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Formulation and evaluation of controlled release matrix tablets of Trimtazidine Dihydrochloride

***Raj Kumar.Marikanti[1], Kiran Joshi.P[2], Vidya Sagar.CH[2], Venkateswara reddy.B[3], Kiran kumar.A[1], Nagaraju.I[1], Srinivasa Rao.P[1]and J.Ravi kiran[1]**

[1]Department of Pharmaceutics, Dr. Samuel George Institute of Pharmaceutical Sciences, Markapur, Prakasam, India
[2]Bellamkonda Institute of Technical Sciences, Kambalapadu, Podili, India
[3]St.pauls College of Pharmacy, Rangareddy, India

ABSTRACT

The purpose of the present study was to formulate the oral controlled release Trimtazidine di hydrochloride tablets by using Polysaccharide B-1459 (14-38%) as rate controlling polymer. The tablets were prepared by direct compression method and coated by the film coating polymers. The powder mixtures were evaluated for angle of repose, loose bulk density, tapped bulk density and compressibility index, shows satisfactory results. All the ingredients were lubricated and compressed using 8mm circular shaped deep concave punches. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, thickness, friability, hardness and In-vitro dissolution studies. Drug content in formulation was determined by HPLC Method . All the formulation showed compliance with Pharmacopoeial standards. The in vitro release study of matrix tablets were carried out in 0.1N Hydrochloric acid with pH 1.2 for 10 hours. The prepared matrix tablets were shown 98.00%, 99.00%, 100.00%, 104.00%, 92.00% and 100.00% release over a period of 10 hours. Formulation F1, F2 and F3 failed to sustain release beyond 10 hours. Among all the formulation, F6 shows 100.00% release at the end of 10 hours. It was observed that the amount of polymer influences the drug release. In vitro release study results revealed that the release of drug was retarded with the proportional increase of the polymer concentration. It was indicated that the using a hydrophilic non-cellulosic polymer in an appropriate combination in tablet could control the rate of drug release.

Key words: Trimtazidine dihydrochloride, Matrix tablets, direct compression, Controlled release.

INTRODUCTION

Trimtazidine di hydrochloride 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.[1] It is quickly absorbed and eliminated by the organism 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.[2] Trimtazidine di hydrochloride is regarded as a safe drug in the long term treatment of chronic ischemic disorders. This compels the necessity of fabricating the immediate release dosage form into a modified release preparation for achieving regular and constant plasma levels, which is also favorable for compliance of the patient to his treatment.

Various types of oral controlled release formulation have been developed to improve the clinical efficacy of drugs having short half-lives as well as to increase patient compliance. [3] These formulations are designed to deliver drugs at a predetermined rate over a wide range of conditions and durations of therapeutic treatments. 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.[4] Using a suitable rate controlling polymer, the matrix can be tableted by direct compression or conventional wet granulation method. Because of their simplicity and cost effectiveness, hydrophilic non-cellulosic polymers in an appropriate combination are extensively used for oral controlled release dosage forms.

Hydration of polymer results in the formation of a gel layer that controls the release rate of the drug. In vitro drug release of water soluble drug is controlled by diffusion out of the gel layer at a rate controlled by the gel viscosity, whereas release for poorly soluble drug is solely by polymer dissolution [5] Polysaccharide B-1459 is used to prepare sustained-release matrix. Polysaccharide B-1459 has also been used to produce directly compressed matrices that display a high degree of swelling due to water uptake, and a small amount of erosion due to polymer relaxation.

The purpose of the present study was to investigate the in vitro performance of compressed matrix tablets prepared by granulating hydrophilic polymeric substance, Polysaccharide B-1459 and Polyethylene oxide to produce a controlled release dosage form containing Trimtazidine dihydrochloride.[6]The effect of the polymer concentration on the in- vitro release rate was studied.

MATERIALS AND METHODS

Trimtazidine dihydrochloride was obtained from (Strides Arcolab, Bangalore). Polysaccharide B-1459, Polyethylene oxide is obtained from (S.D. Fine Chemicals, Mumbai). Magnesium strearate and Anhydrous calcium di hydrogen phosphate was obtained from (Loba Chemicals, Mumbai). All other ingredients used were of analytical grade.

Preparation of matrix tablets

Matrix tablets were prepared by direct compression method. The composition of various formulations was shown in **Table 1.** Trimtazidine Di Hydrochloride, Polysaccharide B-1459 Colloidal anhydrous silica, Polyethylene oxide and anhydrous calcium hydrogen phosphate through #30 mesh and Magnesium stearate through #40 mesh and collect separately in polyethylene bag. Tablets were compressed at 210 mg weight on a 16-station rotary tablet punching machine (Cadmach Machinery pvt. Ltd,) with 8mm circular shaped deep concave punches plain on both sides [7] After compression, the matrix tablets were film coated with a non-cellulosic polymer, namely Opadry II Pink, containing PVA, for good appearance and to protect the tablet from environment. [8] Six different formulae, having different concentrations were developed to evaluate the drug release and to study the effect of polymer concentration on drug release.

Table- 01: Composition of formulation of modified release tablets of Trimtazidine Di Hydrochloride

S.No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Trimtazidine Di Hydrochloride	35.00	35.00	35.00	35.00	35.00	35.00
2	Calcium hydrogen phosphate anhydrous	135.00	115.00	85.00	90.00	40.00	60.00
3	Polysaccharide B-1459	30.00	50.00	80.00	-	50.00	30.00
4	Polyethylene oxide WSR 303	-	-	-	75.00	75.00	75.00
5	Colloidal silicon dioxide	8.00	8.00	8.00	8.00	8.00	8.00
6	Magnesium stearate	2.00	2.00	2.00	2.00	2.00	2.00
	Average weight	**210.00**	**210.00**	**210.00**	**210.00**	**210.00**	**210.00**

Evaluation of blend:

The angle of repose was measured by using fixed funnel method, which indicates the flowability of the granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using the formula: LBD= height of the powder / volume of the packing. TBD= weight of the powder / tapped volume of the packing. Compressibility index of the granules was determined by using the formula: CI (%) = [(TBD-LBD/TBD)] ×100.The physical properties of granules were shown in **Table 2**. [9]

Table- 02: Data's for evaluation of properties of the blended powder for Trimetazidine di Hydrochloride Modified release Tablets

S.No	Formulation Code	Angle of repose	Loose Bulk Density	Tapped Bulk Density	Hauser ratio	Compressibility index
1	**F1**	35 ± 0.65	0.4546	0.5234	1.15	13
2	**F2**	40 ± 0.72	0.4350	0.5346	1.23	19
3	**F3**	47 ± 0.77	0.4168	0.5684	1.36	27
4	**F4**	28 ± 0.29	0.4521	0.5012	1.11	10
5	**F5**	33 ± 0.81	0.4438	0.5213	1.17	15
6	**F6**	30 ± 0.72	0.4321	0.4751	1.10	9

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

Evaluation of Tablets:

Thickness:

Thickness of the tablets was determined using a vernier caliper (For-bro engineers, Mumbai, India). [10]

Weight Variation Test

20 tablets of each formulation were weighed using an electronic balance (Sartorius electronic balance: Model CP-2245, Labtronic), and the test was performed according to the official method. [11]

Hardness

Hardness generally measures the tablet crushing strength. Hardness of the tablets was determined by using a hardness testing apparatus (Monseto Type). [12]

Friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai, India). Tablets of a known weight (W0) or a sample of tablets 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. The weight loss should not be more than 1% w/w.10

$$\% \text{ Friability} = (W0\text{-}W)/\ W0 \times 100$$

Tablet properties of the different formulations of Trimtazidine Di Hydrochloride controlled release core and coated matrix tablets were shown in **Table 3** and **4** respectively.

Table- 03: Tablet properties of the different formulations of Trimtazidine Di Hydrochloride controlled release core matrix tablets

S.No	Formulation code	Hardness	Thickness (mm)	Avg.wt (mg)	Drug content(%)
1	F1	8.12 ± 1.1	4.2±0.11	210±2.0	98.2 %
2	F2	8.24 ± 1.0	4.2±.0.11	211±1.4	99.1 %
3	F3	8.02 ± 0.5	4.3±0.03	211±1.2	98.6 %
4	F4	8.56 ± 0.4	4.3±0.12	211±1.5	99.3 %
5	F5	8.65 ± 0.5	4.2±0.10	211±2.0	99.1 %
6	F6	8.98 ± 0.7	4.3±0.09	212±1.6	99.4 %

Table- 04: Tablet properties of the different formulations of Trimtazidine Di Hydrochloride controlled release film coated matrix tablets

S.No	Formulation code	Hardness ($kg/cm^{2)}$	Thickness(mm)	Friability(%)	Avg.wt (mg)
1	F1	9.32 ± 0.7	4.3±0.03	0.34 %	217.76±1.5
2	F2	9.58 ± 1.2	4.3±.0.04	0.14 %	217.72±1.1
3	F3	9.25 ±1.1	4.3±0.02	0.06 %	216.31±1.5
4	F4	9.74 ± 1.4	4.3±0.02	0.05 %	216.58±1.5
5	F5	9.85 ± 0.8	4.4±0.10	0.09 %	217.63±2.5
6	F6	9.96 ± 0.7	4.4±0.03	0.08 %	218.31±1.4

Drug content (Assay)

Drug content was determined by HPLC method by using Inertsil ODS-3; 150mmx4.6mm; 5µ or equivalent as coloum and mixer of 50:50 buffer and methanol was used as mobile phase, wave length 231nm, flow rate 1.2ml/min, coloum temperature 50^0 C.[13]

Procedure

Separately inject equal volumes (about 20 µl) of diluent as blank, five injections of standard solution and Test solution into the chromatograph, record the chromatograms, measure the drug peak Response. Drug content values were shown in **Table 3.**

***In Vitro* Release Studies**[14]

In vitro dissolution studies were carried out using USP apparatus type II (at 50 rpm. Dissolution medium consisted of 0.1N hydrochloric acid with pH 1.2 from 30mins to 10 hours maintained at 37°C ± 0.5°C. Drug release at different time intervals was measured by UV-visible spectrophotometer at 231 nm. *In vitro* drug release profile of all batches was compared with market product drug release profile shown in **fig.1, 2,3**.

Fig 1: Comparative invitro dissolution profile for different formulation of Trimtazidine Di Hydrochloride drug

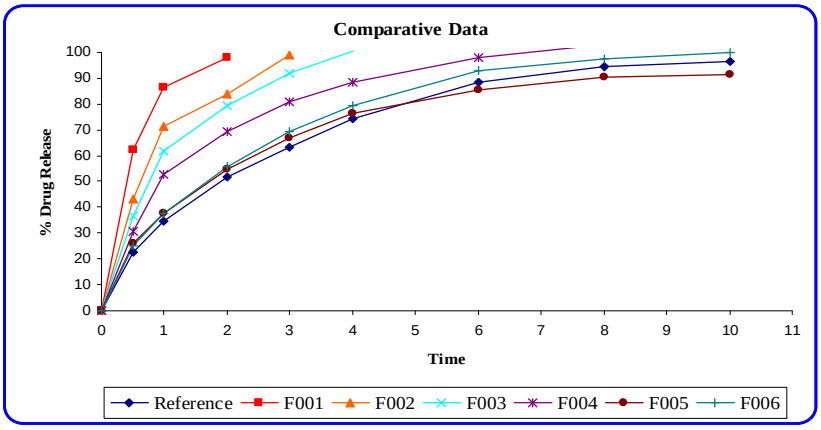


Fig 2: Comparative invitro dissolution profile for market sample and final formulation of Trimtazidine Di Hydrochloride drug

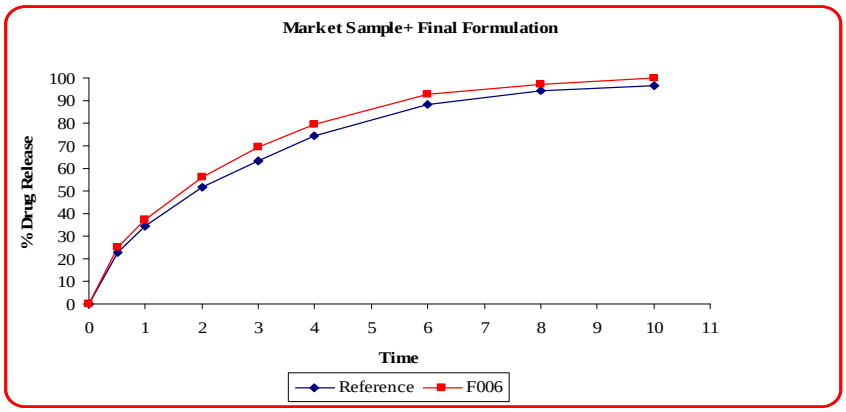
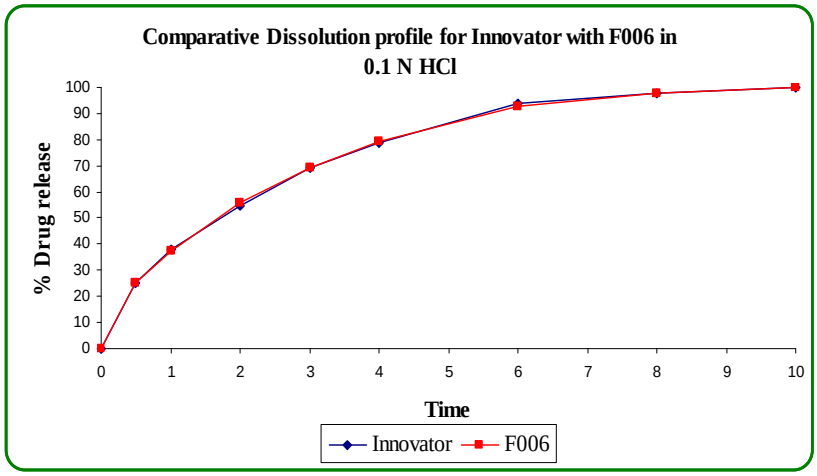


Fig 3: Comparative dissolution profile for innovator with F006 in 0.1N HCl



RESULTS AND DISCUSSION

Evaluation of modified release core tablets

The matrix tablets of various batches formulated were evaluated for test such as uniformity of weight, hardness, thickness, friability and drug content. The weight variation tests were performed according to as per procedure given in British pharmacopoeia. The average percentage deviation of all tablet formulation was found to be (F1: -1.5 to +2.0; F2: -1.7 to +1.4; F3: -1.8 to +1.2; F4: -1.6 to +1.5; F5: -2.0 to +2.0; F6: -1.9 to +1.6) which was found to be within the pharmacopoeial limit of ± 7.5 % hence all formulation passed the test for uniformity of weight. The thickness of the matrix tablet was found to be in the range of 4.1 to 4.4 mm. The hardness of all batches ranged from 8.02 to 8.98 kg/cm^2. Another measure of tablet strength is friability. The friability of all formulation ranged from (0.06 % to 0.34%) which was below 1% limit as per the British pharmacopoeia indicating that the friability is within the specification limit[15]. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house/BP specifications for weight variation, drug content, hardness and friability.

Evaluation of Film coated Tablets

After compression, the matrix tablets were film coated with a non-cellulosic polymer, namely Opadry II Pink, containing PVA, for good appearance and to protect the tablet from environment. The film coated matrix tablets were evaluated for test such as uniformity of weight, hardness, thickness, friability and drug content. The average percentage deviation of all tablet formulation was found to be (F1: -1.5 to +1.5; F2: -1.4 to +1.1; F3: -1.3 to +1.5; F4: -0.9 to +1.5; F5: -1.3 to +2.5; F6: -1.8 to +1.4) within the pharmacopoeial limit. The thickness of the matrix tablet was found to be in the range of 4.3 to 4.4 mm. The hardness of all batches ranged from 9.25 to 9.96 kg/cm^2.

***Invitro* evaluation of modified release film coated tablet**

The performance of modified release formulation has been reported to be greatly affected by physicochemical properties of polymer. The amount of polymer may influence the release of drug from the formulation.

In vitro release study performed in 0.1N HCl with 900 ml, paddle, 50 rpm, reveals that the release of drug was retarded with the proportional increase of the polymer concentration. When the hydrophilic matrix tablets of Class III drug come into contact with the dissolution medium, they take up water and swell, forming a gel layer around the matrix. Then the dissolved drug diffuses out of the swollen hydrophilic matrix at a rate determined by the amount and viscosity of Polysaccharide B-1459 and Polyethylene oxide in the tablet formulation. The hydrophilic polymer swells quickly & completely providing a stronger gel to prevent the immediate tablet disintegration and controlling the diffusion of the drug.

In vitro release study data indicate that duration of release of drug is dependent on the percentage of selected polymer used in the formulations. 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.[16]

Initially tablets prepared with drug to polymer ratio of 1:0.8 with Polysaccharide B-1459 in formulation F1 released 100% of drug within 2 hrs. Hence the polymer concentration was increased in the further trials of F2 and F3 with drug to polymer ratio of 1: 1.4 and 1: 2 respectively, which released 100% drug at 3 & 4 hrs respectively, which states that the amount of polymer incorporated was not adequate to control the release of drug from the formulation. Hence in Formulation F4, the polymer Polysaccharide B-1459 was replaced with another non cellulosic polymer namely Polyethylene oxide with drug to polymer ratio of 1: 2. But the rate of drug release was not matching with that of innovator, releasing (100 %) at the end of 6 hrs. Hence formulations F5 and F6 were designed with the combination of two polymers namely Polysaccharide B-1459 & Polyethylene oxide in the ratio of 1.4: 2 & 1.08: 2 respectively. Formulation F5 was found to release the drug more than 12hrs which was not matching with the innovator as the release of drug was more retarded than the innovator release profile. Hence next trial F6 formulated showed a comparable release profile releasing the drug of 100% at 10hrs matching with innovator. when compared with the marketed product F6 showing similarity factor(f_2)70. F6 shows significant similarity with the marketed product.

CONCLUSION

From the foregoing investigation it may be concluded that the release rate of drug from the matrix tablets can be governed by the combination of hydrophilic polymer namely Polysaccharide B-1459 and PEO when used in an appropriate concentration and maintaining the impurity limit within the proposed specification. Slow, controlled and complete release of Trimtazidine di hydrochloride over a period of 10hr was obtained from the matrix tablets formulated by employing Polysaccharide B-1459 and PEO . Hydrophilic matrix tablets of Trimtazidine di hydrochloride can successfully be employed as a once a day oral controlled release drug delivery system.

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REFERENCES

[1] Onay-Besikci A et al., *Cardiovascular Therapeutics* 26 (**2008**) 147–165
[2] David A. Fairman et al., *Circ Res*. **2003**; 93:e26-e32. Jul 17, 2003
[3] Sunil Kamboj et al., *Pharmainfo*, **2009** Vol.7 Issue 6.
[4] R.K.Khar, S.P.Vyas (**2002**) "*controlled drug delivered*". Pg. no .1-50.
[5] Jain N.K., "Controlled and Novel Drug Delivery" CBS 1-2, **2002**, pg.no.676-698.
[6] Mohammad Mahiuddin Talukdar et al., *International Journal of Pharmaceutics* 129 (**1996**) 233-241.
[7] Sung-Up Choi*et al., Drug Development and Industrial Pharmacy* **2003**, Vol. 29, No. 10, Pages 1045-1052
[8] Rowe RC. *J Pharm Pharmacol* **1977**; 29: 723–726.
[9] Aulton ME, and well TI. Pharmaceutics: The Sciences of Dosage form Design, London, England; Churchill Livingstone; **1998**.
[10] Chang R, Robinson JR. Sustained release from tablets and particles through coatin. In : Libreman HA, Lachman L and Schwartz JB (Eds). Phamaceuticls Dosage form Tablets. 2nd Edn, vol.3, Marceel Dekker ; **1990**: 199-302.
[11] Hadjiioannou TP, Christian GD, koupparis MA. Quantitative calculations in pharmaceutical practices and Research New Dehli, NY: VCH publishers INC; **1993**: 345-348
[12] M. A. Naushad et al., *Journal of Analytical Chemistry* Volume 63, Number 10 / October, **2008**.
[13] Chowhan ZT. *J Pharm Sci* **1980**; 69: 1–4.
[14] Hiremath PS, Saha RN. *AAPS PharmSciTech*. **2008**;9(4):1171-8. Epub 2008 Nov 19
[15] Saleh M. Al-Saidan et al., *AAPS PharmSci- Tech* (1) Article 5, 30 June **2005**.
[16] Manish Shivadas Wani, *Pharmainfo* Vol. 6 Issue 1 **2008**.