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Research Article

Design, development and evaluation of trimetazidine dihydrochloride sustained release matrix tablets

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ABSTRACT

This work aims at investigating the use of natural gum locust bean gum as matrix agent in an attempt to formulate sustained release matrix tablets containing trimetazidine dihydrochloride. The sustained release (SR) tablets of trimetazidine dihydrochloride were prepared by direct compression method. The excipients used in this study did not alter the physicochemical properties of drug, as tested by the FTIR spectrometry. The prepared matrix tablets showed good mechanical properties in terms of hardness and friability. Locust bean gum based tablet formulations alone showed high release retarding efficiency as compared to immediate release formulation. The *in vitro* release studies indicated that the drug release can be modulated by varying concentrations of polymer. Mathematical analysis of the release kinetics indicated the nature of drug release from optimized formulation matrix tablets followed non-fickian diffusion obeying first order kinetics.

Keywords: Trimetazidine dihydrochloride; sustained release; locust bean gum; hydrophilic matrix; drug excipient compatibility.

INTRODUCTION

Increased complications and expenses incurred in marketing of new drug entities, has focused greater attention on the development of sustained release or controlled release drug delivery systems (Talulkdar MM et al., 1986).Among these delivery system, matrix system is the most innumerable method employed in the development of sustained release formulation. It is the system, which prolongs and controls the release of drug that is dissolved or dispersed. In fact, a matrix is defined as a well composite of one or more drugs with a gelling agent i.e hydrophilic polymer (Salsa T et al., 1997). Hydrophilic matrix are an interesting option when developing an oral sustained release formulation. They can be used for the development of controlled release of both water soluble and water insoluble drugs. The release behavior of the drugs varies with the nature of matrix and it is the complex interaction of swelling, diffusion and erosion process (Colombo P et al., 1995). Release of drugs from such matrices is governed by their physical properties, choice of gelling agent and setting up the conditions for fabrication (Vazquez MJ., 1992)

Among hydrophilic polymers, polysaccharides are the choice material due to their non-toxicity and wide regulatory acceptance (Bhardwaj TP et al., 2000. Billa N et al., 2000.Munday DL et al.,2000) Polysaccharides like cellulose ethers, locust bean gum, scleroglucan and guar gum are some of the natural polysaccharides which have been evaluated in hydrophilic matrix for drug delivery system (Ford JL et al., 1987.Risk S et al.,1994.Sujja Areewath J et al., 1996.).

Locust bean gum (LBG) is a plant seed galactomannan, composed of a 1-4 linked β-D-mannan back bone with 1-6-linked α-D-galactose side groups (Khullar P et al1998). It is a nonionic molecule consisting of nearly 2000 residues and similar to that of guar gum but less soluble and less viscous. In LBG, the ratio of mannose and galactose is higher than guar gum. It is not affected by ionic strength or pH, but will degrade at extreme pH and high temperature. The physicochemical properties of galactomannan are strongly influenced by galactose content and distribution of galactose units along the main chain. LBG structure contains long stretches of bare mannose backbone which is responsible for synergistic interactions with other polymers and greater functionality. Locust bean gum is also used in the

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Table 1: Composition of Trimetazidine dihydrochloride Sustained Release Tablets

Fa	Trimetazidine dihydrochloride	Locust bean gum gum	Avicel PH 101	Magnesium Stearate	Aerosil	Total weight (mg)
F-1	60	7.5	129.5	2	1	200
F-2	60	15	122	2	1	200
F-3	60	22.5	114.5	2	1	200
F-4	60	30	107	2	1	200
F-5	60	37.5	99.5	2	1	200
F-6	60	45	92	2	1	200
F-7	60	52.5	84.5	2	1	200

Fa – Code of formulations

(F-1-3.75%, F-2-7.5% and F-3-11% F-4-15%, F-5-19% F-6-23% and F-7-27 w/w)- Developed sustained release tablets with varying concentrations of locust bean gum.

treatment of elevated plasma cholesterol in healthy subjects (Dea ICM et al., 1975.Krishnaiah YSR et al., 2002. Morris ER 1990).

Trimetazidine dihydrochloride a piperazine derivative used in the treatment of angina (Launay B et al.,1986) and it is characterized by the rapid clearance due to shorter half-life. Therefore, a sustained release formulation for prolonged action is needed to improve the patient compliance. Hence, the purpose of our present study was to investigate the *in vitro* performance of compressed matrix tablets prepared by direct compression of hydrophilic polymeric substance locust bean gum to produce a sustained release dosage form containing trimetazidine dihydrochloride. The effect of polymer concentration on the *in vitro* release rates were also proposed to be studied.

MATERIALS AND METHODS

Trimetazidine dihydrochloride was obtained as a gift sample from Cipla Ltd, Mumbai. Locust bean gum was obtained as gift sample from Kathago Ltd, Bangalore, India. Microcrystalline cellulose (Avicel PH 101) was a gift from Signet Chemicals, Mumbai and Aerosil was procured from Degussa Ltd, Mumbai. All other chemicals used in the study were of analytical or HPLC grade.

Drug–Excipients Interactions

The physicochemical compatibilities of the drug and excipients were tested by FTIR spectrometry. FTIR spectras of the drug alone and drug-excipient physical mixtures (1:1 w/w) were derived from a Schimadzu FTIR.

Development of trimetazidine dihydrochloride sustained release (SR) tablets

Sustained release matrix tablets of trimetazidine dihydrochloride were prepared by using drug and different gum ratios viz (F-1-3.75%, F-2-7.5% and F-3-11% F-4-15%, F-5-19% F-6-23% and F-7-27 w/w). Locust bean gum was used as matrix forming material, while microcrystalline cellulose was used as diluent. Magnesium stearate and aerosol was incorporated as lubricants. All the ingredients were screened through a #120 sieve, weighed and blended. The lubricated formulations were compressed by a direct compression technique using 8 mm concave punches on a 10 station rotary tablet press (Rimek, Ahmedabad, India) and the compression force of a 9 KN (preliminary work) or 12 KN (experimental design) was kept for all the formulations. For the preliminary work, batches of 50 tablets were prepared (drug content in the tablet was 60 mg). The composition of trimetazidine dihydrochloride sustained release tablets are given in table 1.

Evaluation of Granules

Angle of Repose

Static angle of repose of powder were determined by the fixed funnel method. The accurately weighed powders were taken in the funnel. The height of funnel was adjusted in such a way that a tip of funnel just touched the apex of heap of the powder. The powders were allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation (Waskell WL et al., 1992)

$$\tan \theta = h/r \qquad (1)$$

Where 'h' and 'r' are the height and radius of powder cone.

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity (2 gm) of granules from each formula, previously lightly shaken to break any agglomerates formed was introduced into a 10 mL measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own height onto a hard surface from a height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in the volume was noted. LBD and TBD were calculated using the following formulas (Cooper J et al., 1986).

LBD= Weight of the powder/volume of the packing (2)

TBD= Weight of the powder/tapped volume of the packing (3)

Compressibility Index

The compressibility index of powder was determined by Carr's compressibility index(Shah D et al., 1997).

$$\text{Carr's index (\%)} = [(TBD-LBD)\times 100]/TBD \quad (4)$$

Hausner's Factor

Hausner found that the ratio D_F/D_O was related to interparticle friction and, as such, could be used to predict powder flow properties (Aulton ME et al 1988).

$$\text{Hausner's Factor} = D_F/D_O \quad (5)$$

Where '$D_F^{'}$ is tapped bulk density and '$D_O^{'}$ is loose bulk density

Evaluation of Tablets

Thickness

The thickness of formulated tablets was determined using digital caliper (Mitutoyo, Japan). Five tablets from different formulations were used and their average values were reported in millimeters. Mean and SD were calculated.

Weight Variation Test

To study weight variation, twenty tablets of different formulations were weighed using an electronic balance (Sartorius AG, Goettingen, Germany). Weight values were reported in milligrams.

Hardness Test

For each formulation, the hardness of six tablets was determined using a hardness tester (Monsanto hardness tester, Cadmach machineries, Ahmedabad, India). Hardness values were reported in kilograms (Kg). .

Friability Test

For each formulation, six tablets were weighed. The tablets were placed in friabilator (Electrolab, Mumbai, India) and subjected to 100 rotations for 4 min. The tablets were then dedusted and reweighed. The friability was calculated as the percentage weight loss (Lachman L et al., 1987)

Friability = [Initial Weight-Final Weight×100]/ Initial Weight (6)

Drug Content

Five tablets from the individual formulations were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to 60 mg drug (200 mg of powder) was extracted with 100 ml of distilled water and sonicated for 15 min. The solution was filtered through a filter paper (Whatmann, 0.22 µm pore size), properly diluted with distilled water and drug content was measured at 243 nm using UV spectrophotometer (Schimadzu, Japan).

***In vitro* Release Studies**

Dissolution studies for the developed SR tablets were monitored. The release experiments were performed in a dissolution media consisted of 900 ml of distilled water maintained at 37°C ±0.5°C and stirred at 50 rpm, using USP dissolution apparatus under perfect sink conditions (Electrolab, Mumbai, India). 5 ml of sample was withdrawn through a 0.45 µm filter and replaced with another 5 mL of a suitable fresh dissolution medium maintained under the same conditions at preselected intervals up to 24 h. The amount of drug was determined as previously mentioned. Each test was conducted in triplicate (6 tablets in set) and the mean values were plotted against time with SD less than 3, indicating the reproducibility of results.

Release Kinetics

Different kinetic equations (zero order, first order and Higuchi's equations) were applied to interpret the release rate of drug from the matrix system. The best fit with higher correlation (r^2>0.98) was found with Higuchi's equation for all the formulations. Two factors, however, diminish the applicability of Higuchi's equation to matrix systems (Lachman L etal., 1987). This model fails to allow for the influence of swelling of the matrix (upon hydration) and gradual erosion of matrix. Therefore, the dissolution data were also fitted to the well-known exponential Koresmeyer – Peppas equation (Koresmeyer RW et al., 1983)

$$M_t/M_\alpha = kt^n \quad (7)$$

M_t/M_α is the fraction of drug release at time't', 'k' is the kinetic constant and 'n' is the release exponent (indicating release mechanism). In addition, for determination of exponent 'n', one must use only the initial portion of the release cure (M_t/M_α < 0.6) (Pharmacopoeia of India1996.Higuchi T. 1963). Ritger and Peppas (Peppas NA. 1985). have defined the exponent 'n' as a function of the aspect ratio (2a/l) defined as the ratio of diameter (2a) to thickness (l). For tablets, depending on the aspect ratios, 'n' values between 0.43 and 0.5 indicates Fickian (case I) diffusion mediated release, non-fickian (anomalous) release, coupled diffusion and polymer matrix relaxation occurs if 0.5<n<0.89, purely matrix relaxation or erosion-mediated release occurs for n=1 (zero order kinetics) and super case II type of release occurs for n>0.89. The release exponent, 'n' is the slope of log fraction of drug release against log time curve. This equation was successfully applied to evaluate the drug release mechanism from hydrophilic, wax and plastic matrix tablets (Peppas NA., 1985)

Due to the differences in drug release kinetics, the constant 'k', through one of the measures of release rate should not be used for comparison. Therefore, to characterize the drug release rates in different experimental conditions, mean dissolution time (MDT) was calculated using the following equation:

$$MDT = \frac{n \times k^{-1/n}}{n+1} \qquad (8)$$

Where 'n' is the release component and 'k' is the kinetic constant calculated from the equation (7).

RESULTS AND DISCUSSION

Drug-Excipients Interaction

Figure 1-3 shows FTIR spectras of trimetazidine dihydrochloride, trimetazidine dihydrochloride with polymer (locust bean gum gum 1:1 ratio w/w) and trimetazidine dihydrochloride matrix tablets with excipients used in the study. The characteristic peaks for trimetazidine dihydrochloride at 1087 (C-O), 1101 (C-N), 2987 (C-H) and 3443 (N-H) were found to appear in drug with polymer. Also, it was found that the characteristic spectra peaks of physical mixture of drug with locust bean gum, or other excipients reflected the characteristic features of trimetazidine dihydrochloride alone. Thus, it was thought to indicate there was no evidence of interactions between trimetazidine dihydrochloride and used excipients.

Physical properties of starting material

The powders were evaluated for angle of repose, loose bulk density (LBD), tapped bulk density (TBD), Carr's compressibility index and Hausner's Factor (HF). The

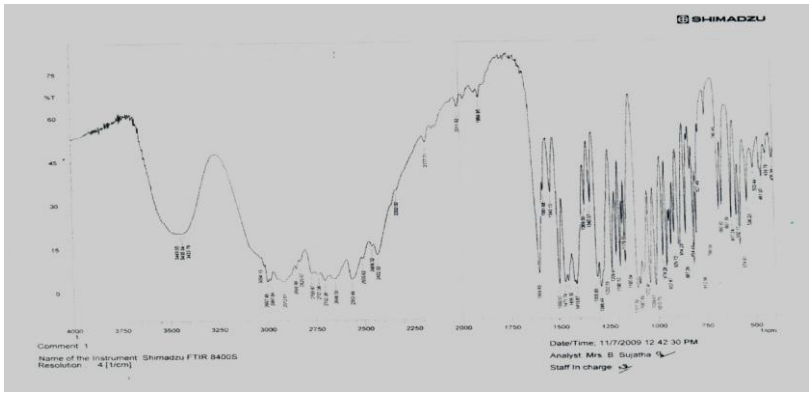

Figure 1: FT-IR Spectra of trimetazidine di hydrochloride

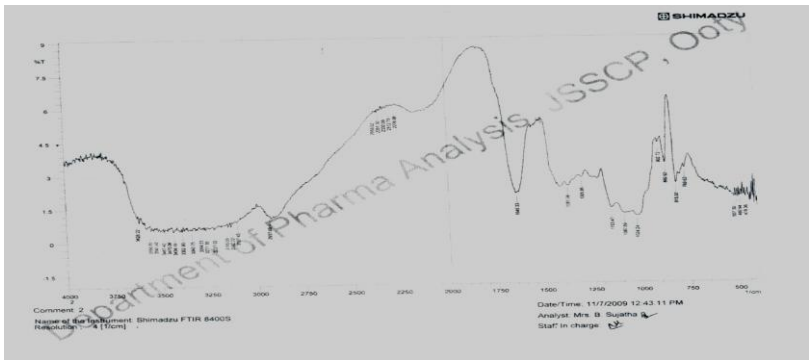

Figure 2: FT-IR Spectra of locust bean gum

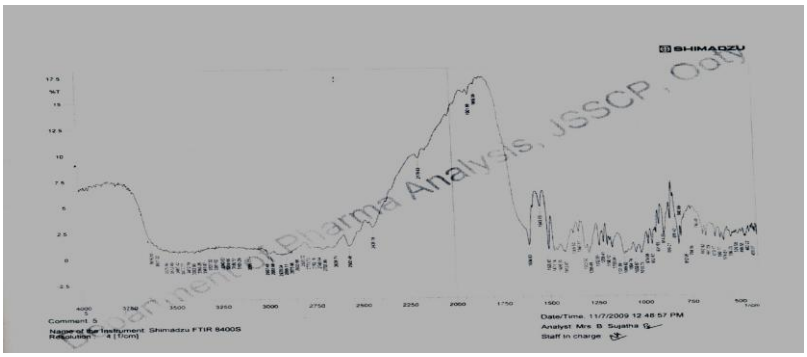

Figure 3: FT-IR Spectra of trimetazidine di hydrochloride and locust bean gum

values of prepared powders ranged from 20.4°± 1.9 to 26.4°± 1.8. HF values of the prepared granules/powders ranged from 1.18 to 1.27 (Table 2). The percentage compressibility, an indirect method of measuring powder flowability from bulk densities developed by Carr, was calculated according equation 4. From the table 2, it was observed that granules and powders exhibited good flowability and compressibili-

Table 2: Powder Properties of Different Formulations of Trimetazidine dihydrochloride

Fa	Angle of Repose (°)**	Loose Bulk Density (gm/cm^3)	Tapped Bulk Density (gm/cm^3)	Carr's Index (%)	Hausner Ratio
F-1	22.5±1.2	0.514±0.04	0.6±0.04	14.3±0.02	1.2
F-2	26.4±1.8	0.54±0.02	0.64±0.03	15.4±0.04	1.18
F-3	20.4±1.9	0.58±0.05	0.7±0.05	16.71±0.05	1.2
F-4	26.4±1.6	0.6±0.04	0.66±0.04	19.2±0.02	1.13
F-5	22.5±2.3	0.53±0.02	0.64±0.02	22.2±0.04	1.2
F-6	24.6±1.1	0.51±0.05	0.64±0.05	21.4±0.05	1.24
F-7	25.3±1.14	0.5±0.04	0.64±0.04	15.72±0.02	1.27

Fa – Code of formulations

(F-1-3.75%, F-2-7.5% and F-3-11% F-4-15%, F-5-19% F-6-23% and F-7-27 w/w of locust bean gum)

**All formulations represent mean ±SD (n=3)

Table 3: Tablet Properties of Different Formulations of Trimetazidine dihydrochloride

Fa	Weight (g) *n=20	Thickness (mm) n=5	Hardness (kg/cm3) n=6	Friability (%) n=6	Drug content (%) n=5
F-1	199.8±1.3	3.67±0.8	6±0.01	0.35±0.04	99.6±1.1
F-2	197.3±1.1	3.67±0.2	6±0.02	0.43±0.02	98.2±1.9
F-3	200.5±1.1	3.68±0.3	7±0.03	0.57±0.03	99.14±1.9
F-4	203.1±2.05	3.69±0.4	6±0.01	0.48±0.04	99.65±1.1
F-5	195.4±1.7	3.72±0.11	7±0.02	0.29±0.02	95.23±1.9
F-6	197.6±0.35	3.7±0.1	7±0.03	0.36±0.04	101.7±1.9
F-7	197.2±1.3	3.71±0.7	7±0.01	0.52±0.04	99.43±1.1

Fa – Code of formulations

(F-1-3.75%, F-2-7.5% and F-3-11% F-4-15%, F-5-19% F-6-23% and F-7-27 w/w of locust bean gum)

**All formulations represent mean ±SD (n=3)

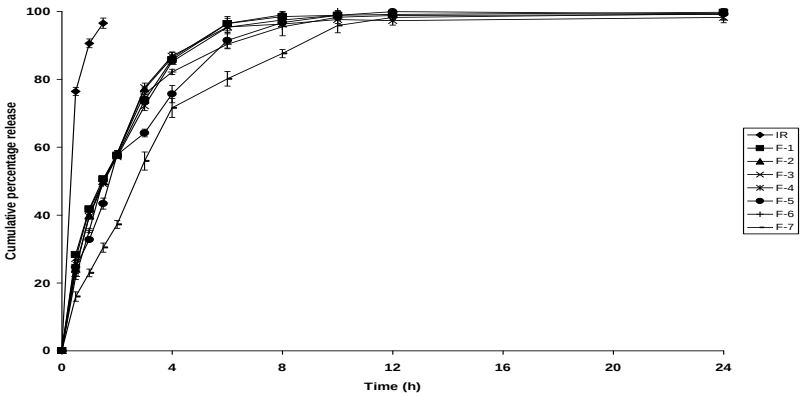

Figure 4: *In vitro* release profile of immediate release (IR) and trimetazidine dihydrochloride sustained release tablets

ty. Finally, both the polymer level did not affect the physical properties of powders markedly.

Physical Properties of Tablets

The compression force and physical properties of tablets are presented in table 3. These properties were studied by determining average weight, thickness, drug content, hardness and friability of prepared tablets, a relative SD of weight was under 3% and SDs were quite uniform, ranging from 0.35 to 2.05. It was also observed that the variation of thickness was minimal. The thickness of tablets ranged from 3.67±0.8 mm to 3.72 ± 0.11 mm. Also, it was observed that increasing the polymer concentrations resulted in no alteration in the thickness of tablet formulations. These results might indicate that the polymer does not alter the binding property of tablets. The friability of tablets fell into a range of 0.29 ± 0.02 to 0.57 ± 0.036 % respectively. The European pharmacopeia states that loss up to 1% is acceptable. There was no marked difference in the friability observed with tablets prepared using different polymer concentration. These findings were in good agreement with the results of thickness measurement, supporting the idea, that the used polymer does not

Table 4: Regression Coefficient (r2) of Trimetazidine dihydrochloride Data from Studied Matrices According to Different Kinetic Models, Diffusion Exponent (n) of Peppas Model and Mean Dissolution Time (MDT)

Fa	First order (r^2)	Higuchi (r^2)	Peppa's		MDT (h)
			n	(r^2)	
F-1	0.9192	0.8823	0.3469	0.9407	1.44
F-2	0.9969	0.9835	0.3943	0.9825	0.746
F-3	0.9971	0.9746	0.3943	0.9822	0.792
F-4	0.8472	0.8717	0.3678	0.9245	1.437
F-5	0.8251	0.9074	0.4013	0.9518	1.518
F-6	0.9026	0.8882	0.3959	0.9274	1.477
F-7	0.9582	0.9837	0.5348	0.9886	1.714

Fa – Code of formulation

(F-1-3.75%, F-2-7.5% and F-3-11% F-4-15%, F-5-19% F-6-23% and F-7-27 w/w of locust bean gum)

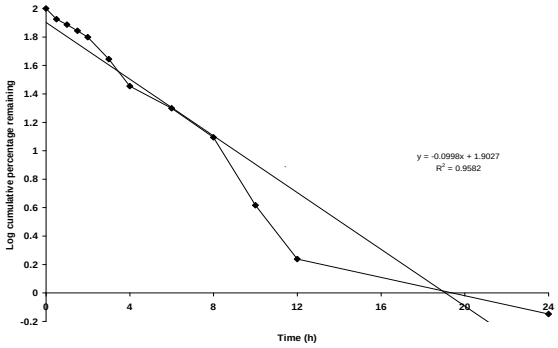

Figure 5: First order plot of trimetazidine dihydrochloride sustained release tablets (F-7)

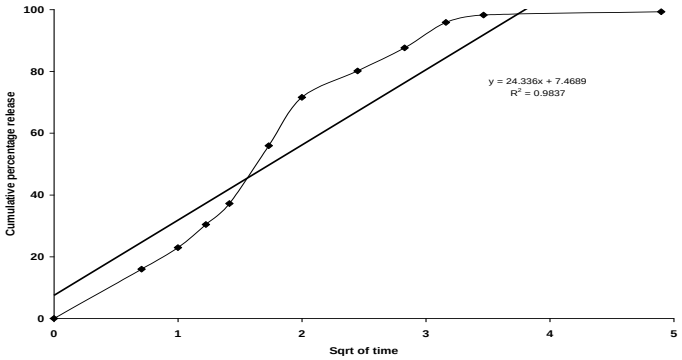

Figure 6: Higuchi's plot for trimetazidine dihydrochloride sustained release tablets (F-7)

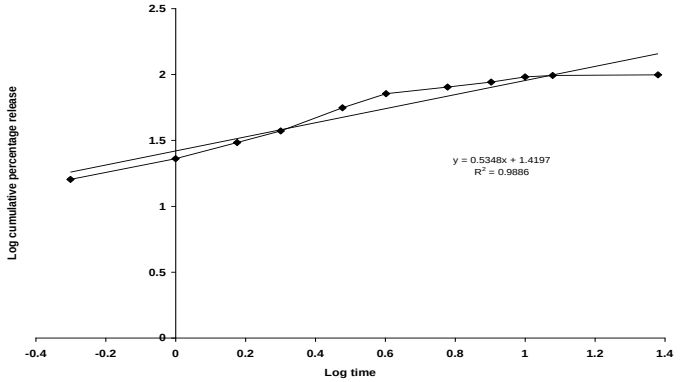

Figure 7: Peppa's plot for trimetazidine dihydrochloride sustained release tablets (F-7)

alter the binding properties. Hardness of tablets fell into the range of 6.00 ± 0.01 to 7.00 ± 0.03 kg/cm^2. These results also revealed that increasing polymer concentration does not alter the hardness of tablet significantly. These results were in good agreement with those of thickness and friability.

***In vitro* release studies**

Figure 4, shows the *in vitro* release profile of trimetazidine dihydrochloride from developed SR tablets. Generally, the drug release rates from developed SR tablets were significantly retarded as compared to the marketed conventional tablets. It is also noted that a drug release rate from locust bean gum based matrix tablets decreased with an increase in the polymer level. This effect might be ascribed to an increase in the extent of gel formation in the diffusion layer and better mechanical properties of locust bean gum.

Release Kinetics

The values of release exponent (n), kinetic constant (k), and MDT calculated from the equations 7 and 8 are presented in table 4. As observed from the table, correlation coefficients (r^2) of all formulation were high enough to evaluate the drug dissolution behavior using equation 8 (r^2= 0.912 -0.986). Irrespective of polymer level, the prepared hydrophilic tablet formulations exhibited non-fickian release, 0.5<n<0.89. Thus, it was proposed that the formulations delivered their active compound by coupled diffusion and erosion. When the hydrophilic matrix tablet enters an *in vitro* dissolution medium, drug particles initially pass into solution from the surface (immediate release). The solid matrix also begins to swell (polymer relaxation) as soon as hydration with solvent molecules, diffusion of the dissolved drug coupled with erosion of gelatinous viscous polymer layer into aggregates or granules, and this in turn deaggregate into fine particles that also release their drug content by dissolution. MDT is used to characterize the drug release rate from the dosage form and retarding efficiency of the polymer. A higher MDT indicates a higher drug retarding ability of the polymer and vice versa. The MDT value was found to be a function of polymer loading. Table 4 shows the higher the polymer level, the higher the values on MDT. These findings were in accordance those already reported by previous investigators (Ritger PL et al., 1985). They investigated the effect of plastic, hydrophilic and hydrophobic types of polymers, their constant level; and drugs of different aqueous solubility values on MDT. The studies showed that a direct relationship could be found with MDT value and polymer loading irrespective of drug and polymer type, and that this relationship was linear.

CONCLUSION

Formulation and evaluation of SR matrix tablets containing trimetazidine difydrochloride was found to be potential, cost effective and satisfactory *in vitro* release studies. In turn, it may enable to release the drug in a sustained manner for prolonged period of time and thereby accompanying some of the benefits like reduction in total dose, frequency of administration, dose related side effects and better patient compliance.

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