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Research Article

OPTIMIZATION AND EVALUATION OF A FORMULATION CONTAINING LOW SOLUBLE ANTIHYPERTENSIVE AGENT

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ABSTRACT

The aim of this project was to develop once daily immediate release tablet of a Telmisartan, an antihypertensive agent. The formulations should have immediate release characteristics and a dissolution showing no essential pH dependency within the physiological relevant pH interval of the gastrointestinal tract. Telmisartan has poor and pH dependent water solubility in order to enhance its dissolution different alkalizers were used in an appropriate ratio. Tablets were evaluated for various parameters like, weight variation, content uniformity, in-vitro dissolution studies were performed using United States Pharmacopeia (USP) apparatus type II. Six batches of immediate release tablet were developed and among them F6 showed satisfactory physicochemical characteristics and drug content uniformity and release of a drug within 60 minutes with maximum release of 99.1% which is comparable to reference product.

Keywords: Antihypertensive agent, Telmisartan.

INTRODUCTION

Telmisartan is an angiotensin receptor blocker (ARB) used in the management of hypertension. It is a competitive antagonist and inverse agonist of angiotensin II, 10000 more selective for AT1 than AT2 receptor. It blocks all overt actions of angiotensin II, viz. vasoconstriction, release of aldosterone and Adr from adrenals, central actions like vasopressin release, growth promoting actions on heart and blood vessels. Telmisartan has a long duration of action, and has the longest half-life of any ARB (24 hours). The usually effective dose of telmisartan is 20,40,80 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, telmisartan dose can be increased to a maximum of 80 mg once daily. The pharmacokinetics of orally administered Telmisartan is nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. The solubility of Telmisartan in aqueous solutions is strongly pH-dependent, with maximum solubility observed at high and low pH. In the range of pH 3–9 it is only poorly soluble. Telmisartan is active as such: it is not a prodrug. The Telmisartan molecule is unusually stable Telmisartan is manufactured and supplied in the free acid form and is has a very poor solubility, and so low bioavailability. Telmisartan is readily ionizable and subsequently the solubility is also pH dependent. Hence, the objective of the present study was to develop Telmisartan (IR) immediate release tablets using NaOH and meglumine and increase the release behaviours. Here NaOH is strong base which is used to dissolve the drug as the drug is soluble in strong base. Meglumine is used as a basic agent which also helps for dissolving the drug so the desired solubility of the formulation can be achieved.

MATERIALS AND METHODS

Materials

Telmisartan, Meglumine, Croscarmellose sodium, Crospovidone XL-10, PVP K-25, Lactose monohydrate (200M) were available from Cadila healthcare ltd., Ahmedabad.

All reagents and solvents used were of analytical grade satisfying pharmacopoeial standards.

Preparation of Telmisartan tablet

Preparation of granulating spray solution

Take a requird quantity of purified water in a tank and dissolve NaOH in it. Then add Telmisartan, PVP K-25, Meglumine in it with stirring till clear solution prepared.

Spray the granulating solution on to the bed of Lactose monohydrate (200M), Crospovidone XL-10/Croscarmellose sodium in a FBE(Pam-Glatt) bowl followed by 15 minutes drying.

Process parameters for granulation step

Inlet air temperature: 40-75 °C

Product temperature: 42-45°C

Exhaust temperature: 25-45 °C

Spraying rate: 50-150 gm/min

Process parameters for drying step

Inlet air temperature: 45-60 °C

Screen the granules on sieve through co-mill containing a mesh size of 1.5 mm.

Blending and compression

Screened granules are finally blended with sorbitol/manitol using a suitable mixer with a revolution of 10 rpm for about 10 minutes followed by 3 minutes blending with sodium stearyl fumarate and 2 minutes blending with magnesium stearate to form a ready for compression blend. Compressed the blend to produce a tablet containing a target weight of 600mg.

Evaluation of tablets

The prepared IR tablets were evaluated for the following parameters.

1). **Hardness** was measured by tablet hardness tester (Pharmatron) in kp (Kilo Pascal),

2). **Thickness** which was measured by Vernier Caliper in millimeter (mm),

3). **Friability** was measured by Roche friabilator (Electrolab) for 100 rpm,

4). **Disintegration** time was measured by Disintegration tester (Electrolab),

5). **Weight variation** (Average weight of ten tablets by electronic weighing balance),

6). **LOD** which was measured by Mettler-Toledo.

***In vitro* drug release studies**

Dissolution studies were conducted using a USP II paddle method (75 rpm, 37 °C, and 900 ml dissolution medium) with a Tablet dissolution tester (Electrolab). Telmisartan tablet (80mg) was exposed in a medium (pH7.5 phosphate buffer). Samples were withdrawn from the dissolution medium at predetermined intervals (10, 15, 20, 30, 45 and 60 min) and then drug concentration was determined by UV (Shimadzu) at 296nm. An equivalent amount of fresh medium was added to maintain a constant dissolution volume.

The reference product and a selected batch(F6) were again taken for a dissolution study in a different media(4.5pH Phosphate buffer, 0.1N HCl, 4.5pH acetate buffer) to compare dissolution profile of a selected batch with a reference product. Dissolution profile in different media was seen in a graph.

Stability study

The selected batch (F6) was kept at 40°C with 75% RH and the samples were withdrawn at 30, 60 and 90 days for physical and *in vitro* evaluation of drug release.

RESULTS AND DISCUSSION

All the tablet formulations showed acceptable pharmacotechnical properties and complied with the range specified by US Pharmacopoeia for Disintegration, weight variation, friability, hardness, LOD.

In first two batches i.e. F1 to F2 mannitol was used as water soluble diluents, povidone used as a binder, croscarmellose sodium is as disintegrant where as sodium carbonate was used as a alkalizer. The desired dissolution profile (more than 90% of the drug should be released in 30 minutes) was not achieved by using sodium carbonate as a alkalizer. In a third batch, sodium hydroxide and meglumine were used as a alkalizer in a proper ratio. In batch F4 to F6, mannitol was replaced with a sorbitol and crospovidone XL-10 was used as a disintegrant. From batch F4 to F6 various ratio of sodium hydroxide and meglumine were used. Among all batches, F6 show comparable dissolution profile with reference product than any other batches. Figure 1 depicts the effect of different alkalizers on the release from tablets. Assay of the optimized batch was carried out by the HPLC method and was found to be 98.4%. Stability studies revealed that there was no significant change in appearance, assay, and drug release profile at 40 °C with 75% RH.

CONCLUSION

When a tablet is ingested it undergoes disintegration, deaggregation and dissolution before being absorbed, the rate and extent of which into the systemic circulation determines its bioavailability. The solubility/dissolution behaviour of a drug is key determinant to its oral bioavailability, being the rate-limiting step to absorption of drugs from the gastrointestinal tract. Consequently poor solubility results in low bioavailability increase in the dosage, large inter and intra-subject variation and large variations in blood drug concentrations under fed versus fasted conditions.

It has been concluded that the Telmisartan IR tablets can be formulated with good release profile for a specified period of time up to 60mins and also have sufficient solubility of the telmisartan in the slightly acidic and neutral pH region. It decreases the frequency of dose administration, prevents nocturnal attack and improves patient compliance by using moderate amount of NaOH and Meglumine.

Table 1: Different formula for Telmisartan tablet 80mg.

Ingredients	Quantity (mg/tablet)					
	F1	F2	F3	F4	F5	F6
Telmisartan	80	80	80	80	80	80
Sodium hydroxide	*	*	6.2	6.5	6.7	6.7
Sodium carbonate	20	26	*			
Meglumine	*	*	26	25	24	24
PVP K 25 (Polyvinyl pyrolidone)	24	24	24	24	24	24
Purified water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Lactose monohydrate(200M)	246	238	231.8	232.5	234.3	234.3
Croscarmellose sodium	10	12	*	*	*	*
Crospovidone XL-10	*	*	12	12	14	12
Mannitol	210	210	200	*	*	*
Sorbitol	*	*		200	197	200
Sodium stearyl fumaratee	*	15	15	15	15	14
Magnesium stearate	10	5	5	5	5	5
Total weight (mg)	**600**	**600**	**600**	**600**	**600**	**600**

Table 2: Physical evaluation of a telmisartan tablet 80mg

Parameters	F1	F2	F3	F4	F5	F6
Disintegration time	11 mins 10 second	12 mins	10 mins 25 seconds	8 mins 10 seconds	7 mins 25 seconds	8 mins 35 seconds
Hardness (kP)	8 to 9	8 to 9	8 to 9	8 to 9	8 to 9	8 to 9
Width (mm)	8±0.2	8±0.2	8±0.2	8±0.2	8±0.2	8±0.2
Length (mm)	17.5±0.2	17.5±0.2	17.5±0.2	17.5±0.2	17.5±0.2	17.5±0.2
Friability	0.12%	0.27%	0.19%	0.22%	0.26%	0.18%
L.O.D.	1.60%	2.10%	1.75%	1.85%	1.55%	1.45%
Avg. wt. of 10tablets(mg)	600.25	600.30	599.90	600.90	600.09	600.15

Table 3: In-vitro dissolution profile of all batches in 7.5pH phosphate buffer, 900ml, paddle, 75rpm

Time (mins)	Micardis	F1	F2	F3	F4	F5	F6
10	54.7	48	56.3	53	59.1	65.9	55.4
15	69.4	59.3	65.9	59.2	79.7	84.8	74.2
20	80.1	64.9	72.1	68.9	90.1	92.0	84.3
30	91.2	78	88.2	88.3	100.5	98.2	94.7
45	96.2	89.3	93.1	97.4	100.3	102.0	96.4
60	99.9	94.3	93.5	97.6	nil	101.0	99.1

Table 4: In-vitro dissolution profile of reference and (F6) in 4.5pH phosphate buffer, 900ml, paddle, 75rpm.

Time (mins.)	Micardis	F6
5	10.4	9.2
10	17.0	17.8
15	20.8	24.6
30	26.6	28.9
45	28.9	35.6
60	45.2	39.6
75	46.3	40.7

Table 5: In-vitro dissolution profile of reference and (F6) in 4.5pH acetete buffer, 900ml, paddle, 50rpm

Time (mins.)	Micardis	F6
5	10.4	9.2
10	17.1	17.9
15	21.2	25.1
30	29.0	35.2
45	45.2	40.1
60	46.9	42.1

Table 6: In-vitro dissolution profile of reference and (F6) in 0.1N HCl, 900ml, paddle, 75rpm.

Time (mins.)	Micardis	F6
5	16.1	11.4
10	29.0	22.5
15	40.1	33.5
30	62.0	60.9
45	74.3	81.0
60	85.3	91.2

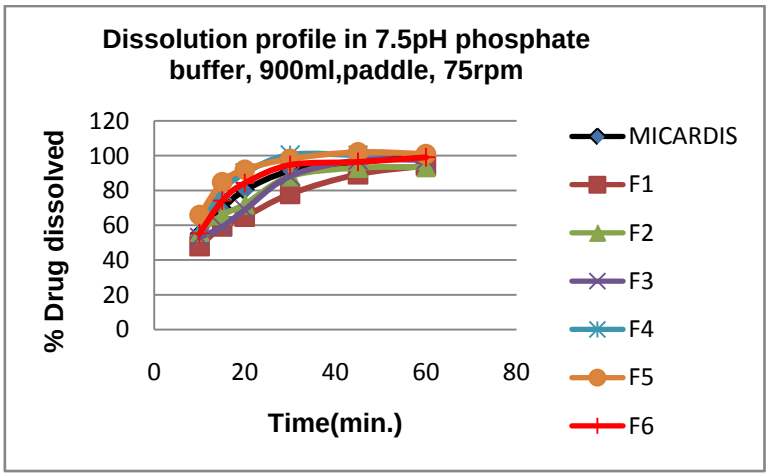

Fig. 1: Dissolution profile of reference product and all batches (F1 to F6) in 7.5pH phosphate buffer, 900ml, paddle, 75rpm

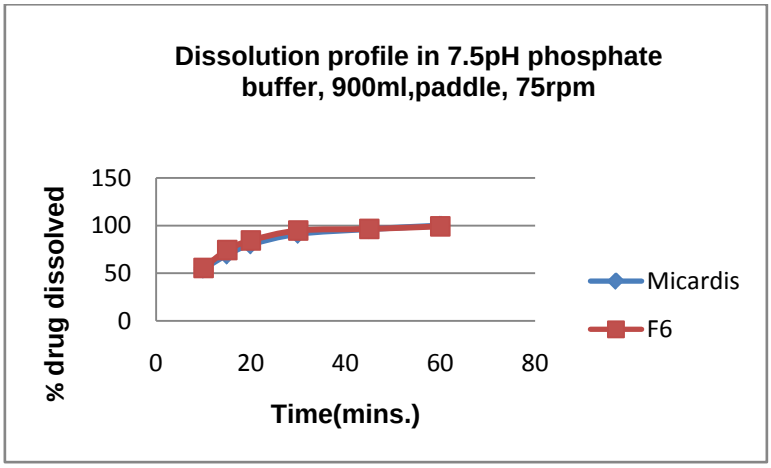

Fig. 2: Dissolution profile of reference product and selected batch(F6) in 7.5pH phosphate buffer, 900ml, paddle, 75rpm

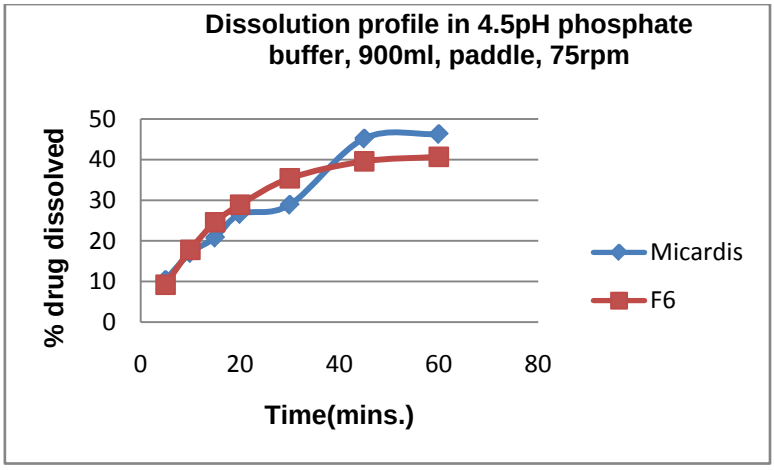

Fig. 3: Dissolution profile of reference product and selected batch (F6) in 4.5pH phosphate buffer, 900ml, paddle, 75rpm

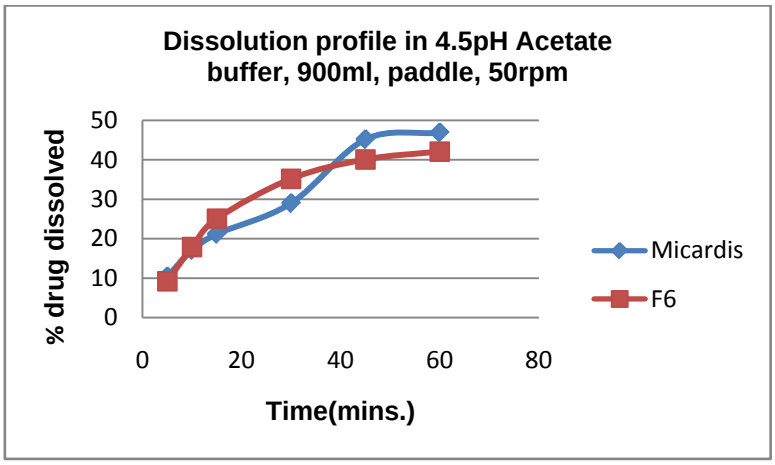

Fig. 4: Dissolution profile of reference product and selected batch (F6) in 4.5pH Acetate buffer, 900ml, paddle, 50rpm

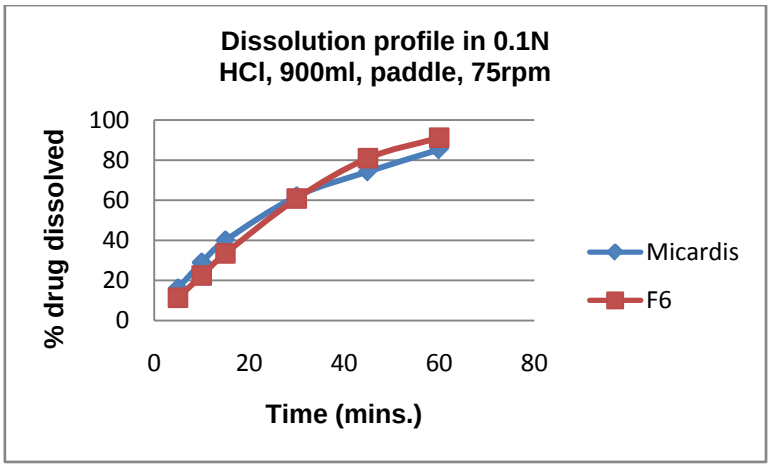

Fig. 5: Dissolution profile of reference product and selected batch(F6) in 0.1N HCl, 900ml, paddle, 75rpm.

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