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Enhancement of The Solubility and The Dissolution Rate of Oral Nimodipine Formulation with Solid Dispersion

Takwa E. Ellakwa[a], Doha E. Ellakwa[b]

[a] *Egyptian Russian University, Physical Chemistry Department, Faculty of Pharmacy, Cairo, Egypt.*
[b] *Al-Azhar University, Biochemistry Department, Faculty of Pharmacy (Girls), Cairo, Egypt.*

Abstract

The present study was an attempt to enhance the dissolution rate of nimodipine (a poorly water-soluble drug), The objective of this study was to evaluate poloxamer 407 as a carrier for nimodipine solid dispersions. The solid dispersions of nimodipine with poloxamer 407 were prepared by the hot melting technique, the molar ratio (3:1). The physicochemical properties of Solid dispersion were investigated by Differential Scanning Calorimetry (DSC), powder x-ray diffraction (PXRD), and Fourier Transform Infrared (FT-IR) spectroscopy. The FT-IR spectra indicated there was no chemical interaction between nimodipine and poloxamer 407 in the solid dispersion. DSC analysis indicated a decrease in the melting point of nimodipine and poloxamer 407 in solid dispersion. Nimodipine tablets were prepared by wet granulation technique using poloxamer 407 and compressed the dried granules of nimodipine into stable tablets. The other objective, the performance of two classes of super disintegrates as croscarmellose sodium (Ac-Di-Sol), and polyvinyl pyrrolidone K30 in the dissolution of nimodipine immediate release and promoting disintegration tablets was evaluated. The in-vitro dissolution was determined by using United States Pharmacopeia (USP) type II dissolution test apparatus. All the results indicated that enhancement of the dissolution rate of nimodipine has been done successfully and drug release Kinetics indicated that the drug dissolution was a diffusion equation.

Keywords: Solid dispersion, Nimodipine, Poloxamer 407, Dissolution rate, Kinetics, Hot melting method.

1.Introduction

Approximately 40 percent of new drugs have poor aqueous solubility, which can lead to low rates of dissolution [6]. Low bioavailability is a health public concern, typically connect to therapeutic failures growing hospital admissions and poor quality of life as a result. In this way, one of the main problems of the pharmaceutical industry is improving drug solubility [21]. There are several techniques for enhancing drug dissolution, including micronization, cyclodextrin complexation, nanoparticle technology, and solid dispersions. [20]. However, few of these approaches will scale up or have good revenue from the operation. In this context, the solid dispersion approach is an excellent alternative for the pharmaceutical industry to increase drug solubility in oral dosage forms [18]. Solid dispersions of drugs are generally produced by two methods, namely, the melting and the solvent methods, each of which had advantages and limitations [8]. The original hot melt method, developed by Sekiguchi and Obiin 1961, had some technical improvements over the years and new methods were developed such as Meltrex and hot-spin mixing [17]. For the solvent method, spray-drying, Rota evaporator, freeze-drying, supercritical fluids, a stream of nitrogen, and vacuum drying are the main techniques used to evaporate the solvent. Both methods are effective in increasing drug solubility since they are capable to produce dispersions [12].

Solid dispersion is characterized on the molecular level using Fourier transform infrared spectroscopy (FTIR) spectra, Powder x-ray diffraction patterns (PXRD), Differential Scanning Calorimetry (DSC), scanning electron microscopy (SEM), and transmission electron microscopy (TEM) and at the bulk level using density, contact angle and Flowability [13,16]. Nimodipine material as a pale-yellow crystalline powder, odorless, tasteless, practically insoluble in water, belonging to the low

*Corresponding author e-mail: takwaellakwa@gmail.com.; (Takwa Ellakwa).
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solubility in the Biopharmaceutics Classification System, a second-high permeability drug, its bioavailability dissolution of the rate-limiting step for such drugs, dissolution is an effective method to improve the bioavailability [1,10]. Nimodipine indicates for cerebral blood vessels and the major therapeutic indication of nimodipine is for the treatment of delayed ischemic neurological disorders [22]. Poloxamer 407 is (poly (ethylene glycol)-block-poly (propylene glycol)-block-poly (ethylene glycol) that acts as a surfactant, and in the last years it has received special attention in a sustained-release gel base and Nano and microparticles preparations considering the advantage of low toxicity, compatibility with other [19,23]. This study aimed to optimize the solid dispersion of nimodipine by poloxamer 407 to enhance the dissolution and so increase the treatment of ischemic neurological disorders by nimodipine. The novelty of this study is the generation of a solid dispersion method using poloxamer 407, which showed a significantly higher solubility and dissolution of the drug in vitro.

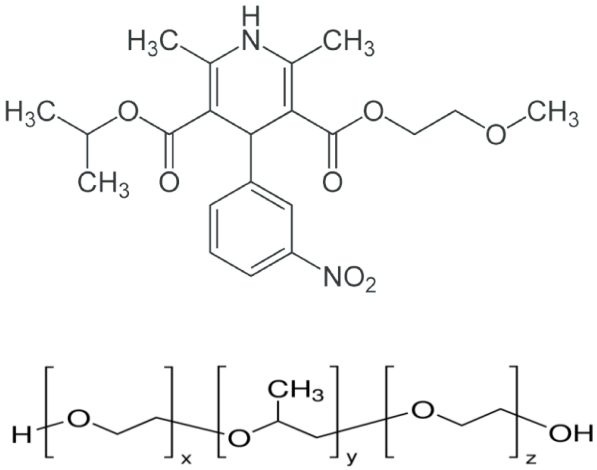


Fig. (1) a. Nimodipine (1,4-dihydropyridine), b. Poloxamer 407 (poly (ethylene glycol)-block-poly (propylene glycol)-block-poly (ethylene glycol).

2. Materials and Methods

2.1. Materials

All pharmaceuticals grade materials were bought from Pharmaceutical suppliers. Nimodipine (active drug) (98.0% -102.0% pure, as required in the USA Pharmacopeial Forum) was purchased from Hetero Drugs Limited (India). Poloxamer 407 was bought from BASF-the Chemical Co. (Ludwigshafen, Germany), Polyvinyl Pyrrolidone K30 (PVP k30), Microcrystalline cellulose (Avicel PH 101), Magnesium Stearate, Lactose monohydrate, croscarmellose sodium was bought from international specialty products (Germany).

2.2 Methods

2.2.1 Preparation of solid dispersion by Hot Melt Method

Solid dispersion of nimodipine and poloxamer 407 containing weight ratio (3: 1) were obtained by the hot melting method as follows. The drug was added to a molten carrier at 60 °C and carefully heated to 130 °C, with continuous stirring, for 15 minutes, until a homogeneous solution was formed. The Solution was immediately cooled on an ice bath and the resulting solid mass crushed in a knife and sieved through a 30-mesh sieve. The samples were put, at 25 C, in a desiccator.

2.2.2 Preparation of nimodipine Tablets

Wet Granulation

The Solid dispersion of nimodipine with poloxamer 407 molar ratio (3:1) is dissolved in purified water, with stirring until complete solubility, then the solution is added to Avicel pH 101 with mixing. In an oven, the final wet granulate is dried at 55-60 ° C and less than 2 percent is checked for Drying Loss (LOD), then granules are sieved through a No. 12 Mesh Screen. Then the dried granules were transported to a mini drum blender and mixed with polyvinyl pyrrolidone K 30 (PVP K 30), magnesium stearate, sodium croscarmellose, Lactose monohydrate, and well blended for 2 minutes. Using a flat, round 6 mm face bevel edge tooling was compressed with the blending. Target weight and hardness, respectively, were 343 mg and 5-8kp.

Table (1) Composition (mg) of nimodipine tablet formulations.

Name of ingredient	Formulation A	Formulation B
Intergranular		
Nimodipine	30	30
Poloxamer 407	10	-
Avicel PH 101	45	45
PVP k 30	6	6
Lactose monohydrate	235	235
Extra granular		
Croscarmellose sodium	13.5	13.5
Magnesium Stearate	3.5	3.5
The total weight (mg)	343 mg	343mg

2.2.3 Characteristics of Tablet Formulations

The active pharmaceutical ingredient(s), fillers, disintegrates, lubricants, are the formulations of a tablet. Past studies show that the addition of magnesium stearate dramatically improved the blending characteristics of the milled batches [7]. It is hydrophobic and may retard the dissolution of a drug from a solid dosage form; the lowest possible concentration is therefore used in such formulations [5, 14]. Weight, hardness, disintegration, friability,

dosage uniformity of material, and dissolution profile were defined for the tablets. As advised by the United States Pharmacopoeia (U.S.P) in 2006, the average weight was estimated at over 20 minutes. The hardness was determined in a Tianjin Guoming Medicinal Equipment Co., Ltd. Hardness Tester (YD-3) over 10 tablets. For each formulation, friability was checked for a sample of 20 tablets in a Tablet friability Tester and a maximum loss of 2 percent of initial weight was the acceptance criterion (U.S.P. 2006). The disintegration was done in a disintegrator (Tianjin) (BJ-2) and the time taken was compared with a traditional tablet acceptance criterion. The dissolution was carried out in a Shimadzu. The drug content of each batch was assayed by high-performance liquid chromatography. Samples were analyzed with UV detection at 274 nm on a Hewlett-Packard 1050 HPLC (Wilmington, DE). The separation was performed on STR BDS HYPERSILC18 – (4.6 x 250 mm) or equivalent column with a mobile phase of phosphate buffer (pH=3.5), acetonitrile (5:5%), delivered isocratically (1mL/min) (Ciavarella USA Patent). Assay validation is indicated in table 2.

Table 2. Assay validation sheet of the proposed method for the determination of nimodipine according to ICH Guidelines

Parameter	Nimodipine	Accepted Limit
Accuracy* (Mean)	99.78	98 – 102 %
Intermediate precision** (RSD)	0.119 %	≤ 3.0%
Range	15 - 45 µg/mL	
Slope	38,124.51062	
Intercept	10,489.81210	
The Correlation coefficient (r)	0.99997	
LOD	0.261 µg/ml	
LOQ	0.790 µg/ml	

*Accuracy (mean) assessed using a minimum of nine determinations over a minimum of three concentration levels covering the specified range.

** The intraday (n = 3), RSD of three concentrations repeated six times in three successive days.

Limit of detection (LOD), Limit of Quantitation (LOQ)

2.2.4 Fourier Transform Infrared Spectroscopy (FTIR)

The Fourier transform infrared spectroscopy (FTIR) spectra were obtained using FTIR spectrometer Schmooze FT-IR 8400S. The samples (nimodipine, poloxamer 407, and Solid dispersion of nimodipine with poloxamer 407 (3:1) were previously ground and mixed thoroughly with potassium bromide. The discs of powders and potassium bromide were obtained in a hydraulic press. Scans were recorded at a resolution of 2 cm^{-1} (K Br as reference).

2.2.5 Differential Scanning Calorimetry

The differential scanning calorimetry (DSC) measurements from nimodipine, poloxamer 407, and solid dispersion of nimodipine with poloxamer 407 (3: 1) were recorded in a differential scanning calorimeter DSC 2920 (TA Instruments, USA) with a thermal analyzer. Samples of approximately 3 mg were placed in sealed aluminum pans with a nitrogen flow rate of 50 ml min^{-1} and heated from 25°C.

2.2.6 X-Ray Powder Diffraction.

Powder x-ray diffraction patterns were recorded on XD-6000 (Shimadzu, Japan) powder x-ray diffractometer. The samples were analyzed with radiation under a voltage of 40 k Vanda current of 40 mA, at a heat ingrate of 2°C min^{-1}. This technique has become an indispensable tool for characterizing the degree of crystallinity of solids and has been used in all work involving the characterization of solid dispersion [9,24].

2.2.7 Flowability testing:

The flowability of the prepared powders was tested by measuring their angle of repose, compressibility index, and Hausner's ratio. experiments are done in triplicate, the average ±S.D.

2.2.7.1. Measuring the angle of repose:

The fixed height cone method was adopted [6] where the diameter of the formed cone (d) was determined according to the following equation:

$\tan \theta = 2h / d$

2.2.7.2 Determination of the initial and tapped bulk densities:

A fixed weight of the powder of drug was poured in a 25 ml graduated cylinder, the powder was allowed to settle with no outer force and the volume occupied was measured as V_I (initial bulk volume). The cylindrical graduate was then tapped on a plan surface at a one-inch distance till a constant volume was obtained. The tapped volume of the powder was then recorded as (V_T). The initial and tapped bulk densities were then calculated according to the following equation [11]

Initial Bulk Density $\rho_I = M / V_I$

Tapped Bulk Density $\rho_t = M / V_T$

Where (M) is the mass of the powder. The percentage compressibility (Carr's index) was then determined from the following equation [21].

Carr's index $= 100 (1 - \rho_I / \rho_T)$

Finally, the Hausner's ratio was obtained by dividing V_I by V_T [4]. The experiments were carried in triplicate and the average angle response; Carr's index and Hausner's ratio of each of the prepared formula were then calculated.

2.2.8 In vitro dissolution studies

Tablet dissolution was assessed in a standard USP 24 apparatus II (paddle) in 900 ml of acetate buffer maintained at 37± 0.5 °C. The speed of stirring was 75 rpm. In the test, a total of six tablets was used. Dissolution was monitored for 30 min; samples were taken at a wide range of time from 5 to 30 min. The dissolution medium was replenished after the collection of each sample with the same volume of fresh medium and analyzed for the percent release of drug by HPLC. A calibration curve was generated from HPLC chromatograms standard solutions.

2.2.9 Stability Study

The tablets were exposed to 40 ˚C /75 % relative humidity for 1, 2, and 3 months. After those tablets were withdrawn at these times to analyze properties such as color, water content, dissolution, assay, etc.

Statistical analysis: The data were analyzed using SPSS software, version 11.5.

3. Results and Discussion

3.1 Infrared spectral analysis:

The IR spectrum of pure drug nimodipine (Fig.2-a) shows a characteristic peak at 3298 cm^{-1} due to N-H stretching and peak at 3224 cm^{-1} due to C-H aromatic stretching and peak at 2981 cm^{-1} due to C-H aliphatic, 1693 cm^{-1} due to C = O, peak at 1647 cm^{-1} due to C=C, 1532, 1346 cm^{-1} due to NO_2 have observed similar peaks for nimodipine at 3298 and 1695 cm^{-1} [25].

The IR spectrum of poloxamer 407 (Fig.2- b) shows a characteristic peak at 3500 cm^{-1} due to O-H stretching and a peak at 2885 cm^{-1} due to C-H alkyl stretching.

Infrared studies (Fig.2-c) reveal that there is no appearance of new peaks and the disappearance of existing peaks, which indicate that there is no interaction between the drug and surfactant used.

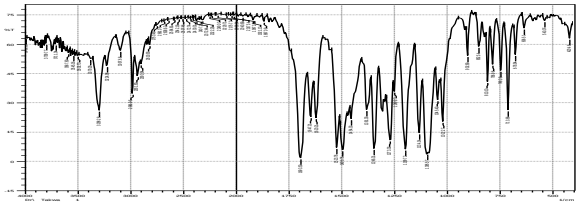


Fig. (2-a): IR spectra of nimodipine

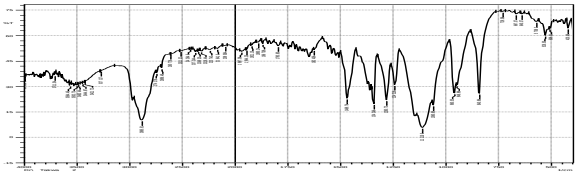


Fig. (2-b): IR spectra of poloxamer 407

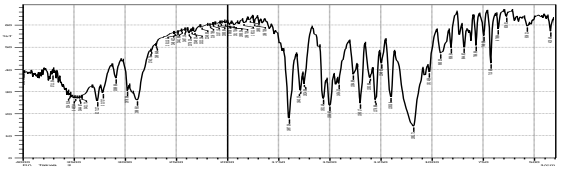


Fig. (2-c): IR spectra of solid dispersion of nimodipine with poloxamer 407 molar ratio (3:1)

3.2. Differential Scanning Calorimetry

Fig. (3-a) shows the DSC thermogram of nimodipine. It shows a sharp endothermic peak at 125.85 ˚C corresponding to the nimodipine melting point [2].

Fig. (3-b) shows the DSC thermogram of poloxamer 407. It shows a sharp endothermic peak at 55.50 ˚C corresponding to the poloxamer 407 melting point.

Fig. (3-c) shows the DSC thermogram of Solid dispersion of nimodipine with poloxamer 407 in a ratio of 3:1 w/w. It shows two endothermic peaks at 106.15 ˚C and 51.30˚C. This melting point was lower than the melting point of nimodipine (125.85˚C) and poloxamer 407 (55.50 ˚C). nimodipine with poloxamer 407 molar ratio (3:1)

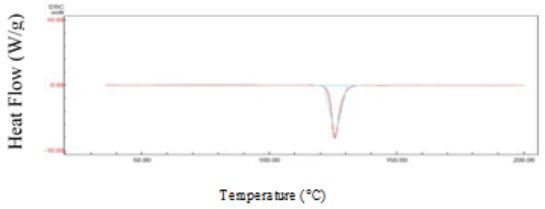


Fig. (3-a) DSC thermogram of nimodipine

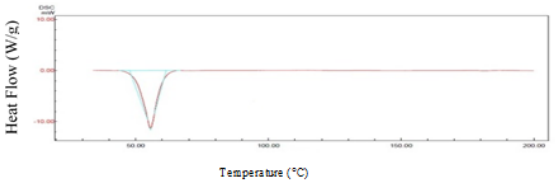


Fig (3-b) DSC thermogram of poloxamer 407

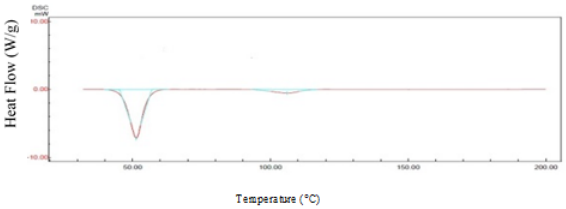


Fig (3-c) DSC thermogram of solid dispersion of

3.3. X-Ray Powder Diffraction

Both nimodipine [15,23], poloxamer 407 [3] are crystalline solids, as demonstrated by sharp and intense diffraction peaks (Fig.4 a-b). PXRD patterns of the Solid dispersion of nimodipine and poloxamer 407 molar ratio (3:1) (Fig.4 c), indicate there is no new diffraction peak; Crystal kept the original structure (No change in crystallinity).

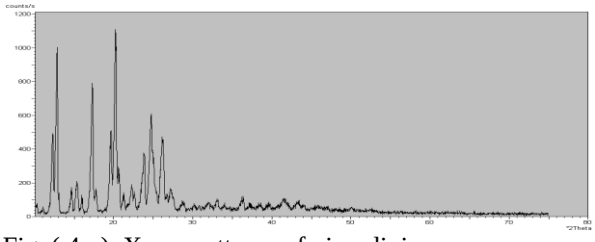
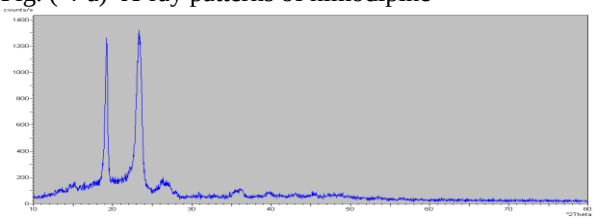


Fig. (4-a) X-ray patterns of nimodipine



Fig(4-b) : X-ray patterns of poloxamer 407

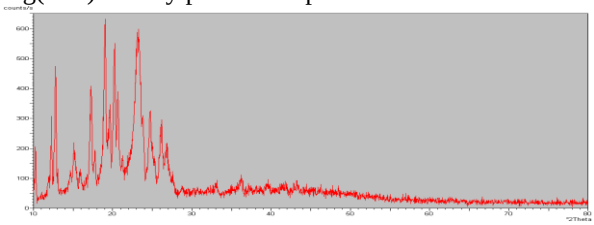


Fig (4-c): X-ray of solid dispersion of nimodipine and poloxamer 407 molar ratio (3:1).

3.4. Flowability testing

Table 4 shows the results of the flowability testing of nimodipine tablets. The angle of repose of all formulation batches from A to B was found in the range of 29.09 to 32.18º. On another hand, the bulk density of formulation batches A to B was obtained in the range of 0.353 to 0.335 g/cm^3 while tapped density was observed in the range of 0.368 to 0.376 g/cm^3. From the data of bulk and tapped density, compressibility index and Hausner's ratio were calculated for formulation batches A to B. Compressibility index was found in the range of 4.076 to 10.910 % respectively, and Hausner's ratio was obtained in the range of 1.042 to 1.122 respectively. Hausner's ratio and Compressibility index of formulation A indicates excellent flow while Hausner's ratio and compressibility index of formulation B indicates good flow as per the Scale of flowability [4]. The results indicate the flow properties of formulation A better than formulation B [4].

Table (3) Scale of flowability:

Compressibility index	Angle of Repose	Huunser's Ratio	Flow characteristics
10	25-30	1.00-1.11	Excellent
11-15	31-35	1.12-1.18	Good
16-20	36-40	1.19-1.25	Fair
21-25	41-45	1.26-1.34	Passable
26-31	46-55	1.35-1.45	Poor
32-37	56-65	1.46-1.59	Very poor
>38	>66	>1.60	Extremely poor

Table (4) Evaluation of Powder Blends of formulation Batches

*Evaluation Parameters**	*Formulation A*	*Formulation B*
The angle of Repose (0)	29.09 ± 0.784	32.18 ± 1 .078
Bulk Density (g/cm^3)	0.353 ± 0.002	0.335 ± 0.002
Tapped Density (g/cm^3)	0.368 ± 0.002	0.376 ± 0.002
Compressibility Index (%)	4.076± 0.400	10.910 ± 0.065
Hausner's Ratio	1.042 ± 0.016	1.122 ± 0.012

All values are mean ± SD

3.5 9 Characterization of nimodipine-loaded Tablets

As shown earlier in Table 1, tablets of all formulation batches A were prepared by wet granulation technique of Solid dispersion of nimodipine with poloxamer 407 molar ratio (3:1) while formulation batch B was prepared by direct compression technique. Tablets with the technique of Solid dispersion showed a greater improvement in dissolution compared to that one without it. Formulation batch A was comprised of Avicel PH 101 as a filler along with two different super disintegrates croscarmellose sodium (Ac-Di-Sol), and PVP k30. While formulation batch B was comprised exactly like that of batch_A but without Poloxamer 407. The reason for this behavior: due to Solid dispersion between drug and poloxamer 407 which enhances the drug release. Therefore, it could be concluded that the poloxamer 407 was improved solubility and dissolution of a drug by solid dispersion. Moreover, as shown in Table 3, The Hardness and thickness of formulation batches A and B were found in the range of 4.14 to 4.06 Kg/cm^2 and 2.92 to 2.83 mm. Friability falls were observed at 0.515 to 0.62 %, respectively, indicating a good mechanical resistance of tablets was obtained. The drug content of formulation batches A and B was calculated at 100.97 to 100.36%. The disintegration time of all formulation batches was found at 5.1 and 6.4 min, respectively. Croscarmellose Sodium (Ac-Di-Sol) was disintegrated tablets into relatively fine particles. Observed results were suggested that the super disintegrates were added into tablet formulations that might cause the penetration of water through the tablet, and the penetration rate of water would be altered. So, to shorten disintegration times in the tablet, the addition of the disintegrate having a property of quick water uptake in the formulation would be preferable to shorten the disintegration times in the tablet.

3.5. Stability Study: Stability studies for the strip-packed tablets of formulation A. The tablets were exposed to 40 °C /75 % relative humidity for 1, 2, and 3 months. After those tablets were withdrawn at these times to analyze properties such as appearance, drug content, and in vitro drug release at 30 min at P<0.01 level. Tablets did not show any significant change. Hence, the stability study for 3 months indicates that nimodipine is stable in the presence of poloxamer 407 and other excipients.

3.6 In vitro dissolution studied: Table 6 shows that the percent of drug dissolved from nimodipine (Formula A) containing 36.08%,70.55%, 88.55 %, and 99.01% after 5 ,10,15 and 30 min. respectively while the percentage of drug dissolved from nimodipine (Formula B) was 30.51%,56.5%, 62.43%, and 72.63% after 5,10,15 and 30 Min. It is evident that the formulation A enhanced nimodipine dissolution than formula B

Table 5: Evaluation of Compressed Tablets for Formulation Batches

Evaluation Parameters*	Formulation A	Formulation B
Weight. Variation (± %)	1.357 ± 0.932	0.916 ± 0.606
Hardness (Kg/cm2)	4.14 ± 0.0565	4.06 ± 0.075
Thickness (mm)	2.92 ± 0.0287	2.83 ± 0.0287
Friability (%)	0.515 ± 0.040	0.62 ± 0.050
Disintegration (min)	5.1 ± 0.024	6.4 ± 0.7985
Drug Content (%)	100.97 ± 0.03	100.06 ±0.723
DP30 (%)	99.01 ± 0.35	62.36 ±1.005

All values are mean ± SD, n=3, DP30 =Drug percent dissolved in 30 min

Table 6: Dissolution profile of Formulation A and Formulation B.

Time (min)	**Tablet 1**		**Tablet 2**		**Tablet 3**		**Tablet 4**		**Tablet 5**		**Tablet 6**		**Mean± SD**	
Formulat	A	B	A	B	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**	A	B
5	36.3	32.3	36.5	29.08	36.8	27.01	36.2	30.05	36.5	36.58	36.3	28.05	36.08± 0.83	30.51±0.49
10	70.8	55.8	70.0	53.5	70.4	60.8	70.3	49.9	70.2	58.8	70.7	6.2	70.55± 0.94	56.5±0.25
15	88.9	59.8	80.8	60.1	80.5	64.2	88.6	69.8	88.8	61.3	80.4	59.4	88.55 ±1.58	62.43±0.78
30	99.3	781	99.5	73.5	99.9	70.8	99.2	69.7	99.8	72.8	99.9	70.9	99.01± 0.35	72.63±0.023

All values are mean ± SD

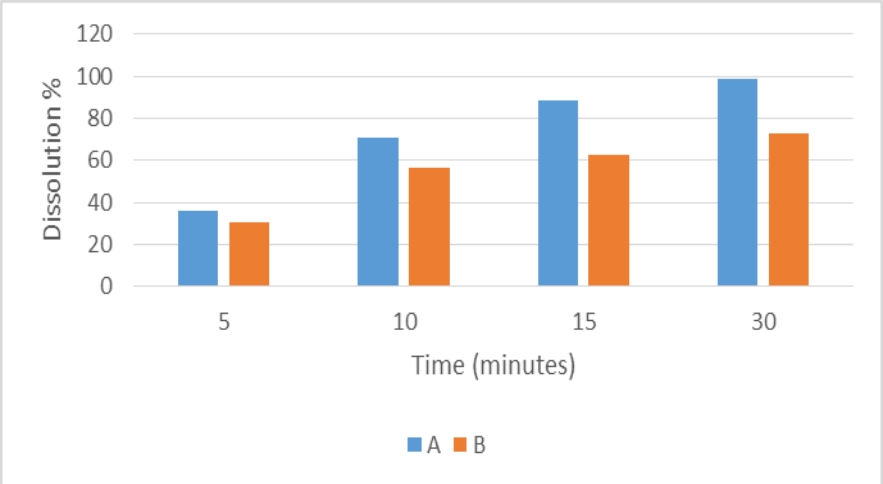


Fig. (5) Dissolution profile of formula A and B

Table 7. Stability profiles of nimodipine tablets (Formulation A) for 3 months at 40 ˚C /75 % RH.

Formulation A	Month	Color	Hardness Kg/cm^2	Friability (%)	Disintegration time (min)	Drug Content (%)	Dissolution % after 30 min.
	0	White	4.14 ± 0.05	0.515±0.04	5.1 ± 0.024	100.97 ± 0.03	99.01 ± 0.35
	1st	White	4.01 ± 0.02	0.501±0.01	5.0 ± 0.011	100.05 ± 0.14	99.0 5± 0.21
	2st	White	4.12 ± 0.01	.501± 0.83	5.1 ± 0.12	99.98 ± 0.23	98.04± 0.13
	3st	White	4.04 ± 0.05	0.5 ± 0.18	5.1 ± 0.024	99.04± 0.17	98.5 ± 0.32

All values are mean ± SD.

3.6 Drug dissolution Kinetics of the prepared nimodipine tablet in acetate buffer

The dissolution data for the prepared tablets are plotted following the Zero-order equation, the first-order equation, Second-order equation, Diffusion equation, and Hixon-Crowell Cube root law,

Fig. 6 show that the linearities are established as R^2 values are close to unity. It is indicated that the amount of nimodipine dissolute is the diffusion equation.

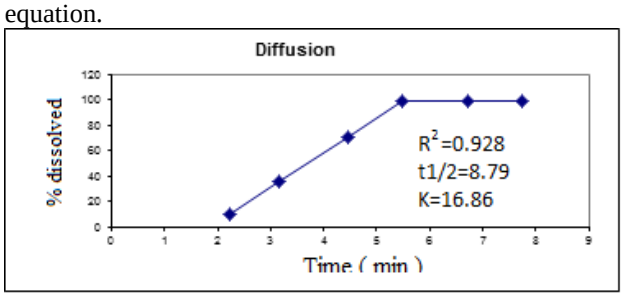


Fig (6) Diffusion plots of nimodipine tablets dissolution in acetate buffer.

4. Conclusion

The Characterization test showed that the Solubility and dissolution of the drug increased in Solid dispersion with a poloxamer 407 molar ratio (3:1) compared to the drug alone.

Conflict of interest

The authors report no conflict of interest; the authors alone are responsible for the content and writing of this article.

5. References

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