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Preparation and Characterization of Sustained Release Tablet Containing Solid Dispersion Granules of an Anti-Hypertensive Drug

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ABSTRACT

The present works was planned with the objective of preparing nifedipine (N) solid dispersion in Poloxamer-188 by using aerosil 300 as adsorbent and were investigated with the view to design sustained release tablets of nifedipine. As nifedipine is practically insoluble in water and aqueous fluids; its solid dispersion in poloxamer 188 has markedly enhanced the dissolution rate of nifedipine. Sustained release tablets were formulated employing nifedipine dispersion in poloxamer 188 and Polyethylene oxide (PEO) was used as rate controlling polymer to control the release of drug from the tablet while coming in contact with the aqueous medium. The sustained release tablets gave slow, controlled and complete release over a period of 14 hrs. Drug release from these tablets followed zero order kinetics and the release was diffusion controlled. The 'n' values obtained from Korsmeyer-Peppas plots were within the range of 0.560-0.825, indicates the drug released by both diffusion coupled with erosion. The FT-IR study were also indicating the absence of strong interactions between the components and suggesting drug- excipient compatibility in all the formulations examined.

Keywords: Nifedipine, solid dispersion, sustained release tablet, poloxamer 188.

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INTRODUCTION

Nifedipine (N) is a calcium channel blocking drug used in the treatment of angina pectoris and hypertension. It is practically insoluble in water and its absorption is dissolution rate limited. Nifedipine has a short biological half-life of 3-4 hrs. and is eliminated rapidly and its anti-hypertensive effect lasts only a few hours. As such sustained release (SR) products are needed for nifedipine to prolong its duration of action and to improve patient compliance. SR products also avoid the vasodilator related adverse effects such as increase in heart rate, flushing and palpitations associated with conventional nifedipine tablets and capsules [1]. There are few reports on the formulation of sustained release products of nifedipine employing coated granules, matrix tablets and Microencapsulation [2].

In the present work sustained release tablets of nifedipine and its solid dispersions in hydrophilic carriers such as poloxamer 188 were formulated employing polyethylene oxide as sustained release polymers and were evaluated with a view to obtain sustain release. As nifedipine is practically insoluble in water, its solid dispersions in poloxamer 188 was prepared to enhance its dissolution rate and to evaluate the feasibility of using these solid dispersions in the formulation of sustained release tablets [3].

MATERIALS

Nifedipine (gift sample received from Mylan Laboratories limited, Bollaram Jinnaram, AP), Poloxamer 188 (purchased from Yarrow Chem Products, Mumbai), Fumed Silicon dioxide (Aerosil 300) (Loba Chemicals, Mumbai), Polyethylene oxide (PEO)(purchased from Alfa Aesar a Johnson Matthey company, MA), MCC (microcrystalline cellulose) (purchased from Thomas baker chemicals Ltd, Mumbai), were used.

METHOD

All experiments were carried out under subdued light to prevent photo degradation of nifedipine.

Preparation of solid dispersions

Solid dispersions of nifedipine in poloxamer 188 using aerosil 300 as adsorbent were prepared by using hot melt method The poloxamer 188 carrier was melted in a china dish at 60 ◦C on a Heater and the drug was added while stirring to obtain a homogenous mixture Various adsorbents (Aerosil 300, MCC) were added gradually to the molten mixture with continuous stirring. The dispersion was cooled at −70 ◦C followed by passing through a sieve 400 µm in diameter. The weight ratio of nifedipine, poloxamer 188 and adsorbent was 1:1:1. A physical mixture (PM) was obtained by mixing Nifedipine, poloxamer 188 and adsorbent using a spatula [4].

Preparation of sustained release tablets

Sustained release tablets each containing 50 mg of nifedipine were prepared by conventional direct compression method employing nifedipine and its solid dispersions in

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PEO and other excipients of the formulation. All the ingredients were passed through sieve #40. Magnesium stearate was then passed through sieve #80, mixed and blended with the initial mixture. The mixed blend of drug and excipients was compressed using multistation rotary rimek minipress I tableting machine to hardness of 6-8 kg/cm2 to produce tablet weighing 300 mg having a diameter of 8.5 mm. The composition of various sustained release tablets was given in table 1.

Table No.1 Formulation compositions (mg) in the preparation of Sustained release tablets Containing Solid dispersion granules.

S.N.	Ingredients (mg/tab)	Formulation Code								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Nifedipine	-	-	-	-	-	-	-	-	50
2.	Physical Mixture	-	-	-	-	-	-	-	150	-
3.	SD1	150	150	150	150	150	-	-	-	-
4.	SD2	-	-	-	-	-	150	150	-	-
5.	Polyethylene Oxide	147	75	50	30	15	147	75	30	30
6.	Microcrystalline cellulose	-	24	31	39	44	-	24	39	73
7.	Lactose	-	48	63	78	88	-	48	78	144
8.	Magnesium stearate	3	3	3	3	3	3	3	3	3
9.	Total	300	300	300	300	300	300	300	300	300

SD1- Nifedipine: poloxamer: Aerosil (1:1:1w/w), SD2-Nifedipine: poloxamer: MCC (1:1:1w/w).
Physical mixture-Nifedipine: poloxamer: Aerosil (1:1:1w/w)

The powder properties were studied which is given in table No. 2

Table No.2 Powder properties of SRT formulations of nifedipine

Batch Code	Parameter				
	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's Index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.487 ±0.03	0.520 ±0.04	6.34 ±0.14	1.06 ±0.06	27.05 ±0.25
F2	0.439 ±0.04	0.476 ±0.06	7.77 ±0.12	1.08 ±0.02	29.74 ±0.24
F3	0.430 ±0.03	0.472 ±0.03	8.89 ±0.15	1.09 ±0.05	27.75 ±0.15
F4	0.449 ±0.07	0.483 ±0.02	7.03 ±0.13	1.07 ±0.03	29.74 ±0.17
F5	0.472 ±0.05	0.536 ±0.03	11.94 ±0.09	1.10 ±0.04	28.05 ±0.26
F6	0.484 ±0.06	0.513 ±0.04	5.65 ±0. 24	1.05 ±0.09	29.30 ±0.14
F7	0.439 ±0.04	0.472 ±0.07	6.99 ±0.20	1.07 ±0.07	29.60 ±0.34
F8	0.402 ±0.05	0.483 ±0.06	16.77 ±0.14	1.20 ±0.06	30.52 ±0.14
F9	0.382 ±0.03	0.452 ±0.06	15.48 ±0.07	1.18 ±0.03	42.05 ±0.26

To minimize processing variables, all batches of tablets were compressed under identical conditions. The compressed tablets were evaluated for physical parameters such as weight uniformity, hardness, friability and drug content [5].

Estimation of Nifedipine

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 340 nm in 1.2 pH and in phosphate buffer of 6.8 pH was used for the

estimation of nifedipine. The method obeyed Beer's law in the concentration range of 0-50 µg/ml.

Dissolution Rate Study on Solid Dispersions

The dissolution rate of nifedipine as such and from various solid dispersions was studied using USP I eight station Dissolution Rate Test Apparatus (Elactrolab TDT-06L) employing a paddle stirrer. In 900 ml of dissolution medium (0.1N HCL containing 10% methanol), a sample of equivalent to 50mg of nifedipine , a speed of 50 rpm and a temperature of 37^0C ±0.5^0C were employed in each test. A sample of 5ml aliquot of dissolution medium was withdrawn through a filter (0.45µ) at different time intervals, suitably diluted and assayed spectrophotometrically at 340 nm using a Shimadzu UV-1700 double beam spectrophotometer [6].

***In Vitro* Drug Release Study on Matrix Tablets**

Release of nifedipine from the tablets was studied using the USP I eight station Dissolution Rate Test Apparatus (Elactrolab TDT-06L) with a paddle stirrer. Dissolution fluid consisted of 900ml of simulated gastro intestinal fluids namely pH 1.2(0-2h) and pH6.8 (2-14h).One sustained release tablet containing 50mg of nifedipine, a speed of 50 rpm was assayed at 340nm for nifedipine. The kinetics of drug release from various matrix tablets were further evaluated with the obtained dissolution data.

Kinetics and Mechanism of Drug Release

To understand the rate and extent of drug release and the mechanism of drug release to compare the differences among the release profiles of these matrix formulations, various plots like log% un dissolved versus time, for first order constant, drug released versus square root of time, for dissolution rate constant (Higuchi constant) log $Mt/M\infty$ versus time (Peppas constant) for 'n' values were plotted. 'n' is the diffusion exponent indicating the mechanism of fickian diffusion, When 0.45 to 0.85 indicates anomalous transport and 0.89 indicates case-II transport and if n > 1indicates for zero order release.

Compatibility Studies Using FTIR- 8700 Shimadzu

Sample preparation

Samples and KBr are taken in the ratio of 1:100. It is triturated using motor and pestle, due precaution is taken not to come in contact with Moisture, which may interfere with the test. The sample along with blank (KBR), Reference standard drug are placed in order on the disk provided peaks obtained in FTIR are compared to that of standard peaks for any significant change in the peaks of the respective drug.

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Table No. 3 Drug Release Kinetics.

Formulation code	Kinetic Models				
	Zero Order	First Order	Higuchi Model	Korsmeyer-Peppas Model	
				R^2	n
F1	R^2 = 0.9829	R^2 = 0.6661	R^2 = 0.9198	0.996	0.767
F2	R^2 = 0.9813	R^2 = 0.0787	R^2 = 0.8454	0.970	0.714
F3	R^2 = 0.9844	R^2 = 0.1383	R^2 = 0.9233	0.946	0.689
F4	R^2 = 0.9889	R^2 = 0.7476	R^2 = 0.8625	0.956	0.740
F5	R^2 = 0.9951	R^2 = 0.1298	R^2 = 0.9551	0.993	0.684
F6	R^2 = 0.9805	R^2 = 0.1293	R^2 = 0.8397	0.993	0.694
F7	R^2 = 0.9958	R^2 = 0.116	R^2 = 0.9677	0.974	0.754
F8	R^2 = 0.9952	R^2 = 0.0094	R^2 = 0.9617	0.987	0.733
F9	R^2 = 0.9916	R^2 = 0.0564	R^2 = 0.913	0.980	0.735

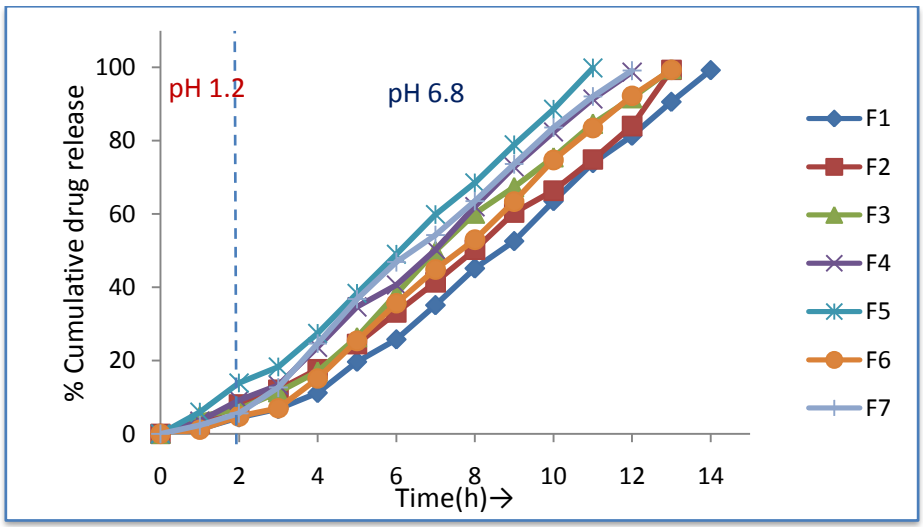

Figure No.1 Comparison of drug release profile of formulations (F1-F7) and studied the effect of PEO amount on Nifedipine release from SD-SR tablet in gastric fluid (pH 1.2) for 2 h and subsequently in intestinal fluid (pH 6.8) for 12 h.

RESULTS AND DISCUSSION

Nifedipine is practically insoluble in water and aqueous fluids due to its highly crystalline natureand exhibits poor dissolution rate. Various attempts made to improve the dissolution of nifedipine include solid dispersions in water soluble carriers such as urea, 4 PVP, 5 PVP-MCC and HPC-MCC and complexation with cyclodextrins.

In the present work solid dispersions of nifedipine in carrier such as poloxamer 188 using aerosil 300 and MCC as adsorbent were tried to improve its dissolution rate. All the solid dispersions prepared gave rapid dissolution of nifedipine when compared to nifedipine itself. With all the solid dispersions, 80% dissolution was observed within 30 minutes. Whereas in the case of nifedipine as such, the dissolution was very low, 20% in 1 hr. The dissolution efficiency was increased from 16.67 percent for nifedipine to 74.46, 83.70, and

90.24 percent in the case of to 70.54, 76.70 and 86.54 in the case of solid dispersions of 1:1:1.

The IR spectrum of pure drug nifedipine showed principle peaks at 1690, 1527, 1496,1310,1225,1120cm^{-1}respectively. The IR spectra of all combinations containing drug and one or more polymers also showed the characteristic peaks same as that of the pure drug at Specific wave no. Sustained release tablets of nifedipine were formulated employing polyethylene oxide (PEO) alone and in combination with Lactose, MCC by direct compression. compressed tablets were evaluated for various physical parameters such as hardness, friability, weight uniformity and drug content. The values of physical parameters evaluated were within the IP specified limits. This indicated that the tablets compressed were stable.

From the *in vitro* dissolution studies, all the sustained release tablets were release the nifedipine over a period of 2 to 14 hours. The dissolution profiles of various formulations (F1 to F7) were shown in figure 3. From the release profile data of the prepared tablets, it was observed that F1 has released least percentage of drug among all formulation so it has more retardant capacity. This is because of higher % of polyethylene oxide in F1 formulation.

Higher PEO content used was correlated with lower drug release due to the formation strong gel layer.as a result different release pattern of Nifedipine from SD-SR tablets were obtained by modifying the PEO content of the tablets. When the amount of PEO in the tablets decreased from 49%(F1) to 7.5%(F5), Nifedipine release increased from 4.42% to 13.9% in gastric fluid after 2h and 73.87% to 100% in intestinal fluid after 12h, further decrease of PEO to 5%(F4) resulted in a drastic increase in Nifedipine release and was unable to sustain drug release over an extended period.

The rate of drug release from all the formulation is shown in FigureNo.1 and are in the following order at the end of 14hrs of *in vitro* dissolution studies. F1 (99.25% 14h)>F2 (99.38% 13h)>F6 (99.37% 13h)>F3 (99.50% 13h)>F4 (98.75% 12h)>F7 (99.12% 12h)>F5 (99.87% 11h) .

Although nifedipine release from SD-SR tablets in gastric fluid was 9.16% higher than that from nifedipine and PM-loaded tablets. The increase drug release from the SD-SR tablets in intestinal fluid is significantly higher at 12 h. Nifedipine release from nifedipine tablets, PM tablets, and the SD-SR tablets were 51.5%, 70.75%, and 100% after 12 h. respectively. This might be ascribed to enhanced drug solubility and faster water penetration from the dissolution medium into the SD-SR tablets compared to nifedipine and PM-loaded SR tablets. This indicates that the SD granules improved the solubility and dissolution of nifedipine at pH 1.2 and could facilitate drug release, leading to pH independent release from the SD-SR tablets, unlike the nifedipine and PM-loaded tablets. The formulations prepared by direct compression method, followed zero order release mechanism and r^2 values obtained were liner. Higuchi plots for all the formulations were linear in drug diffusion process and r^2 values were also linear. The 'n' values obtained were in between 0.55 to 0.85 indicates the anomalous transport with erosion coupled with diffusion [7-15]. The data were depicted in table 3.

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CONCLUSION

Solid dispersions of nifedipine in poloxamer 188 have markedly enhanced the dissolution rate of nifedipine. Slow, controlled and complete nifedipine release over a period of 14 hrs was obtained from tablets formulated employing its solid dispersions in poloxamer 188. it can be concluded that the formulated sustained release tablets of nifedipine using widely accepted and physiologically safe polymers and other excipients was capable of exhibiting sustained release properties. They reduce the dose intake, minimize the blood level oscillations, dose related adverse effects and ultimately improve the patient compliance and drug efficiency.

The results of study also suggest that all the main objectives of the study were met and the formulation can be commercially exploited.

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