INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

Volume: 2: Issue-1: Jan-Mar -2011 IJABPT *ISSN 0976-4550*

DEVELOPMENT, CHARACTERIZATION AND SOLUBILITY STUDY OF SOLID DISPERSION OF NIFEDIPINE HYDROCHLORIDE BY SOLVENT EVAPORATION METHOD USING POLOXAMER 407

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ABSTRACT: The present research endeavor was towards the enhancement of solubility of nifedipine by solid dispersion method, were prepared by solvent evaporation method and polymers Poloxamer 407 was tried with different proportion with drug and increasing the different sodium lauryl sulphate (SLS) percentages. There was significant increase of dissolution rate of nifedipine, in SD of nifedipine + Poloxamer 407 (1:4) than nifedipine + Poloxamer 407 (1:2) and nifedipine + Poloxamer 407 (1:3). Solid dispersion of nifedipine was evaluated by solubility test, DSC, IR and dissolution characteristics. Solid Dispersion of Nifedipine in Poloxamer 407 improved the dissolution rate of nifedipine, which helps to enhancing solubility of Nifedipine. Dissolution rate of pure nifedipine increased, with increasing the various Polymers content and with increasing the various sodium lauryl sulphates (SLS) content. The solubility of pure nifedipine was observed in pH 7.2 ± 0.2 buffer solution, with increasing the polymer ratio as 1:2, 1:3, 1:4 and with increasing the SLS percentage(%) as 1%, 3% and 5% respectively.

Keywords: Nifedipine, Poloxamer 407, solid dispersion method.

INTRODUCTION

Nifedipine is a drug belonging to a class of pharmacological agents known as the calcium channel blockers. Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. Nifedipine is used in the management of vasospastic angina, chronic stable angina and hypertension. Nifedipine was having extensive first pass metabolism, and relative Elimination half-life of about 7 hrs. (extended-release) and associated with frequent dosing of conventional dosage form makes it suitable candidate for sustained release dosage form for patient compliance. Compound with poor aqueous solubility are extremely challenging to be developed as new drugs. It is well known that drug dissolution rather than permeation through the epithelia of the gastro intestinal tract is responsible for a low oral absorption. One of the pharmaceutical strategies to improve the oral bioavailability is formation of solid dispersions. Solid dispersion can able to improve their dissolution by increasing drug-polymer solubility, amorphous fraction, particle wettability and particle porosity.

In this project work, nifedipine was selected as model drug, because it is having poor aqueous solubility and low dissolution rate. Although the formulation of SD is generally accepted as a method to enhance the dissolution characteristics, only few products using SD are marketed, mainly because of stability problems.

In this present study, the solubility of pure nifedipine was enhanced, with increasing the dissolution rate of pure nifedipine. Based on these facts, dissolution rate of pure nifedipine increased, with increasing the various Polymers content and with increasing the various sodium lauryl sulphate (SLS) content. The solubility of pure nifedipine was observed in pH 7.2 ± 0.2 buffer solution, with increasing the polymer ratio as 1:2, 1:3, 1:4 and with increasing the SLS percentage(%) as 1%, 3% and 5% respectively. The SD of nifedipine with Poloxamer 407 was prepared successfully by solvent evaporation method in different ratio. *In-Vitro* dissolution showed that, there were increased in dissolution rate in case of SD of nifedipine with Poloxamer (1:4 ratio). It was observed that complex formed between nifedipine with Poloxamer (1:4 ratios) had change the structure of the drug. It has been well illustrated by the DSC curve of the drug polymer and SD. Solid Dispersion of nifedipine PXM 407 improved the dissolution rate of nifedipine, which helps to enhancing solubility of nifedipine.

The Poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula HO (C_2H_4O) a (C_3H_6O) b (C_2H_4O) a H. It has the molecular weight ranging from 2090-14600. Poloxamer 407 has the molecular weight 9840-14600. Chemical Name is α-Hydro-ω-hydroxypoly(oxyethylene), poly (oxypropylene), poly (oxyethylene) block copolymer.

Table 1: Typical Poloxamer grades.

Poloxamer	Physical form	a	b	Average molecular weight
124	**Liquid**	**12**	**20**	**2090-2360**
188	**Solid**	**80**	**27**	**7680-9510**
237	**Solid**	**64**	**37**	**6840-9510**
338	**Solid**	**141**	**44**	**12700-17400**
407	**Solid**	**101**	**56**	**9840-14600**

MATERIALS AND METHODS:

Preparation of Solid dispersion of nifedipine with Poloxamer 407

Solid Dispersion of nifedipine in Poloxamer 407 containing three different weight ratios (1:2, 1:3, 1:4) was prepared by the solvent evaporation method. An appropriate amount of nifedipine was added to a solution of Poloxamer 407 in Methanol. The solution stirred at 25°c for 2 hrs, and the solvent was removed under vaccum at 40°c in a vaccum tray dryer (VTD) for 12 hrs. The solid residue was pulverized and sieved using #40 mesh. The solid dispersions are stored in light resistant container[1, 2].

Drug content

SDs equivalent to 25 mg of nifedipine were weighed accurately and dissolved in 50 ml of Methanol. The drug content was analysed at 236 nm by UV spectrophotometer. Each sample was analysed in triplicate. The assay for SD of nifedipine + Poloxamer 407 (1:2) ratio was found out to be 101.67%,that of SD of nifedipine + Poloxamer 407 ratio was 102.19% and SD of nifedipine + Poloxamer 407 (1:4) ratio was 103.10%.

Fourier transforms infrared (FTIR) spectroscopy:

FTIR was employed to characterize the possible interaction between the drug and the carrier in the solid state on an FTIR multi scope spectrophotometer by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000-400 cm^{-1} with a resolution of 4 cm^{-1}.

Differential Scanning Calorimetric (DSC) Studies[3, 4]:

DSC analysis of the drug, carrier SD was carried out on the samples using DSC (Mettler). Samples (5mg) were heated under nitrogen atmosphere on an aluminum pan at a rate of 10°C/min over the temperature range of 30°C and 300°C. Thermal data analysis of DSC thermogram was conducted using STAR software (version 8.10). The DSC thermogram of each component exhibited a sharp endothermal peak corresponding to melting point. Nifedipine shows a sharp peak at 174.8°C, Poloxamer 407 shows at 59.76 °C. The thermogram of SD containing the nifedipine & Poloxamer 407 demonstrated endothermic transactions at 52.18°C.

In Vitro Dissolution Studies[5, 6]:

The dissolution behavior of pure nifedipine and SD with PEG 4000 in various weight ratios(1:2, 1:3, 1:4) and various SLS percentages(1%, 3%, 5%) have been shown in terms of dissolution efficiency at 0, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 minutes (0.15, 0.30, 0.45, 0.60, 1.30, 2.00, 3.00, 4.00, 5.00, 6.00 hours) in buffer pH 7.2 dissolution medium, in USP-1(Paddle) apparatus, at time point 0, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 minutes (0.15, 0.30, 0.45, 0.60, 1.30, 2.00, 3.00, 4.00, 5.00, 6.00 hrs).

RESULTS AND DISCUSSION:

In case of extended release tablets, the drug is taking long time for its release, so for decrease the drug release time, the dissolution rate of pure drug should have to be increase. For increasing the dissolution rate of pure drug, the solubility of the pure drug will have to be increased. In a chemically non interacting system, the water-soluble carrier dissolves rapidly, followed by the release of drug molecules. The mechanism of drug release will thus be governed by relative differences in drug and carrier properties and on their proportion in the solid dispersion. Accordingly, two mechanism of drug release from the solid dispersion have been proposed. 1) Carrier-controlled dissolution - The drug release is dependent on the properties of the carrier because the carrier may be the major component of solid dispersion. The hydrophilicity, molecular weight, viscosity grade, etc. of the carrier may have a pronounced effect on drug release from solid dispersion. 2) Drug-controlled dissolution - The release is dependent on the properties of the drug, as it may be the major component of solid dispersion. From a glassy solution, the carrier molecules dissolve first, followed by the exposure of drug molecules to the dissolution medium. Depending upon the environment, the drug may either crystallize or remain amorphous. Thus, the physical form the drug in terms of its crystallinity will dictate its dissolution kinetics[7, 8]. There was significant increase of dissolution rate of nifedipine, in SD of nifedipine + Poloxamer 407 (1:4) than nifedipine + Poloxamer 407 (1:2). The results were showed in the **Table 2** and **Table 3.** The DSC thermogram of each component exhibited a sharp endothermal peak corresponding to melting point. Nifedipine shows a sharp peak at 174.8°C, Poloxamer 407 showed at 59.76°C. The thermogram of SD containing the nifedipine & Poloxamer 407 demonstrated endothermic transactions at 52.18°C. It was observed that complex formed between nifedipine with Poloxamer (1:4 ratios) had change the structure of the drug.

The physicochemical characterization by DSC studies revealed that, the enhancing effect of SD on the dissolution was mainly attributed to the transformation of nifedipine into the amorphous state. Improvement of increased solubility also contributed to the result. In addition, the IR spectra indicated the possible intermolecular hydrogen bonding between the drug and the carriers. DSC curve of nifedipine showed an endothermic peak at 174.8°C. DSC curve of SD is 52.18°C. This is due to the change in crystal lattice of the SD. The results were showed in the **Fig. 1**

Table2. Drug dissolution from SD in buffer pH 7.2 with 1% SLS as Dissolution Medium with PXM 407 (1:2) ratio.

Sl No.	Time (in minute)	Absorbance	Conc.	Conc. in 10ml (mg)	Cum. Conc. in 10ml	Conc. in 900ml	Cum. Conc. in 900ml	% Nifedipine Released
1	0	0	0	0	0	0.00	0	0.00
2	15	0.031	3.266	0.327	0.327	29.39	29.39	14.70
3	30	0.046	5.165	0.516	0.843	46.48	46.81	23.40
4	45	0.052	5.924	0.592	1.435	53.32	54.16	27.08
5	60	0.064	7.443	0.744	2.180	66.99	68.42	34.21
6	90	0.08	9.468	0.947	3.127	85.22	87.39	43.70
7	120	0.106	12.759	1.276	4.403	114.84	117.96	58.98
8	180	0.135	16.430	1.643	6.046	147.87	152.28	76.14
9	240	0.154	18.835	1.884	7.930	169.52	175.56	87.78
10	300	0.161	19.722	1.972	9.902	177.49	185.42	92.71
11	360	0.164	20.101	2.010	11.912	180.91	190.81	95.41

Table3. Drug dissolution from SD of nifedipine and PXM 407 (1:4) ratio in buffer pH 7.2 with 1% SLS as Dissolution Medium.

Sl No.	Time (in minute)	Absorbance	Conc.	Conc. in 10ml (mg)	Cum. Conc. in 10ml	Conc. in 900ml	Cum. Conc. in 900ml	% Nifedipine Released
1	0	0	0	0	0	0.00	0	0.00
2	15	0.034	3.646	0.365	0.365	32.81	32.81	16.41
3	30	0.045	5.038	0.504	0.868	45.34	45.71	22.85
4	45	0.056	6.430	0.643	1.511	57.87	58.74	29.37
5	60	0.072	8.456	0.846	2.357	76.10	77.61	38.81
6	90	0.079	9.342	0.934	3.291	84.08	86.43	43.22
7	120	0.095	11.367	1.137	4.428	102.30	105.59	52.80
8	180	0.138	16.810	1.681	6.109	151.29	155.72	77.86
9	240	0.165	20.228	2.023	8.132	182.05	188.16	94.08
10	300	0.171	20.987	2.099	10.230	188.89	197.02	98.51
11	360	0.172	21.114	2.111	12.342	190.03	200.26	100.13

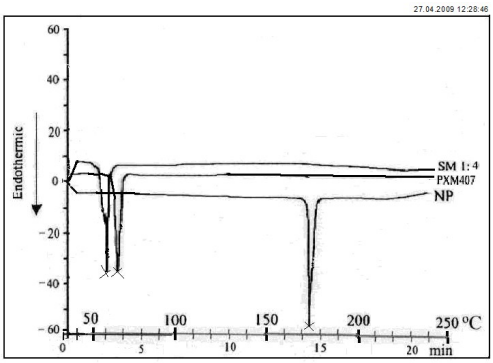

Fig. 1: DSC curve of nifedipine(NP), Poloxamer 407(PXM) and nifedipine + Poloxamer 407 SD (SM).

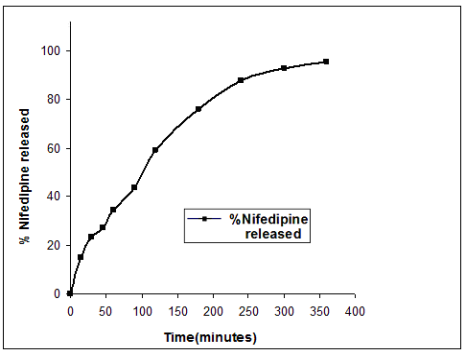

Fig. 2: Dissolution curve of SD of nifedipine + PXM407(1:2 ratio)+ buffer pH 7.2 with 1% SLS as Dissolution Medium.

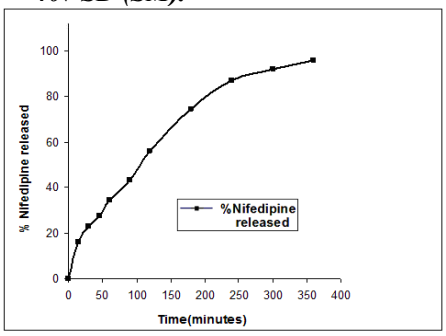

Fig. 3: Dissolution curve of SD of nifedipine + PXM407(1:2 ratio)+ buffer pH 7.2 with 3% SLS as Dissolution Medium.

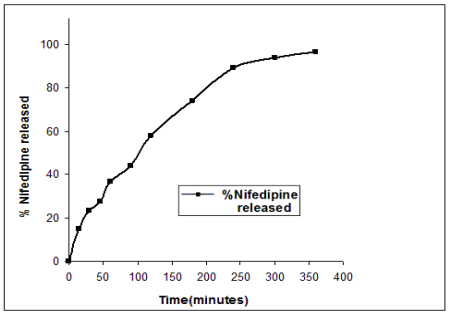

Fig. 4: Dissolution curve of SD of nifedipine + PXM407(1:2 ratio)+ buffer pH 7.2 with 5% SLS as Dissolution Medium.

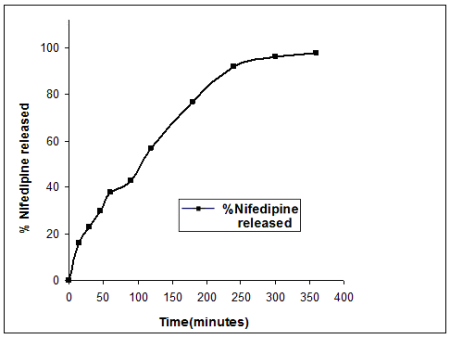

Fig. 5: Dissolution curve of SD of nifedipine + PXM407(1:3 ratio)+ buffer pH 7.2 with 1% SLS as Dissolution Medium.

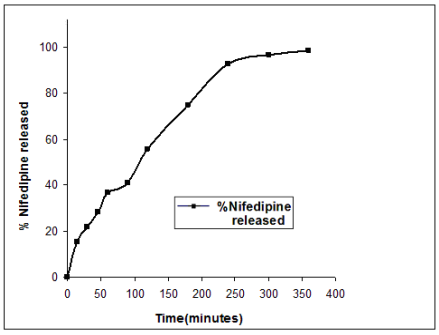

Fig. 6: Dissolution curve of SD of nifedipine+ PXM407(1:3 ratio)+ buffer pH 7.2 with 3% SLS as Dissolution Medium.

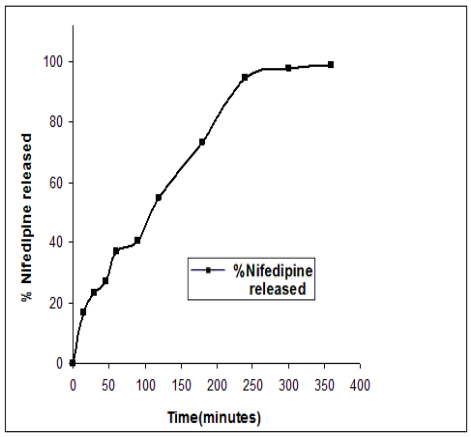

Fig. 7: Dissolution curve of SD of nifedipine + PXM407(1:3 ratio)+ buffer pH 7.2 with 5% SLS as Dissolution Medium.

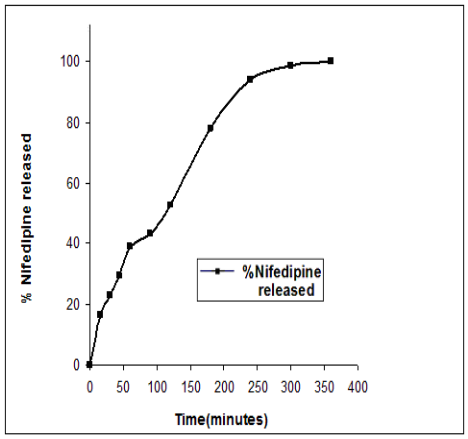

Fig. 8: Dissolution curve of SD of nifedipine+ PXM407(1:4 ratio)+ buffer pH 7.2 with 1% SLS as Dissolution Medium.

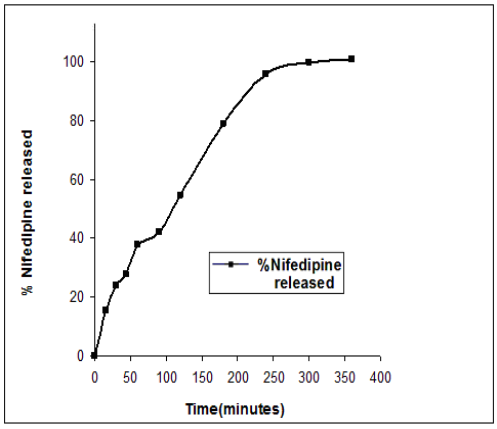

Fig. 9: Dissolution curve of SD of nifedipine + PXM407(1:4 ratio)+ buffer pH 7.2 with 3% SLS as Dissolution Medium.

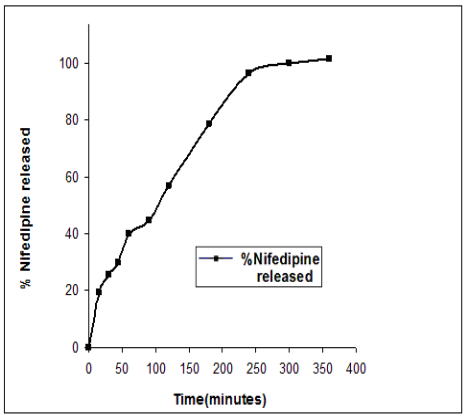

Fig. 10: Dissolution curve of SD of nifedipine + PXM407(1:4 ratio)+ buffer pH 7.2 with 5% SLS as Dissolution Medium.

CONCLUSION:

Solid dispersion of nifedipine in PXM 407 improved the dissolution rate of nifedipine, which helps to enhancing solubility of drug. Effects of the preparation methods and the mixing ratios on the dissolution were clearly observed.

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