Research Article
CODEN (USA): IJPLCP

[Dhiman *et al.*, 3(11 Suppl.): Nov., 2012]
ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Formulation and *In-Vitro* evaluation of fast dissolving tablets of telmisartan

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Abstract

Telmisartan is a Anti-hypertensive drugs which is insoluble in water, hence the drug may be slowly or incompletely dissolves in the gastro-intestinal tract. So the rate of dissolution and therefore its bioavailability is less (bioavailability 42%). In the present study an attempt has been made to prepare Fast Dissolving tablets of Telmisartan by using Superdisintegrants– Cross carmellose sodium, Microcrystalline cellulose and sodium starch glycolate, level of addition to increase the rate of drug release from dosage form to increase the dissolution rate and hence its bioavailability. The tablets were prepared by Direct Compression methods and the prepared blend and tablets were evaluated for their physicochemical properties and In-Vitro dissolution study. The evaluation studies were performed such as Weight Variation, Thickness, Hardness, Disintegrating Time, Wetting Time, and In-Vitro Drug Release. The Disintegration time of Fast Dissolving tablets were increased by the addition of concentration of Superdisintegrants.

Key-Words: Direct compression, *In vitro* dissolution and *In vitro* disintegration time, Fast dissolving, Telmisartan

Introduction

Orally disintegrating tablets offer great advantages for patients having difficulty in swallowing. The condition in which patient suffers from difficulty in swallowing is known as 'Dysphagia'. It is common among all age groups, especially in elderly patients. Disorder of dysphagia is associated with many medical conditions including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy . There is an important role of drinking water in the swallowing of oral dosage forms but some time people experiences an inconvenience in swallowing. The problems can be resolved by means of Mouth Dissolving Tablets (MDTs), when water is not available as during journey, also in case of the motion sickness (kinetosis) and sudden episodes of coughingduring the common cold, allergic condition and bronchitis. MDTs are also abbrevated as "fastmelting, fast-dissolving, oral disintegrating or orodisperse tablets".

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The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations . Recently European Pharmacopoeia defines the term "Orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing in less than three minutes.

Oral drug delivery remains the most preferred route for administration of various therapeutic agents. Recent advances in technology prompted researchers and scientists to develop oral disintegrating tablets (ODTs) with improved patient convenience and compliance. ODTs are solid unit dosage form which dissolve or disintegrate rapidly in the mouth without water or chewing. Novel ODT technologies address many patient and pharmaceutical needs such as enhanced life cycle management to convenient dosing particularly for pediatric, geriatric and psychiatric patients who have difficulty in swallowing (Dysphagia) conventional tablet and capsules. Technologies used for manufacturing of ODTs are either conventional technologies or patented technologies. This review depicts the various aspects of ODT formulation, superdisintegrants and technologies developed for ODT, along with various drugs explored, evaluation tests and marketed formulations in this field.

Telmisartan is a nonpeptide Angiotensin Receptor II (Type- ATI) Antagonist, That Cause Inhibition Of the action of Angiotensin II on Vascular Smooth Muscle in the Symptomatic Treatment of Hypertension. The Bioavailability of Telmisartan is Poor About 45%, which due to Extensive First Pass hepatic metabolism; The Bioavailability can be increase by Fast Dissolving Formulation. Conventional Telmisartan tablets available in market are not suitable where quick onset of action is required. To provide the patients with the most conventional mode of administration, there was a need to develop rapidly disintegrating dosage form, particularly one that Disintegrates and dissolves/disperses in saliva and can be administered without need of water.

Material and Methods

Telmisartan was used as active pharmaceutical ingredient which is angiotensin receptor II antagonist.Microcrystalline cellulose, Croscarmellose sodium and Sodium starch glycolate was used as superdisintegrants. Mannitol was used as diluent, Sodium Lauryl Sulphate as solubility enhancer and Magnesium Stearate as lubricant.

Preparation of fast dissolving tablets of Telmisaratan

The drug, Telmisartan equivalent to 40 mg and mannitol were mixed thoroughly in glass mortar using a pestle. Superdisintegrants (Microcrystalline cellulose, Croscarmellose sodium and Sodium starch glycolate) were incorporated in the powder mixture and finally magnesium stearate was added as lubricant and SLS was added as solubility enhancer. The whole mixture is then passed through sieve no.60 twice. Tablets were prepared using 8 mm round flat-faced punch of the rotary tablet machine compression force was kept constant for all formulation.

Evaluation of Telmisartan Fast Dissolving Tablets

Weight variation test

To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

Thickness

The thickness of the tablets was determined using a Micrometer screw gauge. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm.

Hardness

The resistance of tablets to shipping, breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured.

Friability

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. A sample of preweighed 6 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable. Percent friability (% F) was calculated as follows:

Uniformity Of Drug Content:-

Five tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 40 mg of Telmisartan was weighed and dissolved in 100 ml of 0.1 N HCl (pH 1.2) This was the stock solution from which 1 ml sample was withdrawn and diluted to 10 ml with 0.1 N HCl (pH 1.2). The absorbance was measured at wavelength 291 nm using double beam UV-Visible spectrophotometer.

Content uniformity was calculated using formula:

% Purity = 10 C (Au / As)

Where, C - Concentration

Au and As – Absorbance of unknown and standard respectively

Wetting Time

A piece of tissue paper folded twice containing amaranth powder on the upper surface was placed in a small Petri dish (ID =6.5 cm) containing 6 ml of 0.1N HCl, a tablet was put on the paper and the time required for formation of pink color was measured as wetting time. The study was performed in triplicate.

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then weighed.

Water absorption ratio R was determined using following equation:

$$R = \frac{(Wb - Wa)}{Wa} \times 100$$

Wa = Weight of the tablet after wetting

Wb= Weight of the tablet before wetting

Disintegration Time

Initially the disintegration time for orodispersible tablets was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets

were placed in the disintegration tubes and time required for complete disintegration, that is without leaving any residues on the screen was recorded as disintegration time.

A modified method was also used to check the disintegration time. In about 6-8 ml of 0.1N HCl (pH 1.2) was taken in measuring cylinder. Tablet was placed in the cylinder and complete dispersion of tablet in the cylinder was recorded as the disintegration time.

In-vitro dissolution study

The release rate of telmisartan from fast dissolving tablets was determined using United State Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1N HCL pH 6.8 dissolution medium, at 37±0.5°C and 75 rpm. Sample volume of 10 ml was withdrawn at regular time intervals from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analyzed spectrophotometrically at 291 nm using 0.1N HCl as a blank. Drug content in dissolution sample was determined by calibration curve.

Results and Discussion

Attempt was made in the present investigation to make a Fast Dissolving Tablet of Telmisartan by direct compression method. The formulation was carried out using two different types of super disintegrants and optimizing their concentration and hardness of the tablet to give the minimum disintegration time and get maximum drug release. The pure drug Telmisartan and various excipients used in formulation were characterized by FT-IR spectroscopy to know their compatibility. The FT-IR spectra did not show the possibility of interaction between Telmisartan and superdisintegrants used in the fast dissolving tablet. Since the flow property of the powder mixture are important for the uniformity of the mass of the tablets, the flow of the powder was analysed before compression of the tablets.

The angle of repose for powder blend was found in the range of 24-28°. Bulk densities were found in the range 0.73-0.77 g/ml, compresibility index were found to be below 20% and Hausner's ratio was ranging from 1.06-1.08. Thus, it can be concluded that the powder blend for all formulations possessed good flowability and compressibilty.

Hardness of tablets of each formulation was measured and found in the range of 3.2-3.9 kg/ cm^2. A difference in tablet hardness reflects differences in tablet density and porosity, which are supposed to be result in to different release patterns of the drug by affecting the rate of penetration of the dissolution fluid at the surface of the tablet. For the friability of tablets the percentage weight loss of the tablets of each formulation was measured and found in the range of 0.05% to 0.09% which was within acceptable limit i.e. <1%w/w. The weight variation from each batch showed uniformity of weight as per IP limits. Drug contents of tablets from each batch were found in the range of 98.06% to 99.87%.

From the data it was found that F6 formulation showed drug release of 99.087%, which is selected as optimum as hardness, friability, DT, wetting time was good as well as percentage cumulative release was more as compared to other formulation and this may be due to increase in wettability of the drug by increasing the surface area of the drug particles (*i.e.*, faster disintegration). The release of F8, F7, F5, F4 was 95.986%, 97.484%, 89.800%, 93.867% respectively. It was concluded that the increase in disintegrant concentration increases friability and hardness was reported less. When compared with the marketed formulation, the % cumulative release of marketed preparation obtained 80.497%. The addition of SLS also enhances the solubility of formulation. It was concluded that the disintegrant concentration should be optimum i.e. not higher or lower to give appropriate drug release.

The stability studies of the optimized formulation F6 of tablets revealed that there was no significant change in the physical parameters when stored at temperature and humidity conditions of 45± 2°C/ 75 ± 5 % RH.

No significant reduction in the content of the active drug was observed over a period of 28 days, however, storage temperature not exceeding 45°C and moisture proof packaging are essential to ensure stability of these formulations.

From the present study it can be concluded that fast disintegrating tablet for Telmisartan was successfully prepared by conventional direct compression method using superdisintegrants and the objective of this study was achieved. For better hardness and disintegration time, combination of Microcrystalline cellulose, Cross carmellose sodium and Sodium starch glycolate is required in the formulation.

Thus, the "patient-friendly dosage form" especially for pediatric, geriatric, bedridden, and non-cooperative patients, can be successfully formulated using this technology, and also provides faster and better drug

release, thereby, improving the bioavailability of drug as compared to the conventional marketed formulation.

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Table 1: Composition of telmisartan fast disintegrating tablets

Formulation Code	Drug (mg)	Sodium starch glycolate (mg)	Cross carmellose sodium (mg)	Micro-crystalline cellulose (mg)
F1	40	4.8	4.8	24
F2	40	4.8	4.8	16
F3	40	9.6	4.8	24
F4	40	9.6	4.8	16
F5	40	4.8	8	24
F6	40	4.8	8	16
F7	40	9.6	8	24
F8	40	9.6	8	16

Table No.2: Physical parameters of powder blend

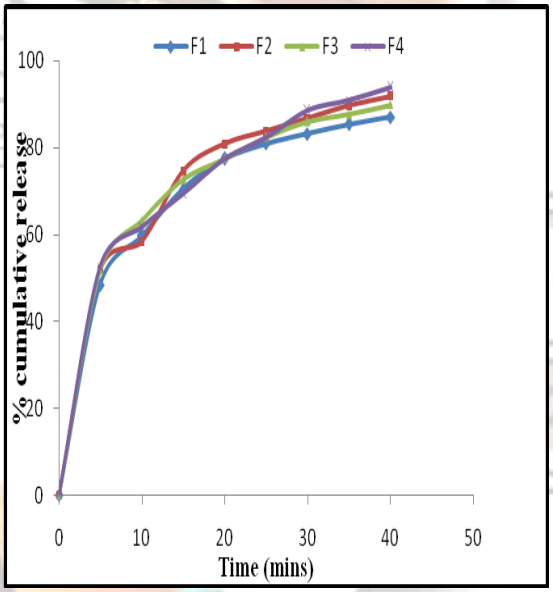
Parameters / Formulations Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Angle of Repose (^{0})	Carr's Index (%)	Hausner's Ratio
F1	0.73	0.79	25.93	7.5	1.09
F2	0.74	0.8	26.71	7.5	1.07
F3	0.74	0.8	26.71	7.5	1.08
F4	0.74	0.8	25.74	7.5	1.08
F5	0.74	0.81	26.31	7.4	1.09
F6	0.75	0.81	27.59	7.4	1.09
F7	0.75	0.81	25.85	7.4	1.06
F8	0.76	0.82	25.63	7.3	1.07

Table 3 : Physical parameters of tablets

Parameters / Formulations Code	Hardness (kg/cm^2)	Thickness (mm)	% Friability	Weight Variation (mg)
F1	3.9	2.94	0.05	164.35
F2	3.8	2.93	0.05	163.62
F3	3.5	2.93	0.05	162.83
F4	3.3	2.94	0.08	164.25
F5	3.6	2.96	0.05	159.73
F6	3.5	2.96	0.05	161.54
F7	3.3	2.98	0.09	159.25
F8	3.2	2.97	0.09	160.23

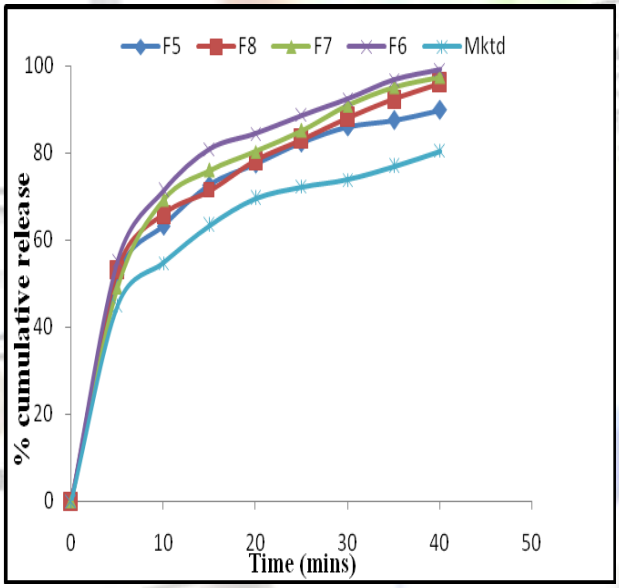
Table 4 : Results of disintegration time, wetting time, water absorption ratio and uniformity of content of fast disintegrating tablet formulation of Telmisartan

Formulations Code	Disintegration time (Sec) mean	Wetting time (Sec) mean	Water absoption ratio mean	Uniformity of content mean
F1	38.23	29.02	84.32	98.72
F2	36.32	31.45	88.92	98.23
F3	38.12	30.63	94.52	99.34
F4	34.87	18.30	97.98	98.99
F5	29.14	29.98	99.66	98.72
F6	25.11	12.02	100.58	98.59
F7	28.66	17.82	77.50	99.21
F8	24.47	13.28	80.80	99.90



1

Fig.1: Dissolution profile of formulation F1, F2, F3, F4 by disintegrant addition technique in 0.1 N HCL



2

Fig.2: Dissolution profile of marketed formulation and formulation F5, F6, F7, F8 by disintegrant addition technique in 0.1 N HCL