount of drug content in the F2 and then drug content of other formulation has the following order.

F2> F1> F5> F3> F4> F6

Table 6.2 Drug Content

Batch Code	Drug Content
F1	98.10 ± 1.2
F2	99.72 ± 2.2
F3	93.20 ± 1.1
F4	91.47 ± 1.5
F5	94.02 ± 1.1
F6	88.80 ± 1.4

CONCLUSION

From the above results it was possible to conclude that the wetting and surface area of lercanidipine was enhanced by making a suspension in PEG 400, the water soluble, non volatile liquid vehicle. Liquisolid system prepared using Avicel PH 102 and Aerosil 200 as a carrier and coating material respectively. A liquid load factor Lf = 0.25, and an excipient ratio R = 20, produced a powder of optimal flow properties. Liquisolid compacts technique is the optimistic alternative for the formulation of water immiscible drugs.

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