AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Studies on Liquisolid System as A technique to modify the Dissolution rate of Nifedipine

Amrutansu Panda*[1], Dinesh M. Biyani[1]

1.Department of Pharmaceutical Sciences, Birla Institute of Technology, Mesra

ABSTRACT

In the present study Liquisolid preparations of nifedipine were prepared by dissolving the drug in a chosen non-toxic, non-volatile solvent and adsorbing onto carrier materials. Various carrier and coating materials were employed in the study. Avicel PH 101 was used as the carrier material and Aerosil was used as the coating material as conventional liquisolid systems, apart from that novel excipients like Fujicalin® and Neusilin® were employed and their effects on the dissolution rate of the drug was studied. The results showed that the solubility of the drug was maximum in polysorbate 20 amongst the selected non volatile solvents i.e. Polyethylene glycol 400, 600, propylene glycol, glycerol and Tween 20. The solution of nifedipine in polysorbate 20 was found to be stable for at least 15 days. It was also found out that Fujicalin® and Neusilin® were much better adsorbents as compared to microcrystalline cellulose. Fujicalin® enhanced the drug release where as Neusilin® when used as an adsorbent retarded the rate of release. Liquisolid systems in general showed enhanced dissolution profile as compared to their directly compressed counterparts. The prepared liquisolid systems were subjected to tests such as FT-IR spectroscopy, differential scanning calorimetry (DSC) and X-Ray crystallography (PXRD) for evaluating the physiochemical properties of the drug in the liquisolid systems. Differential scanning calorimetry and X-Ray crystallography conclusively proved the loss of crystalline structure of nifedipine in the liquisolid systems, thus confirming the enhanced solubility. The optimized liquisolid compact was then compared with commercially available soft gelatine capsules.

Keywords: Dissolution Modification, Liquisolid, Nifedipine, Neusillin, Fujicalin

*Corresponding Author Email: amrutansu@gmail.com

Received 23 December 2012, Accepted 31 December 2012

Please cite this article in press as Panda A., Studies on Liquisolid System as A technique to modify the Dissolution rate of Nifedipine. American Journal of PharmTech Research 2013.

INTRODUCTION

It is well established that the therapeutic effectiveness of a drug depends upon the bioavailability which in turn is dependent on the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown[1].

The poor dissolution rates of water insoluble drugs pose a substantial problem confronting the pharmaceutical industry. Many new and possibly beneficial molecules fail to reach to the general population because of their inadequate dissolution property and poor bioavailability.

Various techniques have been employed to formulate oral drug delivery system that would enhance the dissolution profile and in turn, the absorption efficiency of poorly water soluble drugs, such as solid dispersion, micronization, lyophilization, solubilization by surfactants etc. Liquisolid system is a promising new technique which promotes the dissolution rate of water insoluble drugs[2].

Liquisolid system is a technique that can be employed to convert liquid medications such as liquid lipophilic drugs or water insoluble solid drugs dissolved in suitable non-volatile solvents into acceptably flowing and compressible powdered form. This is achieved by using selected powdered excipients called carriers and coating materials. Various grades of microcrystalline cellulose are used as carrier and very fine particle sized silica can be employed as coating materials[3].

Various studies have been carried out using liquisolid systems using drugs such as prednisolone[1], piroxicam[4], carbamazepine[5], naproxen[6], famotidine[7], repaglinide[8] etc.

In the present investigation nifedipine was chosen as a model drug and the effect of various excipients on the rate and extent of drug release was examined using liquisolid system as a dissolution modification technique.

MATERIALS AND METHODS

Materials:

Nifedipine was provided by J.B. Chemicals and Pharmaceuticals, India as gift sample. Avicel PH 101, Aerosil 200, Fujicalin(R), Neusilin(R), Explotab(R) were provided by Aurobindo Laboratories, India as gift samples. Other chemicals were used from the laboratory such as Lactose, PEG 400, PEG 600, Propylene glycol, Glycerol and Polysorbate 20 (Central Drug House, Delhi), Methanol and HCl (Merck Chemicals, Mumbai).

Solubility Studies:

The solubility study of nifedipine was carried out in various non volatile solvents to select the solvent possessing the maximum solubilizing power. The solvents screened were PEG 400, PEG 600, Propylene glycol, Glycerol and Polysorbate 20. In the study, 50mg of nifedipine was mixed with 1.0 ml of the solvents and then the mixture was kept in the dark with intermittent mixing for 6 hours. The solution was diluted to 100 ml using 0.1N HCl and then filtered. The filtrates were then analysed using UV- Visible spectrophotometer at wavelength 237.6 nm using the respective solvent as the blank to determine the concentration of the nifedipine in solution. Then percentage of nifedipine in solution was found out for each solvent. This procedure was repeated for 3 times. Then the solvent showing the maximum solubilizing effect on nifedipine was chosen for further studies.

Stability study of nifedipine in selected solvent*:*

Since nifedipine is a photosensitive drug it was imperative to study the stability of the drug in the selected solvent. For the study a solution of the drug was made by dissolving 50mg of the drug in 2 ml of the chosen solvent and kept in a closed container for 15 days in dark at room temperature. After the stipulated time period the solution was diluted to 10ml using methanol and then the volume was made up to 100 ml using 0.1N HCl and then analysed spectrophotometrically.

The resulting spectrum was studied for any changes in it as compared to the original spectrum of nifedipine. The drug content was also analysed to ensure that the amount of drug has not decreased appreciably. Another study was carried out by keeping the solution of the drug in the selected solvent in dark for 24 hours and was compared with a similar solution diluted with 0.1N HCl kept on the working place exposed to light and the change in spectrum was noted.

Powder absorption studies:

The loading factor was found out by taking 1.0 ml of the selected solvent in a mortar and then adding the selected powder excipients in small increments with constant mixing, till a free flowing powder was produced. The weight of the excipients required to produce the free flowing powder was found out. The corresponding loading factor was then calculated using the formula$L_f = \frac{W}{Q}$. Where L_f is the loading factor, W is the weight of the liquid medication and Q is the weight of the adsorbents. The coating material (Aerosil) was also added where required to get the required powder flow property. The various excipients that were employed were Lactose, Microcrystalline Cellulose (Avicel PH 101), Dibasic calcium phosphate anhydrous (Fujicalin®), Magnesium meta aluminium silicate (Neusilin®), Combination of the above excipients.

Flow Properties:

The solvent loaded powders as prepared above were studied for their flow properties. The various parameters that were studies for the powder flow properties were bulk density, tapped density, angle of repose, Carr's Index and Hausner's Ratio.

Development of formulations:

200 mg of nifedipine was taken and dissolved in 1.0 ml of the selected non volatile solvent. After a few hours of intermittent mixing in the mortar, the selected adsorbents were added slowly with continuous mixing and scraping using a metal spatula. The powder so formed was lightly triturated using pestle to break any agglomerates. Then the extra carrier/coating materials (if any) were added and mixed with spatula. The prepared formulation was kept in sealed air tight bags for at least 24 hours. The super disintegrant was later added and then the liquisolid systems were compressed into tablets using a single punch tableting machine. Various combinations of Fujicalin® and Neusilin® were tried to produce tablets having required dissolution characteristics as well as hardness. The list of formulations prepared for the study is presented in Table 1.

Table 1 List of formulations prepared for study

	Materials Used (All values are in milligrams)							
S.n	**Codes**	**Avicel**	**Aerosil**	**Fujicalin**	**Neusilin**	**Tween20**	**Explotab**	**Nifedipine**
1	DCT 1	4000	200	-	-	-	220	200
2	LS 1	4000	200	-	-	550	275	200
3	DCT 2	-	50	2500	-	-	137.5	200
4	LS 2	-	50	2500	-	1100	192.5	200
5	DCT 3	-	50	-	2000	-	112.5	200
6	LS 3	-	50	-	2000	1100	167.5	200
7	DCT 4	-	50	2000	500	-	137.5	200
8	LS 4	-	50	2000	500	1100	192.5	200
9	DCT 5	500	50	1500	500	-	137.5	200
10	LS 5	500	50	1500	500	1100	192.5	200
11	DCT 6	1000	50	1500	-	-	137.5	200
12	LS 6	1000	50	1500	-	1100	192.5	200

Evaluation:

The formulations were evaluated for the various parameters such as hardness, friability, drug content, disintegration test and dissolution study. Standard pharmacopoeial guidelines were followed in these studies.

Instrumental Analysis*:*

The formulations were analyzed using FT-IR spectroscopy, Differential Scanning Calorimetry and X-Ray Diffraction.

RESULTS AND DISCUSSION

Solubility studies:

From the solubility data, it was found out that the drug nifedipine showed maximum solubility in Tween 20 (24.830% of nifedipine was soluble in Tween 20) as compared to the other solvents used in the solubility studies i.e. glycerol (0.863%), propylene glycol (1.696%), polyethylene glycol 400 (1.867%) and polyethylene glycol 600 (2.362%).

Tween 20 was therefore selected as a suitable solvent for all further investigation because of its higher solubilizing power for nifedipine.

Stability study of nifedipine in Tween 20:

The spectrum showed no appreciable change as compared to the initial 10 µg/ml spectrum. The absorbance value also had not changed appreciably in the fifteen days of storage period. This is indicative of the fact that the drug was stable in the Tween 20 solution for at least 15 days. In Figure. 1 the stability data is shown.

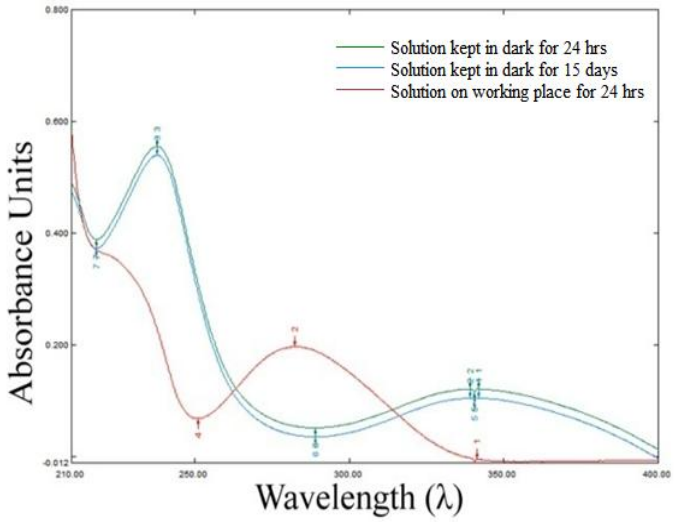

Figure. 1. Overlay spectra for stability of nifedipine for varying amount of time in different environmental conditions.

Powder absorption studies:

From the values of loading factor it is evident that Neusilin ® has the best carrying capacity. With Lactose it was not possible even with 12 times the amount for Tween 20 to be absorbed. Apart from these, various other combinations were also tried to get acceptable hardness and disintegration time for tablets, because other formulations (except with lactose) showed acceptable flow characteristics. In Table 2 the loading factors of the various formulations are shown.

Table 2 Loading factor of various excipients and its influence on the Angle of Repose.

Sl. No	Tween 20 (in mg)	Carrier material	Weight of carrier (in mg)	Aerosil(Coating material) (In mg)	5%Explotab	Total weight of adsorbents (In mg)	Loading factor $Lf = \frac{W}{Q}$	Angle of Repose
1	550 mg	Avicel PH 101	4000	200	210	4410	0.1247	36.5 º
2	550 mg	Lactose	6000	300	315	6615	0.0831	39.5 º
3	1100 mg	Fujicalin ®	2500	50	127.5	2667.5	0.4123	27.22 º
4	1100 mg	Neusilin ®	2000	50	127.5	2177.5	0.5051	28.25 º
5	1100 mg	Fujicalin®+ Neusilin® (3:2)	2300 (2500)	50	127.5	2477.5	0.4439	27.61 º

Flow properties:

Table 3 shows the flow properties of the various formulations. It was found the flow properties of DCT1 and LS1 with MCC as carrier and Aerosil ® as coating material were poor as compared to all the other formulations. The liquisolid formulation of microcrystalline cellulose showed the highest angle of repose of 36.51º. The formulation for DCT 1 also showed the highest angle of repose amongst the other directly compressed formulations.

Table 3 Flow properties of formulations

Sl. No.	Formulation Code	Angle of repose	Bulk Density ρ_B	Tapped Density ρ_T	Carr's Index $(1-(\frac{\rho B}{\rho T})x100$	Hausner's Ratio $\left(\frac{\rho T}{\rho B}\right)$
1	DCT 1	34.15 º	0.32	0.44	27.27	1.38
2	LS 1	36.51 º	0.37	0.54	31.48	1.46
3	DCT 2	27.56 º	0.33	0.45	26.66	1.36
4	LS 2	28.25 º	0.57	0.67	15	1.09
5	DCT 3	26.55 º	0.15	0.21	28.57	1.40
6	LS 3	27.22 º	0.21	0.32	34.37	1.52
7	DCT 4	28.91 º	0.29	0.38	23.68	1.31
8	LS 4	28.19 º	0.40	0.56	28.57	1.40
9	DCT 5	28.15 º	0.35	0.44	20.45	1.26
10	LS 5	28.75 º	0.41	0.52	21.15	1.27
11	DCT 6	29.82 º	0.33	0.47	29.78	1.42
12	LS 6	29.91 º	0.39	0.48	18.75	1.23

Formulations with only Neusilin® acting as the carrier and coating material (DCT 3 and LS 3) showed the best flow properties amongst all other formulations, with an angle of repose of 26.55º and 27.22º for DCT 3 and LS 3 respectively. They also showed low values for Carr's index. LS3 though containing higher proportion (1 ml) of non volatile solvent showed the lowest value of Carr's index (15) amongst all the formulations as well as if compared to its own directly compressible counterpart.

Evaluation of formulations:

Weight variation test:

From the a weight variation test it was inferred that all the tablets prepared passed the test for weight variation and are well within the pharmacopoeial (IP 2007) limit of ±7.5% for tablets weighing between of 80 – 250 mg.

Hardness test:

In the hardness test LS compacts containing only Fujicalin® as the carrier and the coating material produced the softest tablets having the hardness of only 0.5 kg/cm^2, 5% PVP was tried as a binder to enhance the hardness of the tablet but it showed no significant increase in hardness. It can be attributed to the fact that Tween 20 oozed outside during compaction producing soft moist tablets in the formulation. On the other hand Liquisolid compacts containing only Neusilin® as the carrier and coating material showed the maximum hardness amongst all the formulations both in the LS and DCT categories.

Drug content test:

All the tablets passed the test for drug content possessing values within the limits of 90-110% as specified by the Indian Pharmacopoeia.

Disintegration test:

The DCT of Fujicalin® showed the fastest disintegration time of around 12 seconds. Whereas Neusilin® showed the longest disintegration time of around 38:09 minutes. It was also found out that all the liquisolid compacts showed increase in disintegration time as compared to their non liquisolid counterparts. This increase in disintegration time may be attributed to the presence of non volatile solvent in the liquisolid compacts which acts as a binder and produces tablets which have greater hardness and increased disintegration time as it was also evident from tablet hardness.

The liquisolid compacts having only Neusilin ® as the carrier and coating material did not disintegrate even after sixty minutes in the disintegration time apparatus. All the other formulations showed acceptable disintegration time i.e. less than 15:00 minutes.

Friability test:

It was found out that except the liquisolid compacts formulated by using Fujicalin® as both the carrier and coating material, all other formulations passed the friability test, since their friability was well within (1%) the prescribed limit for loss of weight in friability testing.

In vitro dissolution test:

The IP paddle apparatus was used for all the dissolution studies using 0.1N HCl as the

dissolution media. The findings of the dissolution are as follows:

Generally all the liquisolid systems showed enhanced drug release as compared to their directly compressed counterparts, with one exception being the formulation LS3, its liquisolid compact showed slowed release as compared to its directly compressed counterpart and was prepared using Neusilin® as the carrier and coating material,. The liquisolid formulation LS5 (500mg of Avicel, 500 mg of Neusilin(R) and 1500 mg Fujicalin(R)) showed the highest amount of drug release as compared to all other formulations. All other formulations showed drug release between the two extremes. It was also found that increase in the amount of solvent (Tween 20) enhanced the release of the drug. It was found that formulations prepared using Fujicalin® showed enhanced drug release where as formulations prepared with Neusilin® as carrier and coating materials retarded the release of the drug.

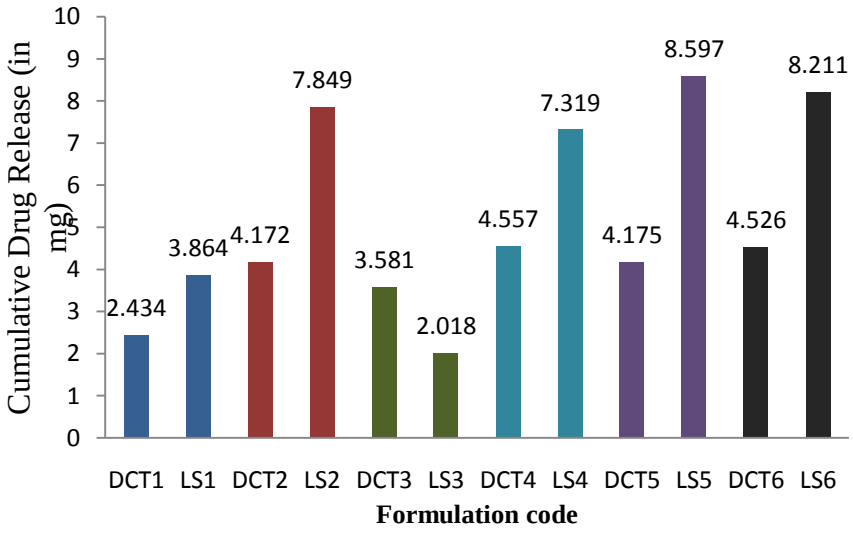

Figure. 2. Bar graph representation of the drug release of the various formulations

Table 4 Cumulative drug release of the various formulations prepared.

DCT		LS	
Formulation Code	**CDR in mg at 120 mins (mean ±SD)**	**Formulation code**	**CDR in mg at 120 mins (Mean ± SD)**
DCT1	2.434 ± 0.003	LS1	3.864 ± 0.051
DCT2	4.172 ± 0.084	LS2	7.849 ± 0.009
DCT3	3.581 ± 0.134	LS3	2.018 ± 0.013
DCT4	4.557 ± 0.550	LS4	7.319 ± 0.340
DCT5	4.175 ± 0.077	LS5	8.597 ± 0.013
DCT6	4.526 ± 0.424	LS6	8.211 ± 0.014

So Fujicalin® can be used to enhance the dissolution rate and Neusilin® can be used to retard the same. These inferences can be correlated to the basic materials of Fujicalin® and Neusilin®. Fujicalin® is dibasic calcium phosphate anhydrous where as Neusilin® is Magnesium Aluminum

Metasilicate. Fujicalin® is already anhydrous in nature and it is a phosphate salt which is quite water soluble where as magnesium aluminum silicates are water insoluble. Calcium salts are dibasic where as aluminum salts are tribasic. In Table 4 the cumulative drug release of the various formulations are shown. Figure. 2 also represent the cumulative drug release.

Comparison with marketed formulations:

The formulation showing the best release LS5 was compared with the commercially available immediate release soft gelatin capsule. It was found that the immediate release liquisolid compact performed much better in the first 5 min as compared to that of the commercially available soft gelatin capsules by releasing 15.29 times more drug as compared to that of the commercial formulation. After the 5 min interval the commercial product showed burst release, releasing almost the entire drug content where as the liquisolid formulation released 85.97% of the drug. The comparative data of the drug release from commercially available soft gelatin capsule and LS 5 is shown in Table 5. The comparative dissolution profile of the two formulations is shown in the Figure. 3.

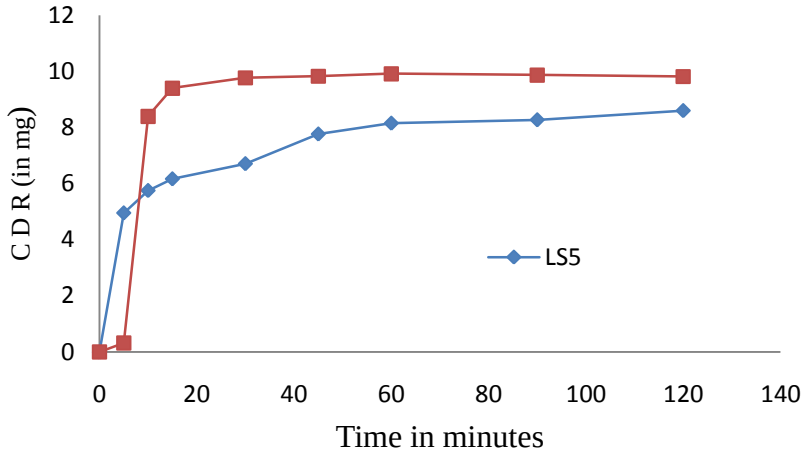

Figure.3. Dissolution profile of LS5 and Marketed formulation (capsule)

Table 5 Comparison of LS5 and Commercially available soft gelatin capsules

Sl. No.	Time in min	Cumulative drug release (marketed)	Cumulative drug release (LS5)
1	0	0	0
2	5	0.324 ± 0.070	4.954 ± 0.083
3	10	8.396 ±0.115	5.751 ± 0.071
4	15	9.402 ± 0.003	6.166 ± 0.057
5	30	9.773 ± 0.035	6.707 ± 0.005
6	45	9.831 ± 0.004	7.764 ± 0.033
7	60	9.918 ± 0.008	8.148 ± 0.001
8	90	9.871 ± 0.001	8.269 ± 0.015
9	120	9.818 ± 0.003	8.597 ± 0.013

FT-IR Spectroscopy:

FT-IR spectroscopy was performed on the pure drug, on the solution of the drug in Tween 20, Tween 20 and Physical mixture of the formulations prepared. In pure nifedipine characteristic peaks were found at 3331.06 cm^{-1}, 1624.06 cm^{-1}, 1120.64 cm^{-1}, 1529.55cm^{-1} and 1228.54cm^{-1}corresponding to N-H Stretching, -C=C- aromatic stretching, C-O ester stretching, C-NO_2 stretching and C-C-(O)-C stretching respectively as represented in Figure.4. All the peaks of nifedipine were retained in the physical mixtures of the drug but The IR spectra of nifedipine in Tween 20 solution showed only one peak of the Nitro group (C-NO_2 stretching) at 1529 $cm^{-1,}$ which may be attributed to the fact that the broad peaks of Tween 20 masked the peaks of the nifedipine. Although IR spectra of nifedipine liquisolid formulation is suggestive of some incompatibility of such system but at the same time the UV spectra of nifedipine solution in Tween 20 indicates the molecular integrity of nifedipine in Tween 20.It can also be supported by the retaining of the absorption maxima and respective absorbance of nifedipine in Tween 20 in section Figure.1.

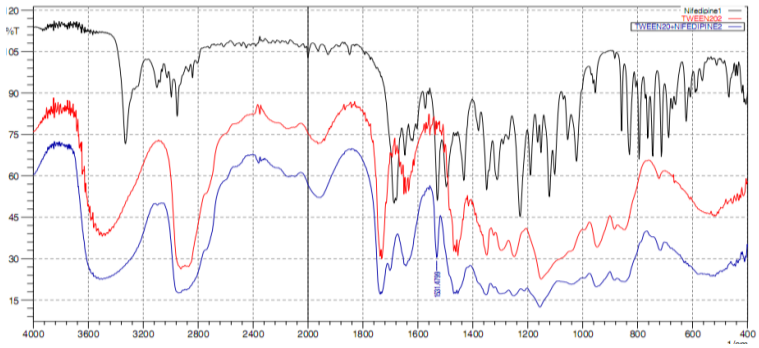

Figure. 4. Overlay FT-IR Spectra of nifedipine (black) Tween 20 (blue) and Solution of nifedipine in Tween 20 (Red)

Differential scanning calorimetry:

In the thermogram in Figure.5 it can be seen that pure nifedipine shows a sharp endothermic peak at 173.2º C which corresponds to the melting point of nifedipine (172ºC -174ºC). In the physical mixtures (directly compressible formulations) of nifedipine with Fujicalin® and Neusilin®, it was found that the peak of nifedipine was preserved, highlighting the integrity of the drug in the given physical mixtures. The thermograms are represented in Figure. 5.

The thermogram of the liquisolid system showed complete loss of the nifedipine peak which is due to the fact that the drug has lost its crystalline structure and is present in its molecularly dispersed form. Hence it can be inferred that nifedipine has been completely solubilized in Tween 20.

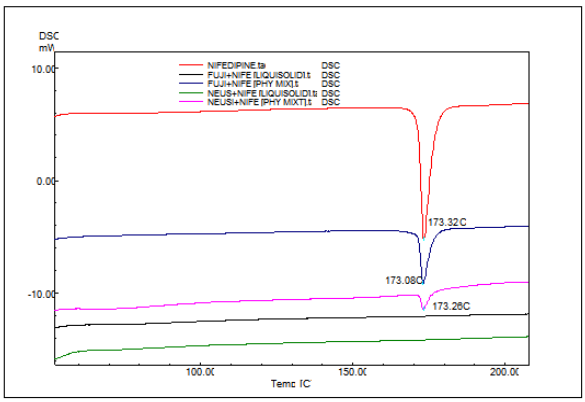

Figure. 5. Thermograms of the drug, drug and physical mixture and liquisolid syste

PXRD Studies:

The API and the prepared formulations prepared were subjected to powder X-Ray diffraction. In the physical mixtures the diffraction patterns of the pure drug were present (though with reduced intensity). But in the liquisolid systems all the peaks of the nifedipine API were lost. So it can be inferred that in the liquisolid system the crystal lattice of the drug were absent suggesting that the drug was present in the molecularly dispersed form in the liquisolid systems. The X-Ray diffraction patterns are shown in the Figure.6, 7 and 8. The peaks of Nifedipine are clearly absent in the X-Ray diffraction pattern of the liquisolid system in Figure. 8.

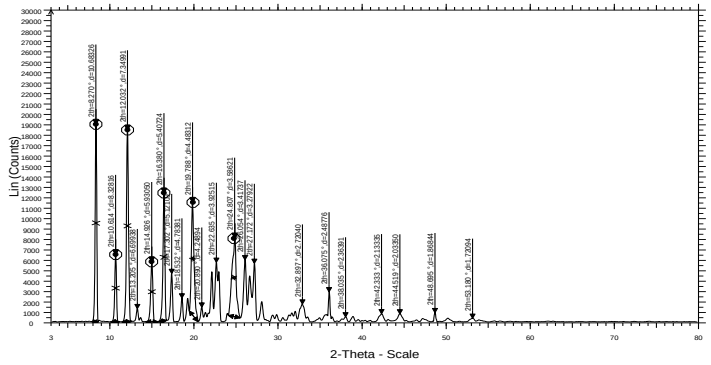

Figure. 6. X-Ray diffraction pattern of pure Nifedipine

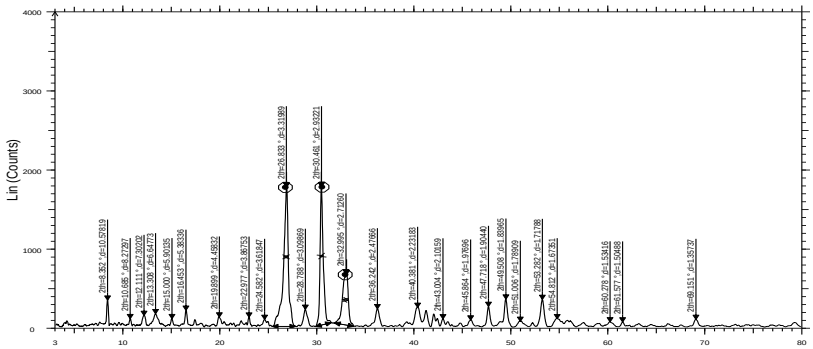

Figure. 7. X-Ray diffraction pattern of physical mixture of Nifedipine and Fujicalin®

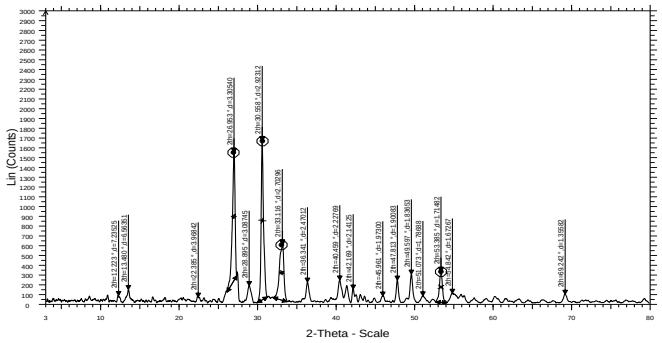

Figure. 8. X-Ray diffraction pattern of nifedipine liquisolid system with Fujicalin® as carrier.

CONCLUSION

In the present study it was evident that the nature of the excipients can influence the rate of release of drug to a large extent in liquisolid systems. It was found that Fujicalin® produced the fastest disintegrating tablets, whereas Neusilin® when used as the only excipient produced hard slow disintegrating tablets. Invariably the liquisolid tablets showed increase in the disintegration time as compared to directly compressed counterparts. Combination of Fujicalin ® 1500 mg, Neusilin (500 mg) and MCC (500 mg) showed the highest drug release, whereas the formulation containing Neusilin ® as the coating and carrier material showed slowed and sustained release. When compared to marketed formulation it was found out that the prepared liquisolid formulation showed 12.2% lesser release but had immediate release within 5 min. So liquisolid systems can be investigated as a viable alternative to soft gelatine capsule.

ACKNOWLEDGMENTS

We express our sincere thanks to J.B. Chemicals and Pharmaceuticals, Daman, India for providing the gift sample of Nifedipine and Aurobindo Laboratories, Hyderabad, India for providing gift samples of Excipients.

REFERENCES

1. Spireas S, Sadu S. Enhancement of prednisolone dissolution properties using liquisolid compacts. Int J Pharm 1998; 166: 177–188.
2. Kulkarni AS, Aloorkar NH, Mane MS, Gaja JB. Liquisolid systems: A review. IJPSN 2011; 3: 1205-1213.
3. Spireas S, Bolton S. Liquisolid systems and methods of preparing same. United States Patent 5968550 1999.
4. Javadzadeh Y, Siahi-Shadbad MR, Barzegar-Jalali M, Nokhodchi A. Enhancement of dissolution rate of piroxicam using liquisolid compacts. Farmaco 2005, 60: 361-365.

5. Javadzadeh Y, Jafari-Navimipour B, Nokhodchi A. Liquisolid technique for dissolution rate enhancement of a high dose water-insoluble drug (carbamazepine). Int J Pharm 2007, 341: 26-34.
6. Tiong N, Elkordy AA. Effects of liquisolid formulations on dissolution of naproxen, Eur J Pharm Biopharm 2009. 373-384.
7. Fahmy RH, Kassem MA. Enhancement of famotidine dissolution rate through liquisolid tablets formulation: in vitro and in vivo evaluation. Eur J Pharm Biopharm 2008. 69: 993-1003.
8. El-Houssieny BM, Wahman LF, Arafa NM, Bioavailability and biological activity of liquisolid compact formula of repaglinide and its effect on glucose tolerance in rabbits. Biosci Trends 2010. 4: 17-24.