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Formulation, characterization and *in vitro* evaluation of Diltiazem Hydrochloride matrix tablets

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Abstract

Matrix tablets of Diltiazem hydrochloride were developed by wet granulation method. Hydroxypropyl methylcellulose; HPMC K4M, HPMC K15M, HPMC K100M were used to prepare the matrix tablets. Na-carboxymethyl cellulose (NaCMC) and ethylcellulose were added to alter the drug release profile or the dimensional stability of the formulation. Formulations were evaluated for preformulation parameters, *in vitro* drug release profile and release kinetics. The formulations were found to have good preformulation characteristics. The release mechanism of Diltiazem hydrochloride from matrix tablets indicated anomalous (non-Fickian) transport mechanism. FTIR spectroscopy indicated the absence of any significant chemical interaction within dug and excipients. DSC studies revealed the presence of other excipients did not affect the drug nature and was well maintained in the selected formulation.

Key words: Matrix tablet, Fourier transforms infrared, Differential Scanning Calorimetry, non-Fickian, Diltiazem hydrochloride.

Introduction

In recent years oral controlled delivery systems have gained increased importance and interest since it is necessary to improve the systemic absorption of the drugs and patient compliance. In addition, controlled release (CR) systems maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs. This is always a challenge, especially when freely water-soluble drugs have to be addressed with constant release rate. Diltiazem hydrochloride (diltiazem HCl), a calcium channel blocker, is widely used in the management of angina pectoris and hypertension [1]. Because of its short biological half-life (3.5 h) and low oral bioavailability (40%) due to hepatic metabolism leading to high frequency drug dosing (Mazzo et al. 2005)[2], the continuous delivery of diltiazem HCl is required. There are several studies where the polymer type, the composition, and tablet characteristics have been studied in order to achieve the desired diltiazem HCl release profile [3-8]. However, matrix CR tablet formulations are the most fashionable and

straightforward to formulate on a commercial scale. A wide variety of polymer matrix systems have been used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Hydroxy propyl methyl cellulose (HPMC), a semisynthetic derivative of cellulose, is a swellable and hydrophilic polymer which has been used as the retarding polymer to sustain the release of several drugs [9-13] Matrix tablets prepared using HPMC on contact with dissolution media or gastric fluids gets hydrated to form a viscous gel layer through which drug will be released by diffusion and/or by erosion of the matrix [14]. However, the use of hydrophilic polymers alone for extending drug release for highly water-soluble drugs is limited due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it becomes essential to incorporate hydrophobic polymers in the matrix system. Among the different polymers, ethylcellulose [15] has been used successfully to formulate appropriate sustained release matrix formulations. The aim of the study was to design a sustained release matrix tablet capable of producing a 12 h sustained release profile for diltiazem HCl.

Materials and Methods

Materials

Diltiazem hydrochloride was obtained as a gift sample from Arvind Remedies, Pvt. Ltd., Thrivallur, Tamil Nadu. Hydroxypropyl methylcellulose (HPMC K4M, HPMC K100M, HPMC K15M) were kindly supplied as gift sample from Colorcon, Goa. Dibutyl pthlate was gifted by Crux fine Chemical, Ahmedabad, Ethylcellulose, Polyvinyl pyrollidone Sodium carboxymethyl cellulose (NaCMC), magnesium stearate and talc were purchased from SD fine chemicals, Mumbai.

Methods: *Preparation of tablets*

Diltiazem HCl, Na-CMC, Ethylcellulose, HPMC K4M, HPMC K100M and HPMC K15M were shifted through mesh no 80. The entire shifted ingredients were mixed thoroughly, for not less than 5 min, until uniformly mixed powder was achieved. Polyvinyl pyrrolidone (PVP K-30) was dissolved in Isopropyl alcohol (IPA) to prepare the solution and in the prepared solution Dibutly phthalate was added. This solution was used to get dough mass of mixed material. The produced dough mass was milled through sieve no 16 and dried by hot air dryer at 40˚C for 2 h to get dry granules and they were further passed through sieve no 18 to get uniform granules.

Table 1. Composition of the various matrix tablets prepared

Ingredients (mg/tablet)	Formulations					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Diltiazem HCl	90	90	90	90	90	90
HPMC-K100 M	15	75	100	115	144	135
HPMC-K15 M	15	35	15	-	-	-
HPMC-K4 M	15	42	35	-	-	-
Ethyl cellulose	12	15	17	-	20	20
Na-CMC	120	-	-	52	3	12

*All tablets contain dibutyl phthalate, polyvinyl pyrrolidone, talc and magnesium stearate 3 mg, 10 mg, 5 and 5 mg respectively. Tablet weight was maintained as 400 mg.

The resulting granules were mixed with magnesium stearate and talc. The lubricated granules were compressed into tablet using 11 mm standard concave punch with 10 station single

rotary Clit (Jemkay) machine and keeping average weight 400 mg. After compression weight variation, friability, hardness, dissolution and assay were carried out.

Prior to compression, granules were evaluated for their characteristic parameters, such as bulk density, tapped density, Carr's index and angle of repose [16] Carr's compressibility index was calculated from the bulk and tapped densities [17] using a tap density apparatus (Galaxy scientific equipments,India).

In vitro dissolution test

To understand the release profiles of the drug from the tablets, dissolution experiments were performed in simulated gastric (0.1 N HCl, i.e., pH 1.2) and intestinal (pH 7.4) conditions. The release of Diltiazem hydrochloride from the tablet was studied using USP XXIII paddle apparatus (Electrolab, Bangalore). Drug release profile was carried out in 750 ml of 0.1N HCl for 2 h and then in 900 ml of phosphate buffer solution (PBS) pH 7.4 maintained at 37 ± 0.5˚C temperature at 100 rpm. Ten ml of samples were withdrawn at predetermined time intervals of every 1 h upto 12 h. The samples were replaced by its equivalent volume of dissolution medium and were filtered through 0.45 µm Whatman filter paper and assayed at 237 nm by UV spectrophotometer (Shimadzu 1601, Japan).

Mechanism of the in vitro release

The drug release data were evaluated by the model-dependent (curve fitting) method. In the present study, the Korsmeyer-Peppas model describing drug release from polymeric system was used. This model takes into account that the drug release mechanism often deviates from the Fick's law and follows anomalous behavior described by the following equation [18]:

$$M_t/M_\infty = k.\ t^n \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where, M_t is the drug released at time t, M_∞ the quantity of drug released at infinite time, k the kinetic constant and n is the release exponent. The value of n is related to the geometrical shape of the delivery systems and determines the release mechanism.

The release data was further treated according to Higuchi equation:

$$Q = k.\ t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where, Q is the percent of drug released at time t and k is the kinetic constant.

The value of n in equation (1) determines the mechanism of drug release. When n approximates to 0.5, a Fickian/diffusion controlled release is implied, where 0.5<n<1.0 non-Fickian transport and for n=1 zero order (case II transport). When n approaches 1.0, phenomenologically one may conclude that the release is approaching zero order [19].

Fourier transform infrared spectroscopy (FTIR study)

Infrared spectrum was taken (FT-IR, 410, Jasco) by scanning the sample in potassium bromide discs. The samples of pure drug and physical mixture containing different polymers and excipients were scanned individually.

Differential Scanning Calorimetry (DSC)

The DSC analysis was carried out to identify the compatibility between the drug and other excipients. DSC scans of about 10 mg, accurately weighed Diltiazem HCl and Formulation F6 were performed by using an automatic thermal analyzer system (DSC 60, Shimadzu, Japan) with TDS tread line software. Sealed aluminum-lead pans were used in the

experiments for all the samples. All the samples were run at a scanning rate of 10 °C/min from 50-350 °C [20].

Results and Discussion

Compressibility, flow property and angle of repose

Prior to compression, granules were evaluated for their characteristic parameters. The bulk densities for the powders of various formulations ranged between 0.516 ± 0.81 gm/ml and 1.627 ± 0.86 gm/ml, as determined by the tap method. This value of bulk density indicates of good packing character. The compressibility index (CI) for all the formulations was found to be below 17 %, indicating desirable flow properties [15]. The flow properties of granules were further analyzed by determining the angle of repose for all granules; it ranged between 27.85° ± 0.96° to 30.26° ± 0.82°. The value indicates good flow property (Martin et al. 2002)[16] of powders.

In vitro drug release

Fig. 1 shows the release profile of all six formulations. All the developed formulations were able to efficiently control Diltiazem HCl release over a time period of 12 h. Formulations F1 showed the release of drug 69.53 ± 2.11 % at the end of 12 h. In F1, 120 mg of NaCMC, 15 mg each of HPMC K4M, HPMC K100M and HPMC K15M, and 20 mg of EC were used. The matrix formed by this combination was so firm that after 12 h complete release of drug was not achieved. In F2 and F3 NaCMC was removed and the combinations were used as shown in Table 1. In these cases also, drug was not completely released after 12 h and showed release of only 80.66 ± 2.51 % and 75.27 ± 3.02 % respectively. In formulations F4 only HPMC K4M and NaCMC were used in quantities of 115 mg and 52 mg respectively. In this formulation drug release obtained after 12 h was higher than previous formulations F1, F2 and F3 but was obtained only 88.7 ± 2.65 % and also failed to complete release. In formulation F5, 144 mg HPMC K4M and 20 mg ethylcellulose were used along with 3 mg of NaCMC and this formulation showed only 83.05 ± 4.01 % drug release.

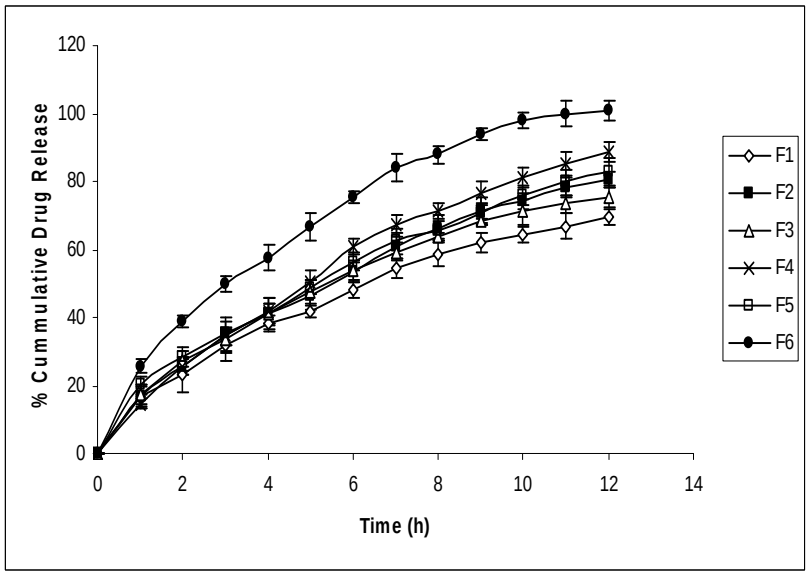

Figure 1. *In vitro* dissolution profile of Diltiazem HCl from formulations F1-F6 (n=3 ± S.D.)

Mechanism of drug release

The reduced release rate was due to the presence of hydrophobic polymer ethylcellolose. In formulation F6 the amounts of HPMC K4M was reduced and NaCMC was increased and taken 135 mg and 12 mg respectively with ethylcellulose 20 mg. In this formulation complete release of drug was obtained of 100.9 ± 2.86 %. So formulation F6 was considered as optimized formulation and further studies of it were carried out.

The drug release data were fitted in various mathematical models. As shown in table 2, the n value for these formulations ranged from 0.5683 to 0.7316 indicating that the release mechanism of propranolol HCl from these formulations is anomalous (non- Fickian). This means that both, drug diffusion from the gelled matrix as well as polymer chain relaxation process were responsible for the drug release [18].

Table 2. Model fitting for the formulations F1-F6

Sl. No	Formulation	Zero Order	First Order	Higuchi	Korsemeyer-Peppas	
		R^2	R^2	R^2	n	R^2
1	F1	0.9441	0.9927	0.9925	0.5941	0.9955
2	F2	0.9610	0.9967	0.9877	0.6479	0.9978
3	F3	0.9402	0.9952	0.9925	0.6038	0.9962
4	F4	0.9647	0.989	0.9798	0.7316	0.9951
5	F5	0.9586	0.9927	0.9913	0.5899	0.9957
6	F6	0.9207	0.7827	0.9927	0.5683	0.9942

FTIR study

Drug polymer interaction was checked by comparing the IR spectra of the physical mixture of drug with the excipients used with the IR spectrum of pure drug. IR Spectral assignments for Diltiazem HCl reveals that it gives characteristic peaks at 3056 cm^{-1}, 3035 cm^{-1}, 2966 cm^{-1}, 2837 cm^{-1}, 2393 cm^{-1}, 1740 cm^{-1}, 1679 cm^{-1}, 839 cm^{-1}, and 781 cm^{-1} frequencies in the region of 400 cm^{-1} to 4000 cm^{-1}. Frequencies of functional groups of pure drug remained intact in physical mixture containing different polymers (figure 2); so it was concluded that there was no major interaction occured between the drug and excipients used in the study. This established the stability of the drug in the formulation which was further confirmed by Differential Scanning Calorimetry (DSC) thermograms.

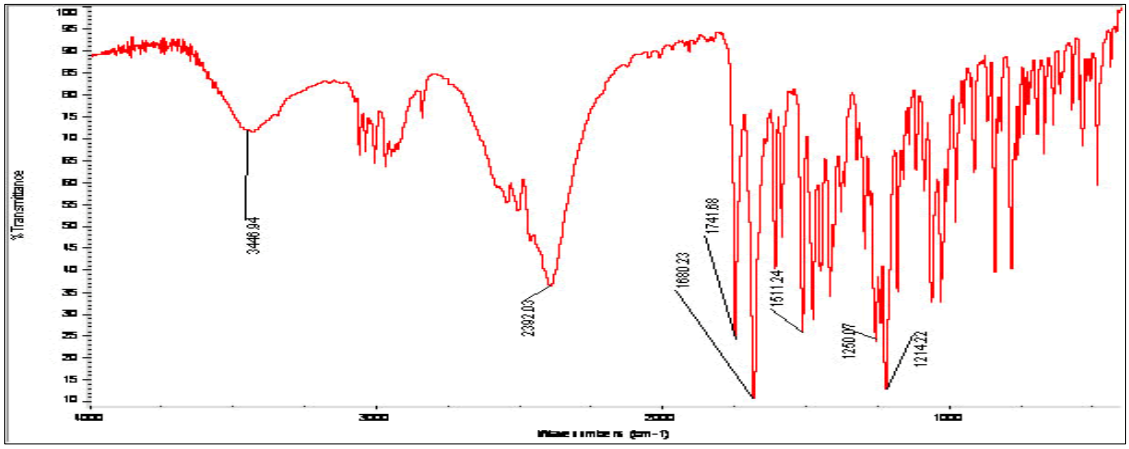

Figure 2. FTIR spectrum of physical mixture of Diltiazem HCl with excipients used.

Differential Scanning Calorimetry (DSC)

Thermograms of the pure drug and the formulation F6 are shown in figures 3. A sharp melting transition of Diltiazem hydrochloride pure drug was observed at 216.20˚C. In formulation F6 melting endotherm at 214.08˚C was observed. This confirmed that the presence of other excipients did not affect the drug nature and it was well maintained in the selected formulation. (Vaghani et al. 2008)[20].

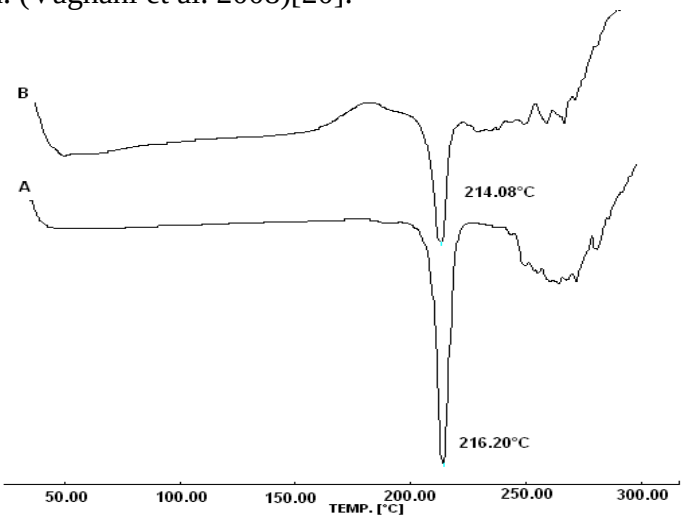

Figure 3. DSC of, A) pure drug Diltiazem HCl and B) Formulation F6

Conclusion

To achieve a sustained release formulation of diltiazem hydrochloride, matrix tablets were developed to be capable to provide prolonged release patterns over 12 h. Formulation containing HPMC K4M, ethylcellulose and Na-CMC was found to satisfy the desired criteria when used in the quantity given for formulation F6. The dissolution profile revealed the dissolution was dependent on type and solubility of polymers. A non- Fickian diffusion was confirmed as the drug release mechanism for these formulations. This meant that water diffusion and polymer rearrangement have essential roles in the drug release.

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