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Formulation and Evaluation of Modified Release Matrix Tablets of Trimetazidine Dihydrochloride

Vinod J*[1], Chenthilnathan A[1], Vijayakumar S[2]

*[1]*Dept. of Pharmaceutical Chemistry, Manonmaniam Sundaranar University, Tirunelveli, Tamil Nadu, India.*

[2]*Kenwell Pharma, Bangalore, Karnataka, India.*

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ABSTRACT

The purpose of the present study was to formulate the oral modified release tablets of Trimetazidine dihydrochloride by using Polyethylene oxide (Polyox WSR 303 LEO) (35-55%) as a rate controlling polymer. The tablets were prepared by direct compression method and coated by using film coating polymers. The powder mixtures were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index and showed satisfactory results. All the ingredients were lubricated and compressed using 8.5mm circular shaped standard concave plain punches. The tablets were evaluated for uniformity of weight, content of active ingredient, thickness, friability, hardness and In-vitro dissolution studies. Drug content in the formulation was determined by UV- Visible Spectrophotometric method. All the formulations showed compliance with Pharmacopoeial standards. The in vitro release study of matrix tablets were carried out in pH 6.8 phosphate buffer for 12 hours. The prepared matrix tablets showed 100.00% release over a period of 12 hours. The dissolution profile of Formulation, F5 was similar to Innovator product in three different media such as pH 1.2, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. It was observed that the amount of polymer in the tablets influences the drug release. In vitro release study results revealed that the release of the drug was retarded with the proportional increase in polymer concentration. It was indicated that the using a hydrophilic non-cellulose polymer in an appropriate concentration in tablet could control the rate of drug release.

KEYWORDS

Trimetazidine dihydrochloride, Matrix tablets, direct compression, Modified release.

INTRODUCTION

Various types of oral modified/controlled release formulations have been developed to improve the clinical efficacy of drugs having short half-lives as well as to increase patient compliance.[1]These formulations are designed to deliver drugs at a predetermined rate over a wide range of conditions and durations of therapeutic treatments.

***Address for Correspondence:**
Vinod J.
Department of Pharmaceutical Chemistry,
Manonmaniam Sundaranar University
Abishekapatti,
Tirunelveli – 627 012
E-Mail Id: vinoddivien2001@yahoo.com

One of the most commonly used methods of developing controlled release formulations for therapeutic agents is to include it in matrix tablets, as they are easy to manufacture. Using a suitable rate controlling polymer, the matrix tablets can be manufactured by direct compression or conventional wet granulation methods. Because of their simplicity and cost effectiveness, hydrophilic non-cellulose polymers in an appropriate combination are extensively used for oral controlled release dosage forms.[2]

Trimetazidine dihydrochloride is a 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.[3, 4, 5] Treatment of angina pectoris involves long term therapy. The conventional dosage regimen is 20 mg thrice daily since Trimetazidine dihydrochloride has a shorter plasma half life of around 0.6 – 1.4 hrs.[6] Hence the objective of our work was to formulate twice daily matrix tablets containing 35 mg of drug with Polyethylene oxide as a rate controlling polymer in order to maintain steady drug blood levels, prolong therapeutic action and improved patient compliance and also the effect of the polymer concentration on the *in-vitro* release rate was studied.

MATERIALS AND METHODS

Trimtazidine dihydrochloride was obtained from Nivedita Chemicals, Hyderabad. Polyethylene oxide (Polyox WSR LEO) was obtained from Colorcon Asia Pvt. Ltd., Goa. , Directly Compressible Lactose (Pharmatose DCL 11), Colloidal Anhydrous Silica and Magnesium stearate were obtained from Loba Chemicals, Mumbai. All other ingredients used were of analytical grade.

METHOD

Preparation of Matrix Tablets

Matrix tablets were prepared by direct compression method**.** Trimetazidine dihydrochloride, Directly compressible lactose (Pharmatose DCL 11), Polyethylene oxide (Polyox WSR 303 LEO) and Colloidal Anhydrous Silica were sifted through #30 mesh. The sifted materials were mixed in an octagonal blender. Magnesium stearate was sifted through #40 mesh and added to the blender was mixed. The tablets were compressed at 200 mg weight on a 16-station rotary tablet punching machine (Cadmach Machinery Pvt. Ltd,) with 8.5mm circular standard concave punches plain on both sides. After compression, the matrix tablets were film coated with a cellulose polymer, Opadry Pink, containing Hypromellose. Six different formulae, having different concentrations of Polyethylene oxide were developed to evaluate the drug release and to study the effect of polymer concentration on drug release. The composition of various formulations was shown in Table: 1

Table 1: Composition of Formulation of Modified Release Tablets of Trimetazidine dihydrochloride (mg)

Sr. No	Ingredients	F1	F2	F3	F4	F5	F6
1	Trimetazidine dihydrochloride	35.00	35.00	35.00	35.00	35.00	35.00
2	Polyox WSR 303	70.00	80.00	90.00	100.00	110.00	120.00
3	Pharmatose DCL 11	87.00	77.00	67.00	57.00	47.00	37.00
4	Colloidal anhydrous silica	6.00	6.00	6.00	6.00	6.00	6.00
5	Magnesium Stearate	2.00	2.00	2.00	2.00	2.00	2.00
Uncoated tablet average weight		200.00	200.00	200.00	200.00	200.00	200.00
6	Opadry Pink	4.00	4.00	4.00	4.00	4.00	4.00
7	Methylene Chloride*	Qs	Qs	Qs	Qs	Qs	Qs
8	Isopropyl Alcohol*	Qs	Qs	Qs	Qs	Qs	Qs
Coated tablet average weight		204.00	204.00	204.00	204.00	204.00	204.00

*Removed during coating process; Qs – Quantity sufficient

Table 2: Evaluation of Physical Properties of the Blended Powder of Trimetazidine dihydrochloride Modified Release Tablets

Sr. No	Formulation Code	Angle of repose (0˚)	Loose Bulk density (g/mL)	Tapped Bulk Density (g/mL)	Hausner ratio	Compressibility index
1	F1	36± 0.65	0.516	0.658	1.275	22
2	F2	33± 0.75	0.538	0.681	1.266	21
3	F3	31± 0.77	0.596	0.694	1.164	14
4	F4	28± 0.29	0.586	0.676	1.154	13
5	F5	29± 0.81	0.543	0.632	1.164	14
6	F6	27± 0.72	0.571	0.649	1.134	12

** All values are expresses as mean ± S.D, n=5*

Table 3: Physical Properties of Different Formulations of Trimetazidine dihydrochloride Modified Release Core Matrix Tablets

Sr. No	Formulation Code	Average weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%w/w)
1	F1	210 ± 2.2	3.7 ± 0.15	8.0 ± 1.3	0.35
2	F2	211 ± 1.3	3.6 ± 0.13	7.6 ± 1.2	0.25
3	F3	210 ± 1.8	3.7 ± 0.11	7.8 ± 1.5	0.31
4	F4	212 ± 1.5	3.6 ± 0.16	8.3 ± 1.2	0.28
5	F5	210 ± 2.5	3.6 ± 0.18	7.9 ± 1.3	0.25
6	F6	209 ± 2.1	3.5 ± 0.12	8.4 ± 1.1	0.22

Table 4: Physical Properties of the Different Formulations of Trimetazidine dihydrochloride Modified Release Film Coated Matrix Tablets

Sr. No	Formulation Code	Average weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Drug content (%w/w)
1	F1	214 ± 2.5	3.9 ± 0.12	9.1 ± 1.2	99.7
2	F2	213 ± 1.8	3.8 ± 0.16	8.8 ± 1.5	98.5
3	F3	214 ± 1.6	3.8 ± 0.14	9.2 ± 1.3	99.1
4	F4	212 ± 1.8	3.7 ± 0.13	9.5 ± 1.1	98.9
5	F5	214 ± 2.1	3.8 ± 0.17	9.0 ± 1.4	99.6
6	F6	213 ± 2.2	3.7 ± 0.19	9.6 ± 1.2	99.2

Evaluation of Blend[7]

The angle of repose was measured by using fixed funnel method, which indicates the flow ability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula:

LBD = height of the powder / volume of packing.

TBD = weight of the powder / tapped volume of packing.

Compressibility index (CI) of the granules was determined by using the following formula:

$$CI = [(TBD-LBD/TBD] \times 100.$$

The physical properties of granules were shown in Table: 2.

Evaluation of Tablets[8]

Thickness

Thickness of the tablets was determined using a vernier caliper (Mitutoyo Digimatic Calliper).

Weight Variation Test

20 tablets of each formulation were weighed using an electronic balance (Mettler Toledo electronic Balance) and the test was performed according to the official method

Hardness

Hardness generally measures the tablet crushing strength. Hardness of the tablets was determined by using a hardness testing apparatus (Erweka Type).

Friability

The friability of the tablets was measured in a Roche friabilator (Electrolab). Tablets of a known weight (W_0) are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below.

$$\% \text{ Friability} = \frac{(W_0 - W)}{W_0} \times 100$$

Tablet Properties of the different formulations of Trimetazidine dihydrochloride modified release core and coated matrix tablets are shown in Table: 3 and 4 respectively.

Drug Content

Drug content was determined by UV-Visible Spectrophotometric method. 10 tablets were weighed and finely powdered. Powder equivalent to 35mg Trimetazidine dihydrochloride was weighed accurately. The powder was transferred to 100ml volumetric flask containing 60 ml of pH 6.8 phosphate buffer. The mixture was shaken for 30 minutes and the volume was made up to 100ml with pH 6.8 phosphate buffer. The suspension was filtered and the absorbance was measured at 270nm using UV-Visible spectrophotometer (Shmazdzu). Drug content values were shown in Table: 4.

In Vitro Release Studies[9]

In vitro dissolution studies were carried out using USP apparatus type I at 100 rpm. Dissolution medium consisted of pH 6.8 phosphate buffer maintained at 37°C ± 0.5°C. Drug release at different time intervals (from 1hour to 12hours) was measured by UV-visible spectrophotometer at 270 nm. *In vitro* drug release profile of all the formulations as well as final selected formulation (F5) were compared with the innovator product (Vastarel). Drug release profiles are shown in Table: 5, 6, 7 and Figure: 1, 2, 3, 4, 5 and 6.

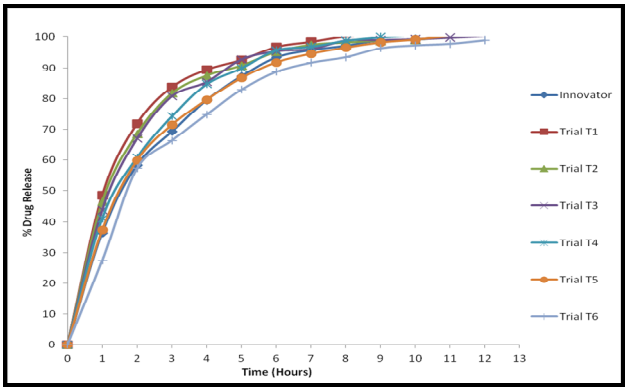

Figure 1: Comparative *invitro* Dissolution Profiles of Different Formulation Trials of Trimetazidine dihydrochloride Modified Release Tablets in pH.6.8 Phosphate Buffer

Table 5: Comparative *invitro* Dissolution Profiles of Different Formulation Trials of Trimetazidine dihydrochloride Modified Release Tablets in pH.6.8 Phosphate Buffer

Time (Hours)	% Drug release of different formulation trials and Innovator Product						
	Innovator	F1	F2	F3	F4	F5	F6
1	36.5	48.5	46.4	43.8	41.2	37.4	27.5
2	58.3	71.8	68.5	66.9	60.8	59.8	57.2
3	69.2	83.7	81.7	80.7	74.2	71.4	66.3
4	79.5	89.4	87.5	85.4	84.7	79.6	74.8
5	87.3	92.6	90.8	92.7	89.9	86.7	82.9
6	93.4	96.8	95.2	95.4	95.8	91.8	88.7
7	95.8	98.4	97.5	96.1	96.9	94.6	91.7
8	97.2	100.1	98.2	98.8	98.8	96.6	93.5
9	98.9	100.4	98.8	98.9	99.9	98.2	96.4
10	99.2	101.5	99.1	99.2	100.5	99.1	97.3
11	100.1	102.1	100.2	99.7	101.4	100.3	97.8
12	100.4	102.9	101.4	100.2	101.8	101.2	98.9

Table 6: Comparative invitro Dissolution Profiles of Final Formulation (T5) of Trimetazidine dihydrochloride Modified Release Tablets in pH 1.2, 4.5 and 6.8 Buffers

Time (Hours)	% Drug release of final formulation (T5)		
	pH 1.2	pH 4.5	pH 6.8
1	35.6	35.8	37.4
2	61.2	59.7	60.8
3	73.5	71.5	72.4
4	75.9	77.6	79.6
5	84.2	86.3	85.5
6	93.5	92.5	91.8
7	94.9	95.4	93.6
8	96.2	96.9	95.6
9	98.1	98.5	97.2
10	99.5	99.8	99.1
11	100.8	100.6	100.3
12	101.5	100.9	101.2

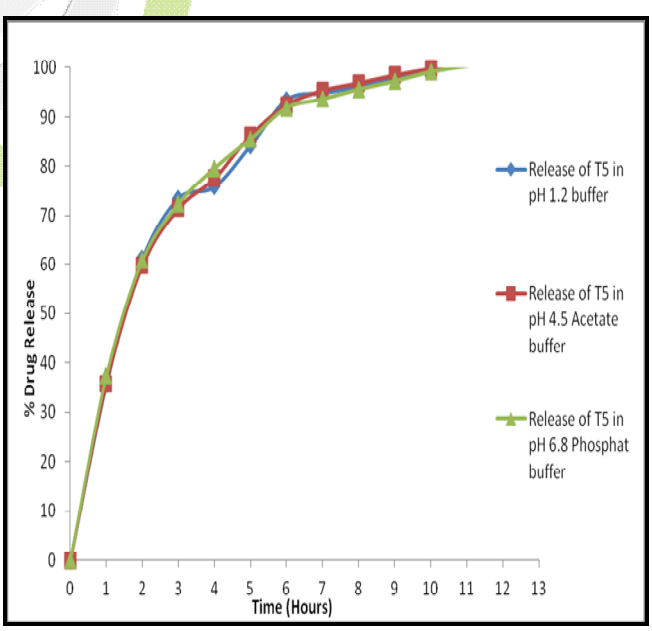

Figure: 2 Comparative *invitro* Dissolution Profiles of Final selected formulation (F5) of Trimetazidine dihydrochloride Modified Release Tablets in pH 1.2, 4.5 and 6.8 Buffers

Table 7: Comparative *invitro* Dissolution Profiles of Final Selected Formulation (F5) of Trimetazidine dhydrochloride Modified Release Tablets with Innovator Product (Vastarel) in pH1.2, 4.5 and 6.8 Buffer

Time (Hrs)	% Drug Release in pH 1.2 buffer		% Drug Release in pH 4.5 acetate buffer		% Drug Release in pH 6.8 phosphate buffer	
	Innovator (Vastarel)	Final formulation (F5)	Innovator (Vastarel)	Final formulation (F5)	Innovator (Vastarel)	Final formulation (F5)
1	33.2	35.6	34.8	35.8	36.5	37.4
2	58.5	61.2	60.5	59.7	58.3	60.8
3	71.6	73.5	67.4	71.5	69.2	72.4
4	74.9	75.9	75.8	77.6	79.5	79.6
5	85.6	84.2	87.5	86.3	87.3	85.5
6	92.8	93.5	91.5	92.5	93.4	91.8
7	95.2	94.9	96.2	95.4	95.8	93.6
8	96.5	96.2	97.3	96.9	97.2	95.6
9	97.8	98.1	98.1	98.5	98.9	97.2
10	99.2	99.5	99.5	99.8	99.2	99.1
11	100.1	100.8	100.2	100.6	100.1	100.3
12	100.8	101.5	101.5	100.9	100.4	101.2

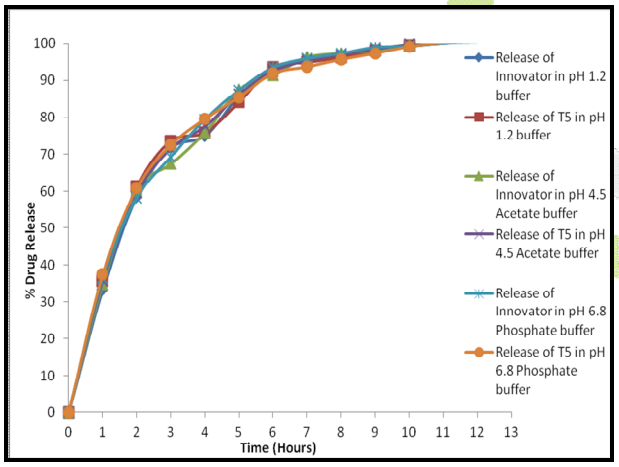

Figure 3: Comparative i*nvitro* Dissolution Profiles of Final Selected Formulation (F5) of Trimetazidine dihydrochloride Modified Release Tablets with Innovator Product (Vastarel) in pH1.2, 4.5 and 6.8 buffer

RESULTS AND DISCUSSION

Evaluation of Modified Release Core Matrix Tablets

The matrix tablets of various formulation trials were evaluated for uniformity of weight, hardness, thickness and friability. The average weight percentage deviation for all tablet formulations were found to be (F1: -2.5 to +2.5; F2: -2.7 to +2.4; F3: -2.9 to +2.2; F4: -2.6 to +2.5; F5: -2.2 to +1.8; F6: -1.9 to +2.6) which was found to be within the pharmacopoeial limit of ± 7.5 %. The thickness was found to be in the range of 3.4 to 3.8 mm. The hardness ranged from 76 to 98N. The friability of all formulations ranged from 0.22 %w/w to 0.35%w/w which was within the pharmacopoeial limit of less than 1%w/w.

Evaluation of Modified Release Film Coated Matrix Tablets

The film coated matrix tablets were evaluated for uniformity of weight, hardness, thickness and drug content. The average weight percentage deviation of all tablet formulations were found to be (F1: -2.5 to +3.2; F2: -2.4 to +3.1; F3: -2.3 to +2.5; F4: -1.9 to +2.5; F5: -2.3 to +2.8; F6: -1.4 to +1.9) within the pharmacopoeial limit. The thickness was found to be in the range of 3.6 to 4.0 mm. The hardness ranged from 7.3 to 10.6 Kg/cm^2.

Invitro Evaluation of Modified Release Film Coated Tablets

In vitro release study of formulation trials were performed in pH 6.8 phosphate buffer (900 ml) using USP apparatus I (basket) at 100 rpm. The release of the drug was retarded with the proportional increase in polymer concentration. An increase in the polymer concentration not only causes increase in the viscosity of the gel but also leads to formation of gel layer with a longer diffusional path. This leads to a decrease in the diffusion of the drug and therefore a reduction in the drug release rate. Initially tablets prepared with polymer concentration of 35% w/w of formulation in trial F1 released 100% of the drug within 8 hrs. Hence the polymer concentration was increased in the further trials from F2 to F6 with polymer concentration ranging from 40 to 55% w/w of formulation. The rate of drug release of trial F5 was similar to innovator in three media viz pH1.2 buffer, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Two dissolution profiles are considered to be similar if the similarity factor (f2) lies between 50-100 and dissimilarity factor (f1) lies between 0-15. The dissolution profile of final trial (F5) and Innovator product was found to be independent of pH. When compared with the Innovator, final trial (F5) showed similarity factor (f2) value of 89 in pH 1.2 buffer, 88 in pH 4.5 acetate buffer 85 in pH 6.8 phosphate buffer.

CONCLUSION

From the foregoing investigation it may be concluded that the release rate of the drug from the matrix tablets can be controlled using hydrophilic polymer namely Polyethylene oxide (Polyox WSR 303) in an appropriate concentration. Slow, controlled and complete release of Trimetazidine dihydrochloride over a period of 12 hours was obtained from the matrix tablets formulated by employing Polyox WSR 303. Hydrophilic matrix tablets of Trimetazidine dihydrochloride can successfully be employed as twice a day oral modified release drug delivery system.

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