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ENHANCEMENT OF SOLUBILITY OF NITRENDIPINE BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

In present study PVA and Poloxamer188 are selected as carrier because of their chemical and pharmaceutical inertness. Solubility behavior of Active pharmaceutical ingredient is one of the most challenging aspects in the formulation development. Nitrendipine is a dehydropyridine calcium antagonist widely used as antihypertensive and antianginal drug but having very low aqueous solubility.The dissolution rate of nitrendipine by solid dispersion was enhanced significantly with increasing the amount of dispersing agents. PVA and Poloxamer188 by virtue of their water solubility may lead to an increase in degree of solubility of poorly water-soluble drug.

INTRODUCTION

The solubility behavior of a drug is a key determinant of its oral bioavailability. Insufficient solubility has presented a challenge to the development of a suitable formulation for oral administration of many drugs [1-3].Aqueous solubility of a drug can be used as first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and hence suffer oral bioavailability problems [2-3]. So if the solubility of the drug is less than desirable, steps are to be taken to improve its solubility [4-5]. There have been numerous reports of the work done for the improvement of the solubility and dissolution behavior of drugs [3]. Several techniques have been developed concerning the optimization of the dissolution rate of poorly water-soluble drugs. Such methods include particle size reduction, solubilization, salt formation etc, but there are several disadvantages and limitations in use of these techniques [4]. The solid dispersion technique for water insoluble drugs developed by Chiou and Reigelman provides an efficient method to improve the dissolution rate of a drug [5]. Solid dispersions can be prepared by various methods depending on the conditions and need like Melting method, Solvent evaporation method, Melting solvent method, Supercritical fluid process, Kneading method, Freeze drying etc [5-9]. Solid dispersion are classified on the basis of their release mechanism into two major types, ie. Sustained release type solid dispersion &Fast release type solid dispersion. Characterization of Solid Dispersion by Thermal analysis ie. Cooling curve method, Thermo microscopic method, Differential thermal analysis, Differential scanning calorimetry; X-ray diffraction method; Spectroscopic method; Microscopic method. Drug dissolution is the dynamic process by which solid material is dissolved in a solvent and solubility describes an equilibrium state where the maximal amount of drug per volume unit is dissolved [10]. Solid dispersion of drug in proper carriers is the most promising approach for enhancing solubility because of the fact that, drug as a molecular or near to molecular dispersion thus giving the both benefits of a local increase in its solubility (within the solid solution) and offering the maximum surface area of

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compound after the dissolution of carrier in dissolution media. Nitrendipine is a dehydropyridine calcium antagonist widely used as antihypertensive and antianginal drug. The major drawback in the therapeutic application and efficacy of nitrendipine as oral dosage form is its very low aqueous solubility (1.9-2.1 µg/ml at 25^0C) [11]. Hence improvement of aqueous solubility of nitrendipine by solid dispersion technique is necessary.

MATERIAL AND METHODS

Nifedipine collected as a gift sample from Concept Pharmaceuticals, Aurangabad. Poloxamer 188 as a gift sample from USV.Ltd. Mumbai, Polyvinyl alcohol, Sodium hydroxide, Potassium dihydrogen phosphate, Disodium hydrogen phosphate, Hydrochloric acid and Ethyl acetate from Research Lab Ltd., Poona. Tween 80, Magnesium sterate, Lactose from Cipla Ltd., Kolhapur, Talc, Microcrystalline cellulose and all other materials and solvents used were of analytical grade.

Methods

Selection of Suitable Method for Preparation of Solid Dispersion

The method for preparing solid dispersion should be such that there is minimum or no loss of the material during preparation and almost all material should easily get recovered with better yield of solid dispersion. The selection of method is also depending on the characteristics of the drug, carriers and solvents used. Nitrendipine decomposes at high temperature, it is freely soluble in ethyl acetate and the solvent is safe. Hence the solvent evaporation method was selected for the preparation of solid dispersions[6].

Preparation of Physical Mixture of Nitrendipine/ PVA and Nitrendipine/Poloxamer188

The physical mixture of nitrendipine with carriers was prepared by mixing the required amount of nitrendipine and carriers for 15 min in a mortar with pestle until a homogenous mixture was obtained. This resulting mixture was sieved through an 100 mesh screen. The powder was stored in a screw cap vial at room temperature [12]. Table No. 1 showed the Composition of physical mixtures.

Preparation of Solid Dispersion of Nitrendipine/PVA and Nitrendipine/Poloxamer188:

Nitrendipine was dissolved in an appropriate amount of ethyl acetate (2.5 times the total weight of drug and polymer) after complete dissolution of nitrendipine solution was dropped onto polymeric carriers PVA and Poloxamer188 respectively. Solid dispersions of different ratios were prepared. The solvent was then evaporated at 45^0C then resulting residue was dried in hot air oven for 1 hour and stored for 24 hours in a desiccators. Subsequently, the dispersion was ground in a mortar and passed through sieve no. 100 [13-14]. Table No. 2 showed the Composition of solid dispersions.

Analysis of Drug Content in Solid Dispersions

The content of nitrendipine in each physical mixture and solid dispersions of PVA and poloxamer 188 was determined using UV spectroscopy. Accurately weighed solid dispersion or physical mixture equivalent to 10 mg of nitrendipine was transferred to 100 ml volumetric flask and diluted to 100 ml with ethyl acetate and sonicated for 30 min for complete solubilization of drug. Solution was filtered with membrane filter paper 0.45 □m, from this 1 ml of this solution was taken and it was diluted to 100 ml with ethyl aceatae and absorbance was taken at 355 nm. Concentration of nitrendipine was determined using calibration curve of nitrendipine in ethyl acetate [15-16].

Phase Solubility Studies

The phase solubility studies were carried out according to the method reported by Higuchi and Connors. Excess amount of nitrendipine was added to the screw capped vials containing 20ml of aqueous solutions of carriers at various concentrations and placed on a water bath shaker and agitated at 37 $\pm$ 0.5^0C for 72 hrs. After equilibrium, the solutions were carefully filtered through Whatman No 41 filter paper and the final solutions were analyzed for the drug content at 355 nm using UV–visible spectrophotometery [16].

Saturation Solubility Studies

The saturation solubility study was carried out to determine increase in the solubility of pure nitrendipine as compared with the physical mixture (PM), solid dispersions (SDs). Weighed amount of solid dispersions were added to the glass vial containing 20 ml of solution. The sealed flasks were shaken for 24 hr at room temperature followed by equilibrium for three days. Then the aliquots were withdrawn through whatman filter paper. The concentration of nitrendipine was determined by UV spectrophotometer at 355 nm [17-18]. The saturation solubilities of drug, physical mixtures and solid dispersions were determined in p H 1.2, 6.8, 7.4 buffer solutions.

Dissolution Rate Studies:

Aim of Dissolution Study: these studies was carried out to check the in-vitro release from the solid dispersions and to get information about the absorption of the drug entity into the systemic circulation [19].

Selection of Dissolution Medium:-

Dissolution of solid dispersion should be seen in pH 1.2, 6.8 and 7.4 buffer solutions [20-21].

Calibration curve in ethyl acetate:

Standard Stock Solution: Nitrendipine, 10 mg was accurately weighed and transferred to 100 ml volumetric

flask. It was dissolved in ethanol and volume was made upto 100 ml.

Working stock solution: A series of nitrendipine solution ranging from 1 to 10 mcg/ml were prepared from standard stock solution. The absorbance of all solution was measured uv-spectrophotometrically at 355 nm[22]. By using USP dissolution apparatus type 2 (paddle type) with Speed of the paddle : 75 rpm having temperature : 37°C ± 0.5°C, dissolution medium : pH 1.2 buffer with 1.5% tween 80 pH 6.8 buffer with 1.5% tween 80, pH 7.4 buffer with 1.5% tween 80, total volume of fluid : 900ml. sample size : equivalent to 10mg of nitrendipine. Samples of 5 ml, was withdrawn at regular intervals. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analyzed spectrophotometrically at 355 nm[23].

Characterization of Solid Dispersion

Differential Scanning Calorimetry

The DSC measurements were performed on a Differential Scanning Calorimetry (Seiko Instruments, Japan) with a thermal analyzer. All accurately weighed samples (about 5 mg of nitrendipine) were placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at a scanning rate of 10^0C/min from 25^0C-250^0C. An empty aluminum pan was used as reference[24-25].

X-Ray Diffraction

X-ray powder diffraction patterns (XRD) were taken by Philips diffractometer with PW 1050/25 goniometer and Co (Kα 30-40 kV, 10-20 mA, λ = 1.79021 ˚A) radiation, and by Huber Diffractometer with Cu (Kα130-40 kV, 10-20 mA, λ = 1.54059 ˚A) [26].

Precompression Parameters of Powder Blend

The powder blend was evaluated for following parameters[27-29].The powder material was evaluated for their texture under microscope

Angle of Repose

The angle of repose of each powder blend was determined by glass funnel method and angle of repose was calculated using the following equation,

Tan Ø = h/r

Where h and r are height and radius of the powder cone respectively.

Bulk Density

Bulk density of solid dispersion granules were determined by pouring gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. The powder was carefully leveled without compacting it and the apparent volume was measured (V0).Bulk density was calculated.

$$\text{Bulk density(g/ml)} = \frac{\text{Weight of sample}}{\text{Apparent volume of packing}}$$

Tapped density

The tapped density was determined by pouring 25 gm sample (solid dispersion granules) through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping was recorded and tapped density was calculated.

$$\text{Tapped density (g/ml)} = \frac{\text{Weight of sample}}{\text{Tapped volume of packing}}$$

Compressibility

It is also one of the sample method to evaluate flow property of a powder by comparing the bulk density and tapped density. A useful empirical guide is given by the Carr's Index:

$$\text{Carr's Index} = \frac{\text{Tapped density – Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

It provides an indication of the degree of densification that could result from vibration of feed hopper. Lower the Hausner ratio better is the flowability.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

RESULTS AND DISCUSSION

The solid dispersion was successfully prepared by using PVA and poloxamer 188 with different concentration and then it was evaluated. The drug content in solid dispersion and physical mixture of PVA and PXM188 with nitrendipine was showed in Fig 1.

PXM188 with Nitrendipine.

PM- Physical mixture PVA- Polyvinyl alcohol SD- Solid dispersion PXM- Poloxamer188

Phase Solubility Studies

Phase solubility studies were performed to determine stoichiometric proportion of nitrendipine and carriers-PVA and PXM188. Phase solubility analysis plot for nitrendipine with PVA and PXM188 are given in Figure 2. Phase solubility studies were carried out to evaluate drug / carrier interaction in liquid state. The Phase Solubility Analysis diagrams showed increase in drug solubility with increase in concentration of PVA and PXM 188. A 5.06 fold increase in solubility of nitrendipine was observed in 18%w/v solution of PVA, also a 6.58 fold increase in drug solubility was observed in 18%w/v solution of PXM188. Both the types exhibited AL type of

plot (Figure 2) indicating 1:1 stoichiometry for dispersion of drug with carriers.

Saturation Solubility Studies

Improved dissolution behavior of solid dispersions of drugs can be attributed to increase in saturation solubility of drug as per Noyes Whitney equation. Solid dispersion systems lead to reduction in particle size of drug because of which there is an enhancement of saturation solubility. This change was confirmed by conducting similar saturation solubility studies on untreated drug as control.

Saturation solubility data for all solid dispersions is given in Figure 3 & Figure 4.

A proportionate increase in the carrier weight fraction resulted in considerable change in the solubility of solid dispersion systems. The solid dispersion has shown increase in solubility by 4.07 to 4.57 folds as compared to Nitrendipine. Between the two types of solid dispersion systems, the one with the Poloxamer 188 carrier showed highest saturation solubility.

Dissolution Studies

Nitrendipine solid dispersions presented better dissolution performance as compared to the pure drug in a given time course. This may be attributed to improved wettability of the drug particles, significant reduction in drug particle size during the formation of the solid dispersions, and the intrinsically higher rate of dissolution of the selected soluble carriers, which could pull insoluble but finely mixed drug particles into the bulk of dissolution medium. The dissolution profiles of Nitrendipine, physical mixtures and solid dispersions of Nitrendipine with PVA and PXM188 are shown in Figure 5 and Figure 6 respectively.

Effect of Concentration of Carrier on Dissolution Rate of Nitrendipine

Three different drug: polymer ratios (1:4, 1:6 & 1:8) were selected to assess the effect of weight fraction of polymer on drug release profiles of solid dispersions. All the dispersions exhibited a definite rise in both rate and extent of drug dissolution with increasing proportions of carrier used. The possible reasons include facilitation of Nitrendipine dissolution by higher amount of soluble carrier and decrease in the particle size of the drug in the dispersion. Figure 7 and Figure 8 show the effect of weight fraction of polymer on dissolution rate of Nitrendipine solid dispersions.

As shown in Figure 9, the solid dispersions with PXM showed better release profile over corresponding PVA solid dispersion at drug: carrier weight ratio of 1: 8.

This phenomenon may be due to the inherent differences between the two polymers in terms of intrinsic rates of dissolution and hydration, and possible complexation of the drug with PXM or decrease in crystallinity of the co-precipitated drug. The initial high drug release was observed in 90 minutes and gets reduced at subsequent time points. The equilibrium concentration that can be achieved with the given formulation in the solution was less than what was achieved at the first dissolution time point. Probably the initial rapid release of drug from the solid dispersion particles to the dissolution medium resulted in high concentration, which was reduced with time.

Characterization of Solid Dispersion of Nitrendipine: Differential Scanning Calorimetric Analysis

DSC Thermogram of nitrendipine shows prominent endothermic peak shown in Figure 10. DSC Thermogram of pure PXM 188 and PVA exhibited single endothermic response in Figure 11 and Figure 12 respectively**.**The partly disappearance of the endothermic peak of nitrendipine from thermogram indicates that nitrendipine is homogenized with the carrier in an amorphous state within solid dispersion.

Dissolution properties of drug particles are affected greatly by nature and extent of crystallinity present in them. An amorphous or the metastable form dissolves faster because of the associated higher levels of internal energy and greater molecular mobility. These together enhance the thermodynamic properties of these forms as compared to crystalline state. X – Ray diffraction studies were performed to reveal the crystallinity of pure drug, carriers, physical mixtures and solid dispersions.

The presence of numerous distinct peaks in X-Ray Diffractogram of nitrendipine (Figure: 31) indicate that nitrendipine as a crystalline material with characteristic diffraction peaks appearing at a diffraction angle of 2θ at 8.79, 9.95, 11.46, 13.93, 21.68, 24.36, 25.92 and 27.52.

Poloxamer (Figure: 32) also exhibited a distinct pattern with diffraction peaks at diffraction angle of 2θ at 19.35, 23.39, 27.27, 28.05 and 26.32. But the spectrum of PVA (Figure: 33) was characterized by complete absence of any diffraction peak.

The diffraction pattern of physical mixture and solid dispersion was found to differ in comparison with drug. Some peaks were disappeared and some peak heights were decreased. The comparison of these spectrum indicate that the molecular state of nitrendipine prepared as drug carrier solid dispersion was changed from crystalline state to microcrystalline state and/or amorphous state and having some peaks retained of drug that might be due to some amount of drug present out of the solid dispersion. It was not dispersed monomelecularly so some peaks of nitrendipine was present on the X-Ray diffractogram in Figure 38 & Figure 39 respectively.

***In vitro* Drug Release from the Solid Dispersion**

The results have shown that solid dispersion of nitrendipine with polyvinyl alcohol released the drug about

79% in 100 min. The solid dispersion of nitrendipine with poloxamer 188 released the drug about 98% in 100 min. This shows that poloxamer 188 has better dissolution rate than polyvinyl alcohol. Thus there is increase in dissolution rate of poorly water soluble drug by using solid dispersion technique. The results were plot accordingly in Figure No. 40-42

Evaluation of Solid Dispersion Tablet Blend

The value of angle of repose was found to be 27^0C which indicate good flow property. Similarly compressibility value was 18.45%.± 0.25 The bulk density of tapped density value was found to be less than one. Hence have good flow property.

Table 1. Composition of physical mixtures

Sr. No.	Physical Mixtures	Ratio for Drug: Carrier
1	Nitrendipine: Polyvinyl alcohol	1:4
2	Nitrendipine: Polyvinyl alcohol	1:6
3	Nitrendipine: Polyvinyl alcohol	1:8
4	Nitrendipine: Poloxamer188	1:4
5	Nitrendipine: Poloxamer188	1:6
6	Nitrendipine: Poloxamer188	1:8

Table 2. Composition of Solid Dispersions

Sr. No.	Solid Dispersions	Ratio for Drug: Carrier
1	Nitrendipine: Polyvinyl alcohol	1:4
2	Nitrendipine: Polyvinyl alcohol	1:6
3	Nitrendipine: Polyvinyl alcohol	1:8
4	Nitrendipine: Poloxamer188	1:4
5	Nitrendipine: Poloxamer188	1:6
6	Nitrendipine: Poloxamer188	1:8

Table 3. Evaluation of Solid Dispersion Tablet Blend (± SD)

	Parameters	Tablet Blend
1	Shape	Circular
1	Angle of repose (□) mean ± SD	27^0 ± 0.5
2	Bulk density (g/ml) mean ± SD	0.673± 0.003
3	Tapped density (g/ml)mean± SD	0.969 ± 0.012
4	Compressibility %	18.45 ± 0.25
5	Housner's ratio	1.25± 0.021

N=3

Figure 1. % Drug Content in solid Dispersion and Physical Mixture of PVA and PXM188 with Nitrendipine

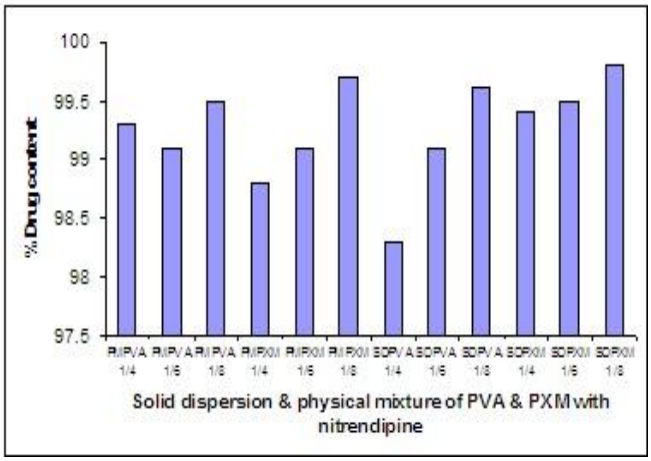


Figure 2. Effect of concentrations of carriers on solubility of Nitrendipine

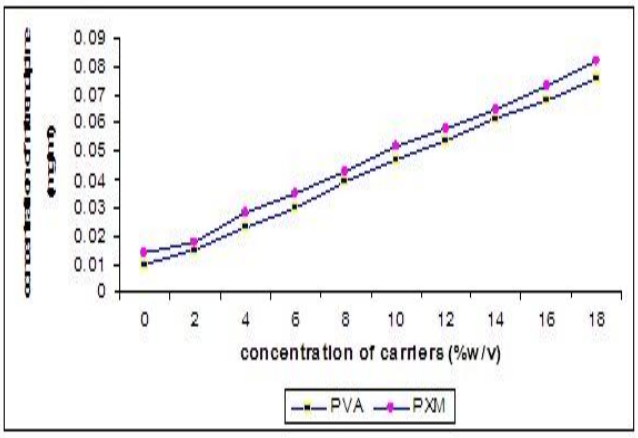


Figure 3. Solubility of Nitrendipine in Physical Mixtures and Solid Dispersions of PVA

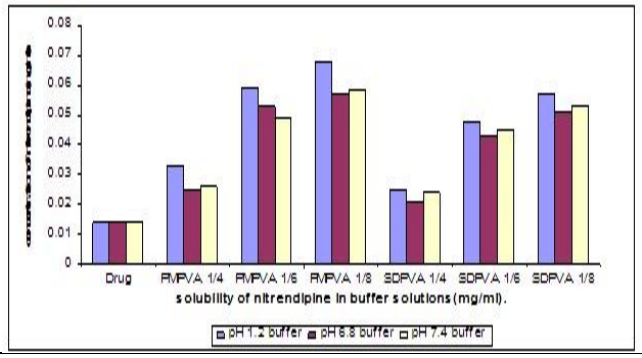


Figure 4. Solubility of Nitrendipine in Physical Mixtures and Solid Dispersions of PXM 188

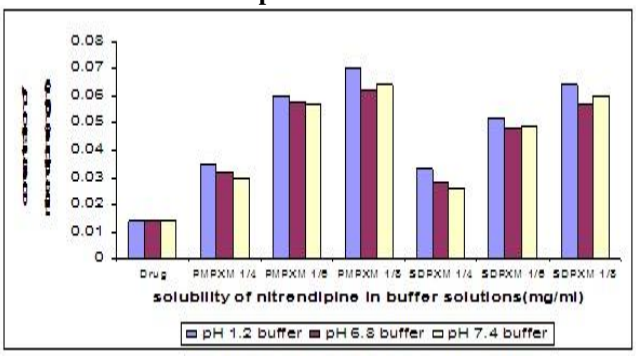


Figure 5. *In vitro* dissolution profile of Nitrendipine and physical mixtures and solid dispersions of Nitrendipine with PVA

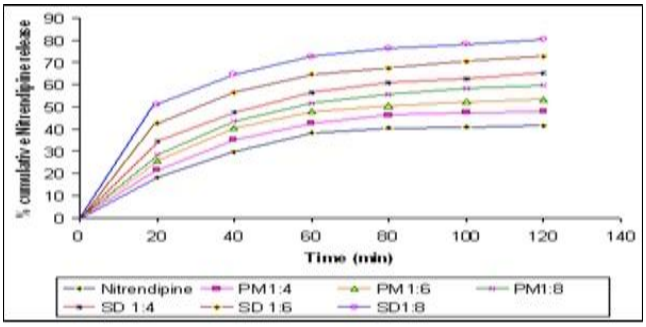


Figure 6. *In vitro* dissolution profile Nitrendipine, physical mixtures and solid dispersions of Nitrendipine with PXM 188

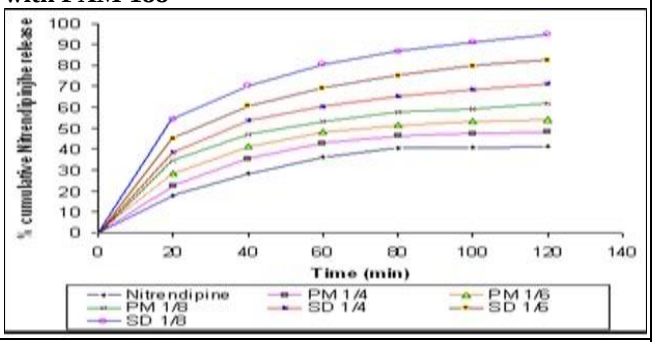


Figure 7. Effect of weight fraction of drug: PVA on Nitrendipine release

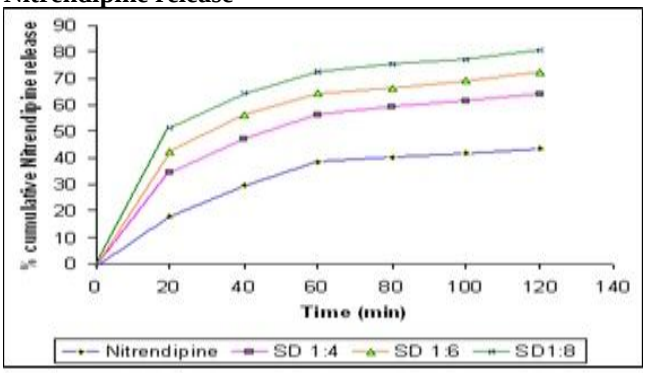


Figure 8. Effect of weight fraction of drug: PXM188 on Nitrendipine release

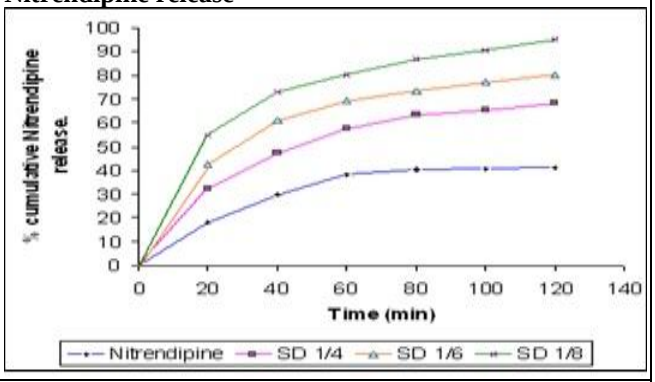


Figure 9. Effect of Type of Polymer on Dissolution Rate of Nitrendipine

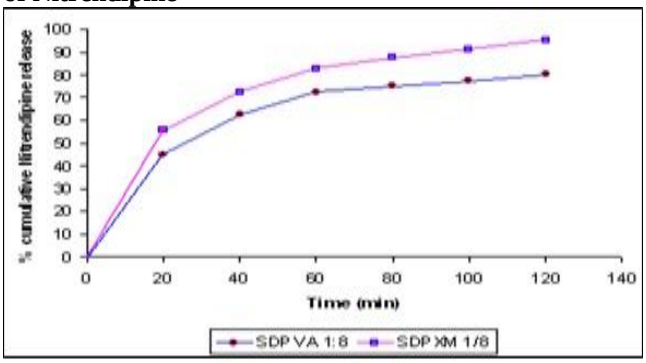


Figure 10. DSC Thermogram of Nitrendipine

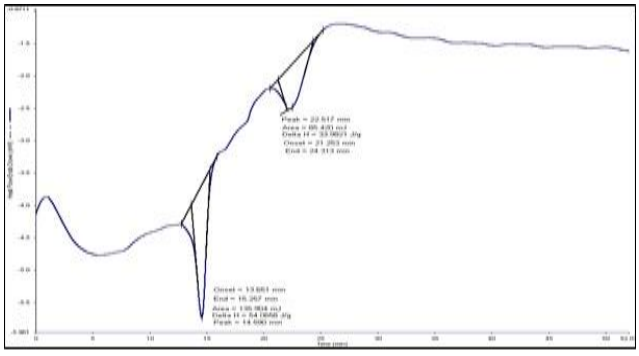


Figure 11. DSC Thermogram of Poloxamer 188

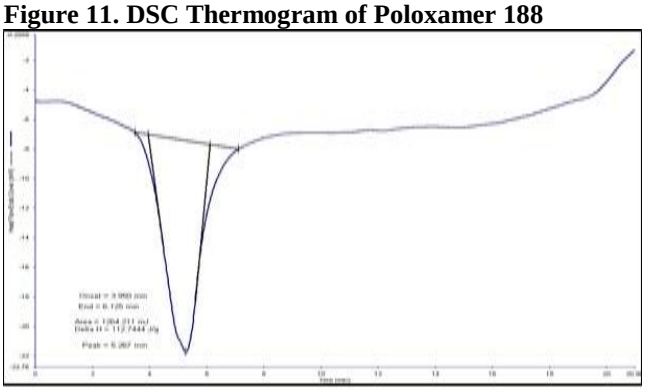


Figure 12. DSC Thermogram of Polyvinyl alcohol

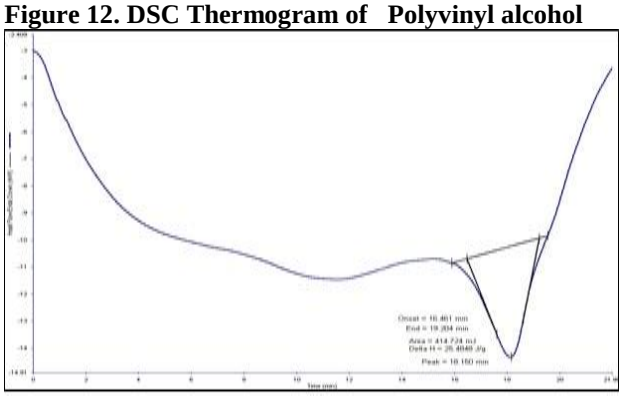


Figure13. DSC Thermogram of physical mixture of PXM (1:4)

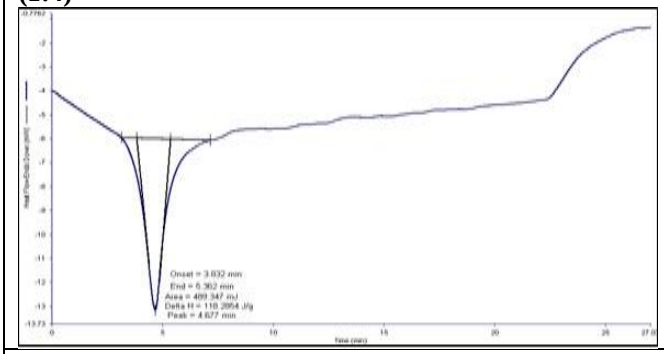


Figure 14. DSC Thermogram of solid dispersion of PXM (1:4)

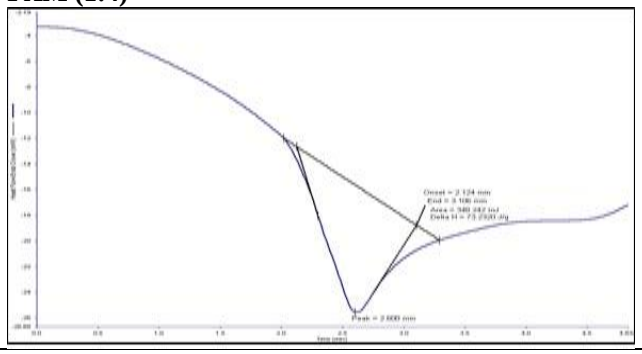


Figure 15. DSC Thermogram of physical mixture of PXM (1:6)

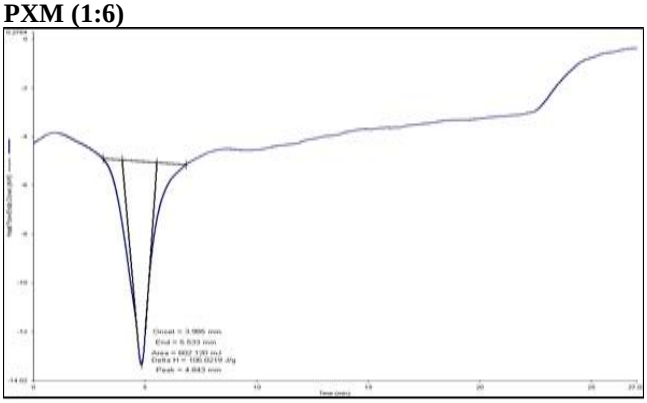


Figure 16. DSC Thermogram of solid dispersion of PXM (1:6)

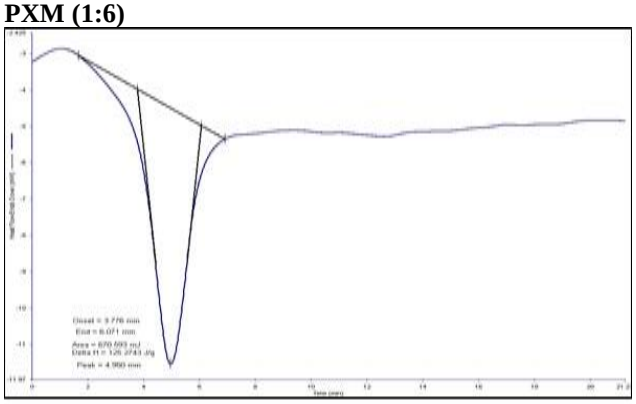


Figure 17. DSC Thermogram of physical mixture of PXM (1:8)

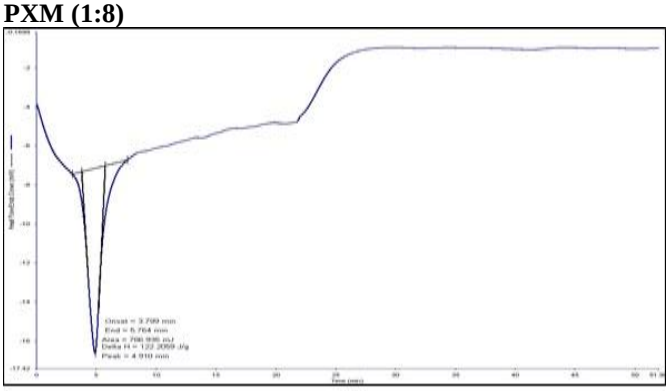


Figure 18. DSC Thermogram of solid dispersion of PXM (1:8)

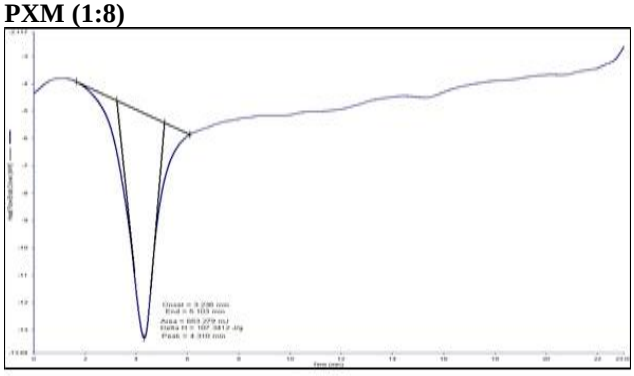


Figure 19. DSC Thermogram of physical mixture of PVA (1:4)

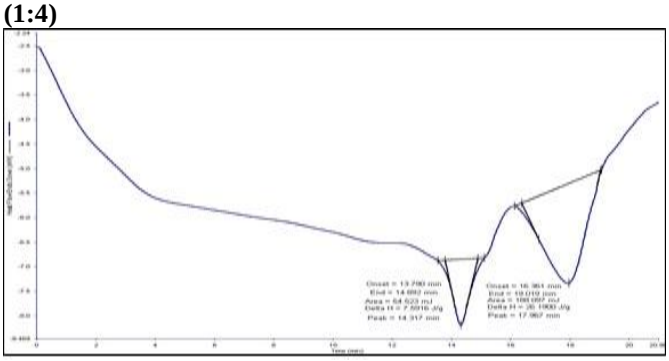


Figure 20. DSC Thermogram of solid dispersion of PVA (1:4)

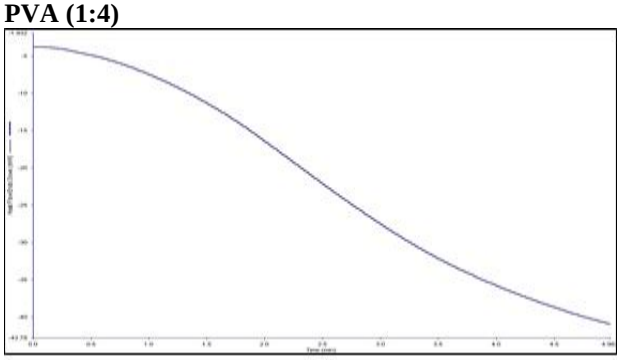


Figure 21. DSC Thermogram of physical mixture of PVA (1:6)

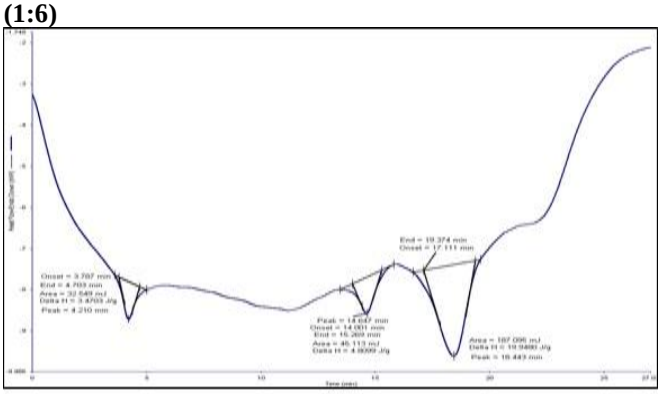


Figure 22. DSC Thermogram of solid dispersion of PVA (1:6)

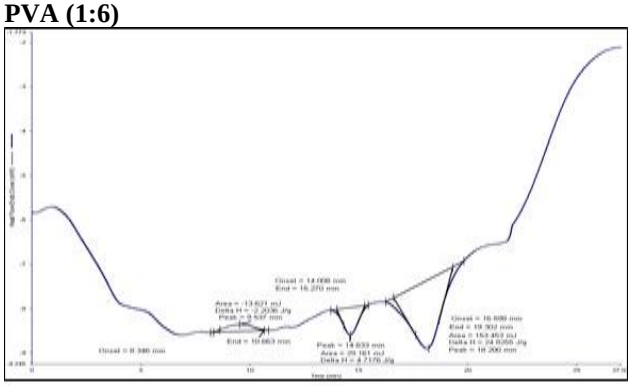


Figure 23. DSC Thermogram of physical mixture of PVA (1:8)

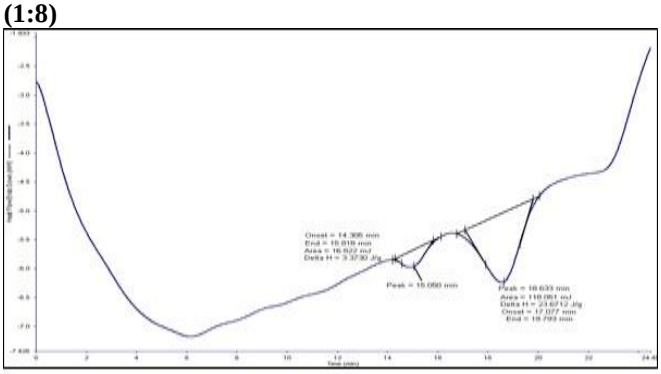
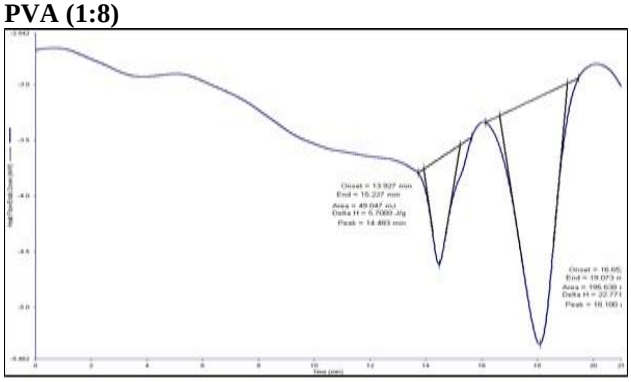


Figure 24. DSC Thermogram of solid dispersion of PVA (1:8)



X-Ray Diffraction Analysis:

Figure 25. X-ray Diffractogram of Nitrendipine

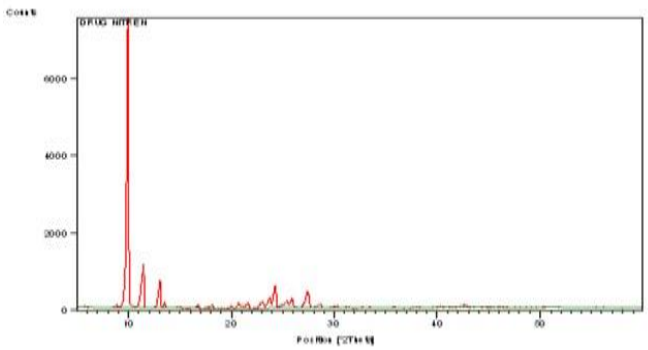


Figure 26. X-ray Diffractogram of Poloxamer188

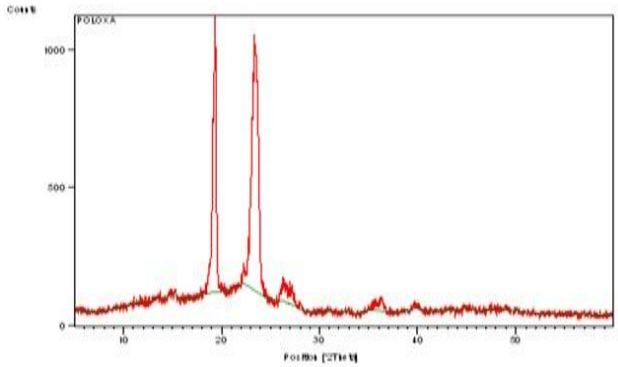


Figure 27. X-ray Diffractogram of Polyvinyl alcohol

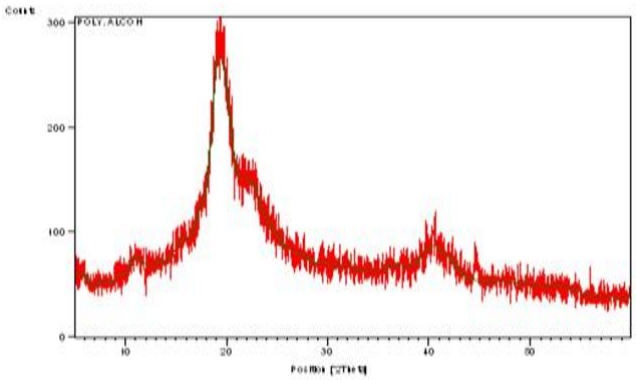


Figure 28. X-ray Diffractogram of Physical Mixture of PXM188(1:4)

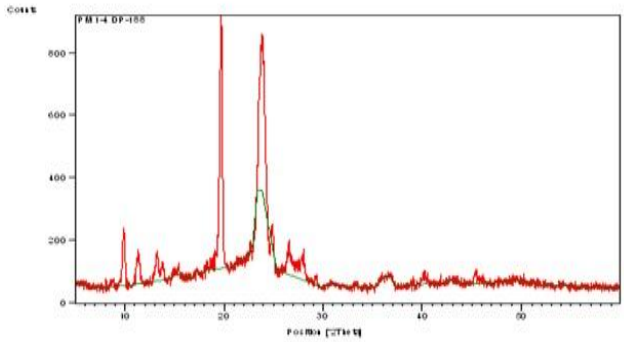


Figure 29. X-ray Diffractogram of Solid Dispersion of PXM (1:4)

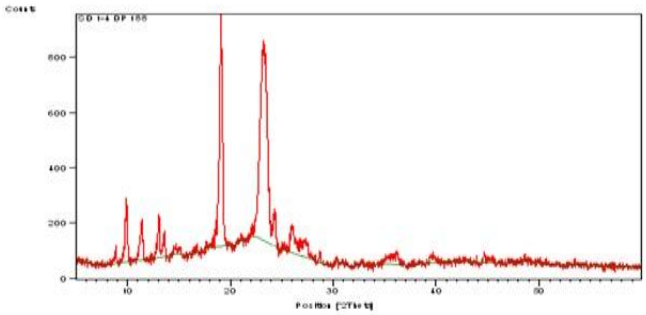


Figure 30. X-ray Diffractogram of Physical Mixture of PXM 188(1:6)

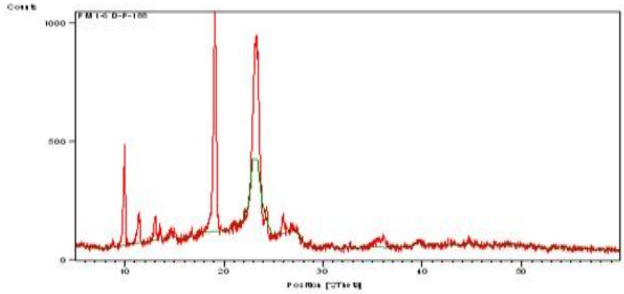


Figure 31. X-ray Diffractogram of Solid Dispersion of PXM (1:6)

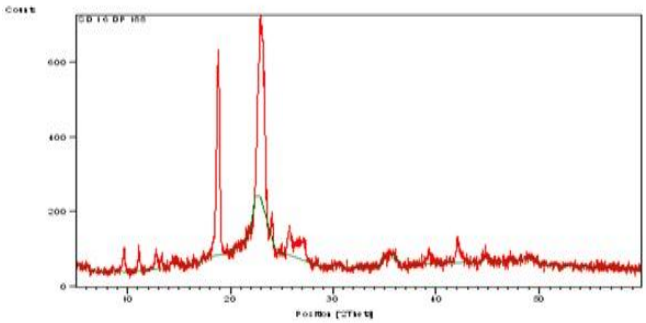


Figure 32. X-ray Diffractogram of Physical Mixture of PXM 188 (1:8)

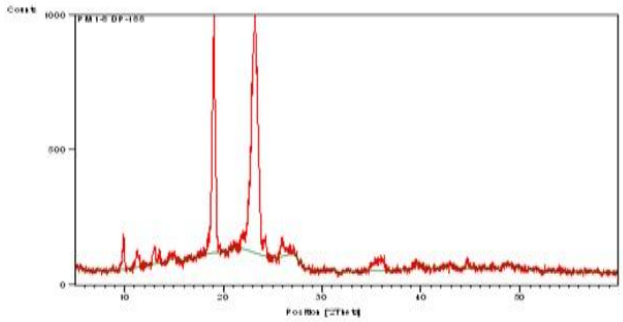


Figure 33. X-ray Diffractogram of Solid Dispersion of PXM (1:8)

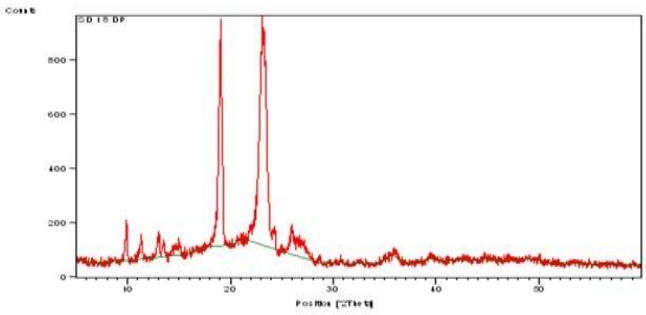


Figure 34. X-ray Diffractogram of Physical mixture of PVA (1:4)

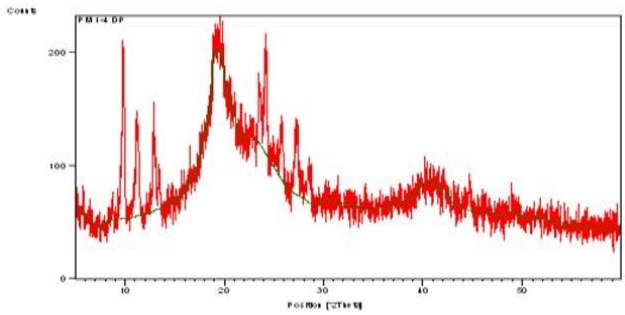


Figure 35. X-ray Diffractogram of Solid Dispersion of PVA (1:4)

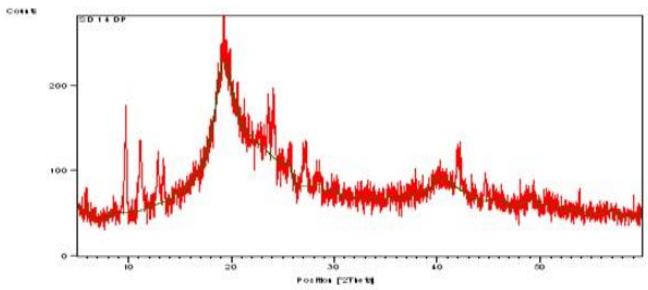


Figure 36. X-ray Diffractogram of Physical mixture of PVA (1:6)

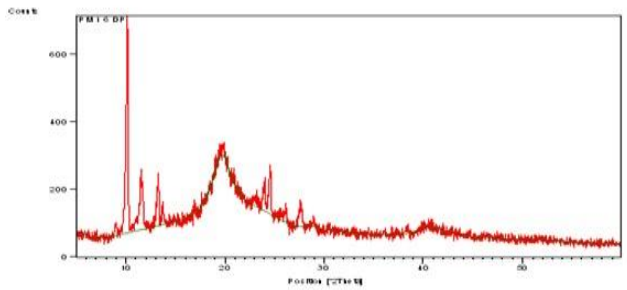


Figure 37. X-ray Diffractogram of Solid Dispersion of PVA (1:6)

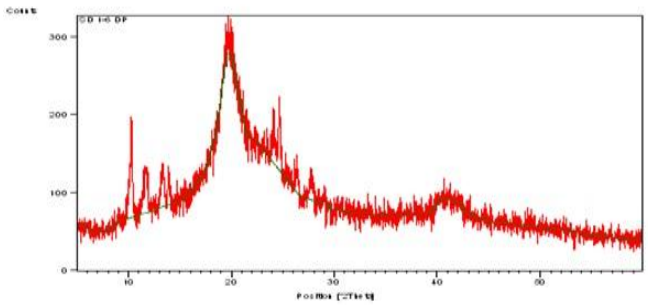


Figure 38. X-ray Diffractogram of Physical mixture of PVA (1:8)

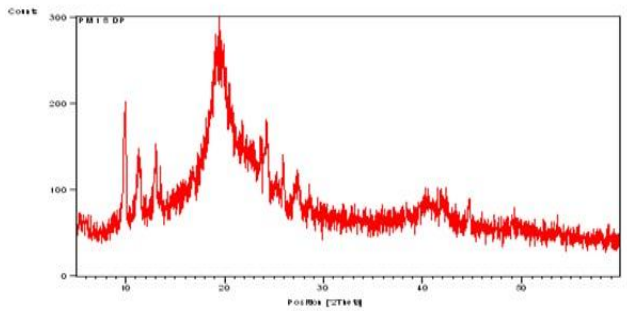


Figure 39. X-ray Diffractogram of Solid Dispersion of PVA (1:8)

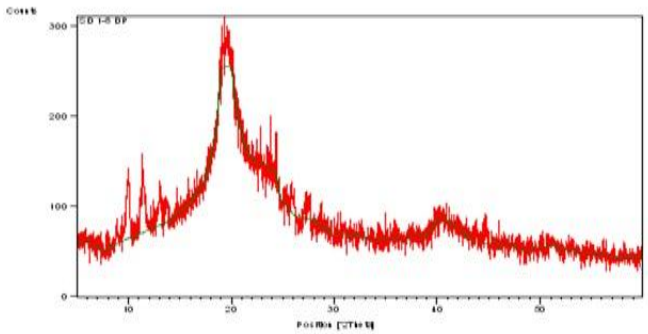


Figure 40. *In-vitro* Dissolution of Solid Dispersion of Nitrendipine with Carriers in pH 1.2

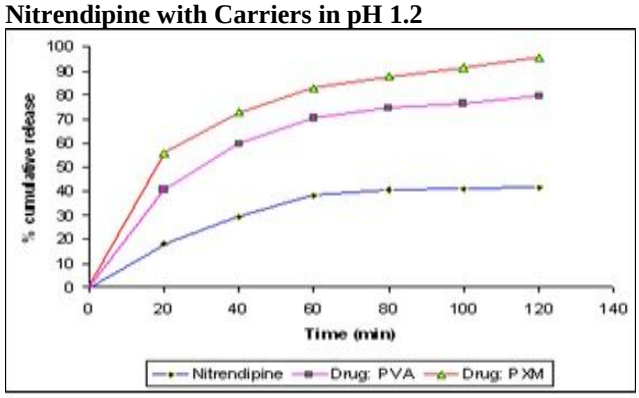


Figure 41. *In-vitro* Dissolution of Solid Dispersion of Nitrendipine with Carriers in pH 6.8

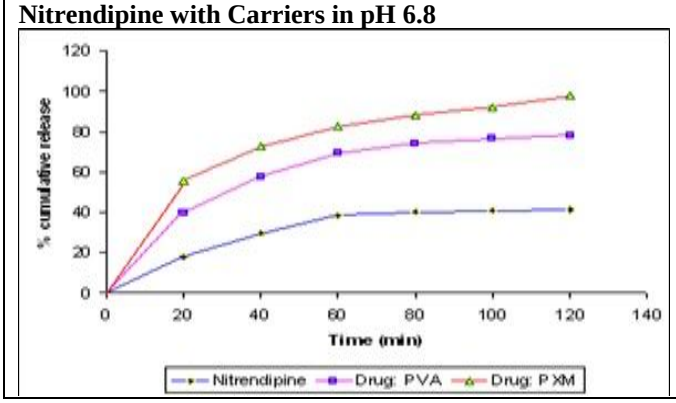
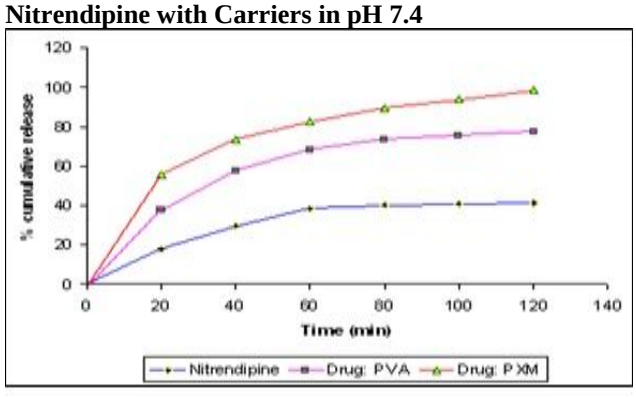


Figure 42. *In-vitro* dissolution of solid dispersion of Nitrendipine with Carriers in pH 7.4



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