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Research Article

DESIGN AND FORMULATION OF TWICE DAILY NIFEDIPINE SUSTAINED RELEASE TABLET USING METHOCEL K15M CR AND METHOCEL K100LV CR

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ABSTRACT

The purpose of the present investigation was to design and evaluate sustained release tablets of a poorly water soluble drug nifedipine, employing hydrophilic polymers Methocel K15M CR and Methocel K100LV CR and to select the best formulation based on pharmacokinetic studies. Direct compression method was used to prepare matrix tablets. The granules were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and drug content. The tablets were subjected to various tests for their physical parameters such as thickness, hardness and friability. *In vitro* release study was carried out for 12 hours using USP paddle type dissolution apparatus in phosphate buffer with sodium lauryl sulphate (pH 6.8). Quantitative evaluation by mathematical model indicates that formulation containing HPMC K15M CR and HPMC K100LV CR in a ratio of 1:3 showed better dissolution properties compared to other formulations. Korsmeyer's plot indicated that the drug release mechanisms from the matrix tablet followed Fickian mechanism. The study indicates that the hydrophilic matrix tablets of nifedipine prepared using Methocel K15M CR and Methocel K100LV CR can successfully be employed as twice-a-day oral controlled release dosage form in order to improve patient compliance.

Keywords: Methocel K15M CR, Methocel K100LV CR, Dissolution, Korsmeyer's plot, Higuchi model, Direct compression.

INTRODUCTION

Nifedipine, a calcium-channel blocking agent, is widely used in the treatment of angina pectoris and systemic hypertension[1]. Half life of the drug is comparatively short[2]. Clinical experiences gained with oral nifedipine formulations with immediate-release (IR) characteristics clearly show that a sudden rise in the drug plasma concentration results in an increase in heart rate and drug-specific side effects[3,4]. Sublingual nifedipine has previously been used in hypertensive emergencies, however, was found to be dangerous, and has been abandoned[3,5,6]. Therefore, it has been generally accepted that sustained-release (SR) formulations are most efficient for routine hypertension therapy with nifedipine. The SR 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 SR 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[7]. 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[8].

HPMC is the dominant hydrophilic vehicle used for the preparation of oral controlled drug delivery[9]. While HPMC could potentially (and therefore control) the release of a soluble drug, it could also facilitate the release of relatively insoluble drug (e.g. nifedipine). In the later case, insolubility of the drug molecule would be the rate limiting step in its release and HPMC's solubilizing effect would facilitate the release. The net result is controlled drug delivery for a prolonged period of time[10].

MATERIALS AND METHODS

Chemicals

Nifedipine (Dr. Reddy's), methocel K15M CR and methocel K100LV CR (Colorcon Asia Pvt. Ltd., India), microcrystalline cellulose-P^{H} 101 (Mingtai Chemical Co. Ltd., Taiwan), colloidal silicone dioxide (Deggusa AG, Germany), magnesium stearate (Chemical Management Co., Germany), methanol (Merck, Germany), disodium hydrogen phosphate (Scharlau, Australia), ortho phosphoric acid (Honeywell Riedel-de Haen®, Germany), sodium hydroxide (Active Fine Chemicals, Bangladesh), sodium lauryl sulphate (Scharlau, Australia), citric acid (EAC Industrial Ingredients (BD) Ltd., Bangladesh) and distilled water.

Instruments

Clit-10 Compression Machine, Agilent HPLC 1100 series, Simadzu-1700 UV Spectophotometer, Digital pH meter, Electronic Hardness Tester, Digital Slide Callipers, Metler Karlfisher Titrator, Electrolab Tablet Dissolution Test Machine, Sartorius Electronic Balance BS-201, 0.2µ Disk Filter.

Preparation of Matrix Tablet

Drug, polymers and other excipients were weighed separately for 200 tablets for each formulation as shown in Table-1. The proposed formulations were coded as F1, F2, F3, F4, F5, F6, F7, F8 and F9. The tablets were prepared by direct compression method. Active ingredient (Nifedipine) and polymers (Methocel K15MCR and Methocel K100LVCR) were passed through #24 sieve and placed in a poly bag. They were hand blended for 20 minutes. Aerosil 200 (1%) and Magnesium Stearate (1%) were passed through #40 sieve and placed in the same poly bag and were blended for another 5 minutes. Blended granules were compressed using "Clit Compress" machine equipped with 6.0mm round biconvex punch and die set. After compression, all the tablets were stored in double polythene bags at room temperature for further study.

Formulation of Nifedipine Matrix Tablets

Evaluation of physical properties of formulation granules

Loose bulk density and tapped bulk density were calculated according to method used in previous study[11]. The compressibility index of the granules was determined by Carr's compressibility index[12]. The diameter of the powder cone was measured and angle of repose was calculated according to Cooper and Gunn[13]. Moisture content of granules was determined using Mettler Karl Fischer Titrator. Flow property was predicted from Hausner ratio and angle of repose measurement. Drug content assay of each of nine proposed formulation granules were determined by UV Spectrophotometer analysis.

Table 1: The active ingredient, polymers and excipients used in the proposed formulations coded as F-1 to F-9

Formulation code	Weight (mg/tab)						
	Nifedipine	Methocel K15M CR	Methocel K100LV CR	Avicel 101	Aerosil 200	Magnesium Stearate	Total
F1	20	5	5	68	1	1	100
F2	20	5	10	63	1	1	100
F3	20	5	15	58	1	1	100
F4	20	10	5	63	1	1	100
F5	20	10	10	58	1	1	100
F6	20	10	15	53	1	1	100
F7	20	15	5	58	1	1	100
F8	20	15	10	53	1	1	100
F9	20	15	15	48	1	1	100

Evaluation of physical properties of matrix tablets

Weight variation test, hardness, friability and moisture content of the prepared matrix tablets were determined. Drug content assay of each of nine proposed formulated tablets were determined by UV spectrophotometric analysis. *In vitro* dissolution studies were conducted according to USP method[14] using 6 assembly paddle type apparatus II at a speed of 50 rpm and the temperature was maintained at 37.0±0.5°C. The total duration of dissolution was 12 hours in which the tablet matrices were subjected to intestinal media (phosphate buffer at pH 6.8 and sodium lauryl sulphate solution).

Preparation of dissolution media

330.9 gm of dibasic sodium phosphate and 38 gm citric acid were taken to a 1L volumetric flask and distilled water was added to dissolve them. After adding 10 mL phosphoric acid the resultant solution was diluted with water to make the volume 1L. 125 mL prepared buffer solution was added to 1L of 1% sodium lauryl sulphate solution and the final volume was made 10 L. The pH was adjusted to 6.8 and 900 mL of solution was taken in each vessel as dissolution media.

***In vitro* dissolution study of the tablet matrix**

In vitro dissolution study was performed in 900mL buffer medium (pH 6.8). The temperature of the medium was set to 37 ± 0.5°C. USP paddle apparatus (Apparatus II) was used with a rotation speed of 50 rpm. After 3hrs, 6hrs, 12hrs definite volume (15 mL) of aliquots were collected for analysis, which were then compensated with equal volume of fresh dissolution medium. The withdrawn volume of dissolution medium was filtered using 0.2µ disk filter and the filtrate was analyzed by UV spectrophotometer at 236 nm. The amount of drug present in the samples was calculated from calibration curve constructed from the standard solution of USP reference standard test drug. The dissolution study was continued for 12 hours to get a simulated picture of the drug release and the percentage of drug release was plotted against time. This drug release profile was fitted into several mathematical models to get an idea of the release mechanism of nifedipine from the matrix tablets.

RESULT

Table 2: Physical Properties of Nifedipine powder blend

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Loose bulk density (gm/mL)	0.424	0.404	0.466	0.480	0.502	0.448	0.525	0.488	0.556
Tapped density (gm/mL)	0.510	0.474	0.556	0.610	0.631	0.533	0.651	0.627	0.699
% of compressibility	20.313	17.188	19.118	24.615	25.758	19.118	23.881	28.571	25.758
Hauser ratio	1.203	1.172	1.191	1.246	1.258	1.191	1.239	1.286	1.258
Carr's index	16.883	14.667	16.049	19.753	20.482	16.049	19.277	22.222	20.482
Angle of repose (◦)	27.02	29.25	28.27	26.78	27.32	27.59	27.98	27.11	28.32
Moisture Content (%)	3.651	3.562	4.826	3.910	3.775	5.310	4.181	2.869	3.739
Assay of Nifedipine (mg/Tab)	21.03	20.45	21.31	20.52	19.85	21.75	20.62	20.83	20.67

Table 3: Physical properties of Nifedipine matrix tablets

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Average weight (mg)	100.62	99.53	98.70	100.78	97.91	100.26	99.83	99.03	99.98
Diameter (mm)	6.00	6.00	5.99	6.00	6.00	6.00	5.99	6.00	5.98
Thickness (mm)	3.55	3.56	3.68	3.23	3.20	3.32	3.21	3.29	3.23
Hardness (kg/cm^2)	5.02	5.28	5.55	6.79	7.10	7.43	9.073	9.18	9.49
Friability (%)	0.46	0.55	0.63	0.32	0.28	0.21	0.08	0.06	0.05
Assay (mg/tab)	19.31	20.64	20.73	21.15	19.56	20.58	20.05	19.88	20.42
Uniformity content (mg/tab)	20.86	20.57	20.05	21.63	19.73	20.81	21.19	19.85	19.39

Table 4: Dissolution kinetics of Nifedipine matrix tablets

Formulation	Zero order		First order		Higuchi	Korsmeyer-Peppas		Hixson- Crowell			Best fit model
	K_0	R^2	K_1	R^2	K_h	R^2	n	R^2	K_{HC}	R^2	
F1	29.68	0.947	-0.389	0.885	26.93	0.996	0.77	0.981	-0.429	0.973	Higuchi
F2	28.57	0.946	-0.336	0.797	25.18	0.939	0.602	0.923	-0.612	0.906	Zero order
F3	26.68	0.968	-0.246	0.851	23.16	0.932	0.48	0.990	-0.696	0.977	Peppas
F4	12.34	0.930	-0.071	0.944	11.24	0.986	0.45	0.921	-0.310	0.910	Higuchi
F5	11.59	0.998	-0.061	0.994	10.04	0.955	0.122	0.961	-0.525	0.978	Zero order
F6	10.20	0.972	-0.053	0.983	9.04	0.973	0.20	0.918	-0.381	0.932	1st order
F7	8.643	0.992	-0.043	0.994	7.504	0.955	0.017	0.931	-0.455	0.95	1st order
F8	6.680	0.991	-0.032	0.993	5.811	0.958	-	0.930	-0.409	0.949	1st order
F9	5.503	0.975	-0.026	0.967	4.772	0.937	-	0.996	-0.414	0.987	Zero order

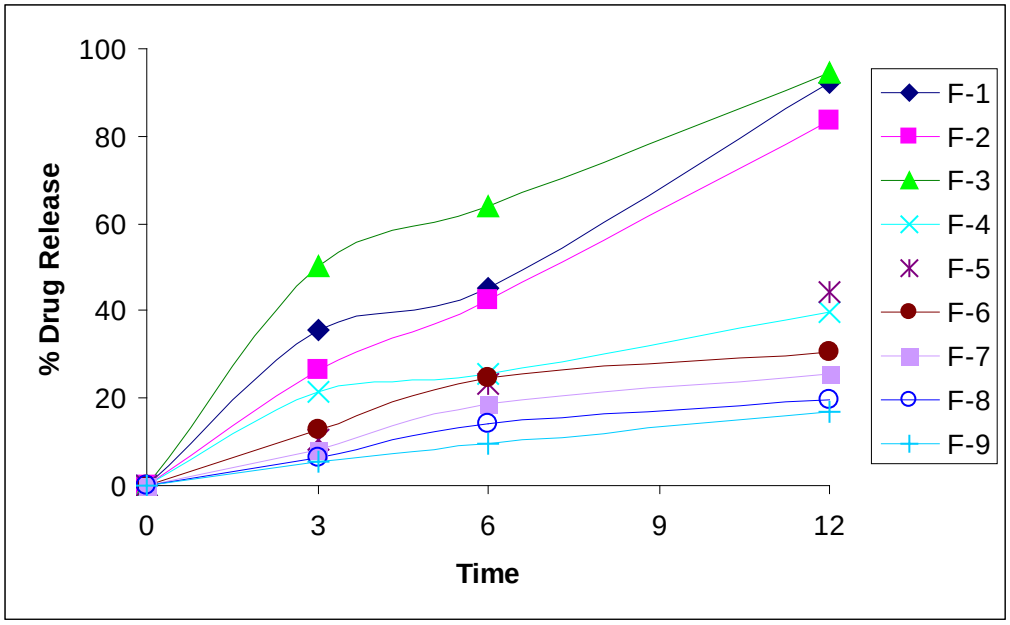

Fig. 1: Zero order plot of release kinetics of nine formulations (F1 to F9) of Nifedipine matrix tablets.

DISCUSSION

Physical properties of powder blend

Physical properties of the powder blend are shown in Table 2. The results of angle of repose (<30) indicated good flow properties of the granules. This was further supported by lower Carr's index and Hausner ratio values. Generally, Carr's index values up to 20% and Hausner ratio values less than 1.25 result in good flow properties, whereas greater than 1.25 indicates poor flow (=33% Carr). Between 1.25 and 1.5, added glidant normally improves flow[12]. The drug content in a weighed amount of granules of all the formulations indicated that the granules possessed satisfactory flow properties, compressibility and drug content.

Evaluation of matrix tablet

The weight variation within batches found less than 0.1%, of the tablets ranged between thickness between 3.19-3.68 mm and hardness was within 5.02- 9.49 kg/cm^2 as shown in Table 3. The hardness of the tablets increased proportionally with the amount of Methocel K15M CR due to binding property of HPMC. The weight variation and friability of the batches complied with British Pharmacopoeia as the tablets were prepared by direct compression the particle size and flow property of the powder blend should be in acceptable range. The flow property was determined by Hausner ratio (1.17-1.28) and Carr's Index (14.66%-22.22%). The data proved that the flow properties and compressibility of blends were satisfactory. Thus all the physical parameters of different batches were within control.

In vitro drug release study

Release parameters of the tablets are summarized in Fig. 1. Nifedipine release from the prepared matrix tablets was slow, spread over more than 12 hours, and depended on the grade of the controlled release polymer. Accordingly, dissolution requirements for Nifedipine SR tablets were specified by the USP. The fraction of drug dissolved using USP Apparatus 2 at 50 rpm is specified for Nifedipine 20 mg SR tablets as 10–30% release at 3 h, 40–65% at 6 h, and not less than 80% at 12 h. Matrix tablets F3 gave a release profile comparable to the theoretical sustained release needed for twice-a-day (12 hours) administration of Nifedipine.

From Fig. 1 it can be observed that drug release from the matrix tablet increased when the polymer Methocel K15M CR and Methocel 100LV CR was present in the formulation in optimum amount. It was observed that when the polymer concentration was increased, the drug release rate decreased. In case of the formulation F9, where the polymer concentrations are very high, drug release rate was too low compared to other formulations. This was due to the lower degree of the swelling because of higher concentration of polymers that suggested that there must be sufficient polymer content in a matrix system to form a uniform barrier. This barrier protects the drug from immediately releasing into the dissolution medium. If the polymer level is too low, a complete gel layer may not be formed.

F1 contained lower concentration of polymer and it was not sufficient to sustain the drug release from the matrix tablet. Gel layer formed on the surface of tablet was relatively thicker when a higher concentration of Methocel K15M CR and Methocel K100LV CR were used. The gel layer formed by the Methocel K15M CR was more viscous than Methocel K100LV CR. So, increasing the quantity of Methocel K15M CR decreased the release rate of drug from the matrix tablet more than Methocel K100LV CR (F4, F5, F6, F8, F9). Water insoluble drug required a smaller amount of polymer to sustain the release compared to the water soluble drug because the hydrophobic nature of the drug restricts the penetration of the solvent inside the matrix, which retarded drug release from the matrix.

Kinetic analysis of dissolution data

Kinetic analysis of prepared sustained release tablets are presented in Table 4. Drug release kinetics indicated that drug release was explained by Higuchi's equation as these plot showed highest linearity (R^2= 0.932-0.996), but a close relationship was also noted with zero order kinetics (R^2= 0.930-0.998). F3 follows Fickian release. Drug release mechanisms as per n value of F2 and F1, follow non-Fickian release mechanism. F4, F5, and F6 follow Fickian release kinetics. Release pattern of F7, F8 and F9 cannot be predicted clearly because the value of release component is beyond the limits of Korsmeyer model[15], as it appears to be a complex mechanism of swelling, diffusion and erosion. Hixson-Crowell plots indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time.

CONCLUSION

The current study indicates that the hydrophilic matrix tablet Nifedipine, prepared using Methocel K15M CR and Methocel K100LV CR, can successfully be employed as twice-a-day oral controlled release dosage form. For F3 formulation, *in vitro* dissolution studies

indicated a steady state sustained release pattern throughout 12 hour of the study which was comparable to theoretical release profile. The result generated in this study showed that the profile and kinetics of drug release were functions of polymer type, polymer content, and physicochemical nature of the drug. Methocel K15M CR and Methocel K100LV CR in combination would be useful in the preparation of sustained release matrix tablets of Nifedipine with desired release profile.

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