

Evaluation of Some Novel Techniques For Dissolution Enhancement of Poorly Water Soluble Drug Nimodipine

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Abstract: Nimodipine (NMP), a Ca^{++} channel blocker, has a low oral bioavailability due to poor solubility and insufficient dissolution rate. In order to improve the same, various techniques were employed viz., evaporative precipitation into aqueous solution (EPAS), spherical agglomeration (SA) and solid dispersion using solvent evaporation and melt-mixing. Formulations so prepared were characterised by differential scanning calorimetry (DSC) and X-Ray powder diffractometry (XRD) and were investigated for drug content studies, solubility studies, in-vitro study and in vivo evaluation of anti-inflammatory activity. The formulations of NMP prepared by spherical agglomeration technique have the good drug content and the formulations with SLS and HPMC show a significant increase in solubility in case of SA technique. In case of solid dispersion, all carriers show improvement in the dissolution rate of the drug. The DSC studies show no change in the polymorphism in most of the formulations. The XRD studies of the formulations show no change in their crystalline form..

Keywords: Nimodipine, evaporative precipitation into aqueous solution, spherical agglomeration, solid dispersion, dissolution.

INTRODUCTION

Poor aqueous solubility of drugs is a major limiting factor with many new drugs in their successful launch in market in spite of their potential pharmacokinetic activity. Poor solubility (less than 10 %) of a drug, leads to poor dissolution in the gastro intestinal tract (GIT) hence, incomplete and erratic absorption ultimately limits its clinical utility. Further, poorly soluble drugs are generally administered at much higher doses than the actual dose in order to achieve necessary drug plasma levels leading to increased adverse reaction & cost of therapy and often yields erratic pharmacological response and hence poor patient compliance. About 40

% of drugs being in the pipeline of pharmaceutical companies are poorly soluble, which emphasizes the need of a technique to overcome such problems.¹ Poorly water-soluble drugs are associated with slow drug dissolution followed by slow absorption leading eventually to inadequate and variable bioavailability. Solubility, one of the key parameter in BCS, as well as dissolution rate is the most essential factors controlling the rate and extent of drug absorption. A poorly water soluble compound is defined which get soluble less than 1 part per 10000 part of water. A poorly water soluble drug, more recently, has been defined in

general terms which require more time to dissolve in the gastrointestinal fluid than it take to be absorbed in the gastrointestinal tract. Thus a greater understanding of dissolution and absorption behaviors of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products.² Nimodipine (NMP), a Ca^{++} channel blocker, was selected as model drug as the drug has low aqueous solubility where its GIT absorption is limited by its dissolution in the gastrointestinal fluids exhibiting a low bioavailability after oral administration.³ A number of approaches are practiced to improve the aqueous solubility poorly soluble drugs viz., solid dispersion (solvent evaporation method, fusion process melt- mixing, freeze-dried, fusion-solvent method, kneading technique, co precipitation),⁴ spherical agglomeration,⁵ evaporative precipitation in aqueous solution,⁶ microcrystallisation,⁷ supersaturation,⁸ pro drug approach,⁹ polymorphism,¹⁰ complexation,¹¹ ph adjustment,¹² co-solvents,^{13, 14} use of surfactant,¹⁵ and particle size reduction.¹⁶ These techniques result into polymorphic changes or changes in crystal structure or hydrophilicity or particle size changes due to formation of molecular dispersion. The formulations were evaluated by the evaluation techniques utilized also focused on studying these changes in drugs along with their solubility, dissolution and other properties. The solubility and *in vitro* study was evaluated by the spectrophotometer in the dissolution media. The polymorphic form of the formulation is evaluated by the differential scanning calorimetry (DSC) & crystal structure determination by the powder X-ray diffraction studies (XRD) at the different angles. In the present investigation the techniques utilized were Evaporative Precipitation into Aqueous Solution, Spherical agglomeration, Solvent evaporation and Melt-Mixing, mainly due to their ease in formulation and versatility in application. All these techniques can be easily accommodated at industrial level and the techniques can be easily incorporated in formulation operations in pharmaceutical industry.

MATERIALS AND METHODS

Materials

Nimodipine was obtained as gift sample from U.S. Vitamins Ltd., Mumbai, India. Polyvinyl pyrrolidone K30 (PVP), Hydroxypropylmethylcellulose (HPMC) and Poly Ethylene Glycol (PEG-4000) were purchased from Qualigens Fine Chemicals (Mumbai, India). All other chemicals were of extra-pure reagent grade and used as and when received.

Methods

Preparation of spherical agglomerates of PEG-4000, HPMC, SLS, PVP

NMP (2.5 g) was dissolved in 40 mL DMF by gentle warming up to 50°C and then cooled to room temperature. A solution of 0.1% w/v of

surfactant/polymer (HPMC, PEG-4000, Sodium Lauryl Sulfate, PVP K-30) in distilled water (30 mL) was then added to drug solution in DMF with stirring (Table 1). The precipitated solid was dissolved by further addition of 30 mL DMF and gentle warming. This solution was added with stirring to 400 mL distilled water contained in the agglomerating vessel. Chloroform (18 mL) was added drop wise with stirring at 900 rpm for 30 minutes. The precipitate obtained was collected and dried in vacuum and stored in desiccator further studies.

Preparation of solid dispersion by solvent evaporation technique

In this technique the proper volume of two solutions were to be taken. NMP (5 wt %) and polymer PEG/SLS/HPMC/PVP (5 wt %), in ethanol were mixed and the mixtures were stirred for 10 minutes at 900 rpm (Table 1). The final solutions were poured onto Petri dish and the solvent was left to evaporate in open air for 2 days. After complete removal of the solvent the solid dispersions were stored at ambient temperature in desiccator.

Preparation of hydrophilic coated drug particles by evaporative precipitation in aqueous solution (EPAS) method

Preheated ($\approx 70^\circ\text{C}$) organic solution of the NMP in Chloroform (1%) is sprayed through a fine nozzle into a preheated ($\approx 70^\circ\text{C}$) (1%) aqueous solution of surfactant/polymer. The rapid evaporation of the organic solvent produces high supersaturation and rapid precipitation of the drug in the form of a colloidal suspension that is stabilized by a variety of low molecular weight surfactant/polymer solution of (SLS, PEG-4000, PVP, and HPMC). The suspensions were then freeze dried (Table 1).

Preparation of solid dispersions by melt mixing method

A physical mixture of NMP and PEG were heated during stirring in a reaction tube immersed in an oil bath to 130°C. When the drug was completely melted and a homogeneous solution was obtained. Solid dispersions with Drug/PEG 20/80, 40/60, 60/40 weight ratios were prepared (Table 1). Next, the tubes were immersed in a water bath to quench the melt. The prepared samples were dried and stored at 25°C in desiccator.

EVALUATION AND CHARACTERIZATION

Differential Scanning Calorimetry

DSC studies of the prepared samples were conducted immediately after preparation as well as after storage for 6 months. A (Q-10, TA) Instrument equipped with an intraocular 2p cooling accessory was used. Samples of 10mg to 5mg were placed in saturated aluminum

pans and sealed with a lid. Heating scans by 10°C /min applied with a purge of 50ml/min. Fast heating rates are preferred to prevent changes during scanning.

X-Ray Powder Diffractometry

X-ray powder diffraction patterns were recorded on a XPERTO-PRO x-ray diffractometer using Ni filtered, using a voltage of 45kV, and a 40mA current. The scanning employed was 1 min- 1 over the 6 to 50 diffraction angle (2θ) range. The relationship used for the calculation of crystallinity was presented by *relative degree of crystallinity*.¹⁷

$$\text{Relative degree of crystallinity (RDC)} = \frac{I_{\text{sam}}}{I_{\text{ref}}}$$

where,

I_{sam} = Peak height of the sample under investigation

I_{ref} = Peak height at the same angle for the reference with the highest intensity.

Drug Content Studies

The individual formulations equivalent to 10mg of drug were weighed accurately and mixed with 100 ml of methanol. After that the solutions is to be 10 times diluted with methanol. The suspension was filtered through 22μm nylon disc filter and drug content was analyzed at 237nm UV spectrophotometer (Perkin Elmer EZ301, USA).

Solubility Studies

In solubility study of the drug and its formulations was done by shaking 10 mg of Std. drug and its formulations (equivalent to 10 mg drug) with 40ml of distilled water (0.1%) in 100ml volumetric flask for 24 hours on water bath shaker. And then make up the volume up to 100ml. After 10 times dilution then filtering and determining spectrophotometrically at 237nm.

In Vitro Study

The dissolution study is to be done of the 10 mg of Std. drug and its formulations (equivalent to 12 mg drug). Formulations (10mg) of Nimodipine were placed in capsule with 200 mg sprayed dried lactose in a rotating basket (USP XXII) and then placed in 900 ml 0.1% SLS solution and stirred at a speed of 50 rpm with temperature maintained at 37 ± 1°C. Aliquots of 10ml were withdrawn at appropriate time intervals and an equal volume of 0.1% SLS was replaced in the vessel. Nimodipine in the aliquot was assayed spectrophotometrically at 237nm.

RESULTS AND DISCUSSION

Differential scanning calorimetric (DSC) study

DSC thermograms of pure drug and corresponding drug carrier system are depicted in Figure 1. The DSC curve of Nimodipine (NMP-16) shows a sharp

endothermic peak ($T_{\text{peak}} = 126.03^{\circ}\text{C}$) corresponding to its melting, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug melting was broadened and shifted toward lower temperature, with reduced intensity, in all the formulations of NMP-01, NMP-07, NMP-012, and NMP-13. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Moreover, the data also indicate there seems to be no interaction between the components of binary system. No significant difference in DSC pattern of dispersions and physical mixture suggests that even in the kneading process could not induce interaction at the molecular level and solid dispersion formed is a physical mixture with highly dispersed drug crystals in carrier.

X-ray Diffraction Study

X-ray diffractometry (XRD) spectra of pure compound and binary systems with carriers are presented in figure 2. The x-ray diffractogram of NMP-16 has sharp peaks at diffraction angles (2θ) 6.54°, 12.87°, 20.28°, 17.36°, and 19.70°. It is showing a typical crystalline pattern. However, all major characteristic crystalline peaks appear in the diffractogram of all the formulations (NMP-01, NMP-07, and NMP-12). The RDC values of NMP-01, NMP-07 and NMP-12) were 0.8281, 1.056 and 0.2239 respectively. Moreover, the relative intensity and 2θ angle of these peaks remains practically unchanged.

Drug content study

The drug content of the prepared formulations of Nimodipine was observed to be varying from 88.4 to 15.1% and it was maximum with formulation (NMP-02) and minimum in formulation (NMP-11) as shown in Table 2. This studies shows that spherical agglomeration technique shows the maximum drug content and the evaporative precipitation in aqueous solution (EPAS) show the minimum drug content.

Solubility studies

For Nimodipine the aqueous solubility of drug was observed to be maximum in the NMP04 formulation is about (6.11±0.02 ug/ml) and is (1.85±0.03 ug/ml) in the NMP02 formulation as shown in Table 2 and Figure 3. Studies shows that spherical agglomeration technique shows the maximum drug solubility with SLS surfactant and with PVP this technique show minimum drug solubility. In the solid dispersion (solvent evaporative) technique the formulation NMP08 show the greater (5.49±0.02 ug/ml) and formulation NMP05, NMP06 & NMP07 show the slightly more solubility. In the Evaporative Precipitation technique in Aqueous Solution the formulation NMP12 show the maximum formulation

NMP-10 shows minimum solubility (4.51 ± 0.04 & 2.11 ± 0.06 ug/ml respectively) as compared to the NMP16. In the solid dispersion (Melt Mixing) technique the formulations (NMP13) show the (3.31 ± 0.03 ug/ml). Over all in the solubility studies show that the spherical agglomeration technique and EPAS is the best method for the increases in the solubility of the nimodipine with SLS.

In vitro dissolution studies

In vitro dissolution studies of the prepared formulations were done on USP-1 apparatus using baskets. The specifications used for dissolution study of the all the prepared formulations were same and described below. In all the formulation, the drug content was taken as 10 mg per capsule in 900 ml dissolution medium, 37°C containing SLS (0.5 % w/v) and at different time intervals, 10ml of the solution was withdrawn until 16 hr.

In Vitro dissolution study of the different formulations of Nimodipine prepared by spherical agglomeration technique, it was observed that the formulation NMP04 show the increase in the %release of the drug from the formulation which are to be kept in the capsule as compared to the std. drug profile. The formulation NMP-02 Show the lesser % release of the drug in the dissolution medium.

In Solid Dispersion (Solvent Evaporation) technique, it was observed that the all formulation NMP-05, NMP-06, NMP-07, NMP-08 show the increase in the %release of the drug from the formulations. In (EPAS) technique, it was observed that the formulation NMP-12 show the increase in the %release of the drug from the formulation which are to be kept in the capsule as compared to the std. drug profile. The formulation NMP-09 Show the lesser % release of the drug in the dissolution medium. In Solid Dispersion (Melt Mixing) technique, it was observed that the formulation NMP-13 show the maximum increase in the %release of the drug from the formulation which are to be kept in the capsule as compared to the std. drug profile. The formulation NMP-15 Show the lesser % release of the drug in the dissolution medium as compared to the std. drug release profile as shown in Figure 4 - Figure 7 and Table 2.

Effect of different carriers on the dissolution of Nimodipine

Spherical agglomeration techniques were developed for improving the solubility of microcrystalline nimodipine. The process involved agglomerating microcrystal using agglomerating solvents. Temp and speed of agitation were optimized to obtain spherical agglomerates in a desired range, which was found to be essential to enhance the solubility. Incorporation of polymer/surfactant (HPMC, SLS) during agglomeration significantly enhanced the dissolution

rate of nimodipine. In additional flow and compressibility properties of the drug is improved.

The enhancement of dissolution of drug from drug carrier systems can be ascribed to several factors. The mechanism of dissolution rate improvement from solid dispersion is lack of crystallinity and particle size reduction considered to be important factors for dissolution rate enhancement. Mixing of drug with a hydrophilic carrier results in greater wetting and increase surface available for dissolution by reducing interfacial tension between the hydrophilic drug and dissolution media. It was noted that drug carrier system sink immediately, while pure drug keeps floating on the surface for a longer time interval.¹⁸

The dissolution parameters of drug (nimodipine) solid dispersion with various carriers (HPMC, PVP K-30, PEG-4000, SLS) in same concentration of each carrier. The dissolution rate of pure drug is low even in the surfactant based medium, as 22.3 % of the drug gets dissolved 360 min respectively.

Solid dispersions formulated with all the carriers exhibited significant improvement in the dissolution parameters of drug. The order of dissolution enhancement with various binary systems was found to be (NMP-08>NMP-06>NMP-07>NMP-05) for nimodipine. The increase in the dissolution rate of the solid mixtures might be due to size reduction and increase in the wettability of the drug molecules in presence of the surfactants. Surfactants also lowering the effect of surface tension, hence increasing the solubilizing effect. This kind of technique can be extended for improvement dissolution rate of drug showing poor dissolution profiles and causing erratic bioavailability.¹⁹

In evaporative precipitation into aqueous solution (EPAS) to form micron to sub-micron sized particles, leading to increased bioavailability relative to larger particles. Soluble stabilizers offer the ability to form submicron particles that have high dissolution rates in aqueous media. The present invention often produces particles having reduced crystallinity as compared to the bulk drug, which enhances dissolution.²⁰

CONCLUSION

Spherical agglomeration is a better technique for the solubility enhancement of Nimodipine because the drug loaded to the carriers in very significant amounts due to which the bulkiness of the dosage form is reduced and the solubility and oral bioavailability of the drug improved nearly twice the pure drug. The EPAS techniques also gave better results in the in vitro studies but their limitation is that the drug content in the formulations is very less, so it enhances the bulkiness of the dosage form. Present investigation successfully enhanced the solubility and dissolution profile of the investigational drug there by enhancing the bioavailability of drugs and improving the patient compliance.

TABLE 1: COMPOSITION OF VARIOUS FORMULATION BATCHES DEPENDING ON THE TECHNIQUES

Sr. No.	Formulations	Techniques	Solvent	Polymers/Surfactant
1	NMP-01	SA	DMF	HPMC
2	NMP -02	SA	DMF	PVP
3	NMP -03	SA	DMF	PEG-4000
4	NMP -04	SA	DMF	SLS
5	NMP -05	SE	Ethanol	HPMC
6	NMP -06	SE	Ethanol	PVP
7	NMP -07	SE	Ethanol	PEG-4000
8	NMP -08	SE	Ethanol	SLS
9	NMP -09	EPAS	Chloroform	HPMC
10	NMP -10	EPAS	Chloroform	PVP
11	NMP -11	EPAS	Chloroform	PEG-4000
12	NMP -12	EPAS	Chloroform	SLS
13	NMP -13	MM	NO	PEG-4000
14	NMP -14	MM	NO	PEG-4000
15	NMP -15	MM	NO	PEG-4000
16	NMP -16	STD	NO	NO

TABLE 2. CONTENT, SOLUBILITY AND % RELEASE OF NIMODIPINE FROM DIFFERENT FORMULATIONS IN COMPARISON WITH ORIGINAL DRUG.

Sr.No.	Formulations	% drug content	Solubility (µg/ml)	% drug released after 6 hrs
1	NMP-01	85.7±0.55	4.03±0.04	39.8
2	NMP-02	88.4±0.30	1.85±0.03	20.5
3	NMP-03	79.3±0.50	2.02±0.03	20.2
4	NMP-04	83.5±0.50	6.11±0.02	45.7
5	NMP-05	64.5±0.20	4.01±0.04	31.3
6	NMP-06	49.5±0.40	3.15±0.01	56.8
7	NMP-07	49.9±0.30	3.53±0.02	45.7
8	NMP-08	47.2±0.40	5.49±0.02	59.6
9	NMP-09	50.7±0.50	2.43±0.03	22.1
10	NMP-10	40.0±0.10	2.11±0.06	25.3
11	NMP-11	15.1±0.20	2.32±0.06	35.6
12	NMP-12	26.2±0.40	4.51±0.04	59.4
13	NMP-13	35.6±0.40	3.31±0.03	35.2
14	NMP-14	40.2±0.20	2.88±0.02	21.2
15	NMP-15	51.0±0.30	2.45±0.04	19.3
16	NMP-16	100±0.00	2.68±0.03	22.3

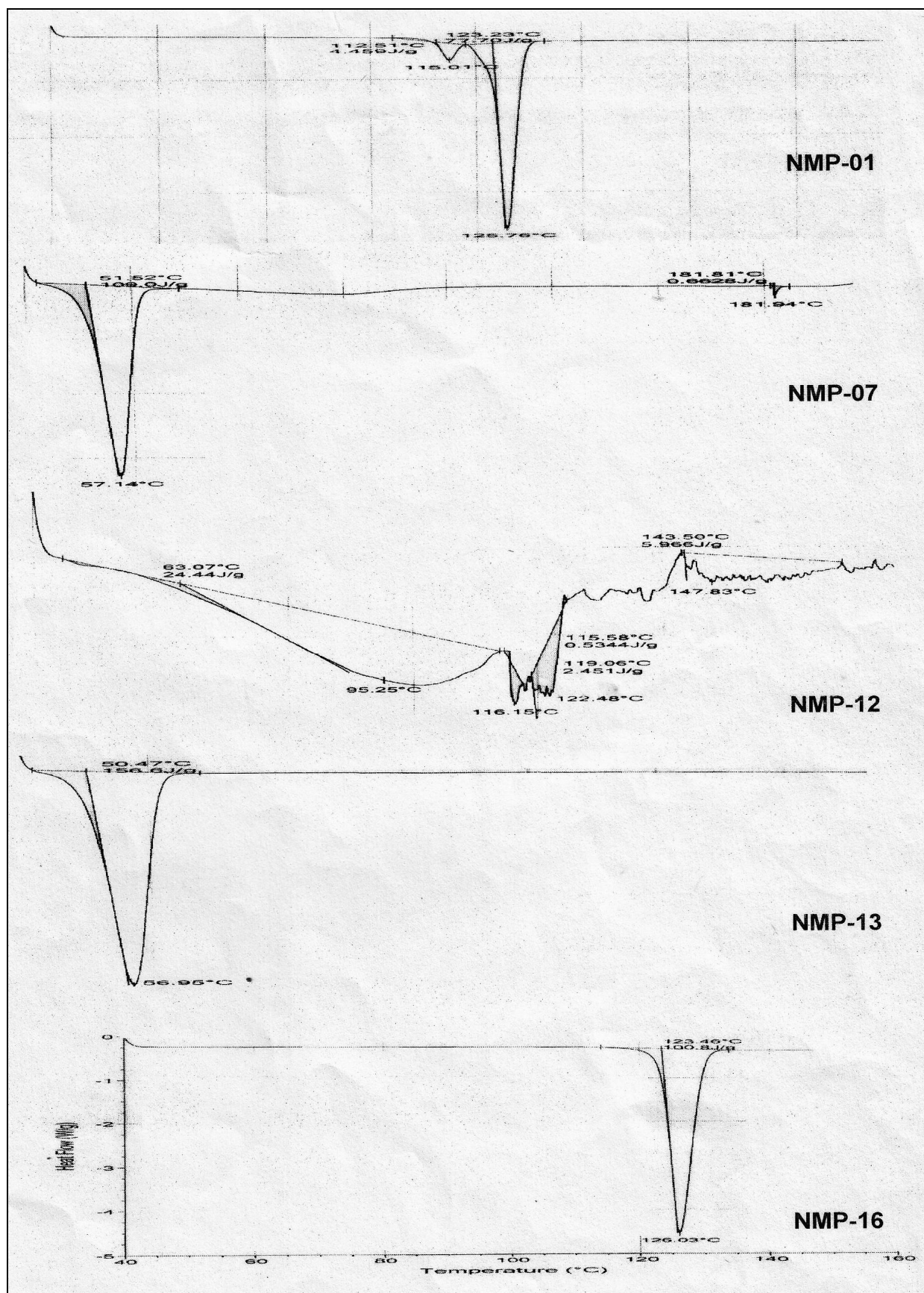


Figure 1: DSC thermogram of pure Nimodipine and its formulations.

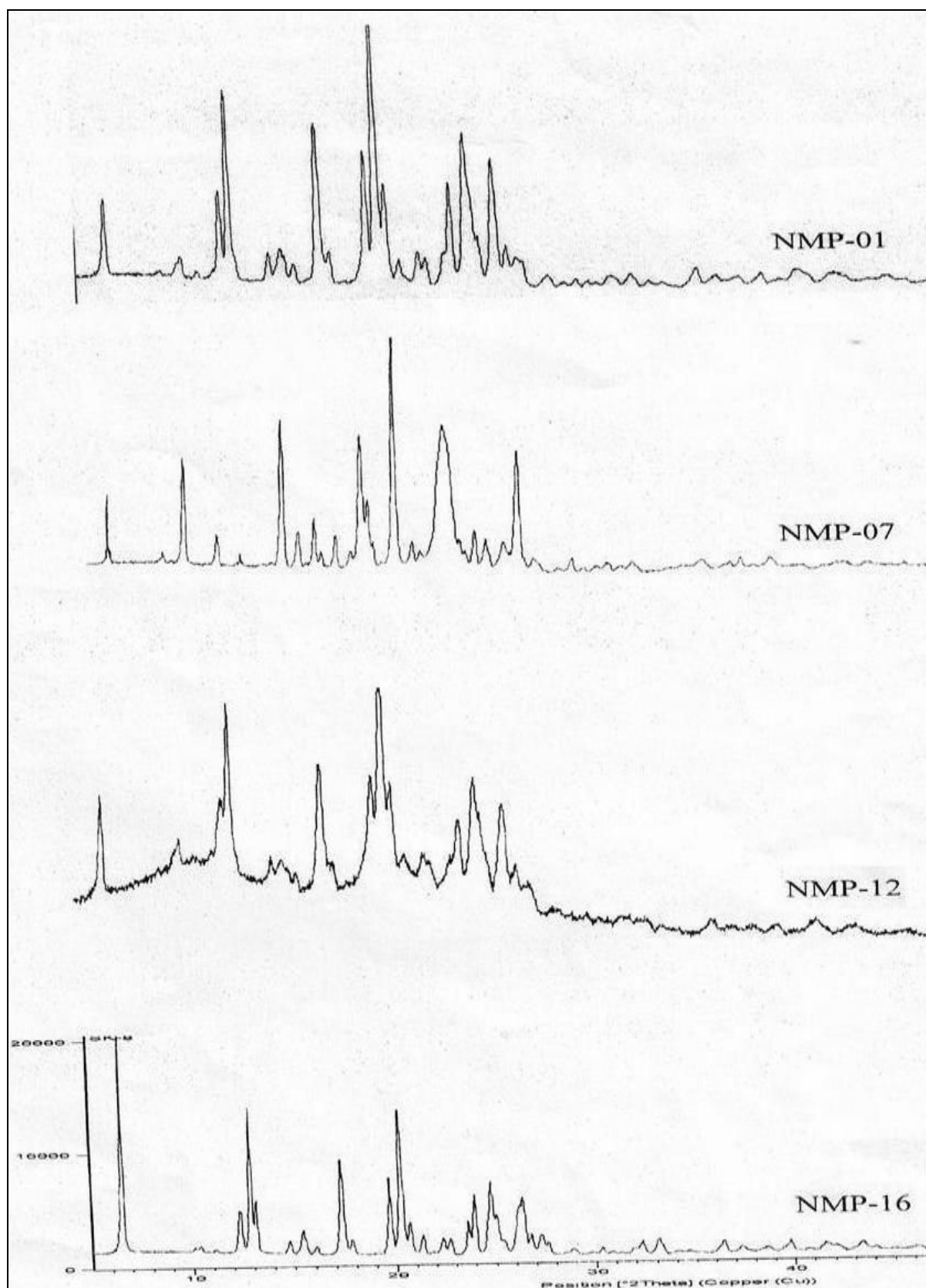


Figure 2: Powder X-ray diffraction spectra of pure Nimodipine (NMP-16), NMP-01, NMP-07 and NMP-12.

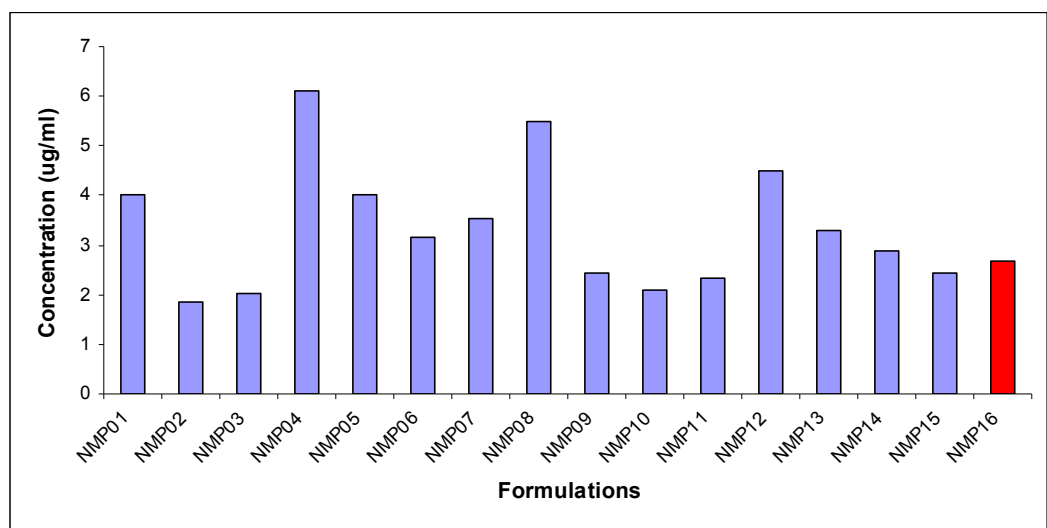


Figure 3: Solubility studies of Nimodipine (NMP 16) and its formulations.

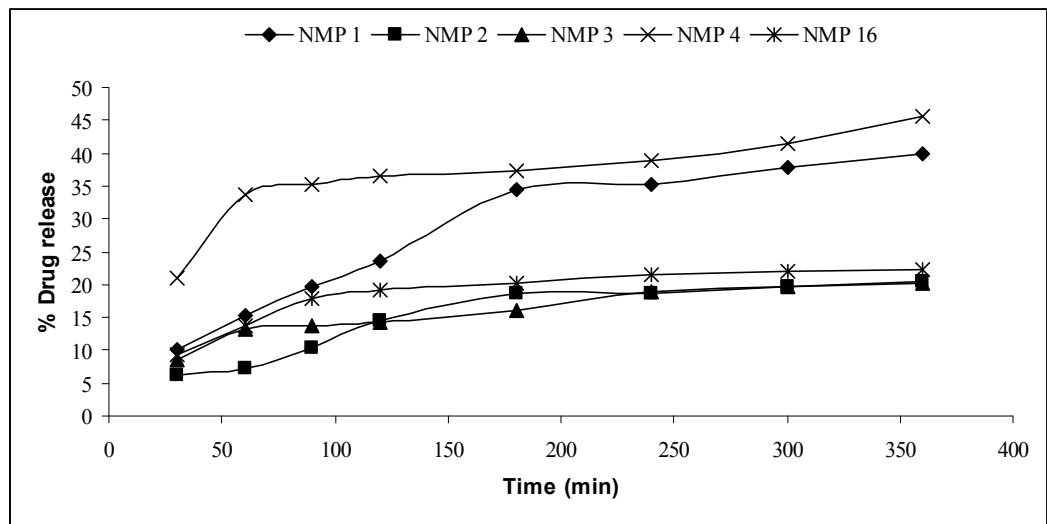


Figure 4: Dissolution profile of pure nimodipine (NMP 16) and its formulations prepared by spherical agglomeration (NMP 1 – NMP 4).

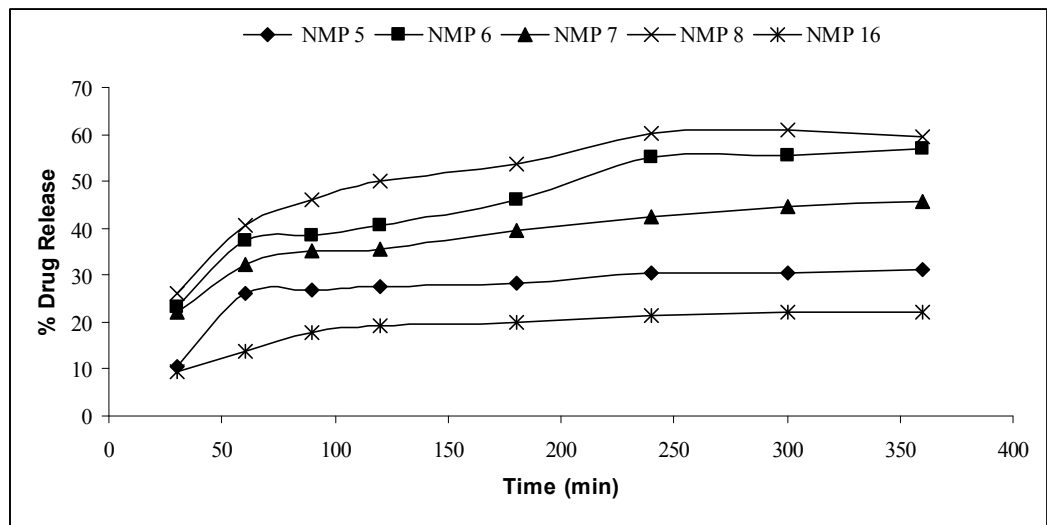


Figure 5: Dissolution profile of pure nimodipine (NMP 16) and its formulations prepared by solvent evaporation (NMP 5 – NMP 8).

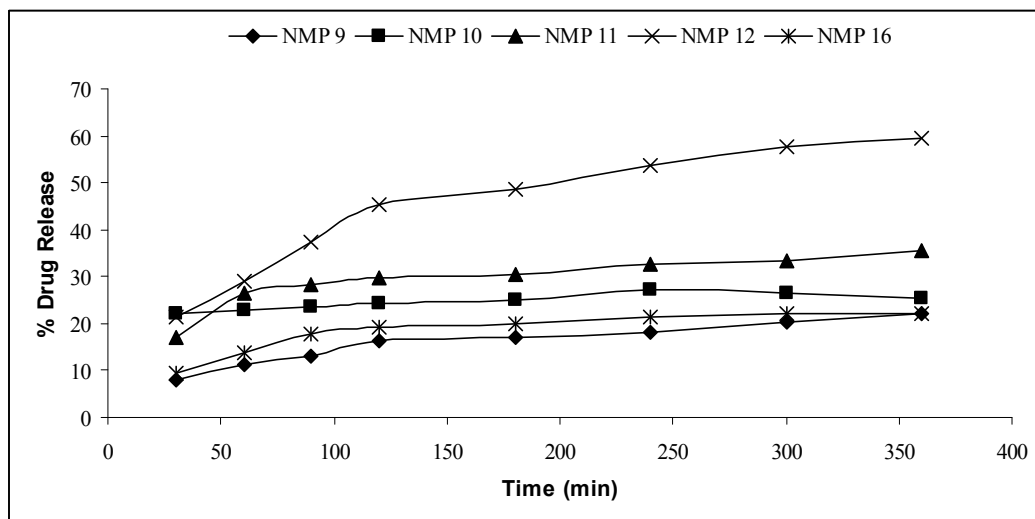


Figure 6: Dissolution profile of pure nimodipine (NMP 16) and its formulations prepared by evaporative precipitation into aqueous solution (NMP 09 – NMP 12).

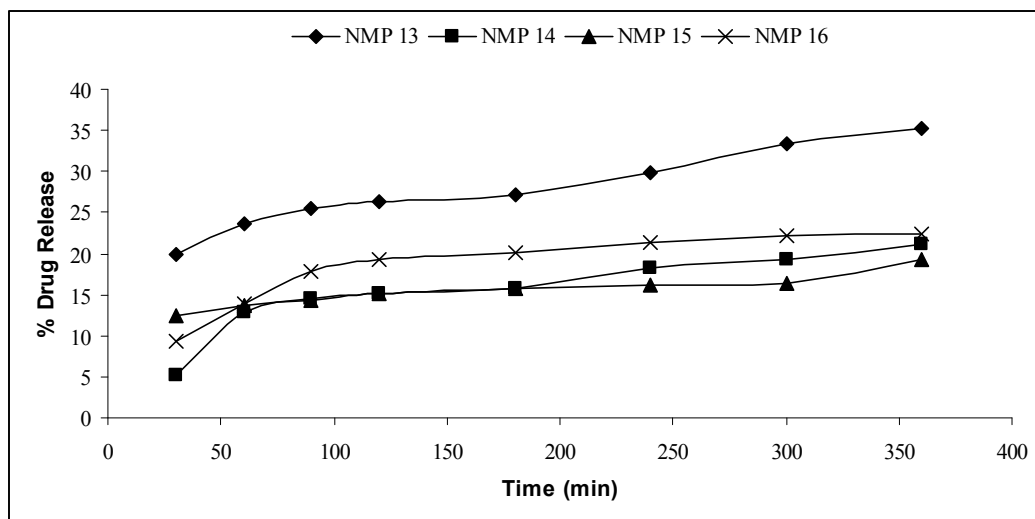


Figure 7: Dissolution profile of pure nimodipine (NMP 16) and its formulations prepared by melt mixing (NMP 13 – NMP 15).

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