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Preparation and evaluation of orally disintegrating tablets of Telmisartan with pH independent release

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Abstract: The objective of the study is to optimize, formulate and evaluate orally disintegrating tablet (ODT) of Telmisartan which disintegrates with in few seconds there by having better patient compliance, and achieve drug release independent of pH. Telmisartan(Angiotensin Receptor Blocker, ARB) is an anti hypertensive agent indicated in patients who cannot tolerate Angiotensin Converting Enzyme (ACE) inhibitors and for patients with LV (left ventricular) dysfunction. The ODTs were prepared using Betacyclodextrin and evaluated for weight variation, thickness, hardness, disintegration and *in vitro* dissolution studies. Stability studies of optimized formulation was carried out as per ICH guidelines at 40 ± 2^0C / 75 ±5% RH for three months and was found stable.

Key words: Orally disintegrating tablets, Anti hypertensive agent, betacyclodextrin.

Introduction:

Among all the routes of administration, the oral route of administration is the most preffered route due because of advantages including ease of ingestion, avoidance of pain, versatility and patient compliance. But the common drawback of tablets and capsules dosage forms for pediatric and geriatric patients is difficulty in swallowing. Nearly 35% of the general population, especially the elderly patients and children suffer from dysphasia which results in high occurrence of noncompliance and ineffective treatment[1]. To overcome the above problems ODTs were developed. Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist.Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT_1-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance[2 3]

ARBs do not block the breakdown of bradykinin, thisaccounts for the lack of cough as a side effect. In patients with type 2 diabetes and nephropathy, ARB therapy has been shown to significantly reduce progression of nephropathy. For patients with LV (left ventricular) dysfunction, ARB therapy has also been shown to reduce the risk of CV (cardio

vascular) events when added to a stable regimen of a diuretic, ACE inhibitor, and β- blocker or as alternative therapy in ACE inhibitor-intolerant patients [4]. ARBs found to have the lowest frequency of side effects compared toother antihypertensive agents.

Telmisartanhas log P=3.2 and is practically insoluble in water, pH range 3-9, soluble in strong acids and in strong bases[2]. The marketed tablets of telmisartan have no consistent release in differentpH i.e. 1.2 pH, 4.5 pH, 6.8 pH and 7.5 pH [5]. In order to improve solubilityand to achieve drug release independent of pH,betacyclodextrin was used in formulation which forms inclusion complex with telmisartan[6]. Thus formation of an inclusion complex with betacyclodextrin fits the criteria for immediate release tablets.

Materials:

Telmisartan was obtained as a gift sample from Verdant life sciences, Hyderabad. Micro crystalline cellulose/Avicel PH 102(diluent) was obtained from PMC polymers. Crosspovidone (super disintegrant), betacyclodextrin (solubiliser) and magnesium stearate (glidant) were obtained from Signet chemicals Pvt. Ltd. India. Sodium carbonate (Rankem), Acesulfame potassium (sweetener) was obtained from Nutrinova. Orange flavour was obtained from Kerry bioscience.

Methods:

Preparation of telmisartan tablets by wet granulation method:

Accurately weighed amounts of Telmisartan and betacyclodextrin were sifted and blended for 30mins. To this, varying amount of sifted avicel pH-101crosspovidone (polyplasydone) and sodium carbonate were added and together blended. Granules were prepared with water which were dried at 60^{o}C for 2hrs, and then sifted through sieve no 22, to get uniform sized granules ready for compression. To the above prepared granules sweetener and flavor were added and blended. Magnesium stearate was sifted through sieve no 60 and added to the prepared granules which were then compressed by a 10.5mm automatic Multi station tablet punching machine[7]. Extra granular materials as mentioned below in table no:1, were added after granulation.

Physico-chemical characterization:[7,8]

The prepared tablets were characterisesd for their physical properties, disintegration time and drug dissolution characteristics as discussed below

1.Weight variation: 20 tablets were randomly selected from the prepared batches and their average weight was calculated using a digitalbalance. Individual weight of each tablet was alsodetermined and compared with the averageweight.

2. Hardness: Erweka hardness tester was used todetermine the tablet hardness for all the formulated batches.

3.Thickness: Vernier calliper was used to determinethe thickness of the prepared tablets. 20 tabletswere randomly selected from each trial batch andwere measured by placing the tablet between the anvils and knob was rotated until the two edges of anvil touch the tablet and the reading was noted.

4. Drug content: 20 tablets were randomly selected from the prepared batch and triturated to get fine powder. 100mg of the powder was taken and dissolved in 100ml of methanol. Absorbance was noted spectrophotometrically at 296nm. Accordingly drug content was calculated.

5. *In vitro* Disintegration test: The various ODT formulations prepared by wet granulation method are subjected to disintegration studies using 900ml water (as a disintegrating medium) and the time taken for disintegration is noted.

6. *In vitro* Dissolution test: [8, 9]*In vitro* dissolution test was carried out by triplicate method using USP Type II (Paddle type) Apparatus. 900ml of Phosphate buffer pH 7.5 was used as dissolution medium, and the paddle was rotated at 75rpm for 1 hr at a temperature of 37^{0}C. Sampling was done at regular intervals and was replaced by water after each sampling interval. The samples are then analysed spectrophotometrically at 296nm.

The *in vitro* dissolution study in different pH i.e. 1.2pH, 4.5 pH, 6.8 pH and 7.5 pH was conducted for optimized formulation with same variables as above.

7. Drug-excipient compatibility:

Differential scanning calorimetry (DSC): DSC- 60 Shimadzu, Japan was used to check the physical, chemical and biological characteristicsof drug substance alone and its combination withvarious formulation excipients used in the final product. The samples (drug and optimized formulation WB-V) were placed in a sealedaluminium pans and heated under nitrogen flow (30 ml/min) at a scanning rate of 5^{0}C/min from25^{0}C to 325^{0}C.

8. Stability studies: Accelerated stability studieswere conducted for the optimized formulation (WB-V) as per ICH guidelines for three months.

Table 1: Composition of Telmisartan ODT batches WB-I to WB-V

Ingredients (%)	**WB-I**	**WB-II**	**WB-III**	**WB-IV**	**WB-V**
Telmisartan	11.42	11.42	11.42	11.42	11.42
Avicel pH 101	57.98	55.98	55.48	42.88	37.88
					5(E.G)
Sodium carbonate	7	7.5	8	8	8
Betacyclodextrin	12.6	12.6	12.6	25.2	25.2
crosspovidone	6	7.5	7.5	3.75	3.75
				3.75(E.G)	3.75(E.G)
Acesulfame potassium	2	2	2	2	2
Orange flavor	2	2	2	2	2
Magnesium stearate	1	1	1	1	1

Evaluation of tablets

Table No:2 Physical properties of tablet batches WB-I to WB-V

S.No	**Formulation**	**Weight variation(mg)**	**Thikness(mm)**	**Hardness(N)**
1	WB-I	350±1.5	4.9±0.2	40-45
2	WB-II	350±1.5	4.9±0.2	40-45
3	WB-III	350±1.5	4.9±0.2	40-45
4	WB-IV	350±1.5	4.9±0.2	40-45
5	WB-V	350±1.5	4.9±0.2	40-45

Table No: 3 Disintegration values of batches WB-I to WB-V

Formulation	**Time(sec)**
WB-I	52
WB-II	45
WB-III	40
WB-IV	32
WB-V	24

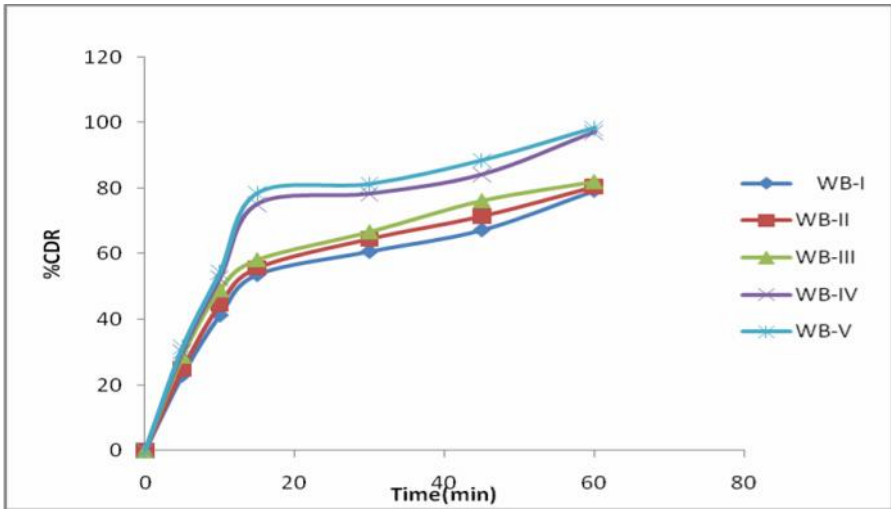

Fig. 1 *Invitro* dissolution of batches WB-I to WB-V

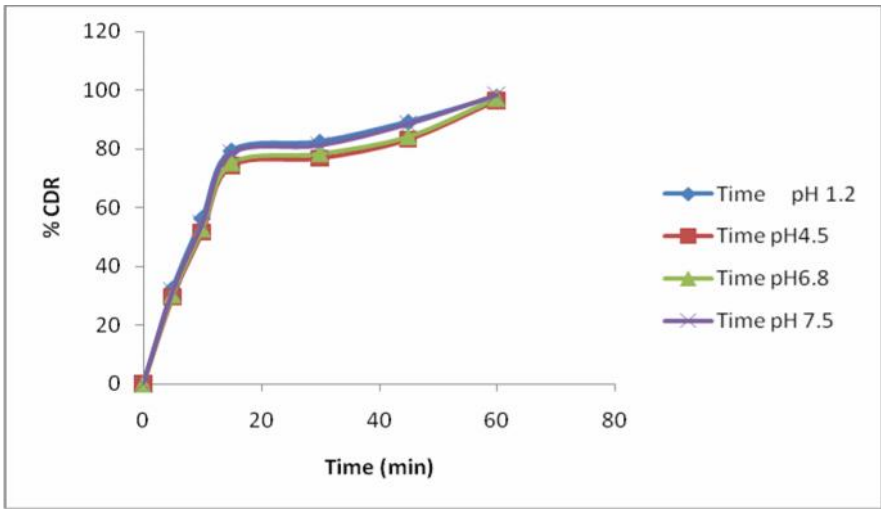

Fig. 2 *Invitro* dissolution of bath WB-V in different pH mediums.

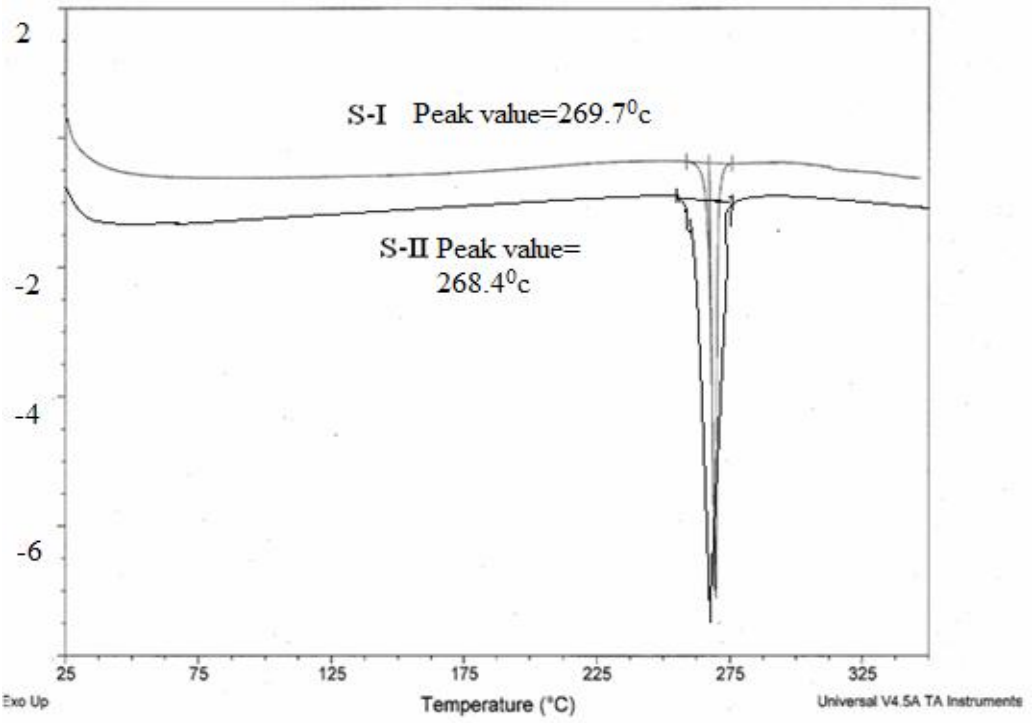

Fig.3: DSC studies of the pure drug (S-I) and optimized formulation (S-II)

Results and Discussions:

Weight variation, Hardness and Thickness: Weightvariation of all the formulated batches shown to be within the limits i.e., 350±1.5 mg. Thickness of tablets found to be 4.9±0.2mm, having a hardness of 40-45N.

Drug content: The drug content was found to beuniform for all the prepared formulations and was found to be 98.1%.

***In vitro* Disintegration test:** From the *in vitro* disintegration test (table 3), WB-V has lower disintegration time (24 seconds).

***In vitro* Dissolution test:** Drug release profile of all prepared immediate release tablets was shown in fig.1.Based on the dissolution data of all the prepared ODTs, the WB-V batch shows 98.40 % drug release in 60 minutes. Based on disintegration time and drug release WB-V was chosen asoptimised formulation. As WB-V was concluded

as optimized formulation, *in vitro* dissolution of batch WB-V was conducted in four different pH i.e. 1.2 pH, 4.5 pH, 6.8 pH and 7.5 pH and the results in fig. 2 with 97.82% in 1.2 pH, 96.44% in pH 4.5, 97.22% in pH 6.8 and 98.40 % in pH 7.5 at the end of 60^{th} minute shows that formulation WB-V has almost similar drug release independent of pH. So the drug will be absorbed even through stomach which meets the criteria for immediate release tablets.

Drug-excipients compatibility:

Differential scanning calorimetry (DSC): The pure drug(S-I) and the optimized Formulation WB-V (S-II) was subjected to the compatibility studies, using Differential Scanning Calorimetry (DSC) which isshown below in fig.3.

The thermograms of mixtures showed no appreciable change in the melting endotherms of the optimized formulation as compared to pure drug (268.4^0C) indicating absence of any interaction.

Stability studies: Formulations found to be stable for one month when tested for its *in vitro* dissolution studies (97.2% release at the end of 60 minutes), which were evident of stability of the product.

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