

Formulation and Evaluation of Trimetazidine Dihydrochloride Extended Release Tablets by Melt Congealing Method

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Javeer, *et al.*: ER tablets of trimetazidine

Trimetazidine dihydrochloride, a cellular antiischemic agent indicated in the management and prophylaxis of angina pectoris is given as 20 mg thrice daily in the conventional dosage regimen. The purpose of the present study was to formulate and evaluate twice a day extended release tablets containing 30 mg trimetazidine dihydrochloride. The method developed to formulate these extended release tablets was melt congealing followed by wet granulation which exhibited uniform sustained release action and overcame the drawbacks of multidosing. The formulation was developed with Methocel® K100M and stearic acid as release retardant.

Key words: Extended release tablets, melt congealing, Methocel® K100M, stearic acid, trimetazidine dihydrochloride

The term 'controlled release' refers to a system that delivers a drug continuously for a predetermined period with predictable and reproducible kinetics, and a known mechanism of release. Controlled release drug delivery systems are usually designed applying physical and polymer chemistry to produce a well characterised and reproducible dosage form that controls drug delivery to the body within the specifications of the required drug delivery profile^[1]. Controlled drug delivery systems can be classified as, continuous release systems, e.g. dissolution^[2], diffusion^[3], ion exchange^[3] and osmotically controlled systems^[4]; delayed transit and continuous release systems, such as density based^[5] and size based bioadhesive based systems^[6]; delayed release systems that include intestinal and colonic release systems^[7]. Melt congealing^[8] is a process, which comprises of forming a molten mixture containing drug and pharmaceutically accepted carrier, delivering the molten mixture to an atomizing means to form droplets and congealing the droplets to form multiparticulates.

Trimetazidine dihydrochloride is cytoprotective antianginal drug that displays antiischemic activity.

It is believed to act through a triple cytoprotective action, restoration of energy production, reduction of energy utilization and opposing the overproduction of free radicals^[9-11]. Treatment of angina pectoris involves long term therapy. Conventional dosage regimen is 20 mg thrice daily. Hence the objective of our work was to formulate twice daily tablets containing 30 mg of drug to maintain steady drug blood levels, prolong therapeutic action and improved patient compliance.

MATERIALS AND METHODS

Trimetazidine dihydrochloride was gifted by Cipla Ltd., Mumbai, India. Methocel® K100M and Ethocel® was gifted by Colorcon Asia Pvt. Ltd., Mumbai, India. All the excipients and chemicals used were of Analytical Reagent (AR) grade.

Preparation of tablets:

All the formulations as shown in Table 1 were developed using direct compression method. Extended release trimetazidine dihydrochloride tablets were formulated by direct compression method. All the ingredients were weighed and passed through 40#. The drug, diluents and polymer were blended in an octagonal blender for 10 min. Then the mixture was lubricated using talc and magnesium stearate in a blender for 5 min. Different polymers were used

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as release retardants such as Methocel® K100M, Eudragit® RSPO, Ethocel® and cellulose acetate. All the batches prepared are summarised in Table 1. The lubricated mixture was then compressed on a Cadmach tableting machine (Cadmach Machinery Co. Pvt. Ltd. Ahmedabad, India) using 10 mm standard concave punches. Tablet weight was set at 250 mg with hardness of 5-6 kg/cm². Release specifications were set at 90% release in 10h.

Formulations T8 to T11 were developed using wet granulation method [Table 2]. All the ingredients were weighed and passed through 40#. The mixture of drug, diluent and polymer were blended in planetary mixer for 20 min. Solution of polyvinyl pyrrolidone was prepared in isopropyl alcohol. This solution was added to form a wet mass along with mixing. The wet mass was passed through multimill having 8 mm screen. The wet granules were dried in fluidised bed dryer at 40° for 30 min. Dried granules were then passed through multimill having 2 mm screen. The dried granules were finally passed through 20#. The dried granules were lubricated using talc and magnesium stearate in a blender for 5 min. The

granules were then compressed using 11 mm round flat faced punches with beveled edges. Tablet weight was set at 250 mg with hardness of 5-6 kg/cm².

Formulations T12 and T13 were developed using melt congealing method. All the ingredients were weighed and passed through 40#. Drug was dispersed in molten stearic acid and congealed. The mass was then screened through 20#. This was blended in a blender with diluent and Methocel® K100M. Solution of polyvinyl pyrrolidone was prepared in isopropyl alcohol and was added to form a wet mass. The wet mass was passed through multimill having 8 mm screen. The wet mass was dried in fluidized bed dryer and dry granules were then passed through 20#. Dried granules were lubricated using talc and magnesium stearate and compressed on cadmach tableting machine on 11 mm round flat faced punches with beveled edges. Tablet weight was fixed at 375 mg with hardness of 4-5 kg/cm².

Evaluation of tablets:

The granules were evaluated for flow properties like Carr's index, Hausner's ratio, density (bulk

TABLE 1: FORMULATION DEVELOPMENT

Batch/Formula	T1 (mg)	T2 (mg)	T3 (mg)	T4 (mg)	T5 (mg)	T6 (mg)	T7 (mg)
Trimetazidine dihydrochloride	30.00	30.00	30.00	30.00	30.00	30.00	30.00
Methocel® K100M	65.00	90.00	125.00	-----	-----	-----	-----
Eudragit® RSPO	-----	-----	-----	15.00	75.00	-----	-----
Ethocel® N - 20	-----	-----	-----	-----	-----	60.00	-----
Ethocel® N - 100	-----	-----	-----	-----	-----	-----	60.00
Avicel® PH102	147.00	122.50	87.50	197.00	137.00	152.00	152.00
Dibasic calcium phosphate	-----	-----	-----	-----	-----	-----	-----
Talc	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Magnesium stearate	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Total	249.50	250.00	250.00	249.50	249.50	249.50	249.50

Table summarizing batches prepared using direct compression

TABLE 2: FORMULATION DEVELOPMENT

Batch/Formula	T8 (mg)	T9 (mg)	T10 (mg)	T11 (mg)	T12 (mg)	T13 (mg)
Trimetazidine dihydrochloride	30.00	30.00	30.00	30.00	30.00	30.00
Methocel® K100M	120.00	-----	-----	-----	120.00	150.00
Ethocel® N - 20	-----	-----	120.00	150.00	-----	-----
Cellulose acetate	-----	120.00	-----	-----	-----	-----
Stearic acid	-----	-----	-----	-----	90.00	180.00
Dibasic calcium phosphate	93.00	93.00	93.00	93.00	2.50	3.75
Talc	5.00	5.00	5.00	5.00	7.50	7.50
Magnesium stearate	2.50	2.50	2.50	2.50	3.75	3.75
Polyvinylpyrrolidone dissolved in Isopropyl alcohol	12.50	12.50	12.50	14.00	-----	-----
Total	263.00	263.00	263.00	294.50	253.50	375.00

Table summarizing batches prepared using wet granulation and melt congealing methods. Batches T8-T11 were prepared using wet granulation, Batches T12-T13 were prepared using melt congealing.

and tap density), angle of repose and loss on drying. The tablets were evaluated for physical appearance, diameter, thickness, hardness, friability, drug content and *in vitro* release studies. Drug content was determined using developed HPTLC method^[12]. *In vitro* release studies were carried out using USP Type I dissolution apparatus containing 200 ml of pH 1.2 hydrochloric acid buffer for 2 h and Phosphate buffer pH 7.2 for remaining 8 h. The apparatus was operated at 100 rpm at a temperature of $37 \pm 0.5^\circ$. 5 ml aliquots were withdrawn at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 h intervals and absorbance was recorded using UV spectrophotometry at λ_{max} of 269 nm.

***In vitro* drug release characteristics:**

The mechanism of drug release from the matrix tablet was analyzed using Korsmeyer-Peppas^[13] equation where M_t/M_∞ is the fractional solute release, t is the release time, k is a kinetic constant characteristic of the drug/polymer system, A is the area of the sample, c_d is the tracer loading concentration and n is an exponent which characterises the mechanism of release of the tracers. $M_t/M_\infty = kt^n$ (1), $dM_t/Adt = nc_dkt^{n-1}$ (2), when the diffusional release exponent (n) is equal to 1 then it characterizes zero order drug release behaviour.

Similarity factor (f_2) analysis:

In vitro drug release profile of the marketed trimetazidine dihydrochloride sustained release tablets was compared with the drug release profile of test product under similar experimental conditions. The data obtained from this drug release studies was used to determine the similarity factor between marketed and test product. Similarity factor was calculated using the formula shown in Eqn. 3, $f_2 = 50 \log \{ [1 + (1/N) \sum (R_i - T_i)^2]^{-0.5} \times 100 \}$ (3), where N is number of time points, R_i and T_i are dissolution of reference and test products at time i . If f_2 is greater than 50 then it is considered that 2 products have similar drug release behavior^[14].

Stability study:

Accelerated stability studies^[15] ensures stability of the product under exaggerated conditions of temperature and humidity. The optimized formulation was strip packed and subjected to stability studies at $25^\circ/60\%RH$, $30^\circ/65\%RH$ and $40^\circ/75\%RH$ at regular intervals for 6 months. The tablets were evaluated for dimension, hardness, friability, drug content and

in vitro release. Degradation was monitored by using stability indicating HPTLC method.

RESULTS AND DISCUSSION

Formulations by direct compression, as shown in Table 1 and fig. 1, formulation T1 to T7 did not exhibit drug release as per desired specifications. So, wet granulation method, as shown in Table 2 and fig. 2, formulation T8 to T11 was tried in order to increase the cohesion and binding by formation of granules, using solution of polyvinyl alcohol in isopropyl alcohol as binder, DCP as diluent, and different polymers as release retardants. Wet granulation method did not give drug release as per set specifications. All the systems gave burst release. Therefore, the method used was melt congealing followed by wet granulation. In order to increase the hydrophobicity of the tablet various wax systems in combination with different polymers were used. Stearic acid and Methocel[®] K100M in different ratios were tried as release retardants (formulation T12 to T13). Batch T13 gave the desired release profile (fig. 3).

The results of the evaluation of tablets for appearance, tablet weight, diameter, thickness, hardness, friability is given in Table 3. The dissolution media used was 200 ml of pH 1.2 hydrochloric acid buffer for 2 h and phosphate buffer pH 7.2 for remaining 8 h. The basket type dissolution apparatus (Electrolab) was operated at 100 rpm; $37 \pm 0.5^\circ$. Formulations prepared using different combinations of polymers were tried and release was observed. Trimetazidine dihydrochloride tablets formulated by direct compression failed to give drug release as per desired specifications. The drug being highly water soluble and a hydrophilic material which allows quicker penetration of water in to the pores of the tablet system, resulted in faster drug release. Increase in cohesion and binding using PVA solution could not help in retardation of drug release. The probable reason of burst release could be insufficiency of hydrophobicity in the matrix. Hence, it was necessary to increase the hydrophobicity of the matrix.

Melt congealing followed by wet granulation was thought to be a better process to increase the hydrophobicity of the matrix. Batch T12 although gave burst release it was quite close to the desired release profile. Further increase in the quantity of stearic acid and Methocel[®] K100M (batch T13) gave

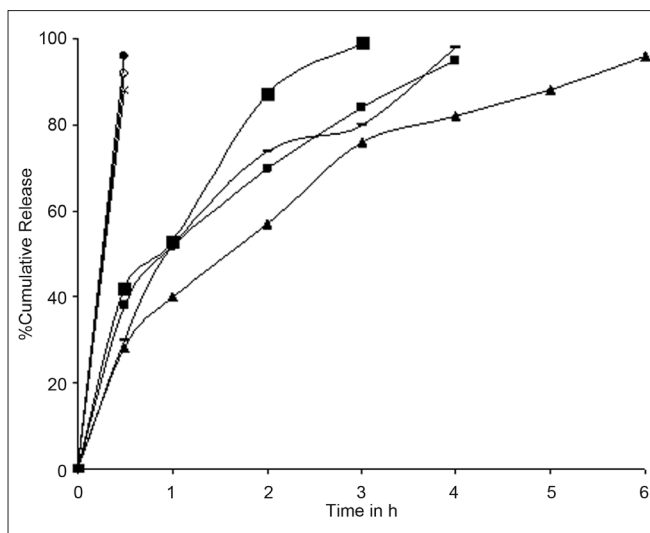


Fig. 1: Release of trimetazidine dihydrochloride from directly compressed tablets

Release of trimetazidine dihydrochloride from trimetazidine dihydrochloride tablets formulated by direct compression method: T1 (---); T2 (-■-); T3 (-▲-); T4(-○-); T5 (-x-); T6 (-●-) and T7 (-■-)

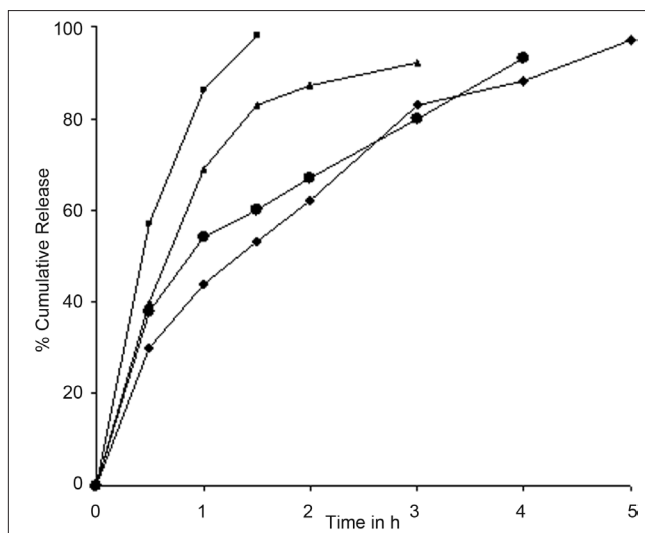


Fig. 2: Dissolution of trimetazidine dihydrochloride tablets formulated by wet granulation

Dissolution profile of trimetazidine dihydrochloride tablets formulated by wet granulation method, T8 (-◆-); T9 (-■-); T10 (-▲-) and T11 (-●-)

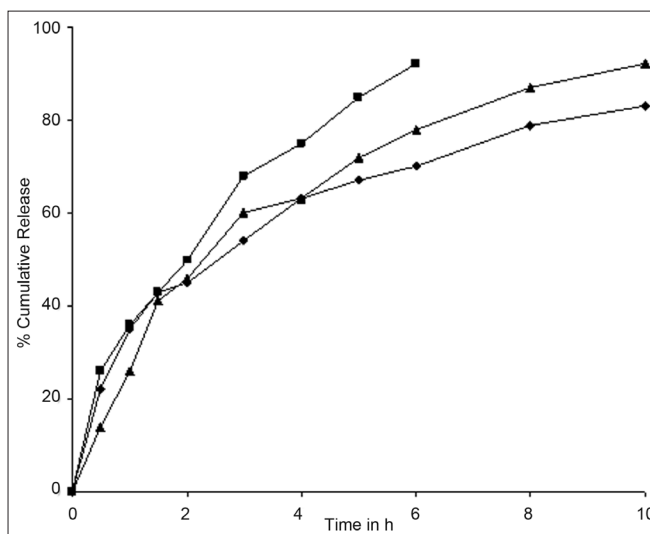


Fig. 3: Release profile of marketed formulation and formulations prepared by melt congealing method

Comparison of release profile of marketed formulation and formulations prepared by melt congealing method. Marketed (◆); T12 (■) and T13 (▲)

desired release profile. Increased quantity of stearic acid could coat the drug to a greater extent to give desired release profile.

Therefore, various wax systems in combination with different polymers were tried in order to increase the hydrophobicity of the system since the drug is highly water soluble. Thus tablets were formulated using Methocel® K100M, stearic acid, a wax system, dicalcium phosphate and other excipients by melt congealing method. Different

TABLE 3: EVALUATION OF THE FORMULATION

Parameter	Result
Appearance	Round, white, flat tablets with beveled edges
Tablet weight (mg)	375±0.018
Diameter (mm)	11±0.044
Thickness (mm)	4.5±0.045
Hardness (kg/cm ²)	4-5
Friability (%)	0.527
Drug content (%)	99.66±1.15

ratios and combinations were tried to achieve a release of about 90% in 10 h.

Level of Methocel® K100M was varied from 120 mg to 180 mg and stearic acid from 90 mg to 150 mg. The amount of dihydrogen calcium phosphate was also varied from 2.5 mg to 3.75 mg. Formulation T13 having Methocel® K100M 180 mg and stearic acid 150 mg gave release according to set specifications and was compared with the marketed preparation. The tablet contains 48% of the polymer and 40% of stearic acid. The optimized formula concludes that not only high molecular weight polymer but also stearic acid wax system was required to obtain the tablet of our interest. The formulation, which gave release as per desired specifications, was subjected to stability studies.

The release exponent (n) indicates the release mechanism of the solute i.e. Fickian diffusion, anomalous non-Fickian diffusion, zero order time independent release and supercase II transport from the tablet. The diffusional release exponent (n) with

their respective release mechanism and solute release rate is given in Table 4.

The diffusional release exponent according to Korsmeyer Peppas Eqn. was found to be $n = 0.6053$, suggesting that the mechanism that leads to the diffusion of trimetazidine dihydrochloride from the sustained release tablets is anomalous (non-Fickian, drug diffusion in the hydrated matrix and polymer relaxation) diffusion^[16-18].

The similarity factor f_2 is the simple measure for the comparison of two dissolution profiles. It ensures the uniformity of product from batch to batch and help to predict bioavailability for formulation development. The similarity factor analysis between prepared tablets and marketed tablets showed the f_2 factor ($f_2 = 66.81$) greater than 50.

The f_2 factor confirms that the formulated preparation T15 shows similar drug release as per marketed preparation. The results are summarized in Table 5. The developed product was found to be stable for 6 months under stability conditions.

TABLE 4: ANALYSIS OF THE DIFFUSIONAL RELEASE MECHANISMS

Diffusional release exponent (n)	Overall solute diffusion mechanism	Time dependence of solute release rate (dM_t/dt)
0.5	Fickian diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Anomalous (non-Fickian) diffusion	t^{n-1}
1.0	Case II transport	Zero order time independent release
$n > 1.0$	Super Case II transport	t^{n-1}

Table indicating the diffusional release exponent (n) with their respective release mechanism and solute release rate

TABLE 5: f_2 FACTOR RESULTS

Time	% Cumulative release		f_2 factor
	Reference	Test	
0.5	22	14	69.23
1	35	26	66.81
1.5	43	41	92.47
2	45	46	97.57
3	54	60	75.00
4	63	63	100.00
5	67	72	78.49
6	70	78	69.23
8	79	87	69.23
10	83	92	66.81

Table indicating comparison of the release profile of marketed and prepared formulation using Similarity Factor (f_2). The factor confirms that the formulated preparation T13 shows similar drug release as per marketed formulation

Twice daily ER tablets of trimetazidine dihydrochloride containing 30 mg of drug were successfully formulated by melt congealing followed by wet granulation method and have a uniform sustained action with increased patient compliance to overcome the drawbacks of multidosing. Tablets which were formulated using drug, stearic acid and Methocel® K100M in the ratio of 1:5:6 gave release as per set specifications. Optimized formulation was subjected to accelerated stability studies at room temperature 30°/65% RH at regular intervals for 6 months. The formulation was found stable with no change in all the parameters and *in vitro* release. HPTLC did not show presence of any degradation products.

ACKNOWLEDGEMENTS

Authors are grateful to the UGC for providing junior research fellowship.

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Accepted 10 November 2010

Revised 14 September 2010

Received 13 June 2009

Indian J. Pharm. Sci., 2010, 72 (6): 704-709