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Formulation and Evaluation of Prolonged Release Matrix Tablets Nifedipine

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ABSTRACT

The aim of the present work is to develop a robust formulation of Prolonged release matrix tablets of Nifedipine.The prolonged release dosage forms should primarily reduce the occurrence of steep rises in plasma concentration of the drug. Another important therapeutic goal that can be achieved with prolonged formulations is the improvement of chronic therapy compliance by prolongation of the dosing intervals. The matrix tablet by direct compression has attracted much attention due to its technological simplicity in comparison with other controlled release systems. It require fewer unit operations, less machinery, reduced number of personnel and processing time, increased product stability and production rate. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. The purpose of controlled release systems is to maintain drug concentration in the blood or in the target tissues at desired value as long as possible.

Key words: Nifedipine Hydroxy propyl methyl cellulose, Hydroxy propyl cellulose, Hydroxy ethyl cellulose Hydrochloric Acid, Sodium hydroxide and Potassium di hydrogen ortho phosphate

Introduction

Nifedipine, a calcium-channel blocking agent, is widely used in the treatment of angina pectoris and systemic hypertension. Because of its short biological half life (3.7±1.2 hrs) frequent administration of dosing is necessary to satisfy the requirement of persistent medication. Prolonged release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve the longer duration of action. Prolonged release dosage forms reduce dosing frequency and improve patient's compliance [1-4]. Treatment for hypertension is a long term therapy where non compliance is high, hence prolonged release dosage forms are useful for quality health care. Matrix tablets were designed to compliment pharmaceutical activity of the medicament in order to achieve the longer duration of action [5-7].

Sublingual nifedipine has previously been used in hypertensive emergencies. It was once frequently prescribed pro re nata to patients taking MAOIs for real or perceived hypertensive crises. This was found to be dangerous, and has been abandoned. Sublingual nifedipine causes blood-pressure lowering through peripheral vasodilation. It can cause an uncontrollable decrease in blood pressure, reflex tachycardia, and a steal phenomenon in certain vascular beds. There have been multiple reports in the medical literature of serious adverse effects with sublingual nifedipine, including cerebral ischemia/infarction, myocardial infarction, complete heart block, and death. As a result of this, the FDA reviewed all data regarding the safety and efficacy of sublingual nifedipine for hypertensive emergencies in 1995, and concluded that the practice should be abandoned because it was neither safe nor efficacious [8-14].

MATERIALS AND METHODS

Nifedipine were obtained from Aarthi Chemicals, Bombay Hydroxy propyl methyl cellulose, Hydroxy propyl cellulose, Hydroxy ethyl cellulose were obtained from S. D. Fine-Chem Ltd.; Mumbai Hydrochloric Acid, Sodium hydroxide and Potassium di hydrogen ortho phosphate were obtained from Qualigenes fine chemicals.

Preparation of controlled release matrix tablets of Nifedipine: All the formulations were prepared according to Table 4.2.2. The tablets are prepared by wet granulation method[35]. Nifedipine and polymer were triturated well and allowed to pass through sieve no. 80 and mixed thoroughly, the powders were granulated using povidone solution. The cohesive mass obtained was passed through sieve no. 12, and the granules were dried at 40 ^{O}C for 2 hours. The dried granules were resieved thorough sieve no.16 and are mixed with talc and magnesium stearate. The granules were punched to get tablets of average weight 150 mg using single punch tableting machine.

Composition of Nifedipine controlled release matrix tablets

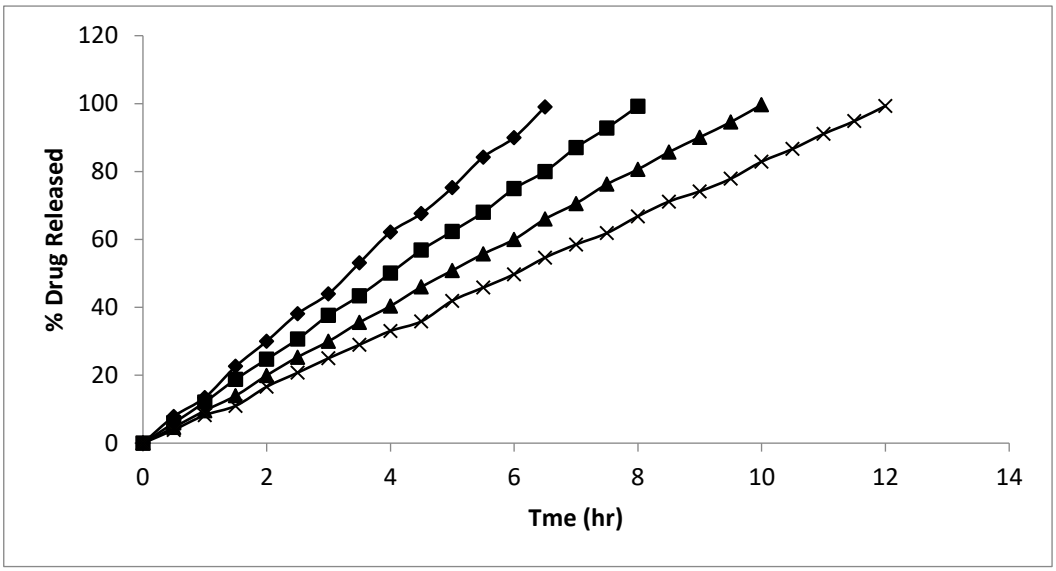
Ingredients (mg/tab)	CF1	CF2	CF3	CF4	CF 5	CF 6	CF 7	CF8	CF9	CF10	CF11	CF 12
Nifedipine	30	30	30	30	30	30	30	30	30	30	30	30
HPMC	15	30	45	60								
HEC					15	30	45	60				
HPC									15	30	45	60
Povidone K 30	5	5	5	5	5	5	5	5	5	5	5	5
MCC PH 101	95	80	65	50	85	85	85	85	85	85	85	85
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total tablet Weight	150	150	150	150	150	150	150	150	150	150	150	150

Physical properties of the Nifedipine matrix tablets Formulated With rate controlling polymers

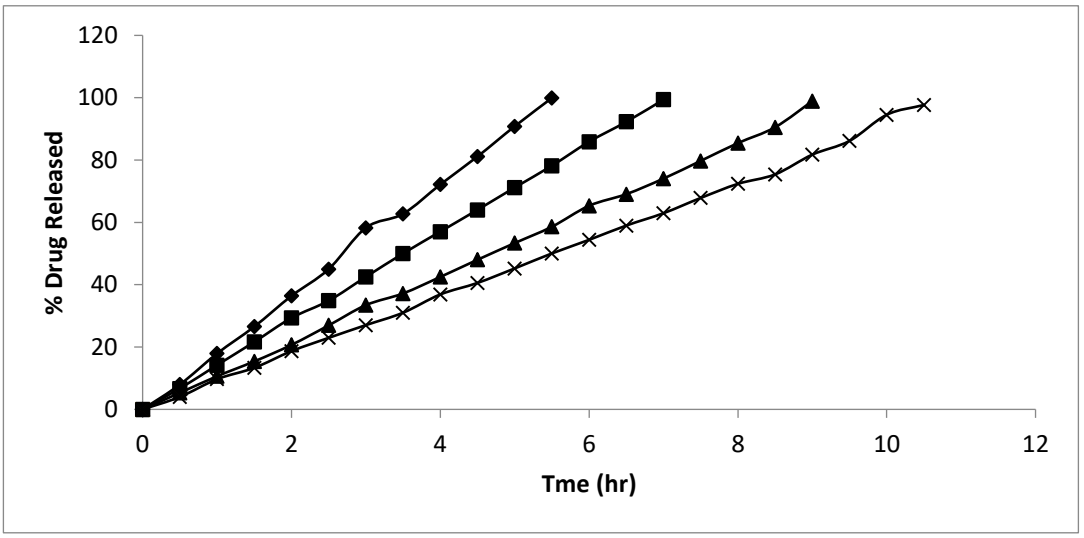
Formulation	Weight variation (mg)	%Drug content	Hardness kg/cm^2	% Friability
CF_1	149.5±0.7	99.23±0.18	7.2±0.02	0.39
CF_2	150.7±0.4	99.85±0.1	7.8±0.25	0.31
CF_3	151.3±0.6	101.39±0.21	7.9±0.34	0.35
CF_4	149.1±0.2	99.93±0.23	8.2±0.12	0.41
CF_5	150±0.5	101.88±0.39	8.8±0.06	0.29
CF_6	151.8±0.8	100.16±0.51	8.9±0.58	0.32
CF_7	152±0.3	99.64±0.63	8.2±0.40	0.38
CF_8	148±0.1	101.24±0.17	8.5±0.24	0.45
CF_9	153±0.6	101.17±0.39	8.9±0.45	0.38
CF_{10}	152.4±0.4	100.16±0.29	7.4±0.40	0.43
CF_{11}	150±0.8	101.06±0.32	8.0±0.25	0.34
CF_{12}	148±0.7	100.26±0.39	7.7±0.35	0.58

***In-vitro* dissolution test:** The release of Nifedipine from the tablet was studied using USP – Type II paddle apparatus. Drug release profile was carried out in 900 ml of 6.8 pH phosphate buffer maintained at 37 ± 0.5ºC temperature at 50 rpm. 5 ml of samples were withdrawn at regular time intervals. The samples were analyzed at 236 nm by UV spectrophotometer[39].

Dissolution kinetics: The rate and the mechanism of release of Nifedipine from the prepared matrix tablets were analyzed by fitting the dissolution data into[40], zero-order equation, $Q=Q_0–k_0t$, where Q is the amount of drug released at time t, and k_0 is the release rate. First order equation, $\text{Ln } Q=\text{Ln } Q_0 – k_1t$, where k_1 is the release rate constant and Higuchi's equation, $Q= k_2t^{1/2}$ where Q is the amount of the drug released at time t and k_2 is the diffusion rate constant. The dissolution data was further analyzed to define the mechanism of release by applying the dissolution data following the empirical equation, $M_1/M_\alpha=Kt^n$ [41], where $Mt/M_\alpha$is the fraction of drug released at time t. K is a constant and n characterizes the mechanism of drug release from the formulations during dissolution process.



***In-vitro* drug release profile plot of Nifedipine controlled release matrix tablets prepared with HPMC in different ratios**



***In-vitro* drug release profile plot of Nifedipine controlled release matrix tablets prepared with HPC in different ratios**

DISCUSSION OF RESULTS

The following conclusions were drawn from the results

1. Wet granulation method was found to be suitable method for the preparation of Nifedipine controlled release matrix tablets.
2. The Nifedipine controlled release matrix tablets release rate was found to be decreased with increase in concentration of polymer.
3. Among the three polymers, controlled release matrix tablets prepared with HPMC shown slow release compared with other polymers.
4. Nifedipine release from the matrix tablets formulated employing HPMC at 1:2 (CF4) ratio shown controlled release for a period of 12 hours.
5. Nifedipine release from the matrix tablets followed zero order kinetics and the mechanism of drug release was governed by super case –II transport diffusion mechanisam.

Conclusion:

From the present study, it was also concluded that controlled release formulation of Nifedipine could be designed by employing hydroxyl propyl methyl cellulose as the release retarding polymer matrix. Release rate of drug from the matrix tablets can be governed by the type of polymer and concentration of polymer employed in matrix tablets. The matrix tablets have successfully extended the release of Nifedipine for a period of 12 hours from its tablet formulations. The manufacturing method employed in the present work is modest and easily adaptable for bulk scale tablet manufacturing units.

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