Formulation and Evaluation of Sustained Release Dosage Form of Nifedipine Hydrochloride Using Hydrophilic Polymers

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A B S T R A C T

Sustained release oral delivery systems are designed to achieve therapeutically effective concentrations of drug in the systemic circulation over an extended period of time. The purpose of the present investigation was to design and evaluate sustained release matrix tablets of nifedipine, a poorly water soluble drug, employing hydroxypropyl methyl cellulose (HPMC) and ethyl cellulose (EC) as hydrophilic polymers. Direct compression method was used to prepare matrix tablets. Drug content uniformity, friability test were performed and the *in vitro* drug release profiles were compared with the innovator product (Procardia) benefiting similarity factor (*f2*) and difference factor (*f1*). In all formulations content uniformity was in the acceptable range. Most of the prepared formulationspassed friability test. Formulation containing HPMC and EC in the ratio of 88.5:5 showed acceptable dissolution properties compared to reference formulation. Fitting the release data to the kinetic models indicated that the best fitted kinetic model for the prepared matrix tablets and Procardia were zero order and Weibull model, respectively. This study indicates that the hydrophilic matrix tablets of nifedipine prepared using HPMC and EC can successfully be employed as sustained release matrix tablet in order to improve patient compliance.

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Introduction

Nifedipine (NF) is a yellow crystalline substance, practically insoluble in water but soluble in ethanol. NF is a selective calcium-channel blocker and a peripheral arterial vasodilator which acts directly on vascular smooth muscle. NF is widely used in the treatment of angina pectoris and systemic hypertension. It is a poorly soluble drug and its absorption from gastrointestinal tract is limited by dissolution rate. It has a short biological half-life (4 hrs). Absorption of NF is poor following administration orally via immediate release dosage forms. It exhibits 45-65% oral bioavability due to hepatic first pass metabolism. Immediate release formulations of NF clearly show fluctuation in drug plasma concentration results in specific side effects like increase in heart rate. Sublingual NF has been used in hypertensive emergencies, however, was found to be unsafe [1-6].

Sustained release formulations are drug delivery systems that are designed to achieve an expanded therapeutic effect by continuously releasing of drug over an extended period of time after administration of a single dose. To reduce the frequency of administration and to improve patient's compliance, a once daily sustained-release formulation of NF is desirable. Most commonly used method to control the drug release is incorporation of drug in a matrix system. The direct compressed matrix tablet has been used for decades due to its simplicity and cost efficiency comparison with other drug delivery systems [2, 3, 7-10]. Hydrophilic polymers are widely used in matrix systems. HPMC is the hydrophilic polymer used for the preparation of oral controlled drug delivery systems as a release retarding carrier. Types, concentration and weight ratio of polymers will lead to high variation of drug release [6, 11-14]. The main objective of this work was to develop and characterize a directly compressed sustained release matrix tablet of NF using HPMC and EC.

Materials and methods

Materials

Nifedipine powder (Sanofichimie, Spain), Hydroxypropyl methyl cellulose, η=16.96 cps (Yocohama, Japan), Ethyl cellulose (Hercules,

Island), Magnesium stearate (Merck, Germany), Methanol (Merck, Germany), Nifedipine film coated tablet 10 mg (Batch: 168, Chimidaru, Iran), Nifedipine soft gel capsules 10 mg (Batch: AM650, Apotex INC, Canada), Procardia tablet 30 mg (Batch: F7754, Pratt, USA).

Tablet preparation and evaluation

Drug and polymers were weighed separately for each formulation as illustrated in Table1. Tablets weight was 500 mg for all formulations. NF and polymers (HPMC and EC) were hand blended for 2 hrs. Magnesium Stearate (MgSt) (0.5%) was added and blended for another 10 min. The mixture was compressed directly using a laboratory single punch machine (Riken, Japan) equipped with 10 mm round punch and die set for three sec at different pressures (Table 1).

Table 1. The composition of the formulations, pressure used for compression and rpm applied in dissolution test

| Formulation code	NF (%w/w)	MgSt (%w/w)	HPMC (%w/w)	EC (%w/w)	Pressure (kg/cm^2)
F1	6	0.5	93.5	0	140
F2	6	0.5	93.5	0	280
F3	6	0.5	93.5	0	415
F4	6	0.5	93.5	0	550
F5	6	0.5	88.5	5	550
F6	6	0.5	83.5	10	550
F7	6	0.5	13.5	80	550
F8	6	0.5	0	93.5	550

The prepared matrix tablets were characterized immediately for friability and drug content. Friability (n=10) was determined in a friabilator machine (Erweka, Germany) for 4 minutes at a speed of 25 rpm. Drug content was analyzed by measuring the absorbance of standard and samples at λ = 233 nm using UV/Visible spectrophotometer (Shimadzu, Japan).

In vitro drug release study

Calibration curve was linear in the range of 0.775-15.5 mg/L in solution of methanol: water (20:80) at two wave length, 238 and 334 nm (r^2=0.9999). Since the excipients of the softgel bared a UV absorption in wave length 238 nm; so therefore, 334 nm was directed for evaluation of drug release from the softgel.

In vitro dissolution studies were conducted using 1000 ml distilled water under stirring rate of 150 rpm for 10 hrs. The temperature was maintained at 37 ± 0.5 °C. At the time intervals of 0.5 hrs, 5 ml of samples were taken out and replaced with water immediately. The withdrawn volume of dissolution medium was filtered using 0.45 μm filter and the filtrate was analyzed by UV spectrophotometer[15]. The amount of drug in the samples was calculated from calibration curve obtained from the standard solution of the drug. The percentage of cumulative drug released was plotted against time. Release profiles of the tablets are summarized in Fig. 1.
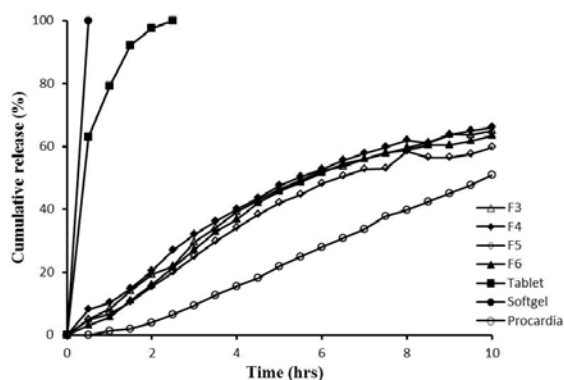
Fig. 1. Drug release profiles for prepared formulations, NF tablet available in the market, softgel and reference product (Procardia).

To evaluate and compare dissolution profiles, the release data was analyzed using dissolution similarity factor (*f*2) and difference factor (*f*1). If *f*1< 15 and 50<*f*2 < 100, two dissolution profiles are verified similar. The equations for calculating *f*2 and *f*1 are given below.

$$f2 = 50 \log \{[1+1/n \; \Sigma \; (R_t-T_t)^2]^{-0.5} \times 100\}$$
(1)

$$f1= \{[\Sigma \; (R_t-T_t)]/ \Sigma \; R_t]\} \times 100 \%$$
(2)

Where R_t and T_t are the cumulative percentage of dissolved drug for a reference and test formulation at time t, respectively, n is the number of time points[14, 16-18].

To find out the mechanism of drug release, the release kinetics data from all matrixes were fitted to various equations including zero order, first order, Higuchi, Peppas, Weibull, linear Wagner, and log Wagner [7, 9, 19, 20]. The accuracy and prediction ability of the models were compared by calculation of squared correlation coefficients (r^2) and percent error (PE).

Results and discussion

Tablet evaluation

Friability of the tablets excluding formulations F1 and F2 were within the acceptable range of <1% specifying that tablet surfaces were strong enough to withstand mechanical force or erosion during storage and transport and until consumption.[15] Formulations F1 and F2 which were compressed under pressures 280 and 415 kg/cm^2 were excluded from further tests. The tablets showed a high degree of drug content uniformity, so that drug content was more than 95% for all the tablets.

In vitro drug release study

The release profiles of NF from different formulated matrix tablets are illustrated in Fig. 1. NF release rate from the prepared matrix tablets was slow and the drug release prolonged more than 10 hours. Matrix tablets F3, F4, F5 and F6 provided a release profile comparable to the innovator's sustained released tablet.

Effect of polymer content on drug release

As shown in Fig. 1, existence of EC in concentration 5% (F5) could sustain release of NF more than formulation F4 containing no EC in its composition. Increasing the amount of EC to 10 % (F6) could not prolonged the drug release rate more than F5 (*f*2=37.46 and *f*1=72.51) indicating that 5% EC could be the optimum amount of polymer to extend NF release from matrix tablets prepared from HPMC and EC.

At higher polymer concentrations, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion of the drug. This indicates that drug/polymer ratio is important factors affecting the rate of drug release from HPMC and EC matrices. In the other word, factors that may contribute to variations in drug dissolution profiles as a function of changes in total polymer concentration include differences in water penetration rate, water absorption capacity and polymer swelling [1, 7, 10, 13, 14, 21-23].

Effect of compression pressure on NF release

Even though the formulations F1, F2, F3 and F4 prepared with the same composition but different compression pressure was applied. Comparative dissolution profiles of F3 and F4 are illustrated in Fig. 1. As shown, release profiles were similar, so that the calculated *f*2 and *f*1 for F3 and F4 were 83.66

and 3.58, respectively indicating similarity between two release profiles. Therefore compression pressures of 415 and 550 kg/cm^2 were found to be adequate pressure for preparation of NF matrix tablets.

Kinetic analysis of dissolution data

In order to describe the kinetics of the drug release process, different models were applied to fit the dissolution data. Squared correlation coefficient (r^2) and percent error (PE) resulted from fitting of the release data to the kinetic models are presented in Table 2. Drug release data for formulations F3, F4, F5 and F6 fitted best to the Weibull equation (r^2= 0.9809-0.9913 and PE= 5.8-9.3), where the predominant model for Procardia was zero order. A high correlation with zero order kinetic was also found to the prepared formulations ($r^2 > 0.9$ and PE < 12).

Table 2. Squared correlation coefficients (RSQ) and percent error (PE) of the kinetic models used for NF matrix tablets

Model		F3	F4	F5	F6	Procardia
Zero order	RSQ	0.9496	0.9458	0.9499	0.9410	0.9899
	PE	11.43	12.68	12.11	10.96	6.31
First order	RSQ	0.9875	0.9868	0.9768	0.9774	0.9744
	PE	12.81	14.20	18.15	18.15	15.33
Higuchi	RSQ	0.9687	0.9750	0.9577	0.9561	0.8794
	PE	12.41	14.91	16.53	13.40	21.54
Peppas	RSQ	0.9807	0.9790	0.9777	0.9678	0.9455
	PE	9.98	14.53	11.94	14.54	12.47
Weibull	RSQ	0.9913	0.9855	0.9837	0.9836	0.9534
	PE	5.87	8.80	9.30	8.65	8.89
Linear probability	RSQ	0.5730	0.5466	0.5754	0.5990	0.5698
	PE	32.09	31.93	35.30	31.78	38.52
Log- probability	RSQ	0.9870	0.9792	0.9773	0.9900	0.9436
	PE	15.92	14.96	16.13	11.39	12.88

Conclusion

The current study indicates that the hydrophilic matrix tablet of NF prepared using HPMC and EC can successfully be employed as an oral controlled release dosage form. For formulations F4, F5 and F6 *in vitro* dissolution studies indicated a sustained release pattern throughout 10 hrs of the study which

was comparable with innovator product's release profile. Although, according to *f*1 and *f*2 values, the prepared formulations could not sustain the drug release similar to Procardia, but they were able to prolong the drug release more than 10 hrs with a parallel release pattern. Results of the present study demonstrated that combination of HPMC and EC would be useful in the preparation of NF sustained

release matrix tablets with desired release profile. The sustained release tablets can be used to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional NF tablets. The formulation method employed is simple and could be adaptable for industrial scale up.

Conflict of interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

Acknowledgement

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