Formulation and Evaluation of Nimodipine Tablet by Liquisolid Technique

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ABSTRACT
Liquisolid technique is novel concept of the drug delivery via the oral route. This technique is applied to poorly water soluble, water insoluble or lipophilic drugs. According to the new formulation method of liquisolid compact, liquid medication such as solution or suspensions of water insoluble drug in suitable non-volatile solvent can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. The present work endeavours is directed towards the development of liquisolid compact for production of immediate release tablet of water insoluble Nimodipine. Liquisolid compacts were prepared by using polyethylene glycol 300 as the liquid vehicle or non volatile solvent. Crospovidone was used as a superdisintegrating agent and PVP K30 as a binder. Microcrystalline cellulose was used as a absorbing carrier and silicone dioxide as adsorbing coating material. The prepared liquisolid system were evaluated for their micromeretic properties and possible drug-excipients interaction. The FTIR spectra study ruled out any interaction between the drug and excipients in preparation of Nimodipine liquisolid compact. The in-vitro dissolution study confirmed enhance drug release from liquisolid compacts by using USP type I basket in 0.5 % SLS in water. The selected optimal formula released 93.86 % of its content in 30 min which is showing immediate release. The results showed that use of superdisintegrants had remarkable impact on the release rate of Nimodipine from Liquisolid compact, enhancing the release rate of the drug from liquisolid compact.

Keywords: Nimodipine, Liquisolid technique, immediate release, Crospovidone

INTRODUCTION
Oral route is most common and popular route of administration of drug because of its systemic effect, patient compliance, less expensive to manufacture, safe and effective etc. Tablet form is the most widely used dosage form because of self-administration and ease in manufacturing. Tablet provides high precision dosing. In most of the cases immediate on set of action is required as compare to conventional therapy. To achieve the rapid onset of action and eliminate the drawbacks of conventional therapy immediate release dosage form is now a days popular and used as a alternative oral dosage form. Immediate release tablets are very quickly absorbed after administration. Basic approach used in development is the use of superdisintegrants which provide rapid disintegration of tablet after administration.1

Nimodipine
belongs to the class of pharmacological agents known as a calcium channel blockers. Nimodipine is used as a anti-hypertensive and in subarachnoid hemorrhage and Arrhythmias. It increases blood flow to injured brain tissues. The bioavailability is 13% by oral route were 95% of protein binding. It get metabolise in liver and biological half life having 8-9 hours and drug is excreted from Faces and urine2.

Many techniques are being employed for the solubility enhancement of poorly soluble drugs to resolve the bioavailability issue due to inadequate dissolution rate. Various approaches make use of hydrophilic polymers as solubility enhancers acting through a variety of mechanisms such as amorphization, co-solvency, micelle formation or inclusion complexes3,4,5. These techniques impart many advantageous effects in the formulation development. But usually these approaches show lack of stability and decreasing success rate over a period of storage. One of the remarkable demerits of solid dispersions, glass solutions, eutectic mixtures and inclusion complexes is formation of sticky and hygroscopic mass resulting in the poor flow characteristics. Due to this set-back, industrial feasibility of the final dosage form becomes very difficult6,7,8.

The liquisolid technology emerged as a new drug delivery system distinguished by its characteristics and ability to deliver variety of drugs9,10. Liquisolid drug delivery system has gained attention of pharmaceutical researchers due to its contribution in the solubility enhancement as well as dissolution retarding approaches depending on the need and design of the formulation11,12,13.
Three major components in the formulation of liquisolid compacts are liquid medication, carrier and coat material. The aim of the present work is to increase the solubility and in-vitro dissolution of water insoluble drug Nimodipine by formulating it into liquisolid tablets. The liquisolid tablets are prepared by using Avicel PH 101, Avicel PH 102, Avicel PH 200 as carrier material, Aerosil as coating material, PEG 300 as liquid vehicle.

MATERIALS AND METHODS
Nimodipine was purchased from Maxwell Life Science Pvt. Ltd. Mumbai, India. Avicel PH101, Avicel PH102, Avicel PH200 were purchased from FMC Biopolymer, Aerosil from Evonik, PEG 300 from Colorcon Asia, Propylene Glycol from Sigma Aldrich, Tween 80 from Merck, Crosspovidone from Nanhang, Sodium Laury Sulphate from Loba Chemical, Methanol from BP Chemicals, Magnesium stearate from Peter Greven. All other materials used were of Pharmaceutical grade.

Solubility studies
For the selection of best non-volatile solvents, solubility studies were performed. In this procedure, pure drug was dissolved in non-volatile solvents (propylene glycol and polyethylene glycol, Tween 80). Excess amount of pure drug was added to the above solvents. Obtained saturation solutions were shaken on sonicator for 1 hours at 25°C under constant vibration. After 1 hours saturated solution were filtered and analyzed by UV spectrophotometer.

Calculation of loading factor (Lf) and “q” value
Loading factors were calculated for different carriers, using various solvents. By using Lf = W/Q formula (W: Amount of liquid medication and Q: Amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. The results showed that if the viscosity of the solvent is higher, lower amounts of carrier and coating materials are needed to produce flowable powder. Based on R value used, the corresponding q (amount of coating material) can be calculated for all formulations using the equation R = Q/q.

Table 1 represents the exact qualitative and quantitative composition for each formulation.

| Ingredients                  | Formulation code (mg) | Formulation code (mg) | Formulation code (mg) |
|------------------------------|-----------------------|-----------------------|-----------------------|
|                              | (1:1 Ratio of drug +  | (1:2 Ratio of drug + | (1:3, 1:4, 1:5 Ratio |
|    (mg)                      | different vehicle)    | different vehicle)    | of drug + PEG 300)    |
| Nimodipine                   | F1                    | F2                    | F3                    |
|                              | 30                    | 30                    | 30                    |
| Tween 80                     | -                     | 30                    | -                     |
| Propylene glycol             | -                     | -                     | -                     |
| Polyethylene glycol 300      | -                     | -                     | -                     |
| MCC 101                      | 55                    | 55                    | 55                    |
| MCC102                       | 140                   | 140                   | 140                   |
| MCC200                       | -                     | -                     | -                     |
| PVP k30                      | -                     | -                     | -                     |
| Aerosil                      | 1.5                   | 1.5                   | 1.5                   |
| Crosspovidone                | 2                     | 2                     | 2                     |
| Magnesium stearate           | 1.5                   | 1.5                   | 1.5                   |
| Total weight of Tablet       | 260                   | 345                   | 500                   |

Manufacturing Procedure:-
1. Dispense all the materials as per formula.
2. Nimodipine API was mixed with different vehicle such as tween 80, Propylene glycol, PEG300 with 1:1, 1:2, 1:3, 1:4, 1:5 ratio.
3. Nimodipine was dispersed in Tween 80 or PG, PEG300, then added Microcrystalline cellulose 101, 102, 200 it absorbed the liquid and get converted into powder form.
4. Then add PVP K30 binder and Crosspovidone and mix properly.
5. After that it get dried in hot air oven at 60°C for 1 hour.
6. Then the blend is pass through sieve no 20.
7. To this blend add aerosil as a coating agent and mix with Magnesium stearate to enhance the flow.
8. After complete mixing compression with punch pressure having size 7.5mm or 10mm.
1. POST COMPRESSION ASSESSMENT OF SUBLINGUAL TABLET
The tablets of all the batches were evaluated for weight variation, drug content, hardness, thickness, disintegration time, wetting time, water absorption ratio, moisture content and in-vitro dissolution study.

- **Weight Variation:** 10 tablets were selected randomly from each batch and weighed individually to check for weight variation. The following percentage deviation in weight variation is allowed as per USP.

| Average weight of a tablet | Percentage deviation |
|---------------------------|----------------------|
| 130 mg or less            | 10                   |
| > 130 mg and < 324 mg     | 7.5                  |
| 324 mg or more            | 5                    |

- **Thickness and Diameter:** The thickness and diameter of 4 tablets from each formulation were recorded during the process of compression using Vernier caliper.

- **Hardness:** Pharmatorn hardness tester was used for the determination of hardness of tablets. Tablet was placed in between the plungers and the force of the fracture was recorded.

- **Friability:** 6.5 gm. of tablets were accurately weighed and placed in the friabilator (Electrolab, EF-2 Friabilator) and operated for 100 revolutions. The tablets were de-dusted and reweighed. Percentage friability was calculated using the following formula

\[
F = \left(1 - \frac{W_0}{W}\right) \times 100
\]

Where,

- \(W_0\) is the weight of the tablets before the test
- \(W\) is the weight of the tablet after the test

The tablets that lose less than 1% weight were considered to be satisfactory.

- **Disintegration Time:** Six tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a one liter beaker containing 900 ml of distilled water and the time of disintegration was recorded. To discriminate between the formulations disintegration was done at room temperature and disk was not used for the study.

- **In-vitro Dispersion Time:** Six tablets were taken for determination of dispersion time. Each tablet was placed in 6 ml 0.5% SDS in Water buffer solution, pH 7.0 ± 0.5°C. Time required for complete dispersion of a tablet was measured. Predetermined time interval 10, 20, 30, 45 min and replaced with same volume of fresh medium 0.5% SDS Water buffer. Absorbance of this solution was measured at 240 nm.

2. **Identification tests for Nimodipine**
   A. **Melting point:** The melting point of the Nimodipine was found to be 125 °C which complies with melting point reported one.

   B. **UV Scanning:** The λmax of Nimodipine was found to be 240 nm. This complies with specified λmax.
C. Infrared Absorption Spectrophotometry:

![FTIR spectrum of Nimodipine](image)

**Fig. No. 3 FTIR spectrum of Nimodipine**

**Table No. 5 FTIR peaks of Nimodipine**

| Sr. No. | Observed Frequency (cm$^{-1}$) | Assignment |
|---------|-------------------------------|------------|
| 1.      | 1307.97                       | C-N        |
| 2.      | 1730.92                       | C=O        |
| 3.      | 745.86                        | C-H        |
| 4.      | 1747.93                       | C=C        |
| 5.      | 1541.14                       | N-H        |
| 6.      | 1646.84                       | C=N        |
| 7.      | 677.02                        | C-Cl       |
| 8.      | 3903.41                       | O-H        |
| 9.      | 824.62                        | C-C        |

A. Drug-Excipients Compatibility Study

Drug-Excipients Compatibility Study was carried out with different excipients with different ratio for initial, 15 days, 30 days.

**Table No. 6 Drug-Excipients compatibility study**

| Sr. no | Combination                        | Initial                  | 15 days                  | 30 days                  |
|--------|------------------------------------|--------------------------|--------------------------|--------------------------|
|        |                                    | Physical Appearance      |                          |                          |
|        |                                    |                          | Open         | closed       | Open         | closed       |
| 1      | Nimodipine                         | Off yellow powder        | Off yellow powder        | Off yellow powder        | Off yellow powder |
| 2      | Nimodipine + Mcc 101(1:1)          | Off yellow powder        | Off yellow powder        | Off yellow powder        | Off yellow powder |
| 3      | Nimodipine + Mcc 102(1:1)          | Off yellow powder        | Off yellow powder        | Off yellow powder        | Off yellow powder |
| 4      | Nimodipine + Mcc 112(1:1)          | Off yellow powder        | Off yellow powder        | Off yellow powder        | Off yellow powder |
| 5      | Nimodipine + 200(1:1)              | Off yellow powder        | Off yellow powder        | Off yellow powder        | Off yellow powder |
| 6      | Nimodipine + Tween 80(1:0.5)       | Off yellow powder        | Off yellow powder        | Off yellow powder        | Off yellow powder |
| 7      | Nimodipine + propylene glycol(1:0.5)| Off yellow powder        | Off yellow powder        | Off yellow powder        | Off yellow powder |
| 8      | Nimodipine + Polyethylene glycol(1:0.5)| Off yellow powder    | Off yellow powder        | Off yellow powder        | Off yellow powder |
| 9      | Nimodipine + PVP K 30(1:0.25)      | Off yellow powder        | Off yellow powder        | Off yellow powder        | Off yellow powder |
| 10     | Nimodipine + Crosprobivdone(1:0.5) | Off yellow powder        | Off yellow powder        | Off yellow powder        | Off yellow powder |
| 11     | Nimodipine + Aerosil(1:0.25)       | Off yellow powder        | Off yellow powder        | Off yellow powder        | Off yellow powder |
3. **PRECOMPRESSION EVALUATION OF LUBRICATED BLEND**

Table No.7: Flowability parameter of Nimodipine Liquisolid compact.

| Sr. No. | Batch Code | Bulk Volume | Tap Volume | Bulk density | Tap Density |
|---------|------------|-------------|------------|--------------|-------------|
| 1       | F1         | 2.1         | 1.9        | 0.9523       | 1.0526      |
| 2       | F2         | 4.8         | 4.3        | 0.4166       | 0.4651      |
| 3       | F3         | 4.7         | 4.1        | 0.4255       | 0.4878      |
| 4       | F4         | 4.9         | 4.2        | 0.4081       | 0.4761      |
| 5       | F5         | 5.1         | 4.4        | 0.3921       | 0.4545      |
| 6       | F6         | 5.4         | 4.3        | 0.3703       | 0.4651      |
| 7       | F7         | 6.1         | 5.0        | 0.3278       | 0.4000      |
| 8       | F8         | 6.2         | 5.2        | 0.3225       | 0.3846      |
| 9       | F9         | 6.4         | 5.5        | 0.3125       | 0.3636      |

Table No: 8. Flowability parameter of Nimodipine Liquisolid compact

| Formulation code | Angle of Repose (°) | Carr’s Index | Hausner’s Ratio |
|------------------|---------------------|--------------|-----------------|
| F1               | 29.03               | 12.18        | 1.13            |
| F2               | 29.05               | 10.42        | 1.11            |
| F3               | 26.86               | 12.77        | 1.14            |
| F4               | 28.62               | 14.28        | 1.16            |
| F5               | 29.08               | 13.72        | 1.15            |
| F6               | 27.15               | 20.38        | 1.25            |
| F7               | 28.17               | 18.05        | 1.22            |
| F8               | 28.96               | 16.14        | 1.19            |
| F9               | 29.63               | 14.05        | 1.16            |

4. Evaluation of Liquisolid tablets:

Table No:9. Evaluation of Liquisolid tablets:

| Formulation Code | Thickness (mm) | Diameter (mm) | Hardness (kg/cm²) | Disintegration time (min:sec) |
|------------------|----------------|---------------|-------------------|-----------------------------|
| F1               | 4.29±0.02      | 7.09±0.01     | 1.06±0.25         | 12 min 51 sec               |
| F2               | 4.28±0.01      | 7.13±0.02     | 2.05±0.19         | 14 min 34 sec               |
| F3               | 4.29±0.07      | 7.10±0.01     | 1.09±0.30         | 11 min 46 sec               |
| F4               | 4.37±0.03      | 10.24±0.10    | 1.28±0.11         | 12 min 32 sec               |
| F5               | 4.38±0.05      | 10.20±0.04    | 2.62±0.28         | 15 min 10 sec               |
| F6               | 4.39±0.01      | 10.05±0.06    | 2.34±0.20         | 19 min 54 sec               |
| F7               | 6.38±0.02      | 10.19±0.03    | 2.44±0.15         | 18 min 59 sec               |
| F8               | 6.78±0.07      | 10.21±0.09    | 2.23±0.55         | 14 min 10 sec               |
| F9               | 8.15±0.15      | 10.22±0.01    | 3.27±0.12         | 23 min 45 sec               |
| Conventional Tablets | 6.12±0.06 | 12.20±0.02   | 9.86±0.16         | 15 min 36 sec               |

Mean ±SD n=3

Table No:10. Evaluation of Liquisolid tablets

| Formulation code | Weight Variation (mg) | Friability (%) | % Drug content |
|------------------|-----------------------|----------------|---------------|
| F1               | 262.6                 | 0.25           | 96.78         |
| F2               | 260.0                 | 0.83           | 95.26         |
| F3               | 262.2                 | 0.22           | 96.20         |
| F4               | 342.1                 | 0.66           | 93.58         |
| F5               | 344.1                 | 0.49           | 97.51         |
| F6               | 345.1                 | 0.86           | 92.26         |
| F7               | 505.2                 | 0.42           | 101.22        |
| F8               | 512.7                 | 0.18           | 99.24         |
| F9               | 542.3                 | 0.36           | 95.18         |
| Conventional     | 547.3                 | 0.16           | 94.96         |

5. **In-vitro Drug Release from Nimodipine Liquisolid Compact.**

In-vitro dissolution studies were carried out using USP apparatus type I at 50 rpm. Dissolution medium consist of 0.5% SLS in water maintained at 37°C. Drug release at different time intervals was measured by UV-Visible Spectrophotometer at 240 nm. In-vitro drug release drug release profile of all batches was compared with conventional formulation for drug release.
Table No: 11. In- vitro release profile of immediate release Liquisolid tablet

| Time in min | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | Conventional Tablet |
|-------------|----|----|----|----|----|----|----|----|----|---------------------|
| 0           | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0                   |
| 5           | 32.34 | 31.98 | 36.67 | 34.67 | 35.89 | 32.34 | 41.61 | 62.51 | 56.94 | 62.46               |
| 10          | 43.45 | 36.18 | 41.45 | 46.65 | 40.01 | 43.45 | 57.45 | 66.37 | 68.57 | 65.96               |
| 15          | 48.89 | 43.39 | 47.47 | 50.91 | 46.13 | 48.89 | 63.45 | 70.86 | 72.31 | 70.98               |
| 20          | 53.76 | 51.27 | 55.68 | 54.87 | 55.58 | 53.76 | 67.91 | 76.82 | 81.89 | 76.02               |
| 25          | 55.85 | 57.89 | 60.76 | 58.76 | 61.19 | 55.85 | 70.15 | 88.31 | 85.64 | 89.41               |
| 30          | 61.14 | 63.86 | 62.21 | 59.98 | 64.91 | 61.14 | 74.19 | 93.86 | 88.49 | 90.56               |

It was observed that F4, F5, F6 prepared by liquisolid techniques using binder PVP K30 to gives 61.14%, 63.86%, 62.21% drug release in 30 min and marketed preparation show 90.56% drug release. F2 give better immediate action.

It was observed that F4, F5, F6 prepared by liquisolid techniques using binder PVP K30 and disintegrants Crosspovidone to gives 59.98%, 64.91%, 61.14 drug release in 30 min and marketed preparation show 90.56% drug release. F5 give better immediate action.
It was observed that F7,F8,F9 prepared by liquisolid techniques using binder PVP K30 and disintegrants Crosspovidone gives 74.19%,93.86%,88.49% drug release in 30 min and marketed preparation show 90.56% drug release. F8 give better immediate action.

It was found that immediate release liquisolid tablet prepared by using binder and disintegrant shows immediate action and greater bioavailability. Formulation no.F8 was found to be optimized batch.

**SUMMARY AND CONCLUSION**

The present work showed that the liquisolid technique can be used for the production of immediate release matrices of water insoluble drug. PEG 300 was used as the liquid vehicle.

The prepared tablets were evaluated for tablet hardness, friability, thickness, weight variation, in-vitro disintegration time and dissolution. The hardness of all tablets was found to be 1.06 ± 0.25-3.27±0.12 Kg/cm². The hardness of all tablets were kept within the above mentioned range to compare the disintegration time of tablets prepared using different vehicle and their varying concentrations. The friability values were found in the range of 0.5-1%, indicating that the tablets were mechanically stable and could handle rigorous of transportation and handling. Thickness of all formulations was between 4.28±0.01 to 8.15±0.15 mm/inch showing fairly uniform tablets. Out of the total formulations, the tablets made by using the Drug: vehicle with ratio 1:4 complex with Crospovidone showed faster disintegration and faster drug release.

From the study, it can be concluded that liquisolid technique showed better disintegration time and drug release. It can also be said that use of 7% crosspovidone as a disintegrating agent gave tablet with faster disintegration time.

In the present work, release studies showed that batch F8 is an optimized batch which gave 62.51%, 66.37%, 70.86%, 76.82%, 88.31%, 93.86% drug release in 0, 5, 10, 15, 20, 25, 30 minutes respectively. On the other hand conventional preparation showed the 62.46%, 65.96%, 70.98%, 76.08%, 89.41%, 90.56% drug release in 30 minutes respectively. Dissolution study was performed using USP Dissolution apparatus I (basket type), using 900 ml dissolution medium 0.5% SLS in water with a rotation speed of 50 rpm.

The release of drug from these formulations provide evidence that PEG 300 play an vital role in immediate release of drug from liquisolid compact.

Thus, it can be concluded that formulation of Nimodipine tablet by Liquisolid Technique with appropriate ratio showed better disintegration time and percent drug release than other formulation. As all parameters were found satisfactory for small scale batch, it need to check commercial feasibility at larger scale. Hence it can be very well recommended for launching the proposed formulation in market with some desirable changes if required.

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