Design fabrication and characterization of controlled released tablets of Trimetazidine di hydrochloride

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ABSTRACT

The purpose of the present study was to formulate the oral controlled release Trimtazidine di hydrochloride tablets by using HPMC and Xanthan gum as rate controlling polymer. The tablets were prepared by direct compression method. 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 UV 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. Formulation F1, F2, F4 and F5 failed to sustain release beyond 10 hours. Among all the formulation, F3 shows 99.63 % 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.

Keywords: Trimtazidine di hydrochloride, Matrix tablets, direct compression, Controlled release.

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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

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60mg daily in divided doses as an immediate release preparation.[1, 2] 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.[3] 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. [4] 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.[5] 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 [6] xanthan gum is used to prepare sustained-release matrix. Xanthan gum 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, Xanthan gum and Polyethylene oxide to produce a controlled release dosage form containing Trimtazidine di hydrochloride.[7] The effect of the polymer concentration on the in- vitro release rate was studied.

MATERIALS AND METHODS

Trimetazidine di hydrochloride was obtained from (Strides Arcolab, Bangalore). Xanthan gum, HPMC is obtained from (S.D. Fine Chemicals, Mumbai). Magnesium strearate and Arosil was obtained from (Loba Chemicals, Mumbai). All other ingredients used were of analytical grade.

Preparation of matrix tablets [18, 19]
Matrix tablets were prepared by direct compression method. The composition of various formulations was shown in **Table 1.** Trimtazidine Di Hydrochloride, Xanthan gum, PVP K30 and Lactose through #30 mesh and add Magnesium stearate and Arosil through #40 mesh and collect separately in polyethylene bag. Tablets were compressed at 200 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 [8] six different formulae, having different

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concentrations were developed to evaluate the drug release and to study the effect of polymer concentration on drug release.

Evaluation of blend:
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 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**. [10]

Evaluation of Tablets:
Thickness:
Thickness of the tablets was determined using a vernier caliper (For-bro engineers, Mumbai, India). [11]

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. [12]

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

Friability
The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai, India). Tablets of a known weight (W_0) 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

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

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

Drug content (Assay)
Five tablets were weighed individually, and the drug was extracted in phosphate buffer. The drug content was determined according to the IP.

***In Vitro* Release Studies** [14-17]
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 **Table 4** and **Fig.1**.

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In vitro drug release profile of best formulation was compared with market product drug release profile shown in Fig.2**.**

Table: 1

S.No.	Ingredients	F1	F2	F3	F4	F5	F6
1	TRIMETAZIDINE DI HYDROCHLORIDE	35.00	35.00	35.00	35.00	35.00	35.00
2	HPMC K4M	60.00	70.00	80.00	-	-	-
3	XATHAM GUM	-	-	-	60	70.00	80.00
4	LACTOSE	93	103	113	93	103	113
5	PVP K30	8.00	8.00	8.00	8.00	8.00	8.00
6	AROSIL	2.00	2.00	2.00	2.00	2.00	2.00
7	MAGNESIUM STEARATE	2.00	2.00	2.00	2.00	2.00	2.00
	Average weight	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**	**200.00**

Table- 2: Data's for Evaluation of Properties of the Blended Powder for Trimetazidine Di Hydrochloride Controlled Release Tablets

S.No	Formulation Code	Angle of repose	Loose Bulk Density	Tapped Bulk Density	Hauser ratio	Compressibility index
1	F1	33 ± 0.65	0.4546	0.5214	1.16	14
2	F2	42 ± 0.72	0.4251	0.5346	1.25	19
3	F3	47 ± 0.77	0.4168	0.5684	1.36	27
4	F4	29 ± 0.29	0.4521	0.5022	1.18	11
5	F5	32 ± 0.81	0.4338	0.5213	1.13	16
6	F6	30 ± 0.72	0.4321	0.4751	1.10	9

* All values are expressed as mean $\pm$ S.D, n = 5.
Tablet properties of the different formulations of Trimtazidine Di Hydrochloride controlled release matrix tablets

Table 3: Data's for Physical Evaluation for Trimetazidine Di Hydrochloride Controlled Release Tablets

S.No	Formulation code	Hardness	Thickness (mm)	Avg. wt (mg)	Drug content (%)
1	F1	8.15 ± 1.0	4.2 ± 0.15	200 ± 2.0	98.3 %
2	F2	8.14 ± 1.1	$4.2 \pm .0.21$	199 ± 1.4	98.1 %
3	F3	8.02 ± 0.5	4.3 ± 0.03	201 ± 1.2	97.6 %
4	F4	8.57 ± 0.3	4.3 ± 0.32	201 ± 1.5	99.1 %
5	F5	8.65 ± 0.4	4.2 ± 0.50	201 ± 2.0	99.3 %
6	F6	8.98 ± 0.7	4.3 ± 0.19	202 ± 1.6	99.4 %

Table 4: Dissolution Profile for Controlled release tablets of Trimetazidine Di Hydrochloride drug

Time (hrs)	% of Drug Release						
	Reference	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
1	36.15±1.02	77.59±0.09	61.58±0.42	48.25±0.52	69.05±0.58	38.02±1.11	39.28±0.28
2	54.20±1.23	88.23±1.36	74.03±1.25	58.07±0.59	86.51±086	53.29±1.25	57.54±1.31
3	64.52±1.28	97.18±1.06	89.28±1.02	67.25±0.02	98.18±1.09	78.87±0.68	68.98±1.58
4	77.31±0.92	-	99.29±1.02	79.27±0.05	-	87.32±1.28	82.65±1.36
6	88.56±0.75	-	-	88.09±1.26	-	98.86±.03	94.56±0.09
8	94±0.83	-	-	95.19±1.26	-	-	99.24±0.52
10	97±1.05	-	-	99..63±1.26	-		-

All values are expressed as mean $\pm$ S.D, n = 5.; F1 -- 5,   F2 -- 70

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Stability Study

Accelerated stability studies (AST) was carried for optimized batch F3 by exposing it to environmental condition like 40 °C/ 75%RH for one month. The sample was taken at different time interval i. e. 7, 14, 21, 28 and 45th day and analyzed for physical parameters like hardness, uniformity of content and percentage cumulative drug release.

RESULTS AND DISCUSSION

Evaluation of controlled release 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/cm2. 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 pharmacopoeial properties and complied with the in-house/BP specifications for weight variation, drug content, hardness and friability.

Invitro evaluation of controlled release 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 HPMC and xanthan gum 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 diffusion 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 with HMPC in formulation F1 released 97.18 % of drug within 3 hrs. Hence the polymer concentration was increased in the further trials of F2 released 99.29% in 4 hours. Hence the polymer concentration was again increased in other trail of F3 released 99.63% in 10 hours.

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Hence in Formulation F4, the polymer HPMC was replaced with another Hydrophilic polymer namely xanthan gum. Tablets were prepared with different concentration of the polymer i.e., F4, F5 and F6 by increasing the polymer concentration. Hence the drug released from formulation of F4, F5 and F6 were 98.18% in 3 hours, 98.86% in 6 hours and 99.24 in 8 hours respectively.

Hence trial F3 formulated showed a comparable release profile releasing the drug of 99.63 % at 10hrs matching with innovator. When compared with the marketed product F3 showing similarity factor (f2)70. F3 shows significant similarity with the marketed product.

Fig No.1: Dissolution Profile for Controlled release tablets of Trimetazidine Di Hydrochloride drug
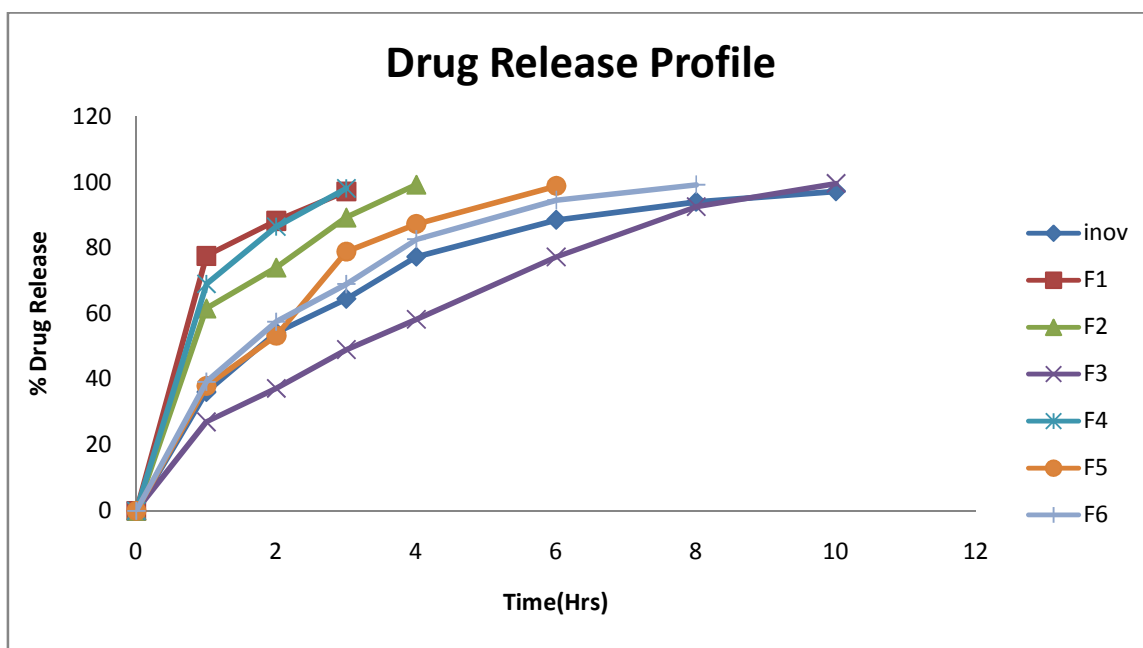
Fig No.2: Comparison of Dissolution of Profile of Innovator with Best Formulation F3

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INNOVATOR Vs F3

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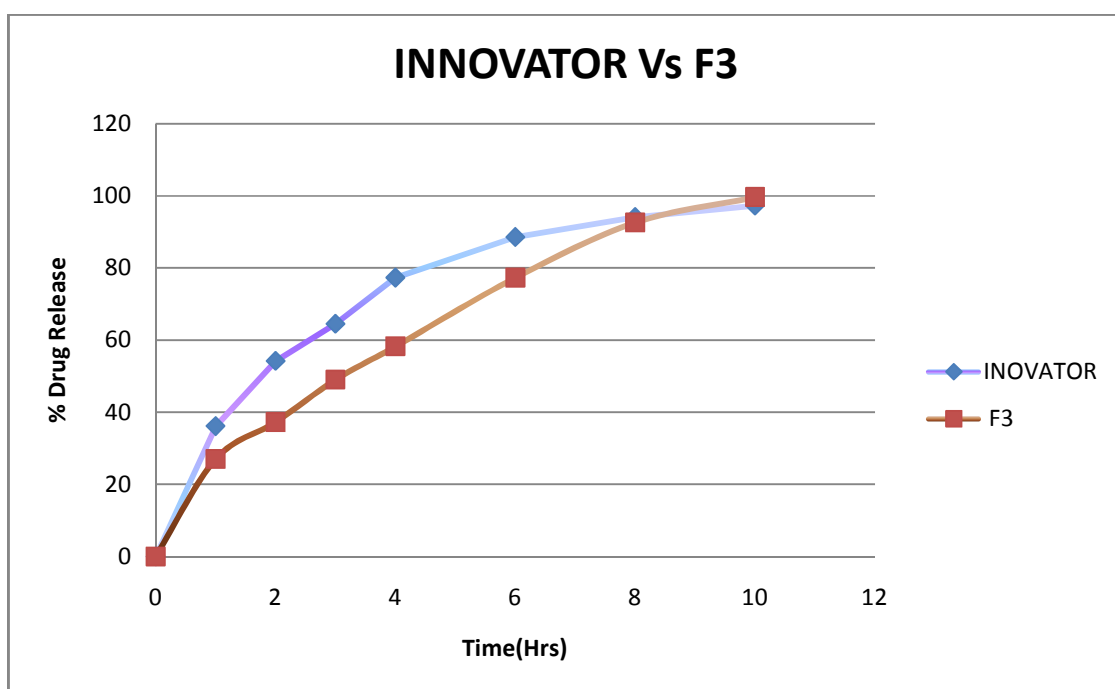
CONCLUSION

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 HPMC and xanthan gum 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 controlled released tablets. 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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