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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF TELMISARTAN USING NATURAL SUPERDISINTEGRANTS

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ABSTRACT
The purpose of the work is an attempt to made formulation and evaluation of fast dissolving tablets of Telmisartan by direct compression method with the aid of natural super disintegrant addition. Telmisartan is a Anti-hypertensive drug which is insoluble in water, hence the drug may be slowly dissolves in the gastro-intestinal tract. So the rate of dissolution and therefore its bioavailability is less (bioavailability 42%). The principal aim of this work is to improve bio availability of the drug, patient compliance & immediate control of hypertension. Fast dissolving tablets of Telmisartan were prepared by direct compression using orange peel pectin and *Plantago ovata* mucilage as super disintegrants. Ten formulations F1 to F6 were developed in such a way that total weight of the tablet remains the same. The tablets were evaluated for their pre and post-compression parameters. It was concluded that among ten formulations F6 showed highest drug release of 99.43% than other formulations and thus selected as the optimized formulation.

KEY WORDS: Telmisartan, Direct compression, Orange peel pectin, *Plantago ovata* mucilage.

INTRODUCTION

Fast dissolving tablets offer the luxury of much more accurate dosing than the primary alternative, oral liquids. This segment of formulation is especially designed for dysphagic, geriatric, paediatric, bed-ridden, travelling and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations [1,2]. Telmisartan is 4′-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl] methyl] biphenyl-2-carboxylic acid. It is an angiotensin II (AT1) receptor antagonist, which shows peak plasma levels approximately one hour after its oral administration and the plasma half-life is about 24 hours [3]. Telmisartan is used mainly to treat high blood pressure (hypertension). It may also delay progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes [4]. The present study is an attempt to develop and formulate fast dissolving tablets of Telmisartan with natural superdisintegrants which disintegrates in matter of seconds in the oral cavity, thereby reducing the time of onset of pharmacological action.

MATERIALS AND METHODS

Telmisartan was received as a gift sample from Aurobindo Pvt Ltd, Hyderabad. Orange peel pectin and *Plantago ovata* were purchased from local market in Hyderabad. Microcrystalline Cellulose, Magnesium stearate, Talc, Aspartame, Mannitol and PVP was obtained from Lobachemie. Pvt. Ltd, Mumbai, India.

Methodology for extraction of *Plantago ovata* mucilage [5]

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- Mucilage was isolated by soaking seeds of Plantago ovata in water (20-30 times) for at least 48 hrs, boiled for 2 hrs subsequently mucilage was released into the water completely.
- With the help of the muslin cloth the mucilage was squeezed out and separated from seeds. The mucilage collected and precipitated using 3 times of 95% ethanol.
- Collected mucilage was dried in the oven at 50-55°. Dried mucilage was scraped and powdered using pestle and mortar. Powder was sieved using mesh no.60.

Extraction of orange peel pectin powder [6]

- Ripped orange peel was obtained from local fruit shop. Peel was carefully washed and dried under shade for 24 h, further dried at 60 °C in a hot air oven.
- Dried fruit peel was cut into pieces and powdered by electric grater. Powdered peel was further passed from sieve No. 20.
- Peel powder, 200 g of was dissolved in 1 L of water and 1 g of citric acid was added to maintain acidic pH 2.
- This solution was subjected to reflux condensation at 70 ºC for 6 h to extract pectin. The extractor thimble was a whatman cellulose thimble with 33 mm internal and 80 mm external length.
- Hot acid extract was pressed in a cheese cloth bag and the concentrated juice was cooled to 4 ºC. Pectin was precipitated by ethanol: water (2:1 v/v) treatment followed by continuous stirring for 15 min and allowed to stand for 2 h.
- Pectin coagulate was filtered through cheese cloth, washed with 95 % alcohol and pressed. Pressed pectin was further dried to constant weight at 35 – 45 ºC. Hard pectin cake was ground and passed through sieve No.60, stored in desiccators for further use.

Characterization of mucilage

Phytochemical characterization like alkaloids, carbohydrates, phytosterols, saponins, phenolic compounds, tannins, proteins and amino acids, gums and mucilage, tannins, flavanoids tests are performed for orange peel pectin and *Plantago ovata* mucilage. Physiochemical evaluation like solubility, LOD, pH, viscosity, swelling index, total ash, water insoluble ash and acid soluble ash was done.

Preparation of Telmisartan tablets

Telmisartan fast dissolving tablets were prepared in 6 formulations from F1 to F6 using the ingredients mentioned in the Table 1. Telmisartan tablets were prepared by using natural polymers like orange peel pectin and *Plantago ovata* to formulate fast dissolving tablets. All the ingredients with drug except magnesium stearate were taken in the mortar. The powder blend was then mixed well by using mortar and pestle for 15 to 30 min, and then each mixture was passed through # 80 sieve. Finally magnesium stearate was added as a lubricant and mixed thoroughly. Tablets were prepared using 8 mm round flat-faced punch of the rotary tablet machine compression force was kept constant for all formulations.

Weight uniformity

20 randomly selected tablets were weighed individually and the average weight and the standard deviation were calculated [7].

Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer [8].

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/cm2. Then constant force was applied by rotating the knob until the tablet fractured [9].

Friability

Friability of the tablets was determined using Roche friabilitor at 25 rpm/min for 4 min. 10 tablets were weighed and loss in weight (%) was calculated.

Friability = (W1 – W2) / W1 X 100

Weight of 10 Tablets = W1,

Weight of 10 Tablets after friability = W2

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

The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 10 cm diameter are placed in a Petri dish with a 10 cm diameter. Ten millimeters of water containing Eosin, a

water soluble dye, is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time [10].

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 . 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.

Dissolution Studies

Dissolution of Telmisartan fast dissolving tablets was studied in Apparatus II as per U.S.P. employing a paddle stirrer at 50 rpm using 900 ml of 0.1 N Hcl pH 6.8 as dissolution medium at 37±0.5°C. One tablet was used in each test. Aliquots of dissolution medium (5 ml) were withdrawn at specific intervals of time and analyzed for drug content by measuring the absorbance at 259 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution 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 [11].

RESULTS AND DISCUSSION

Fast dissolving tablets of Telmisartan were prepared by adding natural superdisintegrants like *Orange peel pectin* and *Plantago ovata* mucilages. Phytochemical, organoleptic and physiochemical characterization of the dried mucilages was done for natural superdisintegrants.

Powders for Effervescent compression were prepared and evaluated for flow properties like Angle of Repose, Carr's consolidation index and Hausner ratio. Those were found to be within in acceptance criteria to indicate good flow properties. The values are shown in Table 3. Post compressional parameters were tabulated in Table 4 & 5.

The angle of repose for powder blend was found in the range of 24-27°. Bulk densities were found in the range 0.73-0.76 g/ml, compresibility index were found to be below 20% and Hausner's ratio was ranging from 1.06-1.09. Thus, it can be concluded that the powder blend for all formulations possessed good flowability and compressibilty. The thickness of the formulations from F1-F6 was found to be 2.91±0.02 to 2.98 ± 0.02 mm and hardness was found to be 2.82±0.021 to 3.55±0.012kg/cm^2 and thus tablets were having good mechanical strength. 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 98.03% to 99.89%. Among all the formulations, F6 showed less than 32 sec. of disintegration time. The wetting time of all the formulations were found to be within 22 to 51 seconds, which complies with the official specifications. The water absorption ratio of all the formulated tablets were found to be 34 to 79.14%.

Graph 1. Percentage cumulative drug release from the tablets

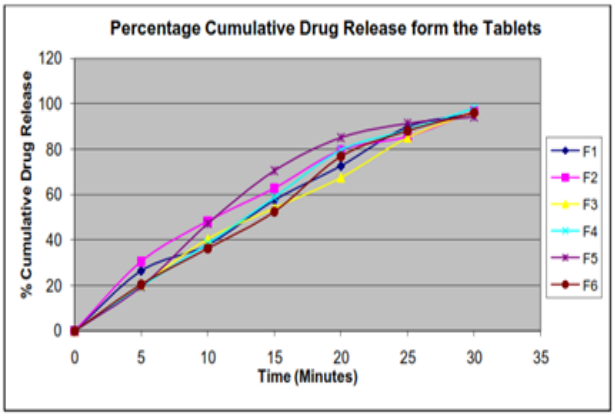

Table 1. Formulation of Telmisartan fast dissolving tablets

Formulation code	Drug (mg)	Orange peel pectin (mg)	*Plantago ovate* mucilage (mg)	Mannitol(mg)
F1	40	6	-	78
F2	40	8	-	76
F3	40	10	-	74
F4	40	-	6	78
F5	40	-	8	76
F6	40	-	10	74

Table 2. Organoleptic and physical properties of Supernatural disintegrants

Parameter	Orange peel pectin powder	*Plantago ovate mucilage*
Appearance	Brown colour	cream coloured
Taste	Mucilageneous	Mucilageneous
Odour	Characteristic	Characteristic
Solubility	Soluble in water, insoluble in acetone, methanol, ether.	Swells in water
LOD	96±0.21%	9%
Swelling index	6.12	6.12
Viscosity	58.79	9.33cps
Total ash	6.89±0.32%	3.00
Water soluble ash	6.15±0.51%	0.67%
Acid soluble ash	0.5±0.34%	0.72%

Table 3. Physical properties of powder blend

Formulation code	(g/ml)	Tapped density (g/ml)	Angle of repose (^{0})	Carr's Index (%)	Hausner's Ratio
F1	0.73	0.8	24.31	7.2	1.08
F2	0.74	0.81	25.20	7.3	1.07
F3	0.76	0.8	25.94	7.4	1.06
F4	0.72	0.8	25.22	7.3	1.09
F5	0.73	0.81	26.53	7.4	1.08
F6	0.74	0.82	27.81	7.4	1.08

Table 4. Physical parameters of Telmisartan tablets

Formulation code	Hardness (kg/cm2)	Thickness (mm)	% Friability	Weight Variation (mg)
F1	2.82	2.91	0.05	160.31
F2	2.91	2.92	0.07	170.55
F3	2.89	2.94	0.08	168.34
F4	3.32	2.95	0.06	154.67
F5	3.45	2.96	0.04	180.11
F6	3.51	2.98	0.08	164.26

Table 5. Comparison of disintegration time, wetting time, Water absorption ratio, Uniformity of content of Telmisartan tablets

Formulation code	Disintegration time (Sec) mean	Wetting time (Sec) mean	Water Absorption ratio (%)	Uniformity of content mean
F1	44	48	34.1	97.14
F2	39	51	42.8	98.34
F3	51	39	60.14	97.56
F4	48	22	70.12	99.38
F5	39	53	59.84	98.34
F6	32	35	79.14	98.97

CONCLUSION

From the data it was found that F6 formulation showed drug release of 99.43%, 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).

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