DESIGN, PREPARE AND IN VITRO EVALUATION OF FAST DISSOLVING TABLETS OF TELMISARTAN

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ABSTRACT : ***The objective of the study was to formulate and evaluate fast dissolving tablet of Telmisartan. Direct compression method was used to formulate fast dissolving tablet of Telmisartan by employing amount of croscarmellose sodium and sodium starch glycolate were used as super disintegrant material along with direct compressible lactose to enhance mouth feel. The prepared batches of tablets were evaluated for hardness, friability, weight variation, disintegration time, drug content and in-vitro dissolution studies. Based on wetting time, disintegration time, the formulation containing croscarmellose sodium and sodium starch glycolate was found to be promising and tested for in-vitro drug release pattern in 6.8 phosphate buffer, short term stability and drug- super disintegrants interaction. F4 Formulation as processed excipient was found to be the best super disintegrants for the preparation of Telmisartan orally disintegrating tablets formulations. Due to it has exhibited faster disintegration time and best dissolution profile when compared to other formulations.***

Keywords: Telmisartan, super disintegrants, FTIR studies, direct compression technique, in-vitro drug release studies.

I.INTRODUCTION

The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional means of taking their medication. Because of physiological changes associated with, especially, elderly and pediatrics are quite unable to swallow (Dysphagia); rather, this is a common problem of all age groups patients[1]. Solid dosage forms that can be disintegrated, dissolved, or suspended by saliva in the mouth resulting in easy swallowing can provide significant benefits to the paediatric and geriatric population, as well as other patients who prefer the convenience of easily swallowable dosage forms.[2] This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva. Recently, pharmaceutical preparations used for elderly patients have been investigated to improve the treatment compliance and quality of life of such patients. A tablet which can rapidly disintegrate in saliva (rapidly disintegrating tablet) is an attractive dosage form and a patient-oriented pharmaceutical preparation.[3] The mouth-dissolving tablets have attracted the interest of many researchers. Many elderly patients have difficulty swallowing tablets, capsules, or powders. To alleviate this problem, these tablets are expected to dissolve or disintegrate in the oral cavity without drinking water.[4] The disintegrated mass can slide down smoothly along the esophagus with the help of saliva, so even people who have swallowing or chewing difficulties can take it with ease. There are two different types of dispersible tablets which have to be distinguished[5] One dosage form disintegrates instantaneously in the mouth, to be swallowed without the need for drinking water, while the other tablet formulation can readily be dispersed in water, to form dispersion, easy to ingest by the patient.[6] The objective of present study is to design and develop a stable solid oral dosage form of telmisartan dispersible tablets to deliver with optimum concentration of drug at desired site at specific time comparable to the innovator product with better stability, high production feasibility, and excellent patient compatibility. Solid oral dosage forms are most convenient from patient as well as from manufacturing chemist's perspective. Dispersible tablets are required to disintegrate within 3 mins in water at 15-25°C.The aim of this study is Formulation and Evaluation of Telmisartan fast dissolving tablets. Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II

receptor blockers (ARBs) such as telmisartan bind to the angiotensin II type 1 (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects. [7,8]

2. MATERIALS AND METHOD

2.1 MATERIALS

Telmisartan was collected as a gift sample from Hetero labs, Hyd, polymers and other excipients were purchased from AR Chemicals, Hyd.

2.2 METHODODOLOGY

Compatibility studies:

The drug-polymer compatibility was ascertained by subjecting the drug and homogenates of drug and polymer to Infrared spectrophotometric study.

Fourier Transform Infrared Spectroscopy (FTIR)[9,10]

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a dosage form. The use of FTIR technique allows pointing out the implication of the different functional groups of drug and excipients by analysing the significant changes in the shape and position of the absorbance bands. In this method individual samples as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a mortar and compressed into disc by applying pressure of 5 tons for 5 mins in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm-1 in FTIR spectrophotometer. Then the characteristics peaks were obtained of all sample as well as mixtures.

Formulation Development

Table-:1 Formulation table

S.No	Ingredient	F-1	F-2	F-3	F-4
1	Telmisartan	200	200	200	200
2	Sodium starch glycolate	10	20	-	-
3	Poloxomer 407	-	-	10	20
4	Lactose	180	170	180	170
5	Aspartame	5	5	5	5
6	Magnesium stearate	3	3	3	3
7	Talc	2	2	2	2
8	Total	400	400	400	400

Preparation technique

Direct compression method

Fast dissolving tablets of Telmisartan were prepared by direct compression. All the ingredients were passed throug h 60mesh separately. Then the ingredients were weighed and mixed ingeometrical order and compressed into table ts of 100mg using 6mmround flat punches on 10- station rotary tablet machine (Rimek)[11].

Evaluation parameters

Precompression parameters[12,13,14,15]

Bulk Density

Bulk density is defined as the mass of powder divided by bulk volume.

It is calculated using the following equation:

Bulk density = weight of sample taken /volume noted

Tap density

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured.

Tapped density = weight of sample taken / tapped volume

Compressibility index

Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index = Tapped density - Bulk density / Tapped density X 100

Hausner's ratio

It indicates the flow properties of the powder. The ratio of tapped density to the bulk density of the powder is called Hausner ratio.

Hausner's ratio = Tapped density / Bulk density

Angle of repose

The flow characteristics are measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\theta = h/r$

Evaluation of tablet

Weight variation

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage[16].

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated[17].

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets were determined.[18]

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.[19]

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Drug Content

The drug content was determined by triturating tablets in a mortar and pestle. The 100 mg of sample powder was dissolved in 6.8 phosphate buffer. The solution was filtered through Whattmann filter paper. The filtrate was analyzed by U.V. spectrophotometer (LAB INDIA) at 295 nm[20].

In Vitro Disintegration Test

The disintegration time of tablets was determined by using Disintegration test apparatus (scientific). Tablets were placed in disintegration test assembly and disc was placed on tablets in each glass tube of assembly. The assembly was dipped in a vessel containing 900 ml distilled water at 37°C. The time for disappearance of tablet residue above mesh was noted as disintegration time.[21]

***In- Vitro* Release study**

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 50 rpm. The

dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for remaining period of time. Temperature maintained at 37±1° C. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. The solution was filtered through Whattmann filter paper. The filtrate was analyzed by U.V. spectrophotometer (Labindia) at 295 nm. The drug release was plotted against time to determine the release profile of various batches.[20]

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The prepared disintegration tablets of Telmisartan were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 30 days.[21]

III. RESULTS AND DISCUSSION

Compatibility Study

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of Telmisartan were obtained at 3500 cm^{-1}, 1084 cm^{-1}, 3095cm^{-1}, 1745cm^{-1}.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

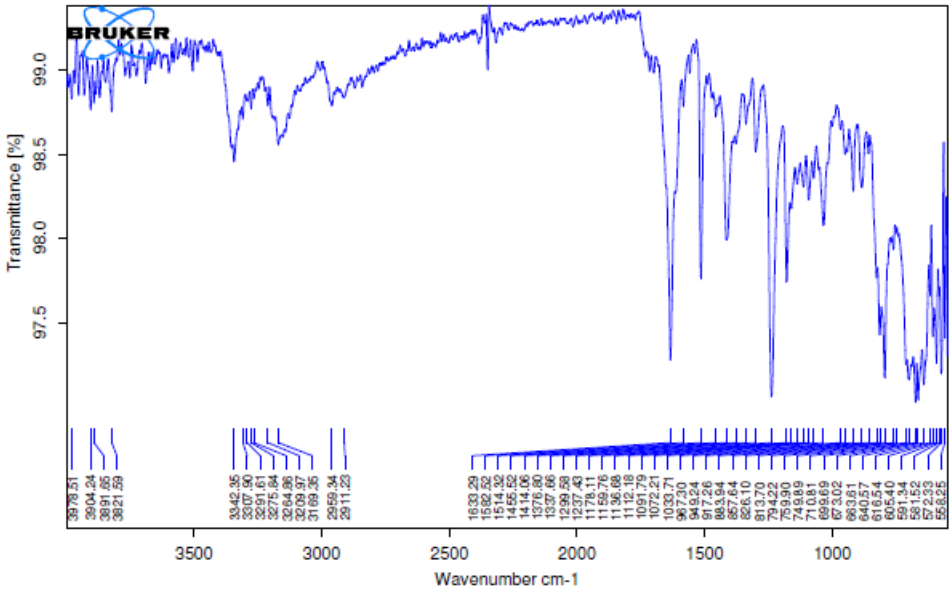

Fig.1. FTIR Spectra of Telmisartan

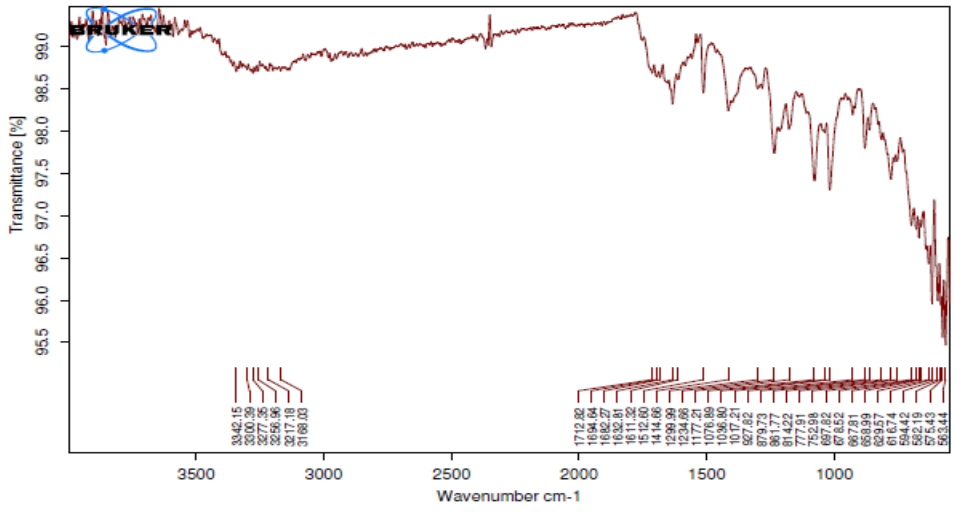

Fig.2. FTIR Spectra of Optimized formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Evaluation Studies

Pre compression Parameters

Evaluation of granules

a) Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.512-0.528.

b) Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.611-0.629.

c) Angle of repose: The angle of repose for the formulated blend was carried out, It concludes that all the formulations blend was found to be in the range of 27 to31^0

d) Compressibility index: Compressibility index was carried out, it found between 10% to 16.9 % indicating the powder blend have the required flow property for compression.

Table -:2 Results of Pre compression parameters of tablets

B. No	**Bulk density**	**Tapped density**	**Compressibility index**	**Hausner ratio**	ANGLE OF REPOSE(0)
F1	0.526	0.629	16.3	1.19	31^0
F2	0.519	0.621	16.42	1.19	29^0
F3	0.523	0.625	16.32	1.19	31^0
F4	0.524	0.624	16.02	1.19	28^0

Post compression parameters

Weight variation

The percentage weight variations for all formulations were tabulated in Table no. All the formulated (F1 to F4) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness

The thickness determined for formulated tablets were tabulated. Tablets mean thickness (n=3) were uniform in F1 to F 4 formulations and were found to be in the range of 3.17mm to 3.31 mm.

Hardness

The measured hardness of tablets of each batch ranged between 6.5 to 7 kg/cm^2. This ensures good handling characteristics of all batches.

Friability

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity

The percentage of drug content for F1 to F 4 was found to be between 94.50% and 99.80% of Telmisartan it complies with official specifications.

Table-:3 Results of Evaluation parameters of tablets

B. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	400	6.12	5.82	0.65	97.82
F2	399	6.15	5.65	0.64	96.42
F3	398	6.18	5.42	0.61	99.80
F4	400	6.23	5.22	0.60	95.82

In-vitro Dissolution Study

Table-: 4 *In vitro* release data of tablet F_1 to F_4

Time	F1	F2	F3	F4
0	0	0	0	0
5	25.65	25.02	24.18	28.14
10	39.56	38.25	37.81	36.58
15	44.28	43.45	42.58	44.27
20	69.35	68.57	67.84	66.28
25	78.56	77.19	78.29	79.14
30	89.25	88.27	90.96	96.88

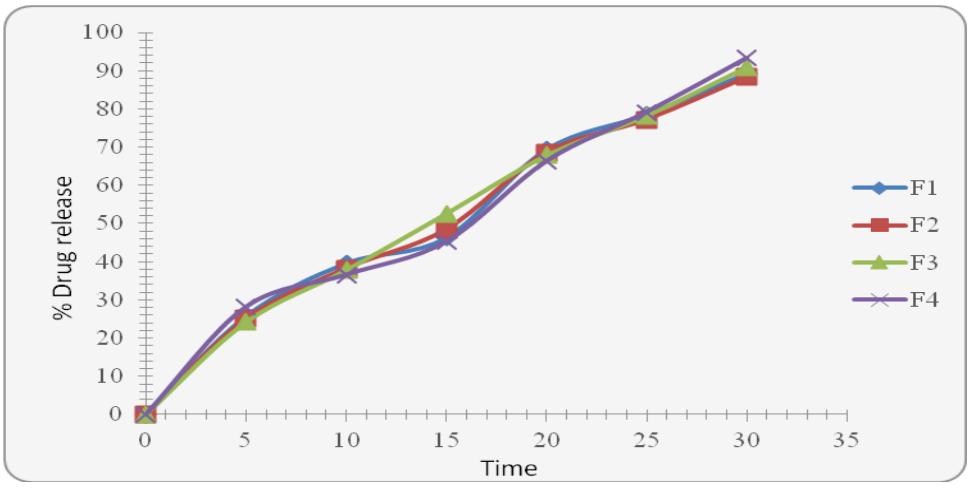

Fig.3. Dissolution Profile of formulations (F1 to F4) Stability Studies

There was no significant change in physical and chemical properties of the tablets of formulation F-4 after 3 months. Parameters quantified at various time intervals were shown

Table no: 5 Results of stability studies of optimized formulation F-4

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-4	25^0C/60%RH % Release	96.88	96.87	96.85	96.82	Not less than 85 %
F-4	30^0C/75% RH % Release	96.88	96.84	96.82	96.81	Not less than 85 %
F-4	40^0C/75% RH % Release	96.88	96.81	96.80	96.80	Not less than 85 %

IV. CONCLUSION

The aim of the present study was to develop an optimized formula for fast disintegrating tablet containing Telmisartan. Pre-formulation studies it was decided to prepare fast dissolving tablets prepared by direct compression method. In the formulation of sodium starch glycolate, and croscarmellose were used as super disintegrants. Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The compressed tablets were also evaluated for weight variation, hardness, friability, drug content, disintegration time, wetting time, in vitro drug release and stability studies. In the above studies F4 formulation showed promising results. It was further supported by FTIR analysis which showed that F4 had no interaction with excipients. The stability studies were carried out for the optimized batch F4 for 90days and it showed acceptable results. So F4 formulation was considered as the optimized formulation.

REFERENCES

1. Zade PS, Kawtikwar PS, Sakarkar DM. Formulation, evaluation and optimization of fast dissolving tablet containing tizanidine hydrochloride. Inter J Pharm Tech Res. 2009; 1:34–42.
2. Ishikawa T, Watanabe Y, Utoquchi N, Matsumoto M. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter-taste-masked granules by the compression method. Chem Pharm Bull. 1999; 47:1451–4.
3. Omaima SA, Mohammed HA, Nagia MA, Ahmed SZ. Formulation and optimization of mouth dissolve tablets containing rofecoxib solid dispersion. AAPS Pharm Sci Tech. 2006;7: E1–9.
4. Simone S, Peter CS. Fast dispersible ibuprofen tablets. Eur J Pharm Sci. 2002; 15:295–305.
5. 5th ed. 1.0. Strasbourg, France: 2005. European Pharmacopoeia 5.0; p. 628.]
6. Habib W, Khankari R, Hontz J. Fast-dissolve drug delivery systems. Crit Rev Ther Drug Carrier Syst. 2000; 17:61–72.
7. https://pubchem.ncbi.nlm.nih.gov/compound/Telmisartan.
8. https://en.wikipedia.org/wiki/Telmisartan.
9. https://en.wikipedia.org/wiki/Fourier-transform_infrared_spectroscopy
10. https://www.mee-inc.com/hamm/fourier-transform-infrared-spectroscopy-ftir.
11. Thomus R. Fast dissolving tablets: an overview. Eur J Pharm Sci 2007;32:58-68.
12. Sreenivas SA, Gadad AP, Patil MB. Formulation and evaluation of ondansetron hydrochloride directly compressed mouth dissolving tablets. Indian Drugs 2006;43:35-7.
13. Bhowmik D, Chiranjib B, Yadav J, Chandira RM, Sampath KP. Emerging trends of disintegrants used in formulation of solid dosage form. Schol Res Lib 2010;2:495-504.
14. Sunada H, Bi Y. Preparation, evaluation and optimization of rapidly disintegrating tablets. Powder Technol 2002;122:188-98.
15. Dey SK, Rahman M, Ahmed A, Khatun A, Siraj A. Phytochemical screening and pharmacological activities of jack fruit seeds. Int J Appl Res Nat Prod 2013;6:34-9.
16. Furie KL. High dose statins should only be used in atherosclerotic strokes. Stroke 2012;43:1994-5.
17. Fateatun N, Jiaur RM, Sultan MM, Sorifa A, Aminul IT, Ahmed M. Physicochemical properties of flour and extraction of starch from Jack fruit seed. Int J Nutr Food Sci 2014;3:347-54.
18. Menaka T, Nagaraja G, Yogesh DB, Sunil Kumar US, Prakash L. Physicochemical properties of flour and isolated starch from Jackfruit seeds (Artocarpus Heterophyllus). Res J Pharm Sci 2011;1:14-8.
19. Okunlola A, Odeku OA. Comparative evaluation of starches obtained from Dioscorea species as intragranular tablet disintegrants. J Drug Delivery Sci Technol 2008;18:4457.
20. Biraju P, Dhaval P, Ramesh P, Chirag P, Tejas S, Sanja SD. Development and in vitro evaluation of fast dissolving tablets of glipizide. Int J Pharm Pharm Sci 2009;1:15-8.
21. Shukla D, Subhashis C, Sanjay S, Brahmeshwar M. Mouth dissolving tablets II: an overview of evaluation techniques. Pharm Sci 2009;77:327–41.