INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

SOLUBILITY ENHANCEMENT OF NIFEDIPINE BY USING LIQUISOLID COMPACT TECHNIQUE

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ARTICLE INFO

Article history
Received 07/02/2017
Available online
14/03/2017

Keywords
Nifedipine;
Liquisolid Compact;
PEG 400;
Carrier Material;
Coating Material;
Poorly Water Soluble Drugs.

ABSTRACT

This study evaluated the feasibility of liquisolid compact as an innovative drug delivery system to improve the solubility of the poorly soluble drug Nifedipine. There are several techniques to enhance the dissolution of poorly soluble drugs. Among them, the technique of liquisolid compact is most promising technique towards novel aim. Several formulations of liquisolid compact having different drug concentration (20-40% w/w) and with varying ratios of carrier and coating material (i.e. different R value, from15-20) were prepared. In this study Polyethylene glycol 400 (PEG400) as a solvent, Avicel PH 102 as a carrier and Aerosil-200 as a coating material were used. The interaction between excipients was examined by Attenuated Total Reflectance infrared spectroscopy. DSC suggested loss of nifedipine crystallinity upon liquisolid formulation, it indicates that drug is held within the power substrate in a solubilised, almost molecularly dispersed state, which lead to enhanced drug solubility. The results showed that liquisolid compacts demonstrate significantly higher drug release rates than those of marketed ones (% drug release of marketed product-19.5% and LS_3-28.5% after 10 minutes). This was due to an increase in wetting properties and surface of drug available for dissolution. Increased wetting properties and dissolution rates lead to enhance solubility. The liquisolid technique appears to be a promising approach for improving the solubility of poorly soluble drugs.

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*Please cite this article in press as **Deeliprao V. Derle** et al. Solubility Enhancement of Nifedipine by Using Liquisolid Comp Technique. Indo American Journal of Pharmaceutical Research.2017:7(02).*

INTRODUCTION

Definition[1,2]

The term "liquisolid systems" refers to powdered forms of liquid medications formulated by converting liquid lipophilic drugs or drug suspensions or solutions of water insoluble solid drugs in suitable non-volatile solvent systems, into "dry" (i.e., dry-looking), non- adherent, free flowing and readily compressible powder admixtures by blending with selected carrier and coating materials.

The term "liquisolid compacts" refers to conventional or immediate or sustained or release tablets or capsules that are prepared using the technique described under "liquisolid systems," combined with the inclusion of appropriate adjuvants required for tabletting or encapsulation, such as lubricants, and for immediate or sustained release action, such as disintegrants or binders, respectively.

The term "liquisolid Microsystems" refers to capsules prepared by the technique described under "liquisolid systems" combined with the inclusion of an additive, e.g., polyvinylpyrrolidone (PVP), in the liquid medication wherein the resulting unit size may be as much as five times less than that of liquisolid compacts.

The "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 the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably flowing liquid/powder admixture.

The term "compressible liquid-retention potential" (Ψ-number) of a powder material describes its ability to retain a specific amount of liquid while maintaining good compression properties. The 'Ψ -value' is defined as the maximum weight of liquid that can be retained per unit weight of the powder material in order to produce an acceptably compressible liquid/powder admixture, i.e., being able to yield tablets of satisfactory mechanical crushing strength (hardness) without presenting any liquid squeezing out of the liquisolid mass during compaction.

The term "carrier material" refers to a preferably porous material possessing sufficient absorption properties, such as microcrystalline and amorphous cellulose, which contributes in liquid absorption.

The term "coating material" refers to a material possessing fine and highly adsorptive particles, such as various types of amorphous silicon dioxide (silica), which contributes in covering the wet carrier particles and displaying a dry-looking powder by adsorbing any excess liquid.

Historical development [1,2,3]

Historically, liquisolid compacts are descendants of "powdered solutions", an older technique which was based on the conversion of a solution of a drug in a non-volatile solvent into a drylooking, nonadherent powder by mainly adsorbing the liquid onto silicas of large specific surfaces. Such preparations, however, have been investigated for their dissolution profiles while being in a powder-dispersion form and not as compressed entities, simply because they could not be compressed into tablets. In later studies on powdered solutions, compression enhancers such as microcrystalline cellulose were added in such dispersions in order to increase the compressibility of the systems. In these studies, however, large quantities of silicas were still being used, and the flow and compression properties of the products were never validated and standardized to industrial specifications and requirements. Specifically, when such modified powdered solutions were compressed into tablets, they presented significant "liquid squeezing out" phenomena and unacceptably soft tablets, thereby hampering the industrial application of such systems. Liquisolid compacts, on the other hand, are acceptably flowing and compressible powdered forms of liquid medications, and they are industrially applicable. In addition, the term "liquid medication" does not only imply drug solutions, as in "powdered solutions", but also drug suspensions, emulsions, or liquid oily drugs. Therefore, in contrast to "powdered solutions", the term "liquisolid compacts" is more general and it may encompass four different formulation systems, namely,

1. Powdered drug solutions,
2. Powdered drug suspensions,
3. Powdered drug emulsions, and
4. Powdered liquid drugs.

Furthermore, the older term of "powdered solutions" seems to be inadequate even in describing the original systems, since it has not been proven that the drug remains in solution in the liquid vehicle after its deposition on the extremely large powder surfaces of silicas used.

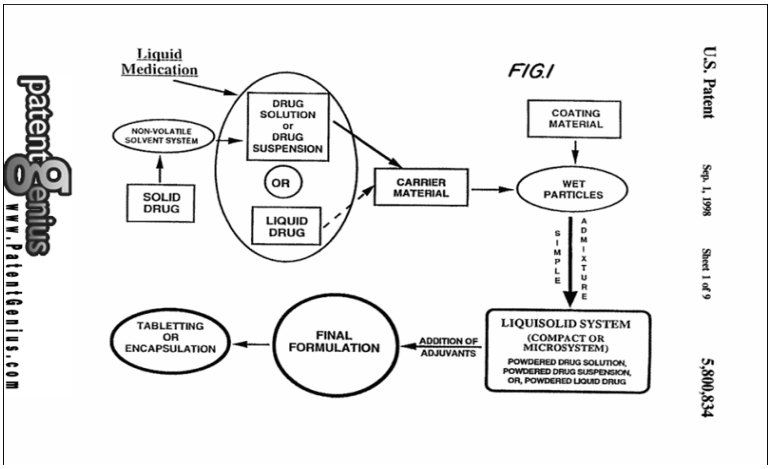


Fig 1: Schematic presentation for the formulation of liquisolid system.(Spireas S.United states patent,2002).

Table 1: Components of liquisolid compact formulation1[4].

Category of components	Examples
Non- volatile solvents	PEG 200, PEG 400, Glycerine, PG etc
Carrier material	Avicel PH 101, Avicel PH 102, Lactose, Eudragit etc.
Coating material	Aerosil 200, Silica
Disintegrant	Sodium starch glycollate, Crosscarmellose Sodium, Cross PVP etc.
Lubricant	Magnesium stearate, Stearic acid.
Glidant	Talc

Preparation of liquisolid compacts [1,2]

The liquisolid systems are acceptably flowing and compressible powdered forms of liquid medication. The first step in the formulation of liquisolid systems is preparation of the liquid medication. The poorly soluble drugs are dispersed in liquid vehicle. Here the liquid vehicle is the non-volatile solvents such as propylene glycol, tween 80, polyethylene glycol 200 (PEG 200), polyethylene glycol 400 (PEG 400), etc. Different drug concentrations in % w/w of drug and liquid vehicle can be prepared.

Liquid vehicle mixed may be heated to sufficient temperature with constant stirring for proper mixing of both. Then the next step is to add binary mixture of carrier and coating material. It is also possible to add carrier material first and then resulting wet mixture is converted into a dry-looking, non-adherent, free-flowing and readily compressible powder by the simple addition and mixing of a calculated amount of coating material.

The carrier material incorporated are microcrystalline cellulose, lactose, starch, sorbitol, etc. which has porous surface and closely matted fibres in their interior that aids for absorbing property to wet itself by the liquid medication. Mainly coarse granular grades of microcrystalline cellulose were used which are better for direct compression process such as avicel PH 102, avicel PH 200. Silicon dioxide (Silica) powder is used as coating material which has sufficient adsorptive property to dry the wet particles of carrier material and make them readily flowable and compressible.

Different grades of silica can be used in liquisolid formulation such as aerosil 200, cab-O-Sil M5, and syloid 244 FP. Finally a disintegrant or binder is added in mixture depending on the type of tablet formulation is to be prepared. i.e. for immediate release, disintegrant such as sodium starch glycolate (explotab), cross-carmellose, etc can be used. The % of disintegrant or binder used in formulation depends on total weight of the tablet and desired property (immediate release or sustain release), appropriate quantity of these excipients can be incorporated. Mixing process can held for sufficient time period up to 10-15 minutes for uniform and proper mixing of powder mixture. The prepared liquisolid powder systems that have simultaneous acceptable flowability and compressibility are compressed into cylindrical tablets of desired weight using tablet press machine. Tablets are prepared with sufficient hardness. The liquisolid powder mixtures are also encapsulated using hard gelatin capsules to aid control and comparison of different formulations.

In short the liquisolid system is prepared as the liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicle is incorporated into the porous carrier material (Fig. 1.3). Inert, preferably water-miscible organic solvent systems with high boiling point such as propylene glycol, liquid polyethylene glycols, or glycerine are best suitable as liquid vehicles. Once the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. Thus, an apparently dry, free flowing, and compressible powder is obtained. Usually, microcrystalline cellulose is used as carrier material and amorphous silicon dioxide (colloidal silica) as coating material. compressibility and markedly higher percentage of drug release than of the marketed tablet and it was found that excipients were compatible with the drug in the prepared liquisolid system that was determined by fourier transform infrared spectroscopy and differential scanning calorimetry.

From this study it was concluded that the liquisolid technique is an effective approach to enhance the dissolution rate of nifedipine.

Objective:

i) To enhance the solubility of poorly soluble BCS class II drug Nifedipine using Liquisolid technique.
ii) To formulate and evaluate liquisolid tablet of Nifedifine.
iii) To compare the dissolution profile of prepared liquisolid tablet of Nifedipine with marketed preparation.
iv) Drug release kinetic study.
v) To find out most optimized Nifeipine liquisolid formulation.

Advantages[1,5]

- Liquisolid technique is used mainly for converting liquid drugs or drug suspensions or solutions of.
- poorly soluble drugs in to solid dosage form.
- It is used to formulate sustained release dosage forms.
- By using liquisolid technique controlled drug delivery systems can be formulated.
- Production cost of liquisolid system is also less as compared to soft gelatin capsules.
- This technique is also applied to convert liquid oily drugs in to solid dosage form.
- It enhances dissolution rate of poorly water soluble drugs by increasing their solubility.
- Liquisolid technique is also used for class II and class IV drugs for enhancing their bioavailability.
- Manufacturing of liquisolid tablets is simple as that of tablet formulation.

Disadvantages[5]

- For maintaining flowability and compressibility of liquisolid powder in an acceptable range high quantity of carrier and coating materials can be required which can result in increase in weight of the tablet more than 1 gm which is difficult to swallow.
- More efficient excipients are required which have high adsorptive properties which can enhance release rates of the drug from the dosage form.
- The liquisolid systems have less drug loading capacity and it also require high solubility of the drug in a non-volatile solvent.

Applications[6]

- It is used for enhancing rate of dissolution of the many poorly soluble drugs by enhancing their solubility.
- Bioavailability of many class II and class IV drugs get enhanced by using liquisolid technique.
- Release rates of many poorly water soluble drugs get increased by using liquisolid system.
- It is also used for designing controlled drug delivery system.
- Liquisolid technique is also successfully used for the formulation of many water insoluble or liquid lipophilic drugs.
- It is also used to formulate sustained release dosage forms.

MATERIAL AND METHOD

Materials

Following materials were used for the research work.

Table 2:List of the chemicals used.

Ingredients	Role	Suppliers
Nifedipine	Antihypertensive	Lupin research Park, Pune
Microcrystalline Cellulose(PH102)	Carrier	Modern Labs. Ltd.
Colloidal silicon Dioxide(Aerosil 200	Coating materil	Modern Labs. Ltd.
Crospovidone	Superdisintegran	BASF
Polyethylene glycol (PEG400)	Non-volatile solvent	Modern Labs. Ltd.
Magnesium stearate	Lubricant	Modern Labs. Ltd.
Methanol solvent	Solvent	Modern Labs. Ltd.
Hydrochloric Acid	Solvent	Modern Labs. Ltd.

Equipements and Instruments used

List of Equipements and Instruments used.

Table 3. List of Equipements and Instruments used.

Sr. No.	Equipments/ Instruments	Models
1.	Analytical Balance	Shimadzu AUX 220
2.	Dissolution Test Apparatus	Lab India disso. 2000
3.	UV spectrophotometer	Shimadzu 2450
4.	ATR spectrophotometer	Bruker
5.	Compression Machine	Rimek
6.	Pfizer Hardness Tester	Cadmach
7.	Disintegration test apparatus	Lab India
8.	Roche Friability Tester	Remi
9.	Differential Scanning Calorimeter	Perkin Elmer

Formulation and development

Based on saturation solubility study Polyethylene glycol was selected as liquid vehicle for preparation of liquisolid compact. Several liquisolid compacts were prepared as follows. The desired quantities of the previously weighed solid drug and the liquid vehicle (PEG 400) was mixed separately to get different drug concentration. The solution was then sonicated for 15 min until a homogeneous drug solution was obtained. Then the calculated weight (W) of the resulting liquid medications (equivalent to 20 mg drug) were incorporated into the calculated quantities of the carrier material (Avicel PH102) (Q) and mixed thoroughly. The resulting wet mixture was blended with the calculated amount of the coating material (Aerosil 200) (q) using a standard mixing process to form simple admixture. The formulations of liquisolid compacts, LS-1 to LS-9 was prepared by varying concentration of drug in liquid vehicle PEG from 20 % to 40 % w/w and excipients ratio 10 to 20 (different R values). Different liquid load factors (Lf) ranging from 0.330 to 0.500 for PEG400 was employed. Finally 5 % w/w of crospovidone as the disintegrants was mixed with the above mixture for 10 min. The required quantities of excipients incorporated are shown in table as follows.

Table 4. Formulation table for Nifedipine liquisolid table formulation.

Liquisolid System	Drug conc. %w/w	Carrier coat Ratio(R)	Liq. Load factor(LF)	Liq. Vehicle PEG 400(mg)	Carrier(Q) Avicel PH 102(mg)	Coating(q) Aerosil 200 (mg)	Disintegrant Crosspovidone (mg)
LS-1	20	10	0.500	80	200	20	16
LS-2	20	15	0.386	80	259	17.175	18.80
LS-3	20	20	0.330	80	302.9	15.12	20.85
LS-4	30	10	0.499	46.66	133.33	13.33	10.66
LS-5	30	15	0.385	46.66	172.70	11.51	12.54
LS-6	30	20	0.329	46.66	202.01	10.1	13.93
LS-7	40	10	0.500	30	100	10	8
LS-8	40	15	0.386	30	129.5	8.63	9.40
LS-9	40	20	0.330	30	151.52	7.576	10.45

RESULT AND DISCUSSIONS

Preformulation Study:

Organoleptic properties :

Nifedipine procured was studied for the organoleptic properties as shown in the following table.

Table 5:Organoleptic properties of Nifedipine.

Parameters	Observation
Colour	Lightish Yellow
Odour	Odourless
Appearance	Crystalline Powder

Melting point of Nifedipine

Melting point of Nifedipine observed was as shown in Table.

Table6: Melting point of Nifedipine.

Sample	Observed Melting Point	Reported Melting Point
Nifedipine	172-174^0 C	169-171^{0}C

UV-Visible Spectrophotometric analysis of Nifedipine

Preparation of standard curve of Nifedipine in distilled water

10 mg of drug was accurately weighed and transferred to 100 ml volumetric flask. Drug was dissolved in 100 ml distilled water. Thus, a stock solution of Nifedipine of 100 µg/ml was prepared.

The solutions were further serially diluted with water to produce solutions of concentrations 10-50 µg/ml.

The UV spectrum was recorded in the range 200-400 nm. The wavelength maximum absorption (max) was found from the scan and then further preparation of calibration (standard) curve was carried out at the detected wavelength of maximum absorption (max).

Preparation of standard curve of Nifedipine in 0.1 N HCL

10 mg of drug was taken in 10 ml volumetric flask and to it was added 4-5 ml of 0.1 N HCl and was sonicated.

Then the volume was made up and 100 ppm stock solution was obtained with 0.1 N HCL. Drug was dissolved in 100 ml 0.1 N HCL. Thus, a stock solution of nifedipine of 100 µg/ml was prepared in 0.1 N HCL.

The solution were futher serially diluted with 0.1 N HCL produce solutions of concentrations 5-25 µg/ml.

The UV spectrum was recorded in range of 200-400 nm. The maximum absorption wavelength (max) was found out from scan and then further preparation of calibration (standard) curve was carried out at the detected wavelength of maximum absorption (max).

UV Visible spectrum of Nifedipine in distilled water: (at 237nm).

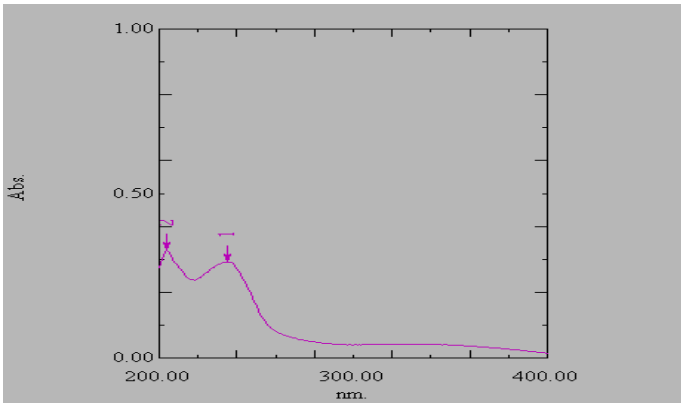


Fig 2. UV Visible spectrum of Nifedipine in distilled water.

Data for UV calibration curve of Nifedipine in distilled water

Table 7. Concentration and absorbance values of Nifedipine in distilled water.

Concentration(ppm)	Absorbance(at 237 nm)
10	0.06
20	0.118
30	0.17
40	0.241
50	0.29

Beer-Lambert's plot for Nifedipine in distilled water: (At 237 nm)

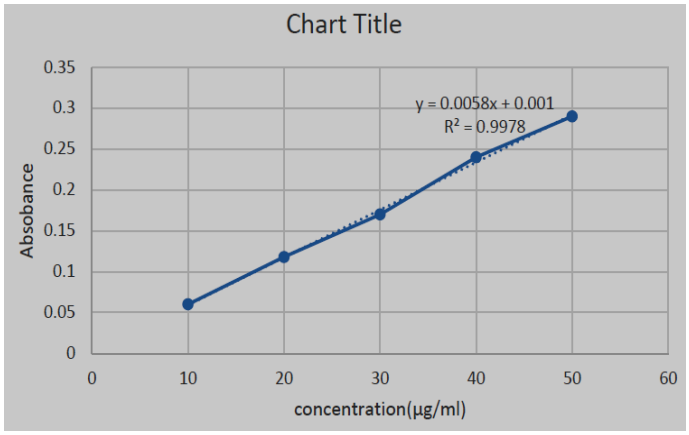


Fig 3. Calibration curve for nifedipine in Distilled water.

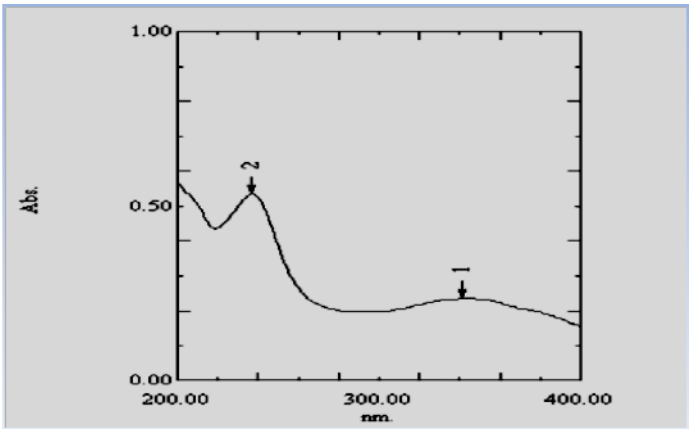


Fig 4.UV Visible spectrum of Nifedipine in 0.1 N HCL.

UV Visible spectrum of Nifedipine in 0.1 N HCL:(at 237 nm).

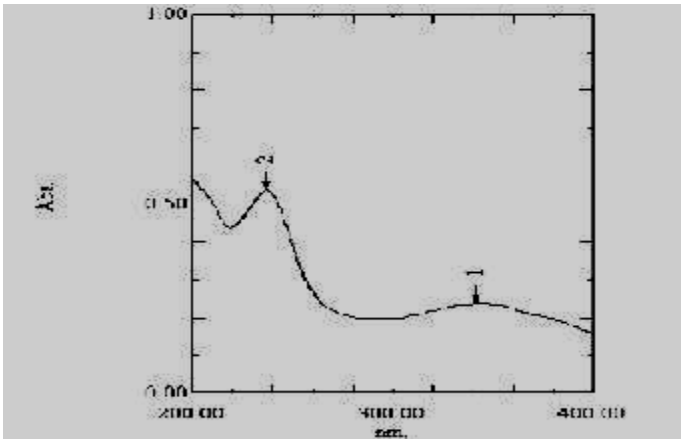


Fig 5 . UV Visible spectrum of Nifedipine in distilled water.

Data for UV calibration curve of Nifedipine in 0.1 N HCL

Table 8. Concentration and Absorbance values of Nifedipine in 0.1 N HCL.

Concentration	Absorbance
10	0.347
20	0.384
30	0.434
40	0.476
50	0.540

Beer-Lambert's plot for Nifedipine in 0.1 N HCL (at 237 nm).

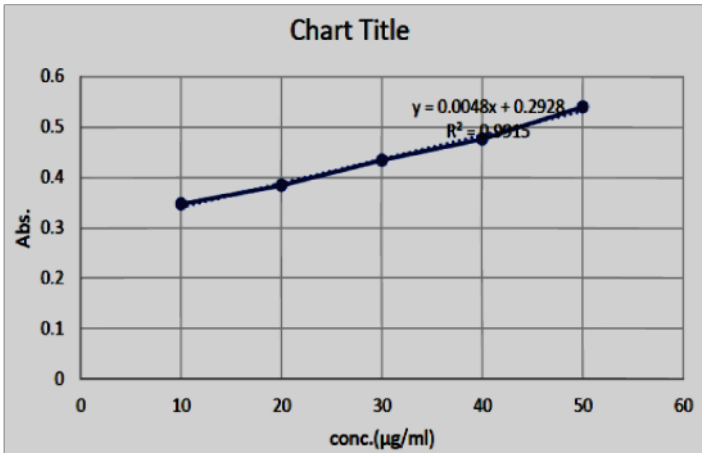
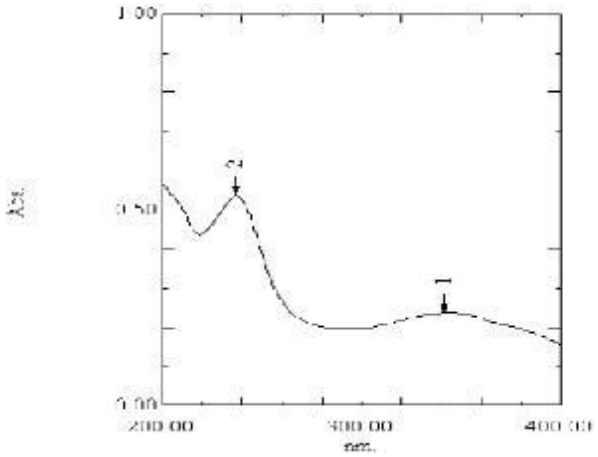


Fig 6. Calibration curve for Nifedipine in 0.1 N HCL



Solubility of Nifedipine

Solubility of Nifedipine is as shown in table as follows.

As PEG 400 showed greater solubility of the drug than the other two solvents, it was selected as the suitable solvent for preparing Nifedipine liquisolid compacts in this study.

Table 9. Solubility of Nifedipine.

Solvent	Reported(mg/ml)	Observed(mg/ml)
PEG 400	0.320	0.328
Propylene glycol	0.534	0.500
Water	0.005	0.004

IR Spectroscopy

IR Spectra of Nifedipine

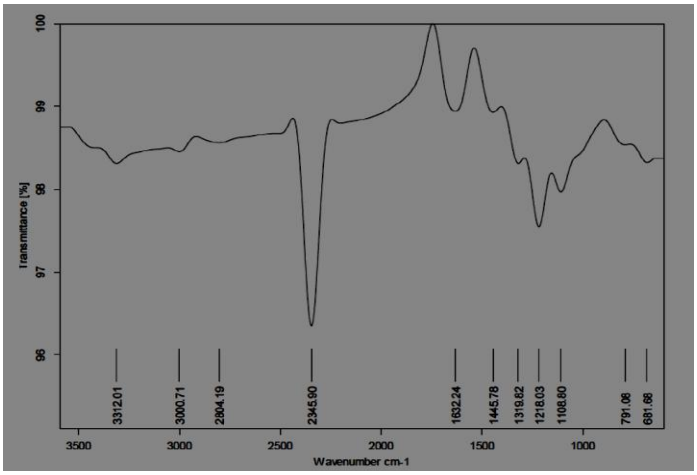


Fig 7. IR Spectra of Nifedipine.

IR Spectra of Nifedipine liquisolid powder

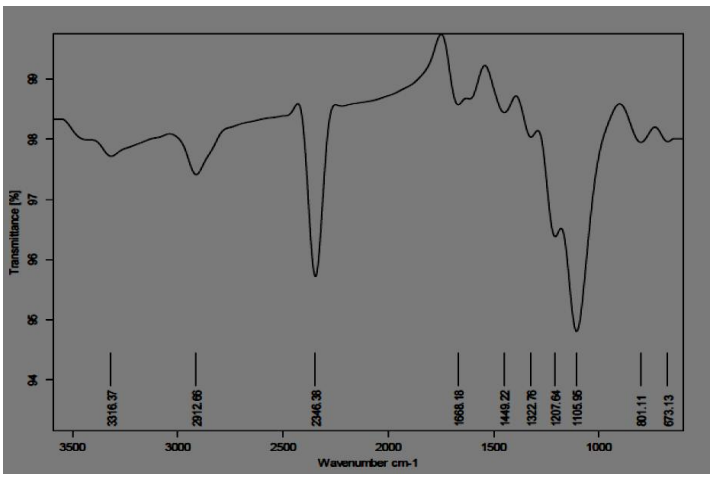


Fig 8. IR Spectra of Nifedipine liquisolid powder.

Interpretation of IR data

Table 10. Wavenumber values for major peaks present in IR spectra of Nifedipine.

Assignment	Peak report(cm^{-1})	Peak Observed(cm^{-1})
N-H stretch	3400-3250	3312.01
=C-H(alkene aromatic)	3000-3100	3000
C-H(alkane strerching)	2960-2862	2345
O-H(carboxylic acid)	3800-2500	2345
C=O Stretch(ester)	1730-1630	1632
N-O Stretch(nitro compound)	1550-1475	1445

IR spectrum of Nifedipine was compared with reference spectrum provided in Indian pharmacopoeia 2010. It showed peaks similar as in the reference spectrum.

Compatibility testing

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) of pure Nifedipine drug.

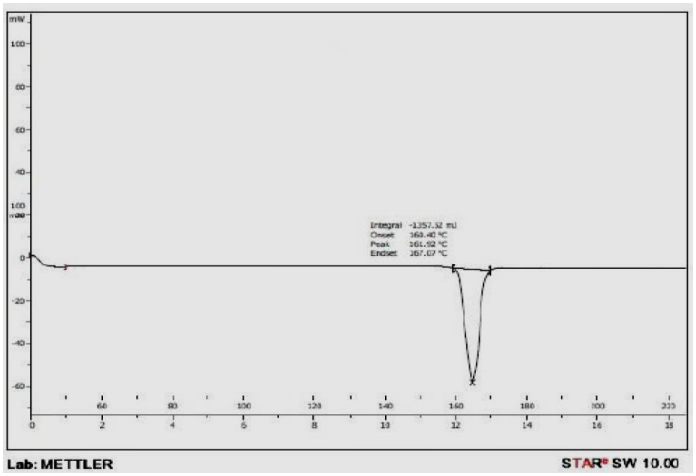


Fig:9. DSC spectra of Nifedipine.

Differential Scanning Calorimetry (DSC) of Nifedipine liquisolid compact

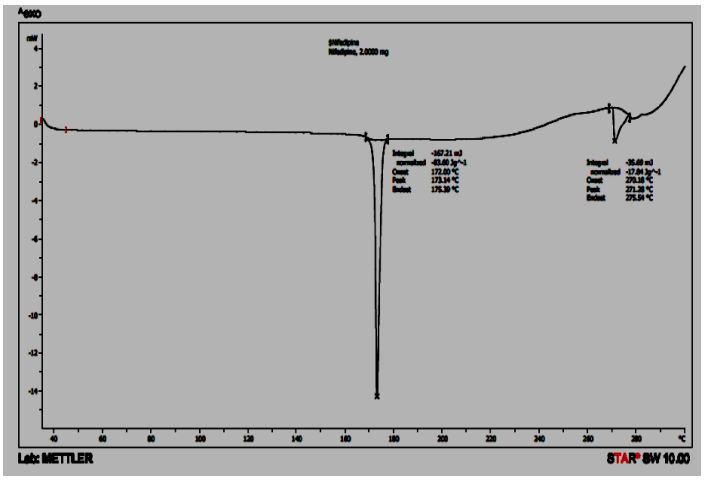


Fig:10. DSC spectra of Nifedipine liquisolid compact powder.

Interpretation of DSC data

The DSC Thermograms of pure Nifedipine and DSC Thermograms of mixture (Nifedipine liquisolid powder) show minor significant difference from their obtained thermograms. It indicate minor shift of endotherm peak from 171 to 161. These obtained results indicate that there was no positive evidence for the interaction between Nifedipine and Excipient material. So, excipients used in nifedipine liquisolid compact can be used for preparation of tablet of Nifedipine.

Solubility study of liquisolid powder systems
Solubility enhancement of drug due to each liquisolid formulations

Table 11. Solubility values of Nifedipine liquisolid powder systems.

Formulation	Solubility in distilled water(mg/mL) (Mean ± SD)
LS-1	0.109± 0.0016
LS-2	0.111± 0.0008
LS-3	0.12±0.002
LS-4	0.064± 0.0017
LS-5	0.095± 0.0012
LS-6	0.096± 0.0009
LS-7	0.077± 0.0033
LS-8	0.084± 0.0024
LS-9	0.099± 0.0005

Disintegration time

The disintegration time test revealed that the liquisolid tablet formula disintegrated within 3 min which is as per specifications given for the dispersible tablets in the IP and result of the test are shown in table. Microcrystalline cellulose has disintegration property which could facilitate disintegration of tablets and dissolution of drug. Because of the presence of a nonvolatile solvent acting as a binding agent in the liquisolid formulation, delayed disintegration time is expected.

However, in the liquisolid tablets containing microcrystalline cellulose, a fast disintegration of tablet occurred which can be explained by the disintegrating property of microcrystalline
cellulose. In addition, use of crospovidone accelerates the disintegration of tablets by virtue of its ability to absorb a large amount of water when exposed to an aqueous environment. The absorption of water results in breaking of tablets and therefore faster disintegration.

Drug content

A fundamental quality attribute for all pharmaceutical preparations is the requirement for a constant dose of drug between individual tablets. Uniform drug content was observed for the formulation which is as per the IP specification (90%-110%).

Table 12. Table for results of drug content of liquisolid formulations.

Formulation	Drug content(%) (Mean± SD)*	DisintegrationTime(Min) (Mean± SD)
LS-1	95.35± 1.4	2.4±0.09
LS-2	97.27± 1.6	2.3±0.03
LS-3	98.87± 1.8	2.3±0.18
LS-4	94.63± 1.6	2.6±0.11
LS-5	95.19± 2.1	2.5±0.07
LS-6	97.41± 2.2	2.1±0.19
LS-7	94.84± 1.9	2.0±0.12
LS-8	95.83± 1.7	2.2±0.18
LS-9	96.91± 1.2	2.1±0.06

Flow properties

Powder flow is a complicated matter and is influenced by so many interrelated factors. Those factors include physical, mechanical as well as environmental factors. Flow properties includes angle of repose, Carr's index, Hausner's ratio as it may affect compressibility, tablet porosity and dissolution.

The effect of liquid load factor (Lf), which is a ratio of mass of liquid (PEG) added to the mass of carrier, Avicel PH 102 on flowability and compressibility of the final admixture of the powder is shown in table.

As a general guide angle of repose greater than 40o has unsatisfactory flow properties whereas minimum angle close to 25o correspond to very good flow property. Powders showing Carr's index up to 21 are considered of acceptable flow property.

Table 13. Results for flow properties.

Formulation	Bulk Density gm/cm3 (Mean± SD)*	TappedDensity gm/cm3 (Mean± SD)*	Carr's Index % (Mean± SD)*	Hausner Ratio (Mean± SD)*	Angle of Repose (θ) (Mean± SD)*
LS-1	0.384 ± 0.021	0.557±0.034	27.41±0.060	1.454±0.026	28.79±1.134
LS-2	0.347± 0.038	0.541±0.022	14.83±0.021	1.416±0.021	24.57±1.164
LS-3	0.356±0.045	0.395±0.025	10.78±0.038	1.120±0.051	26.96±1.560
LS-4	0.346±0.037	0.317±0.021	20.22±0.012	1.174±0.031	27.10±1.422
LS-5	0.367±0.012	0.405±0.013	16.27±0.045	1.237±0.012	25.22±1.121
LS-6	0.317±0.024	0.413±0.027	27.13±0.080	1.177±0.029	26.49±1.433
LS-7	0.334±0.035	0.393±0.018	19.78±0.019	1.191±0.018	24.12±1.214
LS-8	0.337±0.031	0.402±0.015	22.31±0.023	1.232±0.016	27.32±1.226
LS-9	0.345±0.029	0.398±0.019	25.21±0.022	1.314±0.033	25.31±1.316

All values expressed as Mean ± SD (n=3).

Table 14: Results for tablet evaluation.

Formulation	Friability test(%fines)	Broken tablet	Hardness(kg/cm2) (Mean± SD)*	Weight variation(%) (Mean± SD)*	Thickness(mm) (Mean± SD)*
LS-1	0.121	None	3.4±0.37	1.7±0.71	2.72±0.037
LS-2	0.135	None	2.7±0.87	2.3±0.98	2.40±0.054
LS-3	0.127	None	3.5±0.32	1.4±0.34	2.63±0.026
LS-4	0.217	None	2.6±0.74	1.9±0.74	2.13±0.065
LS-5	0.136	None	4.1±0.96	2.1±0.14	2.71±0.070
LS-6	0.152	None	3.8±0.23	2.0±0.11	2.11±0.052
LS-7	0.174	None	2.9±0.39	1.2±0.68	2.87±0.036
LS-8	0.245	None	3.7±0.53	1.3±0.34	2.74±0.028
LS-9	0.110	None	2.9±0.14	1.8±0.67	2.56±0.043

In-vitro drug release

The results of in vitro percentage amount of drug released at different time intervals plotted against time to obtain the release profiles. The liquisolid compacts showed higher drug release than marketed tablet formulation. The enhanced dissolution rates of liquisolid compact compared to marketed tablet formulation may be attributed to the fact that, the drug is already in solution in PEG while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica). Thus, its release is accelerated due to its markedly increased wettability and surface availability to the dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compact. PEG facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface. The dissolution profiles of the selected Nifedipine liquisolid tablet formulation together with the dissolution profile of marketed tablet formulation tablets (MT) are presented.

In-Vitro dissolution study of Nifedipine liquisolid compacts in 0.1 N HCl

Apparatus : USP type 2 (Paddle type)
Media : 0.1 N HCl
Volume of media : 900 mL
Paddle RPM : 50
Temperature : 37±0.5 oC
λmax : 237 nm

Table for drug release profile for all the Nifedipine liquisolid formulations alongwith it's marketed tablet for the comparison point of view.

Table 15. Results of % drug release from Nifedipine liquisolid formulations.

Formulation	% Drug release in 10 mins.	% Drug release in 1hr.
Marketed Tablet	19.5	69.79
LS-1	21.0	93.25
LS-2	30.0	94.95
LS-3	28.5	96.26
LS-4	26.25	80.27
LS-5	29.25	87.62
LS-6	29.25	90.09
LS-7	21.75	83.30
LS-8	22.50	85.36
LS-9	30.00	91.02

Graphical presentation of drug release profiles of all the liquisolid formulations.
liquisolid formulations LS-1,LS-2,LS-3,LS-4,LS-5

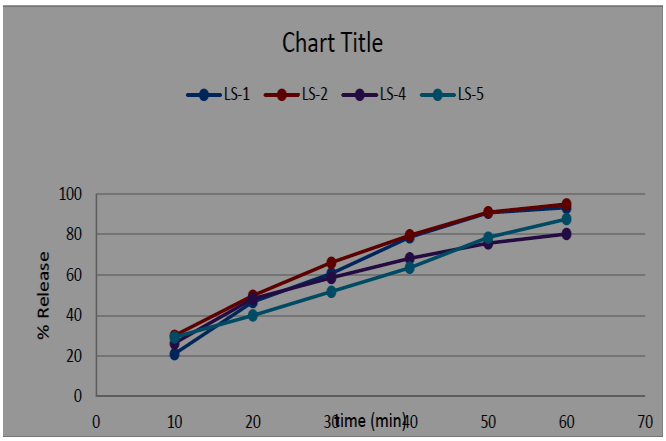


Fig 11. Representation for release profiles of drug from liquisolid formulations.

Liquisolid formulations LS-6,LS-7,LS-8,LS-9

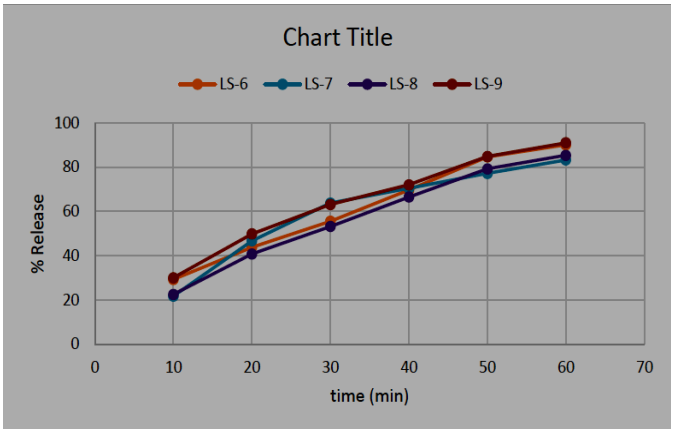


Fig 12. Representation for release profiles of drug from liquisolid formulations.

Results for mathematical modelling and release kinetics of Nifedipine liquisolid formulation

Table 16: Results for mathematical modelling and release kinetics of Nifedipine liquisolid formulation.

Formulation Code	Correlation coefficient (R2)	Best fit model	N value
LS-1	0.986	Hixon-crowell release model	0.0295
LS-2	0.995	Hixon-crowell release model	0.0096
LS-3	0.994	Korsemeyer peppas release model	0.693
LS-4	0.982	Hixon-crowell release model	0.0171
LS-5	0.997	Zero order release model	1.1973
LS-6	0.994	Korsemeyer peppas release model	0.6454
LS-7	0.971	Hixon-crowell release model	0.0194
LS-8	0.997	Higuchi release model	14.033
LS-9	0.996	Higuchi release model	13.336

Stability testing

From the stability data Table 9.13. and Table 9.14. It can be concluded that stability of pure nifedipine and liquisolid compact did not differed significantly at 5.0% level of significance in any parameter, so optimized batch are said to be stable. Hence, this product can be kept for a period of one year or more. The objective of present work was to enhance the solubility of poorly soluble drug Nifedipine. Polyethylene glycol 400 was used as non-volatile vehicle for enhancing the solubility of Nifedipine since the solubility studies revealed that the drug is soluble in it.

Table 17: Result of Stability Testing- i) 40 + 2 o C and RH 75 % + 5.

Formulation	Parameter	Initial	40°C/75% RH 7days	40oC/75% RH 14 days	40oC/75% RH 1 Month	40oC/75% RH 2Month	40oC/75% RH 3Month
LS-3	Hardness(Kg/cm^2)	3.5±0.32	3.02±0.66	3.06±0.65	3.04±0.48	3.09±0.23	3.15±0.18
	Friability (%)	0.127±0.01	0.131±0.04	0.129±0.10	0.125±0.03	0.146±0.05	0.132±0.08
	D.T.(Min.)	2.3±0.18	2.21±0.25	2.32±0.26	2.2±0.43	2.13±0.40	2.11±0.21
	Drug Content	98±1.6	97.52±2.45	97.41±1.90	97.16±2.11	97.08±2.0	97.91±2.15
	Avg.Wt. (Mg)	1.4±0.34	1.37±0.12	1.49±0.29	1.3±0.22	1.42±0.05	1.18±0.18

Table 18:Result of Stability Testing-ii) 30 + 1 o C and RH 65 % + 5%.

Formulation	Parameter	Initial	30oC/65% RH 7days	30oC/65% RH 14days	30oC/65% RH 1Month	30oC/65% RH 2Month	30oC/65% RH 3 Month
LS-3	Hardness(Kg/cm^2)	3.5±0.32	3.3±0.25	3.06±0.43	3.06±0.16	3.05±0.23	3.1±0.18
	Friability (%)	0.127±0.01	0.131±0.08	0.120±0.09	0.145±0.09	0.126±0.05	0.123±0.08
	D.T.(min)	2.3±0.18	2.1±0.21	2.2±0.20	2.00±0.43	2.23±0.40	2.21±0.21
	Drug Content	98±1.6	97.65±2.45	97.40±1.90	97.16±2.11	97.13±2.0	97.07±2.15
	Avg. Wt. (mg)	1.4±0.34	1.47±0.12	1.1±0.29	2.1±0.22	1.6±0.67	1.8±.18

SUMMARY AND CONCLUSIONS:

The objective of present work was to enhance the solubility of poorly soluble drug Nifedipine. Polyethylene glycol 400 was used as non-volatile vehicle for enhancing the solubility of Nifedipine since the solubility studies revealed that the drug is soluble in it.

For the formulation of the liquisolid compacts a number of excipients are available. The selection of the optimum carrier and coating material was done by formulating the liquisolid powder system of the drug with each carrier and coating material and then determining the solubility of Nifedipine in water by carrying out the saturation solubility studies for 24 hours.

From this study it was found that the highest solubility enhancement yielding formulation containing Avicel PH 102 as a carrier material and Aerosil 200 as a coating material. Then the various liquisolid powder systems were made from the two obtained optimum carrier and coating material. Again the solubility enhancement of each formulation was studied by saturation solubility studies for 24 hours. The optimized formulation was selected and was compressed into compact and then was subjected for tablet evaluations.

Nifedipine: Polyethylene Glycol 400 liquisolid compact:

From the findings of the study, the results can be summarized as follows -

The UV absorption spectrum of Nifedipine showed maximum absorption at 237 nm in 0.1 N HCL.

The melting point of Nifedipine by open capillary method was found to be 169-171 ^{o} CThe saturation solubility of Nifedipine in 0.1 N HCL was found to be 0.0382mg/mL.

The compacts, as investigated with ATR, were found to show absence of any well-defined chemical interactions. DSC analysis data concludes that compacts of Nifedipine showed enhancement of dissolution due to the conversion of Nifedipine to a less crystalline and/or amorphous form.

Kinetic treatment of drug release data revealed that the korsmeyer-peppas model is most appropriately fits the in-vitro dissolution data and gives an insight in to the possible drug release mechanisms invariably predominant by diffusion mechanism of liquisolid compact in distilled water. Liquisolid compact with batch LS-3 shows better drug solubility in distilled water. Dispersible tablet is formulated using superdisintegrant crospovidone of concentration 5 %. Prepared tablets were evaluated for hardness, friability, average weight, thickness, D.T.

IR data indicated no interaction of drug with the excipients. Hence, this product can be kept for a period of one year or more.

The in-vitro release profile of liquisolid compact of Nifedipine prepared in PEG was compared separately with marketed tablet formulation. The results shows that liquisolid compacts of Nifedipine made in PEG shows better dissolution rate. Drug release profiles on model fitting follows first order model as best fit model.

Table 19 formulation Result of drug release profile of selected LS-3 formulation and marketed tablet.

Formulation	% Drug release in 10 mins	%Drug release in 1 Hr.
Marketed formulation	19.50	69.79
LS-3	28.50	96.26

Tablet 20: Results of Comparision study of solubility pure drug with nifedipine liquisolid formulation in distilled water and 0.1 N HCL.

Solvent	Pure Drug	Liquisolid formulation	Fold increases solubility
Distilled water (mg/ml)	0.004	0.120	30 fold
0.1 N HCL (mg/ml)	0.0382	1.956	51 fold

Such away Nifedipine is BCS class II drug having High permeability but low solubility. Due to this formulation with liquisolid. technique Nifedipine get shifted to BCS class I with high solubility as well as high permeabili**ty.**

ACKNOWLEDGMENTS

We would like to thank to NDMVP's College of pharmacy Nashik for providing required chemicals and Instruments. We would like to express the gratitude to all those our friends and also the teaching and non teaching staff who supported us directly or indirectly for completion of this research work. We also thankful to Lupin Laboratories Pune who provide API Nifedipine and also BASF and Modern Labs who provide required chemicals as a gift sample.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

%	Percentage	DSC	Differential Scanning Calorimetry
Mg	Microgram	cm-1	Per centimeter
^{0}C	Degree Celsius	MEC	Minimum Effective Concentration
CAS	Chemical abstract services	CRDF	Controlled Release Drug Formulation
Mm	Millimeter	CPOPT	Controlled Porosity Osmotic Pump
Cm	Centimeter	ATR	Attenuated Total Reflectance
mmHg	Millimeter of Mercury	mg	Milligram
MSC	Maximum Safe Concentration	kg	Kilogram

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