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EFFECT OF HYDROPHILIC AND HYDROPHOBIC POLYMERS ON RELEASE PROFILES OF TRIMTAZIDINE DI HYDROCHLORIDE FROM SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT
The current study aimed to develop a matrix type sustained release Trimtazidine dihydrochloride, using hydrophilic and hydrophobic polymer. Three different hydrophilic polymers, that is, HPMC K4M, HEC and Sodium CMC and Cetosteryl alcohol (CA) as hydrophobic polymer were used in various proportions as release controlling factor. Matrix tablets were prepared by melt granulation technique. The physicochemical properties of the granules and tablets were evaluated. *In vitro* dissolution studies of prepared matrix tablet were performed at pH 1.2 and pH 6.8 phosphate buffer at 75 rpm at 37 ± 0.5°C. The dissolution data were fitted to Zero‐order, First‐order, Higuchi, and Korsmeyer-Peppas' equations. The prepared matrix tablets were within house specifications for all the physicochemical properties. *In vitro* release data shows individual low polymer concentration of HPMC K4M, HEC and Sodium CMC with Cetosteryl alcohol sustain the drug release only up to 8hrs but at higher concentration of hydrophilic polymers with Cetosteryl alcohol sustained the drug release more than 12hrs. It was found that formulations containing CA with HPMC K4M showed better dissolution properties with respect to formulations containing HEC and Sodium CMC. Mathematical analysis of the release kinetics indicated that drug release mechanism was fickian diffusion. The present study demonstrated that Trimtazidine dihydrochloride, could be successfully prepared using an appropriate amount of HPMC K4M, HEC and Sodium CMC and CA in the form of matrix tablets.

Keywords: Trimetazidine dihydrochloride, HPMC K4M, HEC, Sodium CMC and Cetosteryl alcohol

INTRODUCTION
Angina pectoris is a characteristic sudden, severe, pressing chest pain radiating to the neck, jaw, back and arms. It is caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to ischemia [1].

Trimtazidine dihydrochloride is used therapeutically in the long term treatment of angina pectoris and it is freely soluble in water. Class III drug is administered orally in doses of 40 to 60mg daily in divided doses as an immediate release preparation. It is quickly absorbed and eliminated from the body with plasma half life of around 0.6 - 1.4 hours. Since it has a shorter plasma half life, in practice 20mg preparation is given twice or thrice a day in order to ensure relatively constant plasma levels but, due to the fact that it is absorbed quickly, these immediate release forms lead to maximum plasma levels immediately after administration and to a very low plasma level at the time of the next dose, resulting in great differences in peak and through plasma levels at steady state. Trimtazidine di hydrochloride is regarded as a safe drug in the long term treatment of chronic ischemic disorders. To reduce the frequency of administration and to improve patient compliance, sustained-release formulations of trimtazidine dihydrochloride are desirable[2]. Trimtazidine dihydrochloride is freely soluble in water, and hence judicious selection of release-retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug[3]. One of the most commonly used methods of modulating the drug release is either swellable hydrophilic polymers or nonswellable lipophilic excipients, like waxes and lipids. Lipophilic matrix agents were frequently used in the preparation of sustained release tablets. Wax matrix dosage forms are utilized to incorporate drugs into inert water-insoluble matrix materials.

Many types of matrix forms, including granules and tablets, have been tried in order to obtain effective sustained release. Waxy materials have major applications in sustained-release systems and the use of wax matrix appears to have several advantages such as being a multiple-unit system, chemical inertness against other materials, and ease of manufacturing with high reproducibility that can be obtained without special instrumentation, as well as low production cost. Moreover, as the matrix delivery system passes through the gastrointestinal

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tract, the active ingredient is slowly released and absorbed [4].

Thus, the current study investigated the development of a matrix type sustain release trimetazidine dihydrochloride tablet, using hydrophilic polymers such as HPMC, HEC, Sodium CMC and hydrophobic polymer cetosteryl alcohol. The physicochemical properties of the developed formulations such as hardness, thickness, friability, and *in vitro* drug release study were evaluated.

MATERIALS AND METHODS

A gift sample of Trimetazidine dihydrochloride was obtained from JPN Pharma Pvt Ltd Mumbai, India. HPMC K4M, HEC and Sodium CMC, Cetosteryl alcohol, Lactose and Talc from SD-fine chemicals limited and all other chemicals used were of analytical grade.

Drug-excipents compatibility studies:

FT-IR studies:

FTIR spectra help to confirm the identity of drug and to detect the interaction of the drug with the excipents. IR spectroscopy of pure trimetazidine dihydrochloride and physical mixture of it with polymers was carried out using shimadzu FTIR to check the compatibility between drug and polymers. The IR spectra of drug with polymers were compared with the IR spectrum of the pure trimetazidine dihydrochloride[5].

Differential scanning calorimeter:

Thermal properties of the powder samples were investigated with differential scanning calorimeter. DSC thermograms were taken for pure drug and respective physical mixtures with various polymers. The dynamic scans were taken in a nitrogen atmosphere at the heating rate of 10^0C/min with flow rate 10ml/min. DSC studies were routinely conduct of drug interaction in the formulations[5].

Formulation of tablets:

Trimetazidine dihydrochloride sustained release tablets were tablets were prepared by hot melt granulation. All ingredients were weighed accurately and passed through 80 mesh sieve. The cetosteryl alcohol was heated up to the 70^0C and the drug was added to molten wax at 50^0 C. The mixture was stirred continuously to get the solid soft mass which was passed through the 16 mesh sieve. The cetosteryl alcohol embedded drug were mixed with the rest of cellulose polymer as shown in table no.1 and passed through 22 mesh sieve and dried. Granules were mixed with weighed quantities of lactose and talc previously passed through 100 mesh sieves and compressed into tablets weighing 250 mg with a hardness of 4.5-6 kg/cm^2 [6].

Table 1: Composition Trimetazidine dihydrochloride sustained release tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Trimetazidine dihydrochloride	60	60	60	60	60	60
Cetosteryl alcohol	100	100	100	100	100	100
HPMC K4M	40	-	-	80	-	-
Hydroxyl ethyl cellulose	-	40	-	-	80	-
Sodium CMC	-	-	40	-	-	80
Lactose	40	40	40	-	-	-
Talc	10	10	10	10	10	10
Total weight of tablet	**250**	**250**	**250**	**250**	**250**	**250**

EVALUATION OF GRANULES

The flow properties of the prepared granules were evaluated by determining the bulk density, tapped density, compressibility index (carr's index), angle of repose, Hausner ratio[7].

Post compression parameters:

*Appearance:*The tablets were checked for presence of cracks, depressions, pinholes etc if any, uniformity of the colour and the polish of the tablets.

Hardness:

Hardness of tablets was tested using Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two

plungers. The lower plunger is placed in contact with the tablet and a zero reading is taken. The upper plunger is then forced against a spring by touring a threaded bolt until the tablet fractures, and then the force of fracture is recorded. In all the cases mean of three replicate determinations were taken. The physical properties of formulations were shown in Table 5.5[8]

Friability test:

Friability test was carried out to evaluate the hardness and stability instantly. In Roche friabilator, 10 tablets were weighed (W_0) initially and put in a tumbling and rotating apparatus drum. Then they were subjected for completion of 4 min or 100 rpm, the tablets were again weighed. The % loss in weight or friability (F) was calculated by the formula given below[8].

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Weight uniformity:

This test was performed to maintain the uniformity of weight of each tablet, which should be in the prescribed range. This was done by weighing 10 tablets at random and average weight was calculated. Not more than two of individual weight deviates from the average weight. The weight data from the tablets were analyzed for sample mean and percent deviation. IP limit for weight variation in case of tablets weighing 130 - 324 mg ± 7.5 % and more than 324 mg ± 5%.[8]

Thickness:

Thickness of tablet was important for uniformity of the tablet size. Thickness was measured using digital screw gauze (mitutoyo).[9]

Uniformity of drug content:

The formulated tablets were tested for their drug content. This test was performed by taking ten tablets randomly, weighed and powdered. A tablet triturate equivalent to 60 mg of drug weighed accurately dissolved in 50 ml of pH 1.2 buffer solutions for 10 min to ensure complete solubility of drug. Further dilutions were done suitably and absorbance was measured at 270nm using UV spectrophotometer[10].

In vitro dissolution studies:

In vitro drug release from tablets was studied using a USP 24 dissolution apparatus type 2 (USP 2000) (Electrolab, TDT-08L) at 75 rpm. The study was carried out in 900 ml pH 1.2 at 37±0.5 ºC for first 2 hours and then in 900 ml of phosphate buffer (pH 6.8) for subsequent hours. Sink condition was maintained for the whole experiment. 5ml of the sample was withdrawn at regular intervals and the same volume of pre warmed (37±0.5 ºC) fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a 0.45 µ membrane filter and the drug content in each sample was analyzed after suitable dilution with a Shimadzu 1700 UV-VIS spectrophotometer at 270 nm [11].

Analysis of release data:

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models.

Stability studies:

The stability of optimized formulation (F4) was studied at 40 ± 2 ^{o}C with 75 ± 5% RH for a period of 3 month. Changes in the appearance and drug content were investigated after storage[12].

RESULTS AND DISCUSSION

Trimetazidine dihydrochloride lipid matrix granules were prepared with the fusion method because this method does not require solvent or water, since the molten polymer acts like a binder. The intense mixing and agitation during fusion also deaggregates particles and improves the content uniformity for the extrudates. It was also reported that the fusion method provided slower release profiles compared to the direct compression or wet granulation method. Generally waxes are inert and have lower melting points than those of polymers. In this study, we used cetosteryl alcohol as lipophilic waxes as thermal binders for the process due to their stability and inertness**.**

The possible interaction between the drug and the excipients was studied by IR and DSC techniques. The IR spectra of pure Trimetazidine dihydrochloride and its physical mixtures revealed no considerable changes in the IR peaks of Trimetazidine dihydrochloride when mixed with excipients and it confirmed absence of any chemical interactions between the drug and polymer (Fig.1-3). The DSC thermogram for the drug gave a sharp melting endotherm at 242.67^{0}C. The individual excipient did not show any characteristic peaks. There was no shift in the endotherm of drug–

excipient mixtures indicating compatibility of the drug with all the excipients. The comparative DSC thermograms of the drug, individual excipient and drug–excipient mixtures are depicted in (Fig.4-6).

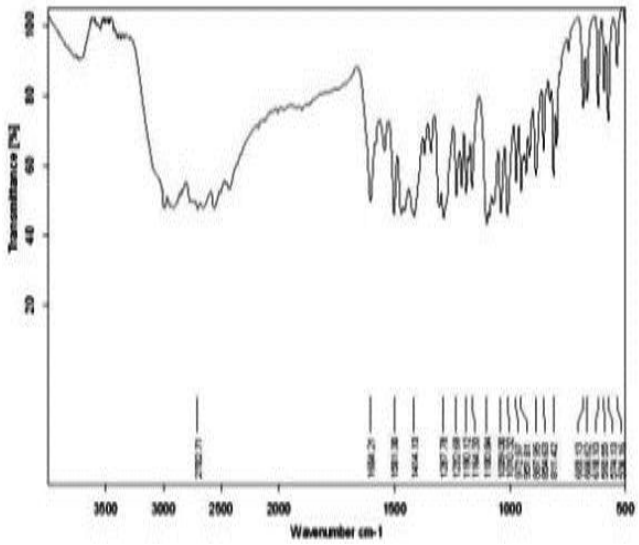

Figure 1: FTIR Spectra of pure Trimetazidine dihydrochloride

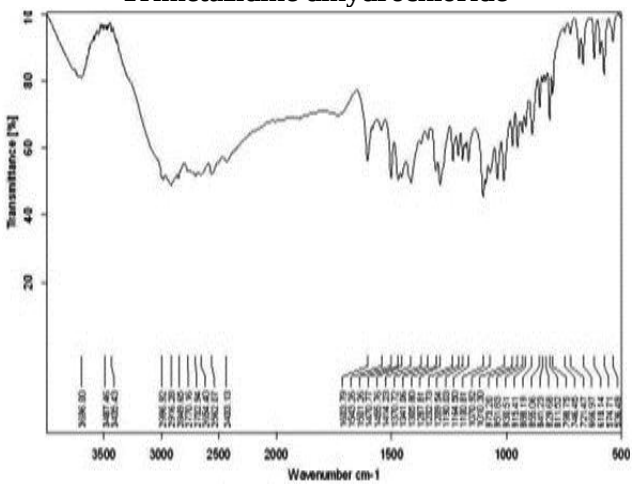

Figure 2: FTIR Spectra of formulation (F4)

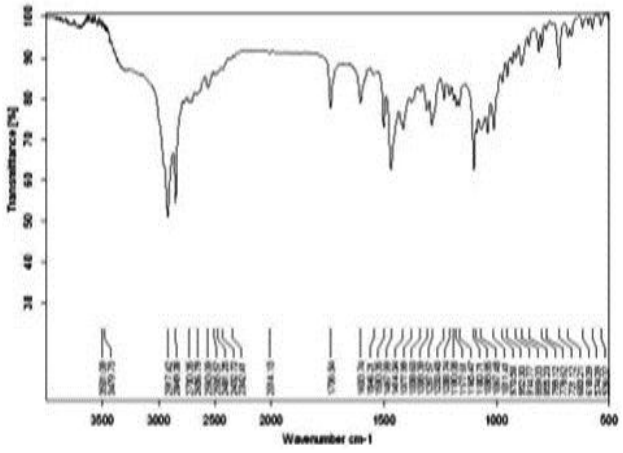

Figure 3: FTIR Spectra of formulation (F5)

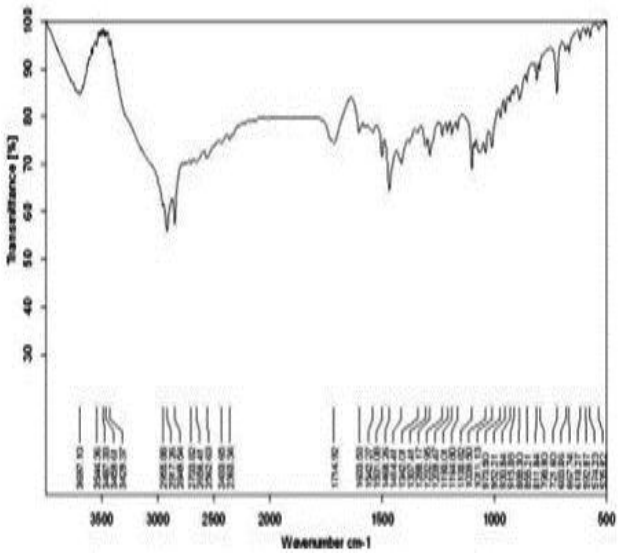

Figure 4: FTIR Spectra of formulation (F6)

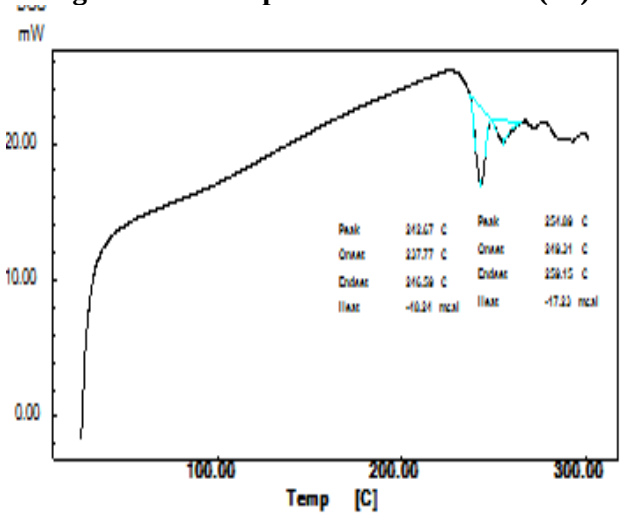

Figure 5: DSC Thermogram of Trimetazidine dihydrochloride

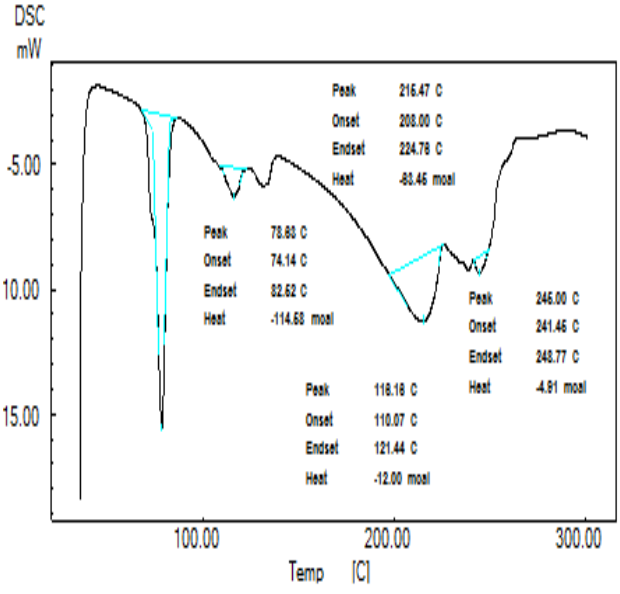

Figure 6: DSC Thermogram of F4

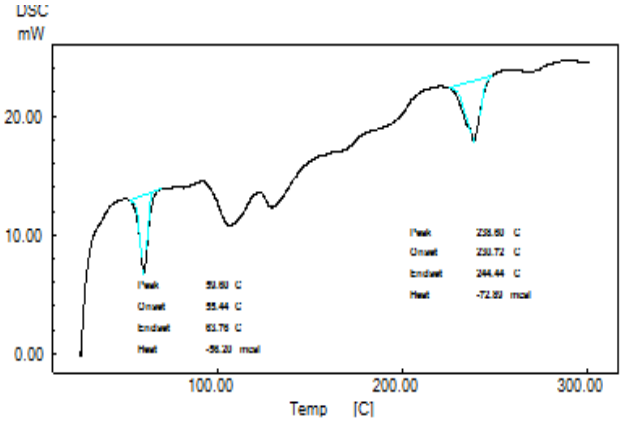

Figure 6: DSC Thermogram of F5

The granules of different formulation were evaluated as Loose Bulk Density (LBD), Tapped Bulk density (TBD), angle of repose and compressibility index (Table 2). The result of LBD and TBD ranged from 0.419±0.006 to 0.479±0.014 and 0.500±0.021 to 0.617±0.015 respectively. The result of angle of repose compressibility index was found to be 19.79±0.778 to 23.69±1.013. An angle of repose of less than 30 degrees indicates good flow properties (Aultron, 1998). This was further supported by the lower compressibility index. Granules with Carr's index values are considered to have fair and excellent flow properties.

Table 2: Precompressional parameters of all the formulations

Formulation Code	Parameters			
	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Angle of repose
F1	0.423±0.012	0.500±0.021	14.00	23.69±1.013
F2	0.419±0.006	0.617±0.015	21.16	22.28±1.233
F3	0.479±0.014	0.562±0.019	15.63	23.64±2.712
F4	0.431±0.011	0.571±0.010	15.33	21.71±1.647
F5	0.452±0.010	0.532±0.006	9.46	20.66±1.584
F6	0.463±0.009	0.566±0.008	16.90	19.79±0.778

Table 3: Post compressional parameters of all formulations

Formulation code	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Thickness (mm)	Drug Content (%)
F1	5.79±0.15	0.279	250.77±0.766	2.720±0.006	96.61±0.003
F2	5.93±0.15	0.33	249.50±0.654	2.774±0.008	96.21±0.004
F3	5.33±0.115	0.45	250.16±0.552	2.761±0.009	97.81±0.003
F4	4.51±0.1	0.79	251.14±1.259	2.728±0.004	94.23±0.002
F5	5.83±0.115	0.22	252.50±1.789	2.742±0.005	95.03±0.003
F6	5.82±0.113	0.31	250.23±0.942	2.729±0.006	98.60±0.004

Table 4: Release kinetics data of all the formulations

Formulation code	Zero order	First order	Higuchi	Korsmeyer peppas	
	R^2	R^2	R^2	n	R^2
F1	0.940	0.913	0.982	0.728	0.954
F2	0.963	0.885	0.892	0.779	0.937
F3	0.971	0.765	0.958	0.816	0.952
F4	0.965	0.881	0.928	0.742	0.975
F5	0.965	0.781	0.917	0.798	0.898
F6	0.976	0.782	0.930	0.837	0.925

The prepared tablets were evaluated for various physical parametric tests. Table 3 gives the physical parameters (thickness, hardness weight uniformity and friability) and content uniformity of all the formulated tablet batches. The thickness and weight uniformity of the prepared tablets was found to be 2.720±0.006 mm and 2.774±0.008 mm, respectively. Friability is an important factor in tablet formulation to ensure that the tablet can stay intact and withhold its from any outside force of pressure. The amount of hydrophobic material was found to have a significant effect on friability and hardness of the prepared tablets. The % friability was found to be ranging from 0.22 to 0.79, clearly indicating friability may be due to hydrophobic material in the matrix tablets. The hardness values are also presented in Table 3. The hardness of the fabricated tablets was found to increase with the increase lipid content. Drug content was found to be uniform among different batches of the tablets and ranged from 94.23±0.002 to 98.60±0.004 %.

Dissolution studies were conducted for all the formulations. All formulations showed very low drug release in 0.1N HCl (pH 1.2). This was due to the low solubility of hydrophobic polymer at pH 1.2, but complete drug release was displayed by all formulations in phosphate buffer (pH 6.8). Here the comparision was established for dissolution profiles of formulations containing different ratios of HPMC K4M, HEC and Sodium CMC along with cetosteryl alcohol. Dissolution results showed matrix tablets containing HPMC K4M showed much better release than HEC and Sodium CMC. Among all the formulations F4 gave release profile slow and sustained over the period of 12 hours and it was selected as the best formulation. Formulations F4 showed linearity with zero order plots having high regression coefficient value than the first order. According to 'n' values obtained from the Korsemeyer peppas plot, it may conclude that the drug release is by super case II transport. From the present study it may conclude that combination of both waxy materials and hydrophilic materials can be successfully used release retarding for water soluble drug.

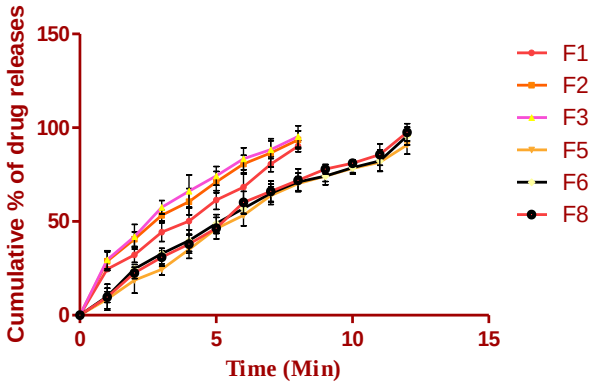

Figure 7: Drug release profiles of Trimetazidine dihydrochloride sustained release matrix tablets

Stability studies:

The stability studies of the optimized formulation (F4) were observed for any physical changes, such as colour, appearance and drug content was estimated at an interval of one month. The physical appearance showed that it does not show any changes when compared to the freshly prepared formulations and there was no significant change in the drug content uniformity during the storage for 90 days.

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