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DESIGN AND EVALUATION OF MATRIX TABLETS OF DILTIAZEM HYDROCHLORIDE

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ABSTRACT

Delayed release matrix tablets of diltiazem hydrochloride were developed employing combination of hydroxypropyl methyl cellulose and stearic acid as the matrix materials in different proportions. Tablets containing 90 mg of the drug were formulated and made by entrapping the drug in a waxy carrier and then by the conventional wet granulation method. Granules prepared were evaluated for loose bulk density, tapped density, compressibility index, Hausner ratio, angle of repose and by determining the constants from a Kawakita plot. The prepared tablets were found to be of optimum hardness, uniform weight and acceptable friability. The release was found to be dependent on the relative proportion of hydroxyl propyl methyl cellulose and stearic acid. Kinetics of the drug release data was evaluated out by employing the relevant equations of first order, zero order, Higuchi square root and korsmeyer-Peppas. The drug release data suggested that the release of the drug is first order and that the drug release is diffusion controlled.

Key words: Diltiazem hydrochloride, Wax matrices, Controlled release, Combined polymers, Kawakita plot.

INTRODUCTION

Diltiazem hydrochloride is a calcium channel blocker, which has been used in the treatment of various cardiovascular disorders, particularly angina pectoris and systemic hypertension[1]. It has a short biological half life[2] of about 3.5 h and is rapidly eliminated. The oral bioavailability of diltiazem is 40% in humans[3]. Because of its low bioavailability and short biological half life, controlled release formulations are needed for diltiazem for extended clinical effects and reducing dosing frequency. As diltiazem hydrochloride is a highly water soluble drug, its formulations into sustained release products is rather difficult. Hydroxypropyl methyl cellulose (HPMC) is a very commonly employed material for the

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preparation of matrix tablets but when employed alone, it is not quite efficient in controlling the release of highly water soluble drugs.

Waxes have been extensively investigated for sustaining the release of drugs. Hydrophobic polymers (waxes) provide several advantages that include good stability at varying pH and moisture levels and effective retardation of highly water-soluble drug from the matrix[4]. In forming a wax matrix system, different processing methods such as dry blending (direct compression), wet granulation, melt granulation and extrusion spheronization are used. In the present study, the water soluble drug is first incorporated in a wax matrix by melt granulation principle and this matrix is subsequently granulated with the hydrophilic polymer HPMC. In this study, it is considered that a combination of the 2 polymers (hydrophobic stearic acid and hydrophilic hydroxyl propyl methyl cellulose) to prepare the matrix tablets will result in a desired slow release profile.

EXPERIMENTAL

Materials and methods

Diltiazem hydrochloride is a gift sample from Tablets India ltd, Chennai; HPMC (HPMC K4M) was obtained as gift samples from Colorcon Asia Pvt Ltd, Mumbai. All other excipients were purchased from M/s. Loba Chemicals, Mumbai. All the solvents and other chemicals are of analytical grade.

Preparation of matrix tablets

The tablets (batch size of 50 tablets) were prepared as per the formula given in Table 1.

Table 1: Details of matrix formulations prepared

Name of the ingredients (mg)	F1	F2	F3	F4	F5	F6
Diltiazem hydrochloride	90	90	90	90	90	90
Stearic acid	25	25	25	37.5	37.5	37.5
HPMC	37.5	75	150	37.5	75	150
Lactose	267.5	230	155	255	217.5	142.5
PVP	20	20	20	20	20	20
Mg stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5

Preparation of wax matrices

Initially, stearic acid is taken in a porcelain dish on a water bath and heated at a temperature of 75^{o}C. In the molten mass, the drug diltiazem hydrochloride is dispersed. The mixture is allowed to cool and solidified at room temperature. The solidified mass is pulverized in mortar and sieved through a 100 # screen.

Preparation of granules by wet granulation

The drug dispersed in the molten matrix is now blended with other accurately weighted ingredients as shown in the Table 1. The blend is now wetted with a solution (1%) of polyvinyl pyrrolidone in isopropyl alcohol as granulating fluid. The cohesive mass obtained is passed through mesh No. 12. The granules obtained are then air dried at room temperature. The coarse granules thus obtained were once again sieved to get more uniform sized granules. Talc and magnesium stearate are now added and blended uniformly and then the granules are compressed employing 10 mm diameter flat punches using a rotary 16 station tablet punching machine. Each tablet is prepared to contain 90 mg of diltiazem hydrochloride.

Evaluation of wax matrices and granules

The flow properties of the prepared wax matrices and the granules were evaluated by determining the bulk density, tapped density, compressibility index (Carr index), angle of repose and Hausner ratio. The flowability and compaction behavior of the granules were also studied by using Kawakita plot.

Evaluation of tablets

The matrix tablets prepared were evaluated for hardness, weight variation, friability and drug content. Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Weight variation test was carried out by following the official procedure[5].

Content of the active ingredient is determined by taking five tablets, which were powdered in a mortar. From this powder, equivalent to 90 mg of drug was taken in a 100 mL volumetric flask and the volume was made up to 100 mL with phosphate buffer pH 7.4. The powder is shaken with the buffer for 2 hours and appropriate dilutions were made and the absorbance was measured at 240 nm against blank employing Elico (Model SL 159) double beam UV spectrophotometer.

This method of estimation followed Beer – Lambert's law in the concentration range of 10-40 µg/mL. Diltiazem hydrochloride, when estimated in distilled water, 0.1N HCl and in phosphate buffer (pH 7.4) repeatedly (n = 6). The relative error and standard deviation were found to be within limits. The excipients did not have any interference with this method of drug content determination.

In vitro drug release study

Drug release study from the matrix tablets was made in 0.1 N HCl (for first 2 hours) and in phosphate buffer of pH 7.4, (for the remaining period) employing USP XXIV Type I dissolution rate test apparatus (Lab India Model). A speed of 50 rpm, temperature of 37^{o}C and volume of 900 mL dissolution medium were employed in each study. 5 mL samples were withdrawn using 0.45 micron filter at various time intervals and the same volume of the medium is replaced. Samples were suitably diluted and assayed for diltiazem hydrochloride by measuring the absorbance at 240 nm employing Elico (Model SL 159) double beam UV spectrophotometer. The dissolution studies were carried out in triplicate.

RESULTS AND DISCUSSION

Formulation of matrix blend and the granules is an important aspect of preparation of matrix tablets for extended release. It is essential that the drug release from the matrix is controlled efficiently. Combined polymers-a waxy material and a hydrophilic matrix former are employed in the present study. A novel approach is first embedding the drug in the hydrophobic material by dispersing the drug in the molten wax material and subsequently blending the dispersion with hydrophilic matrix former HPMC to form the granules employed in this study. The drug-wax dispersions should be easily handled during manufacture, while the powders are being converted into granules. This is evaluated from the study of the flow properties as follows :

The flow properties of the various wax matrices prepared were studied by determining the bulk density, tapped density, compressibility index (Carr index), angle of repose and Hausner ratio. The values are reported in the Table 2. The data given in the table indicate that the flow properties of the wax matrices are satisfactory[6]. The corresponding values for the prepared granules are also shown in the Table 2. Angle of repose and compressibility index values for all granules ranged from 19.65 to 23.45 and 21.15 to 23.32, respectively. These values suggested good flow properties for the granules prepared.

Table 2: Flow properties of wax matrices and granules

	F1 Wax matrix	F1 Granules	F2 Wax matrix	F2 Granules	F3 Wax matrix	F3 Granules
Bulk density (g/cc)	0.495	0.535	0.527	0.556	0.515	0.528
Tapped density	0.630	0.712	0.712	0.733	0.713	0.756
Carr index	28.57	21.21	28.27	23.23	28.15	22.56
Hausner ratio	1.42	1.23	1.38	1.33	1.39	1.28
Angle of repose	29.31	23.54	29.05	19.66	27.75	22.45

The flowability and compaction behavior of the granules was also studied by using Kawakita plot[7]. The reduction in volume after tapping (using measuring cylinder) was noted. The plot of number of tapings vs the degree of volume reduction was plotted and the values of ‘a’ and ‘b’ were calculated by using equation-

$$N/C = N/a + 1/ab$$

Here: a = Carr's index and b = Constant related to cohesiveness and shear strength.

Where, ‘n’ is the number of tapping and ‘c’ is the degree of volume reduction equal to $C = (V_o - V_{oo})/V_o$

Where, V_o is initial volume before tapping and V_{oo} is volume after tapping.

Kawakita plot is used to analyze the behavior of powder from the bulk density state to the tap density state. The constants ‘a’ and ‘b’ of Kawakita plot were determined from the slope and intercept of graph of n/c versus number of tapping. The value of ‘a’ indicates compressibility or densification due to tapping and ‘b’ indicated good flowability and small cohesiveness. The results of the Kawakita plot are shown in Table 3.

Table 3: Flow properties of wax matrices and granules

	F4 Wax matrix	F4 Granules	F5 Wax matrix	F5 Granules	F6 Wax matrix	F6 Granules
Bulk density (g/cc)	0.513	0.535	0.527	0.556	0.515	0.523
Tapped density	0.725	0.712	0.712	0.733	0.713	0.789
Carr index	27.76	21.68	28.27	20.56	28.15	21.16
Hausner ratio	1.39	1.23	1.38	1.33	1.39	1.22
Angle of repose	29.81	20.94	29.05	20.73	27.75	20.75

The various prepared tablets were evaluated with respect to their hardness, friability, drug content and weight variation. The hardness of tablets of all formulations was in the range of 5.6 ± 0.57 Kg/cm^2.

The friability of tablets of all formations was in the range of 2.5 ± 0.01 to 0.35 ± 0.03 % i.e. less than 1%. The tablet formulations in all the prepared batches contained diltiazem hydrochloride within 100 ± 5% of expected hardness, friability and drug content. All tablets complied with pharmacopoeial specifications for weight variation.

The drug release is found to be slow and extended over a period of 12 hours. The drug release profiles of different matrix tablets are shown in Fig. 1. It was observed that in case of matrix tablets with a fixed amount of waxy polymer and increasing proportion of hydrophilic polymer, there is only a small decrease in the release rate; whereas with higher amount of the wax, there is a considerable decrease in the release rate with a similar raise in HPMC proportion. For example in case of formulations F1 and F2, the percent released at various times is higher than that of formulations F4 and F5, which indicated that waxy polymers are quite effective in controlling the release. However, it is to be noted that with smaller proportion of stearic acid but higher amount of HPMC (as in F2), the release is found to be same as that of F5, which shows that it is not only the hydrophobic carrier that influences the release rate but the hydrophilic matrix former can also significantly retard the release in combination with a waxy matrix former. The use of hydrophilic polymer alone for controlling the release of highly water soluble drugs is probably restricted due to the high and rapid diffusion of the highly soluble drug through the gel layer formed. Employing hydrophobic polymers will retard the drug release of such drugs with high water solubility.

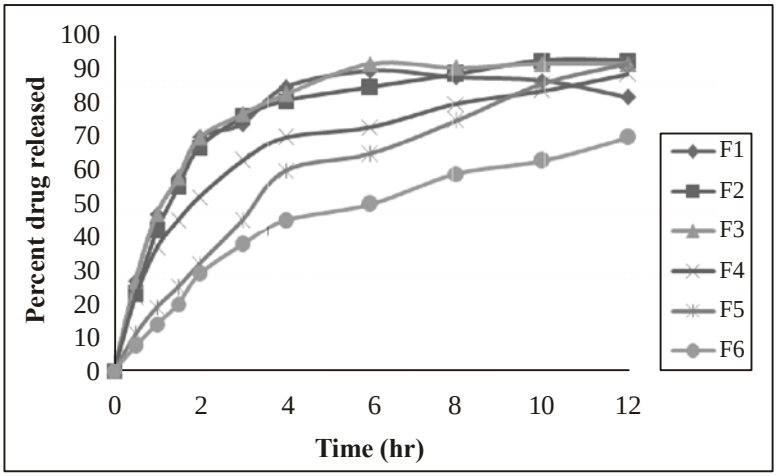

Fig. 1: Drug release profiles from various formulations

The presence of stearic acid, the waxy polymer, provides a complimentary environment in controlling the drug release. The drug particles in the waxy dispersion (which is blended with HPMC to prepare the granules) are probably surrounded by stearic acid resulting in lowered water penetration into the core of the matrix tablet; thus, retarding the release further.

Table 4: Values m, a and b from Kawakita plots

Formulation	m (slope)	a	b
F1	3.9512	0.3465	0.4256
F2	4.2794	0.3261	0.4331
F3	4.9912	0.2976	0.3965
F4	6.8245	0.2516	0.4286
F5	7.7870	0.2413	0.4296
F6	8.1240	0.1956	0.4462

To know the mechanism of drug release from these formulations, the data were treated according to first-order (log cumulative percentage of drug remaining versus time), Higuchi's (cumulative percentage of drug released versus square root of time), and Korsmeyer's (log M_t/M_{oo} vs log time) equations, along with zero order (cumulative amount of drug released versus time) pattern. The release rate kinetic data for all the equations are given in Table 5. When the data were plotted according to the zero-order equation, the formulations showed linearity with correlation coefficient values between (0.8383 and 0.9337). When the data were plotted according to the first-order equation, the formulations showed a good linearity, with significantly higher correlation coefficient values than the zero order plots, (0.9799 to 0.9913). Although, it is desirable for a controlled release device to deliver the drug in zero-order kinetics, it is extremely difficult to attain such pattern as the kinetics of release is affected by the physico-chemical composition of surrounding medium and processing variables. The release from all the products in this study could be expressed by Higuchi's diffusion equation as the plots of the amount released vs the square root of time showed a good linearity (Fig. 2).

The matrix system employed here is a combination of hydrophilic swellable polymer and a hydrophobic wax based on stearic acid. According to the n values (between 0.5 and 1), obtained in the Peppas plot (Table 5), one may conclude that the drug release is controlled by both; diffusion of the drug through the hydrated matrix and the erosion of the matrix

itself, that is, a non-Fickian (anomalous) solute diffusion mechanism. This sort of release behavior is reported for similar wax matrices previously by Lourdes et al.[8]

Table 5: Drug release kinetic parameters of different formulations

Product	Zero order		First order		Higuchi plot		Peppas plot	
	K_0	R	K_1	R	K_H	R	n	R
F1	5.5	0.8383	0.23	0.9799	41.98	0.9123	0.75	0.9223
F2	7.3	0.8564	0.25	0.9866	30.04	0.9567	0.77	0.9867
F3	5.7	0.9124	0.12	0.9902	22.56	0.9934	0.76	0.9932
F4	6.4	0.9187	0.16	0.9876	26.87	0.9732	0.65	0.9775
F5	5.6	0.9215	0.12	0.9913	20.87	0.9986	0.83	0.9923
F6	4.8	0.9337	0.05	0.9854	18.21	0.9954	0.87	0.9843

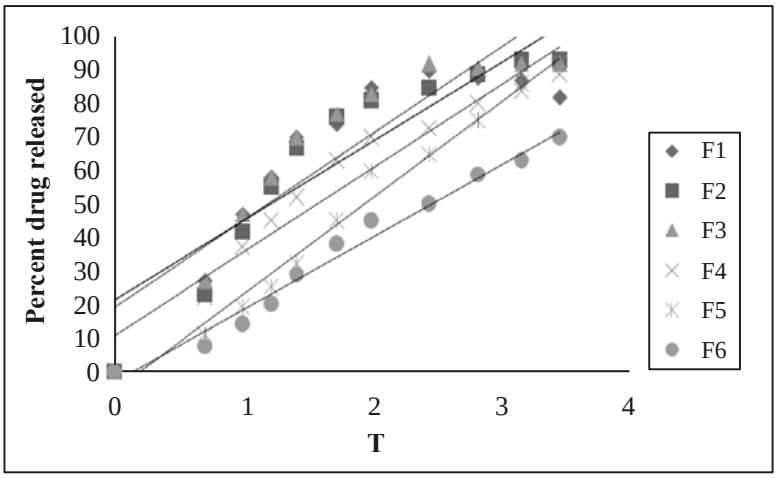

Fig. 2: Plot of percent drug released vs √ T

CONCLUSION

From the results of the present study, it could be concluded that a slow and sustained release spread over a period of 12 hours, of the water soluble drug diltiazem hydrochloride can be obtained by employing a combination of release retarding materials – a hydrophobic stearic acid and a hydrophilic HPMC. Changes in the nature of the matrix material will significantly influence the release of water soluble drugs. It was observed that an optimum

combination will result in the desired release spread over 12 hours. Compared to F1 and F6, which had lowest and the highest amounts of the 2 matrix formers giving relatively very high and slow release rate, respectively; F5 gave a release profile, which is slow and sustained over a period of 12 hours.

Thus, the ratios of the wax and hydrophilic material can be suitably modified to obtain a complete and controlled release of the water soluble drug diltiazem hydrochloride from the matrix tablets.

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