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Studies On Effect of Super disintegrant and Ph Modifiers in Formulation Of Telmisartan Fast Disintegrating Tablet

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ABSTRACT

Telmisartan is an ARB receptor blocker and is a class II drug having low solubility and high permeability. Fast disintegrating tablet of Telmisartan was formulated by incorporating drug in solid dispersion using carrier PEG 6000. Effect of superdisintegrant i.e., Croscarmellose sodium amd pH modifier i.e., sodium carbonate was investigated in the formulation. 32 factorial design was employed in the formulation. Compatibility of drug with excipients was analysed by DSC and FTIR. Pre-compression evaluation of blend showed good flowability and compressibility. Post-compression evaluation of formulated tablets showed suitable hardness, friability, disintegration and drug release. Optimised formulation F4 reported drug release of 94.01% and disintegration time of 115 seconds. Optimised formulation F4 in comparison with marketed product showed better bioavailability and drug release. Short term stability studies concluded formulation to be stable. Hence fast disintegration tablets of Telmisartan were potential and effective to provide drug with enhanced solubility.

Keywords: *Telmisartan, solid dispersion, FDT's, superdisintegrant, pH modifier*

INTRODUCTION

Oral drug delivery is the most commonly used drug administration strategy over all those investigated for the systemic delivery of medication via diverse pharmaceutical products of varied dosage forms. Because they are portable and have a low manufacturing cost, tablets are often employed for self-administration, enhanced stability, accurate dosing, convenience of handling, diversity regarding drug kind and dosage, and suitability for scale-up. Additionally, solid oral delivery systems are less expensive to manufacture because they don't need to be sterilized.[1]

As an alternative to traditional dosage forms, fast-dissolving or orally disintegrating tablets have gained popularity.These tablets are also known as quick dissolve, fast dissolving, rapid disintegrating, mouth dissolving, melt in the mouth, orodispersible, or orally disintegrating tablets.[2,3]

The importance of 24 h blood pressure control has been endorsed in the current European Society of Hypertension/European Society of Cardiology guidelines.[4]

Telmisartan (TLM) is an antihypertensive agent which is a nonpeptide angiotensin receptor II antagonist, that causes inhibition of the action of angiotensin II on the vascular smooth muscle in the symptomatic treatment of hypertension. Chemical name of Telmisartan is [4- [[4-methyl-6-(1- methylbenzimidazol-2-yl)-2-propylbenzimidazol-1-yl] methyl] 1, 1-biphenyl] - 2 carboxylic acid.[5] Telmisartan, an angiotensin II receptor blocker, as well as having a terminal elimination half-life of 24 h.Telmisartan is categorized as a BCS Class II molecule because of its low aqueous solubility (0.09 µg/mL) with dissolution rate-limited absorption. Additionally, Telmisartan is highly ionizable (pKa 4.45 ± 0.09) and shows pH-dependent solubility behaviour, i.e., sparingly soluble in strongly acidic media but readily soluble at strong alkaline conditions. Its highly pH-dependent and poor solubility features cause inconsistent absorption and insignificant bioavailability (~43%).[6]

Another feature distinguishing Telmisartan from other ARBs is its high lipophilicity. This enhances tissue penetration, intracellular absorption and bioavailability.[7] Fast disintegrating dosage forms/Immediate release [IM] dosage forms are defined as drug delivery systems that dissolve or disintegrate within seconds to a few minutes. The fast disintegrating dosage forms systems include tablets, films, wafers, caplets, granules, and powders. Disintegrants are agents added to tablets and some encapsulated formulations to promote the breakup of the tablet and capsule "slugs' into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix.[7] Examples of such superdisintegrants are Sodium starch glycolate, Crospovidone, Croscarmellose sodium, etc. Another important approach to improve the solubility of pH-dependent, poorly soluble drugs is pH adjustment. Incorporating a pH modifying material into formulations or tablets is a promising way to create a suitable microenvironment pH that leads to improved solubility and the release of pH-dependent drugs. For example, poorly soluble weakly basic drugs can solubilize more when using acidifiers and vice versa.[8]

In view of improving solubility and dissolution characteristics and facilitating faster onset of action an attempt has been made to formulate fast disintegrating tablets of Telmisartan by incorporating superdisintegrant and pH modifier.

Aims and Objectives

- To develop and optimize fast disintegrating tablets of Telmisartan.
- To perform pre-formulation studies for formulation
- Comparison of in-vitro dissolution studies of optimized formulation with marketed product
- To perform Stability studies.

MATERIALS AND METHODS

The following materials that were either AR/LR grade were used as supplied by the manufacturer.

TABLE 1: List Of Chemicals With Grade And Manufacturers

Sr.No	Materials	Grade	Manufacturer
1	Telmisartan	Lr	Apotex Research Private Ltd. Bangalore
2	Peg 6000	Lr	Sd Fine Chemical Limited
3	Croscarmellose Sodium	Lr	Hi Media Mumbai
4	Sodium Carbonate	Lr	Sd Fine Chemical Limited
5	Starch	Lr	Molychem
6	Talc	Lr	Hi Media Mumbai

TABLE 2: List of Instruments Used In The Research Work

Sr.No	Instrument	Manufacturer
1	Electronic Balance	Sartorious Bs/Bt, Mumbai, India
2	Uv-Visible Spectrophotometer (Model Uv-1201)	Shimadzu Uv-1900
3	Differential Scanning Calorimetry	Shimadzu Corporation, Japan
4	Ir Spectrophotometer	Shimadzu Corporation Japan.
5	Tablet Compression Machine	Rimek, Ahmedabad, India.
6	Monsanto Hardness Tester	Cambell Electronics, Mumbai, India.
7	Friability Test Apparatus	Systonic Lab, India
8	Vernier Caliper	Campbel Electronics, Bombay, India
9	Tablet Disintegration Tester	Labtronics,Panchkula,India
10	Tablet Dissolution Tester	Lab India, Mumbai
11	Stability Chamber	Kesar Control Systems. India

Preformulation Studies

Preformulation study is carried out before the development of the dosage form of a particular drug substance. It is "an investigation of physical and chemical properties of drug substance, alone and when combined with excipients." This helps in designing a formulation by evaluating its physicochemical properties.

Identification Of Pure Drug

Determination Of Melting Point

The melting point of the drug was determined by the capillary method using Thiel's tube apparatus. The procedure was conducted in triplicates to get the average reading. Average temperature was noted when sample begins to melt.

Determination Of Absorption Maxima(Λmax)In Ph 0.1n Hcl Buffer:[35]

Accurately weighed 100mg of Telmisartan was transferred to a 100ml volumetric flask containing 0.1N HCl which givesa stock solution of 1000µg/ml. From this stock solution, 10ml was pipetted out into a 100 ml volumetric flask and volume was made up to 100ml with buffer to get a concentration of 10 µg/ml. This solution was scanned in the range of 200-400nm by using a UV spectrometer. It was found that Telmisartan showed maximum absorbance(λmax) at 291 nm.

Solubility Analysis

Solubility studies of the drug was performed in 0.IN HCl buffer. Saturation solubility was determined to know the maximum amount of drug dissolved in a solvent. In a beaker 100mg of the drug is dissolved in 25 ml of buffer in it. The beaker was kept in a metabolic shaker for 24 hrs after 24 hrs the sample was sonicated for half an hour. The sample was filtered and the filtrate was analysed by UV spectrophotometer at λmax 291nm.

Preparation Of Calibration Curve Of Telmisartan In 0.1 N Hcl

100mg of Telmisartan which is accurately weighed was transferred to a 100ml volumetric flask and was diluted up to the mark with 0.IN HCl buffer to get a concentration of 1000µg/ml of stock solution. In 100 ml of volumetric flask aliquots of 0.2ml, 0.4ml, 0.6ml, 0.8ml, and 1ml respectively of stock solution werepipetted& diluted with buffer up to the mark, to get a solution in the concentration range of 2-10ug/ml. The absorbance of the solution was carried out atλmax 291nm against 0.IN HCl as blank. A standard curve was then plotted by taking absorbance on Y-axis and concentration on X-axis.[9]

Drug-Excipient Compatibility Studies

Ir Spectroscopy

The FTIR spectrum of the Telmisartan drug IR was obtained by the KBR probe methodusing IR spectrophotometer(SHIMADZU CORPORATION, JAPAN) and obtained spectra was compared with reference standard.

Ftir Spectroscopy

The compatibility of the drug with superdisintegrants and excipients is analysedby infrared spectral analysis. Samples were mixed with KBr. The spectra obtained were scanned between 400-4000 cm^{-1} at a resolution of 4 cm^{-1} frequenciesand were compared with standard frequencies of functional spectra of drug.

Differential Scanning Calorimetry (Dsc) Analysis

API and excipients were placed in aluminium pans which were crimped and heated under nitrogen flow at a scanning rate of 5°C/min from 30°C to 230°C. An empty pan was used as a reference. The heat flow was measured for both drug-polymer, observed for endothermic peaks as a function of temperature.

Preparation Of Telmisartan Solid Dispersed Product By Fusion Method

The melting or fusion method is the preparation of a physical mixture of a drug and a water-soluble carrierand heating it directly until it melted. Weighed quantity of polymer (PEG 6000) and drug(TLM) are taken. The polymer was melted in a china dish. Slowly drug was added to the melted polymer mass.The melted mixture is then solidified rapidly on an ice bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved.

Experimental Design:[43]

Through experimental design, the fast disintegratingTelmisartan tablets were optimized using design expert 13.0.11.0 version software.A 3^2 randomized full factorial design was used. In the model evaluation, 2 factors were selected each at 3 different levels were varied with the help of design expert 13.0.11.0 version software, to study the effects of the independent variables on the dependent variables.Based on the outcomes of optimization for the independent variables X1 and X2, as well as the response variables Y1 and Y2, the software creates optimised solutions.

Variables

Independent variables

X1=Amount of croscarmellose sodium[6-12mg]

X2=Amount of sodium carbonate [18-24]

Dependent Variables [response]

Y1=Disintegration time

Y2=Cumulative drug release [%CDR]

TABLE 3: Coded Levels Of The Variables

Coded levels	**Actual values (mg)**	
	X1	X2
-1	6	18
0	9	21
+1	12	24

TABLE 4: Formulation Table Of Telmisartan Fast Disintegrating Tablet Prepared Using Doe Software

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Telmisartan	40	40	40	40	40	40	40	40	40
Peg 6000	80	80	80	80	80	80	80	80	80
Cross Carmelose Sodium	12	6	9	12	6	9	6	9	12
Sodium Carbonate	18	24	21	24	18	24	21	18	21
Starch	20	20	20	20	20	20	20	20	20
Talc	30	30	30	30	30	30	30	30	30

Formulation Of Fast Disintegrating Tablet Of Telmisartan

Direct compression method is used to prepare the fast disintegrating tablets. Drug, superdisintegrants and all other excipients were passed through mesh # 40. The drug was mixed with a proper portion of super disintegrant. The care was taken to ensure the proper mixing of

drug and superdisintegrant. Excipients, glidant and lubricant were then added, mixed and triturated by using mortar and pestle. This is then passed throughmesh # 60. The obtained blend was compressed into tablets with 8mm round flat punches using the rotary tableting machine (RIMEK, AHMEDABAD, INDIA). The fast disintegrating tablet was prepared by using different concentrations of superdisintegrant and pH modifier. The tablet weight was 200 mg.

TABLE 5: Melting Point Determination Of Telmisartan Fast Disintegrating Tablet By Thiele's Tube

Sl No	**Starting Melting Point**	**Ending Melting Point**
1	262 °C	263°C
2	261°C	263°C
3	262°C	264°C
MEAN	262±0.471°C	263±0.471°C

TABLE 6: Solubility Analysis Of Telmisartan Fast Disintegrating Tablet

Medium	**Solubility (Mg/Ml)**
Distilled Water	8.43±0.54
0.1N HCl	18.32±0.42
4.0 pH Buffer	3.81±0.35
7.4 pH Buffer	9.56±0.84

TABLE 7: Standard Calibration Curve Of Telmisartan In 1.2PH 0.1n Hcl Buffer.

Concentration(µg/Ml)	**Absorbance**			
	TRIAL 1	TRIAL 2	TRIAL3	AVERAGE
0	0	0	0	0
2	0.11	0.12	0.11	0.11±0.004
4	0.217	0.218	0.218	0.217±0.005
6	0.311	0.311	0.313	0.311±0.009
8	0.415	0.417	0.415	0.415±0.001
10	0.546	0.544	0.546	0.546±0.009

TABLE 8: Ftir Spectral Analysis Of Pure Drug (Telmisartan) And Mixture (Telmisartan+Peg 6000)

Structural Characteristics	**Absorption Bands (cm-1) (PURE DRUG)**	**Absorption Bands (cm-1) (MIXTURE)**
O-H hydrogen bond	3474.91	3474.91
C-H aromatic	3060	3061.16
C-H aliphatic	2963.75	2956.04
C=O stretching	1381.09	1381.09
C=C stretching	1600	1600.02
C-N stretching	1695.50	1695.50
C=N stretching	1460.18	1457.28

TABLE 9: Pre-Compression Parameters Of Telmisartan Fast Disintegrating Tablet

Formulation code	**Angle of repose (θ)**	**Bulk density (gm/cm3)**	**Tapped density (gm/cm3)**	**Carr's compressibility (%)**	**Hausner's ratio**
F1	28° 57′±0.08	0.61±0.01	0.731±0.01	17.90±0.36	1.21±0.02

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F2	25° 17′±0.24	0.63±0.04	0.697±0.03	13.91±0.37	1.16±0.01
F3	31° 36′±0.26	0.61±0.01	0.714±0.02	15.90±0.61	1.19±0.02
F4	30°12′±0.36	0.6±0.06	0.714±0.03	15.90±0.12	1.19±0.04
F5	31°36′±0.46	0.64±0.04	0.697±0.01	13.90±0.49	1.16±0.04
F6	28°07′±0.43	0.64±0.05	0.652±0.02	13.91±0.80	1.08±0.02
F7	28°28′±0.61	0.61±0.01	0.675±0.03	11.11±0.36	1.12±0.01
F8	29°52′±0.39	0.65±0.05	0.731±0.01	17.90±0.63	1.21±0.04
F9	28°05′±0.23	0.63±0.03	0.712±0.02	15.73±0.46	1.18±0.02

TABLE 10: Post Compression Parameters Of Telmisartan Fast Disintegrating Tablet

Formulation code	**Thickness (mm)**	**Hardness Kg/Cm²**	**Friability (% w/w)**	**Weight variation (mg)**	**Disintegration time (sec) (1.2pH)**
F1	3.3±0.081	2.1± 0.014	0.5±0.004	197±0.81	130±0.47
F2	3.4±0.047	2.1 ±0.041	0.6±0.006	196±0.47	206±0.48
F3	3.5±0.047	2.13± 0.043	0.5±0.004	194±0.48	174±0.94
F4	3.4±0.081	2.2 ±0.047	0.5±0.003	195±0.91	115±0.81
F5	3.4±0.094	2.1±0.047	0.6±0.005	196±0.95	240±0.48
F6	3.3±0.081	2.2±0.043	0.5±0.008	195±0.82	165±0.81
F7	3.5±0.047	2.1±0.041	0.6±0.007	196±0.52	227±0.82
F8	3.3±0.094	2.1±0.043	0.5±0.010	197±0.82	183±0.94
F9	3.4±0.081	2.2±0.014	0.4±0.011	196±0.86	123±0.81

TABLE 11: Drug Content Analysis And Ph Determination Of Telmisartan Fast Disintegrating

Formulation Code	**Drug Content (%)**	**Change In Ph**
F1	95.99±0.86	5.1±0.01
F2	94.49±0.74	6.3±0.03
F3	96.55±0.84	5.6±0.04
F4	98.23±0.56	6.4±0.01
F5	97.11±0.28	5.2±0.04
F6	97.67±0.45	6.4±0.03
F7	99.73±0.37	5.7±0.02
F8	98.98±0.46	5.2±0.01
F9	99.92±0.40	5.6±0.03

TABLE 12: In-Vitro Dissolution Studyof Telmisartan Fast Disintegrating Tablet

Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
5	33.88	24.61	18.85	32.25	32.6	36.75	35.99	32.00	27.49
10	51.44	34.42	31.94	37.39	42.17	58.32	47.82	65.21	47.73
15	69.00	47.80	56.38	63.13	66.46	63.49	66.41	76.27	73.87
30	86.55	70.98	76.45	78.57	75.14	82.47	73.16	78.83	83.15
45	90.07	81.68	85.18	94.01	76.01	88.51	77.39	82.23	91.58

Data expressed are average of triplicate (n=3 ± SD)

TABLE 13: Comparison Of In-Vitro Drug Release Of Optimized Formulation Of Telmisartan Fast Disintegrating Tablet With Marketed Product

Time (Min)	**% Cumulative Drug Release Of F4 Formulation**	**% Cumulative Drug Release Of Marketed Formulation**
0	0	0
5	32.45±0.05	20.46±0.45
10	38.17±0.12	41.38±0.62
15	63.78±0.35	57.42±0.84
30	79.34±0.24	69.56±0.75
45	93.65±0.38	78.96±0.53

TABLE 14: Stability Profile Of Optimized Formulation (F4)

Parameters	**F4 Formulation**		
	Initial	Accelerated Temperature 400C ± 20C / RH 75 ± 5%	
		15 Days	30 Days
Hardness (kg/cm2)	2.2	1.9	1.78
% Drug Content in 0.1N HCL	98.2	96.46	95.47
% DR at 45min	94	93.74	91.87

The current study has been successful made to formulate Telmisartan fast disintegrating tablet with the solid dispersion for the treatment of hypertension**.**

Based on the outcomes of the experiments, study concludes

- There was no interaction between the medication and the polymers, as shown by the IR spectra and DSC thermograms, hence they were compatible.Telmisartan has a comparatively high solubility in 1:2 pH 0.IN HCl
- Pre-compression evaluation results indicated that compression blend was free-flowing and suitable for compression.
- The post-compression evaluation of formulated Telmisartan fast disintegrating tablet results complied with the Indian Pharmacopoeia limits. The drug content of Telmisartan fast disintegrating tablets had a uniform drug distribution.The pH for formulation occurred in the range of 5-7 which is the desired pH for absorption of Telmisartan drug.
- The data of the in-vitro drug release study of formulations at the end of 45 min showed increased %CDR as the superdisintegrant and pH modifiers concentrations increases.
- Optimized formulation F4 was compared with the Marketed formulation (TELMA 40) for the In-vitro dissolution study. Optimised formulation showed better drug release.
- Stability studies were performed andTelmisartan fast disintegrating tablets were stable after 30 days of stability studies.
- Thus, the prepared Telmisartan fast disintegrating tablets were safe and effective for oral route delivery in the treatment of hypertension.

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