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Design, development and in vivo pharmacokinetic of telmisartan loaded oral disintegration tablets

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ABSTRACT

Orodispersible Tablets (ODT) is a novel tableting technology which is formulated, and it overcomes the difficulties of other multi compressed tablets. Telmisartan has a bioavailability of 42-100 percent and a 24-hour elimination half-life. It excretes the majority of drugs through the faeces, which accounts for 97 percent of total drug excretion. The objective of this research is to formulate and evaluate Telmisartan loaded ODT and to prove the enhancement of dissolution and bioavailability of Telmisartan. From the DSC studies, it was confirmed that Telmisartan and excipients used in the formulation are compatible to each other and suitable for the manufacturing process. Telmisartan loaded ODT was formulated by wet granulation technique and evaluated for powder characteristics and release characteristics. About 9 formulations were formulated in each ODT, and all the formulation obeys a good powder flow characteristic from the angle of repose, Carr's index and Hausner's ratio. All the experimental formulation batches have been subjected to various evaluations viz, average weight, friability, disintegration, thickness, hardness, dissolution, content uniformity. Among this nine Telmisartan ODT formulations (F1-F9), F7 possess an expected release pattern and disintegration time in a short time period (i.e., 101.8 ± 2.72 in 5^{th} min and disintegration time at 5 seconds), which may fastens the absorption and bioavailability of Telmisartan. It was concluded that ODT was a suitable dosage form to enhance the solubility at the same time the bioavailability of BCS class II drugs like Telmisartan.

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INTRODUCTION

Orally disintegrating tablets (ODTs) is solid dosage types that dissolve in less than one minute in the mouth. The residual is simple to consume. The word "Orodispersible tablet" was coined by the European Pharmacopeia to describe a tablet that disperses or dissolves in even less than three minutes. The current article focuses on ideal features, benefits and drawbacks, different ODT technologies, assessment processes, as well as recent research and future prospects. Solid dosage formulations are commonly

used for a variety of purposes, including cheap price, ease of operation, powerful dosage self-medication, pain avoidance, and, most importantly, patient compliance. The most common solid dosage forms are tablets and capsules (Dey and Maiti, 2010; Singh and Verma, 2020). The medication is released into the mouth for absorption through local or mucosal tissue, as well as the gastrointestinal tract's gastric (stomach), (GIT) pre-gastric (oral cavity, pharynx, and oesophagus), and post-gastric (small and large intestine) parts (Hannan *et al.*, 2016; Vishali and Damodharan, 2020).

Orodispersible tablets, simple dissolving tablets, mouth dissolving tablets, fast-dissolving tablets, rapid dissolving tablets, porous tablets, and rapid melts are all terms used to describe ODTs. The United States Pharmacopoeia (USP) has designated these dosage forms as ODTs, based on the foregoing. The word Orodispersible tablet was invented by the European Pharmacopoeia to describe tablets that spread easily in the mouth within 3 minutes before being swallowed (Anjan *et al.*, 2013; Kakar, 2018).

Many ODT manufacturers will face challenges in the future, such as lowering costs by using conventional equipment, using flexible packaging, and improving mechanical strength and taste-masking capabilities (Brniak *et al.*, 2015; Gupta *et al.*, 2020). ODTs may be useful for oral delivery of drugs like protein and peptide-based therapeutics that have poor bioavailability when taken as tablets. Furthermore, controlled release ODTs prepared with various drug carriers have the potential to be created (Dangore *et al.*, 2020).

Telmisartan is an antihypertensive non-peptide angiotensin II receptor antagonist derived from benzimidazole. Telmisartan selectively inhibits the binding of angiotensin II to the AT1 subtype receptor found in vascular smooth muscle and the adrenal gland. The antagonism induces vasodilatation and inhibits angiotensin II-mediated aldosterone production, resulting in decreased sodium and water excretion and increased potassium excretion, lowering blood pressure. Angiotensin II receptor antagonist Telmisartan is used to treat hypertension. There were no reports of acute liver injury associated with Telmisartan, despite the fact that it has been related to a cheap cost of temporary serum aminotransferase elevations. Telmisartan has a bioavailability of 42-100 percent and a 24-hour elimination half-life. It excretes the majority of drugs through the faeces, which accounts for 97 percent of total drug excretion (Reiter, 2004).

The objective of this research is to formulate and evaluate Telmisartan loaded ODT and to prove the enhancement of dissolution and bioavailability of Telmisartan.

MATERIALS AND METHODS

Telmisartan was acquired as a gift sample from Aurobindo Pvt ltd. PEG 4000. Crosspovidone XL10, Cross Carmellose Sodium, Sodium bicarbonate, Citric acid, Aspartame, Avicel PH 101, Magnesium stearate, Mint flavor purchased from Himedia Pvt. Ltd.

Methodology

Preformulation Studies

Preformulation studies use DSC to determine the fundamental characteristics of the medication and excipients, such as solubility and drug-excipients compatibility.

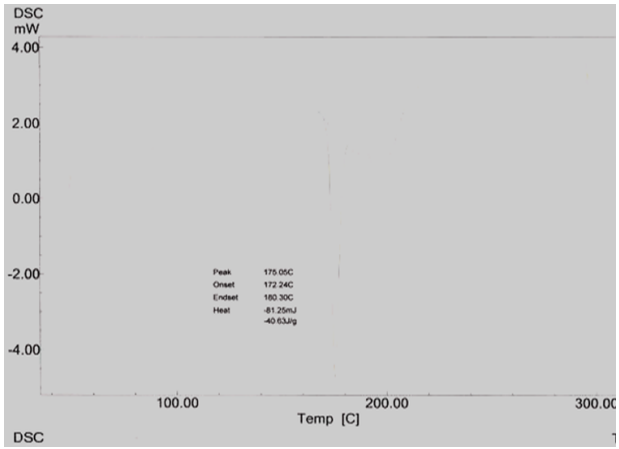

Figure 1: DSC thermogram of Telmisartan

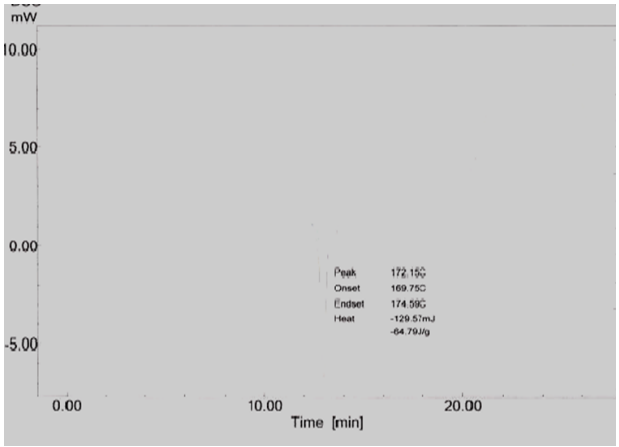

Figure 2: DSC thermogram of Telmisartan with ODT excipients

Studies on solubility

By the concentration of the drug, the solubility of the drug was measured in water and various solvents such as ethanol, methanol, ether, 1.2 pH 0.1N

Table 1: Formulation of Telmisartan ODT

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Telmisartan	20	20	20	20	20	20	20	20	20
P E G 4000	10	10	10	10	10	10	10	10	10
Crosspovidone XL10	5	10	15	-	-	-	2.5	5	7.5
Cross Carmellose Sodium	-	-	-	5	10	15	2.5	5	7.5
Sodium bicarbonate	16	16	16	16	16	16	16	16	16
Citric acid	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Aspartame	10	10	10	10	10	10	10	10	10
Avicel PH 101	10	10	10	10	10	10	10	10	10
Magnesium stearate	11.50	11.50	11.50	11.50	11.50	11.50	11.50	11.50	11.50
Mint flavor	5	5	5	5	5	5	5	5	5
Purified water	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total(mg)	100	100	100	100	100	100	100	100	100

Table 2: 2^3factorial design for optimization of Telmisartan ODT

Run	Independent variables					
	Factor A: (CP: CCS) X1 (mg)	Factor B: ($NaHCO_3$) X2 (mg)	Factor C: (Citric acid) time X3 (min)	Factor A: X1 (mg)	Factor B: X2 (mg)	Factor C: X3 (mg)
F1	1	-1	-1	2.5:2.5	5	5
F2	1	1	-1	2.5:2.5	10	5
F3	1	1	1	2.5:2.5	10	10
F4	-1	1	1	1.5:1.5	10	10
F5	-1	1	-1	1.5:1.5	10	5
F6	-1	-1	1	1.5:1.5	5	10
F7	1	-1	1	2.5:2.5	5	10
F8	-1	-1	-1	1.5:1.5	5	5

Table 3: Solubility studies of Telmisartan in various solvents

Medium	Percentage	mg/ml
Dematerialized Water	100.9%	0.45
0.1 N HCl	101.5%	0.46
Acetate buffer	100.1%	0.48
Phosphate buffer	100.1%	0.49

Hydrochloric acid, and others. It's then enabled to degrade in 10 mL of lipid before optimum saturation is reached. The lipid solubility of the drug was calculated in milligrams per millilitre (Khan *et al.*, 2012).

Differential Scanning Calorimetry (DSC) Analysis

The melting point of samples was determined using DSC tests. It aids in the reporting of drug purity as well as drug-excipients compatibility. The DSC-70, a Schimadzu model instrument, was used to conduct DSC experiments on pure drugs (Telmisartan) and their mixtures with excipients. The samples were measured at 5 mg and heated at a rate of 20°C/min in aluminium pans with dry nitrogen as the effluent gas at a temperature of 20-200°C. An exothermic or endothermic peak was used to determine the melting point (Kantharao *et al.*, 2019).

Formulation of Telmisartan for selection of variables

Weighed the required quantity of API, sodium bicarbonate, citric acid, aspartame, avicel, half of the required quantity of disintegrants. Sieve all the ingredients through sieve no 40 to make it a uniform size distribution. Blend it in mortar and pistil to get

Table 4: Particulate properties of Telmisartan ODT granules

Batch	Angle of repose (θ) (Mean ± S.D.)	Bulk density (g/ml) (Mean ± S.D.)	Tap density (g/ml) (Mean ±S.D.)	Carr's Index	Hausner's ratio
F1	$28^o27' \pm 0.04'$	0.48 ± 0.86	0.55 ± 0.95	15.87 ± 0.543	1.1887 ± 0.018
F2	$29^o69' \pm 0.06'$	0.55 ± 0.41	0.52 ± 0.86	17.02 ± 0.432	1.2051 ± 0.020
F3	$26^o32' \pm 0.06'$	0.43 ± 0.64	0.48 ± 0.54	17.93 ± 1.465	1.2185 ± 0.016
F4	$28^o96' \pm 0.04'$	0.51 ± 0.78	0.54 ± 0.46	14.40 ± 0.537	1.1682 ± 0.025
F5	$27^o52' \pm 0.06'$	0.52 ± 0.43	0.57 ± 0.10	13.26 ± 0.693	1.1529 ± 0.032
F6	$26^o64' \pm 0.08'$	0.47 ± 0.76	0.58 ± 0.32	13.70 ± 0.426	1.1588 ± 0.028
F7	$27^o39' \pm 0.04'$	0.38 ± 0.90	0.64 ± 0.67	13.79 ± 1.231	1.1620 ± 0.042
F8	$27^o66' \pm 0.06'$	0.50 ± 0.30	0.44 ± 0.81	15.34 ± 0.954	1.1812 ± 0.031
F9	$25^o38' \pm 0.04'$	0.51 ± 0.65	0.58 ± 0.73	17.01 ± 0.742	1.2050 ± 0.035

Table 5: Evaluationof Telmisartan ODT tablets

Formulations	Thickness (mm)	Weight Uniformity(mg)	Hardness Kg/cm^2	Friability (%)	Uniformity of Drug Content(%)	Disintegration time (Sec)
F1	5.00±0.002	109.56 ± 1.78	6.4	0.229	97.64±0.62	45 ± 5
F2	5.021±0.002	104.24± 1.84	5.2	0.258	99.25±0.5	36± 2
F3	4.069±0.002	110.42 ± 1.78	5.2	0.291	98.72±0.35	24 ± 4
F4	5.041±0.002	106.25 ± 1.76	5.4	0.252	96.38±0.5	42 ± 2
F5	5.046±0.002	110.52 ± 1.46	6.2	0.268	98.64±0.49	30 ± 2
F6	4.077±0.002	109.56 ± 2.12	5.4	0.256	95.68±0.6	18 ± 2
F7	5.029±0.001	110.56 ± 1.64	5.0	0.285	100.56±0.2	5 ± 5
F8	5.022±0.001	112.82 ± 2.82	6.2	0.246	99.25±0.3	5 ± 5
F9	5.042±0.002	106.82± 2.64	6.0	0.222	97.2±0.31	5 ± 5

Table 6: 2^3 factorial design for optimization of Telmisartan ODT

Run	Telmisarta	Independent variables			Dependent variables		
		Factor A: (CP: CCS) X1 (mg)	Factor B: (Sodium bicarbonate) X2 (mg)	Factor C: (Citric acid) time X3 (min)	Y1 Disintegration time (sec)	Y2 % amount of Drug release	Y3 Time of drug release
F1	20	1	-1	-1	12	78.5	5
F2	20	1	1	-1	10	85.3	5
F3	20	1	1	1	5	101.8	5
F4	20	-1	1	1	25	84.1	5
F5	20	-1	1	-1	30	76.6	5
F6	20	-1	-1	1	45	78.5	5
F7	20	1	-1	1	5	102.1	5
F8	20	-1	-1	-1	42	76.6	5

Table 7: Comparative *in-vivo* pharmacokinetic studies data between Telmisartan formulations treatment groups

Parameter	Telma (4 mg/kg) (Marketed Telmisartan plain formulation) - Oral administration	Telmisartan ODT (F7) (4 mg/kg)- Oral administration
Tmax (min)	10	5
Cmax (μg/ml)	0.141	0.152
AUC 0-α (μg/ml/h)	4.682	12.920
F rel= $(AUC)_{drug.}\ (Dose)_{std}$ / $(AUC)_{std.}\ (Dose)_{drug}$		Bioavailability enhanced by 2.49%

Note: Increase in $AUC_{0-\infty}$; decrease in Tmax; increase in Cmax in Telmisartan ODT shows better bioavailability and faster duration of therapeutic action than other marketed Telma® dosage form.

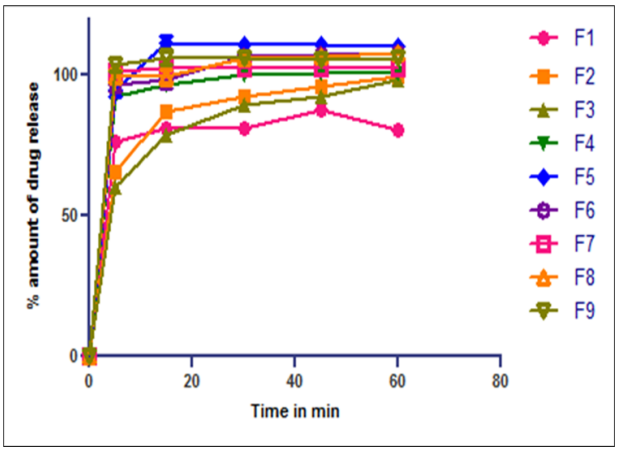

Figure 3: Dissolution profile of Telmisartan ODT (F1 toF9) formulation in 6.8pH Phosphate buffer

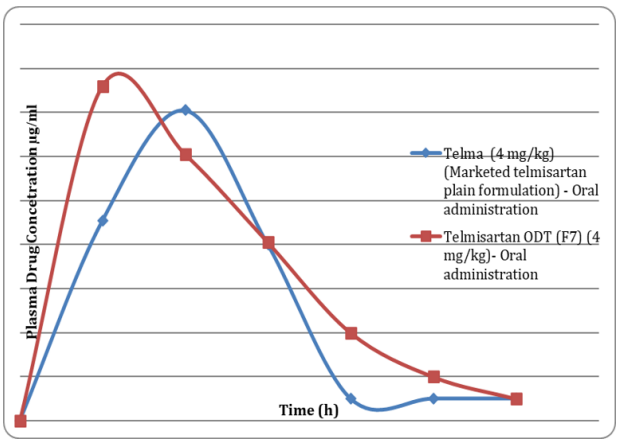

Figure 4: Graph of Comparative in-vivo Pharmacokinetic study data for Telmisartan formulations

a homogenous mixture. Add the required quantity of the above taste-masking solution to the homogenous mixture. Sieve the wet mass through sieve no 10 followed by 22. Dry it in a tray dryer at 60ºC for 10 min and to the dried granules, add a remaining quantity of super disintegrants, glidants, lubricants. Punch it in a 16/32 punch to get ODT (Hoffmann *et al.*, 2020; Singh and Verma, 2020; Singh and Sharma, 2020).

Optimization by 2^3 factorial designs for a selection of best Telmisartan ODT

The elected re-optimized variables were fixed in 2^3 factorial designs as shown in Tables 1 and 2, was designed with the help of Design Expert 9 Software, Stat-ease, Inc. USA, 17 formulation runs 8 factorial runs were generated. It was used to determine the effects of changes in the dependent variables corresponding to the independent variables. In this optimization design, the elucidation of the effect outcome was based on a 2^3 factorial design. Selected independent variables from pre-optimization parameters are given as X1 for Crosspovidone: Crosscarmellose sodium ratio in Telmisartan ODT; X2 for Sodium bicarbonate in mg with different concentration; X3 for different Citric acid concentration for both the Optimization design at 2-different levels code as low (-1) and high (+1). By using the above variables, the ODT formulation was formulated and evaluated the effect on dependent variables like Y1 –Disintegration time in seconds, Y2 - % amount of drug release (dissolution rate) and Y3 – time of drug release in min (Ramu *et al.*, 2014; Joshi and Bhadauria, 2020).

Pre-compression parameters

Angle of repose

The frictional force in powder can be calculated using the angle of repose. The angle of repose is measured using the fixed funnel process. A graph paper was placed on a flat surface, and a funnel was

attached to a stand so that the funnel's lower tip was 2.5 cm above the surface. The mixture was funneled onto the graph paper and allowed to fall freely until the tip of the heap formed just met the funnel. The heap's radius was measured, and the angle of repose was calculated using that data. The angle of repose can be calculated using this equation (Paul and Tyagi, 2011).

$$\theta = \tan\ \tan -1 \left(\frac{h}{r}\right) \quad (1)$$

Where h is the height of the heap in centimeters and r is the radius of the heap in centimeters.

Bulk Density

A sample of about 2g was poured into a 10 ml graduated cylinder to determine bulk density. The cylinder was lowered three times from a height of 2.5 cm onto a hard wooden surface at a 2-second interval. The bulk density was calculated using the formula after the volume was counted (Nitesh *et al.*, 2011).

$$Bulk\ density = \frac{weight\ of\ the\ sample\ taken}{Volume\ occupied\ by\ the\ sample}$$

Tapped Density

A 2g sample was gently poured into a 10 ml graduated cylinder. The cylinder was lowered from a height of 2.5cm at 2-second intervals. The final volume after 100 taps on a wooden surface was used to measure the tapped density (Mahesh and Raman, 2020).

$$Tapped\ density = \frac{Weight\ of\ the\ sample\ taken}{Volume\ noted\ after\ 100\ tapings}$$

Compressibility Index

The granules' packing capacity was determined by measuring the volume shift caused by rearrangement and packing during tapping. It is measured as follows and is expressed as Carr's Compressibility Index (CI percent) (Karthik *et al.*, 2020).

$$CI\ \% = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

Evaluation of tablets

Thickness

The thickness of the pills was measured with a verniercalliper. The average values were determined after evaluating five tablets from each formulation.

Weight variation test

To calculate weight variance, 20 tablets of each type of formulation were individually weighed on an electronic balance, the average weight was calculated, and the weight difference was calculated by comparing the real tablet weight to the average value (Hamilton and Luts, 2005).

Hardness

The hardness value of six pills for each type of formulation was determined using a Monsanto hardness tester.

Friability

The Roche friabilator was used to perform the friability test. The friabilator was filled with a preweighed sample of tablets and spun at 100 revolutions. After that, the tablets were dusted and reweighed. Friability limits are usually less than 1% (Kuchekar *et al.*, 2001).

$$\%\ Friability = \frac{preweight\ of\ the\ sample - Final\ weight}{Pre\ weight} \times 100$$

Content uniformity

By precisely weighing five tablets and crushing them in a mortar, the content uniformity of the tablets was calculated. The powder was then correctly measured and transferred to a 100 ml volumetric flask, equating to 100 mg of substance. 70 mL water was applied, and the mixture was shaken for 15 minutes. With distilled water, a volume of up to 100 mL was formed. Whatmann filter paper was used to filter the solution. The first few milliliters of the filtrate were discarded. With distilled water, 10 mL of the filtrate was diluted to 100 mL. Then, using distilled water, 10 mL of the resulting solution was diluted to 100 mL. In a UV spectrophotometer, the absorbance of the resulting 10 g/ml solution was measured at 234 nm for Telmisartan [64]. Content uniformity was calculated using the formula (Bi *et al.*, 1996).

$$\%\ Purity = 10X\ concentration\ (Absorbance's\ obtained\ from\ s\,\text{tan}\,dard\ preparation\ /\ Absorbance's\ obtained\ from\ s\,\text{tan}\,dard\ preparation)$$

Percentage water content by (Karl Fischer Titration)

To titrate with Karlfischer reagent, fill the titration vessel with 35-40ml of the methanol mixture and titrate to the electrometric end-point. To absorb any moisture that may be present, use powder from 5 tablets ground to a fine powder in a temperature and relative humidity known not to affect the outcome (disregard the amount absorbed, as it does not enter into the calculation). Weigh and carefully pour 300mg of powder into the titration vessel. Mix and titrate with the Karl Fischer reagent to meet the electrometric end-point. Using the formula, determine

the water content of the specimen in milligrammes.

$$S \times F \times 100 \div W$$

S= The amount of reagent absorbed in millilitres during the titration.

F= is the karlfischer reagent's water equivalence factor.

W= is the weight of the sample.

Water Absorption Ratio

In a shallow Petri - dish 6 ml of water a folded pieces of tissue paper was inserted twice. The time it took too fully wet the paper was recorded using a tablet mounted on the paper. After that, the wetted tablet was measured.

$$Water\ absorption\ Ratio = Final\ weight/- Initial\ weight/Final\ weight\ x\ 100$$

Wetting Time

The internal structure of the tablet, as well as the hydrophilicity of the excipients, affect the wetting time. Pore sizes shrink as compression force or porosity decreases and wetting time increases. In a petriplate consisting 6ml of water that contains water-soluble eosin dye, a double-folded piece of tissue paper was placed. The time it took to absolutely wet the tablet was calculated in seconds after it was put on the paper (El-Arini and Clas, 2002).

Wetting volume

The tablet was put in the centre of the Petri dish, and distilled water was applied drop wise to the tablet using a 5ml pipette. The wetting volume was defined as the volume needed to fully disintegrate the tablet (El-Arini and Clas, 2002).

***In vitro* dissolution studies**

The dissolution in vitro was done with a USP type II dissolution apparatus (paddle method). 900 mL of 1.2pH HCL was used as the dissolution medium. By holding the dissolution medium at a temperature of $37^0C \pm 2^0C$, the paddle speed was set to 50 rpm.

The apparatus was started after the tablets were put in the dissolution medium. 5 ml aliquots were removed at intervals of 5, 10, 20, 30, 45, and 60 minutes and replaced with equivalent quantities of fresh dissolution medium held at the same temperature.

Whatmann filter paper No-41 was used to filter each 5 mL aliquot. The absorbance of 1 ml of sample in 100 ml distilled water was measured at 234 nm for Telmisartan.

The concentrations of drugs in the sample were measured using a normal calibration curve (Klancke, 2003).

***Invivo* Pharmacokinetic studies**

Grouping and treatment of animals with Telmisartan ODT

In a parallel plan, rats were divided into three groups of six rats each. The control group is made up of only normal rats eat a daily diet and have free access to water. The second group received a proportionate dose of commercial Telmisartan tablets (Telma), while the third group received Telmisartan oral disintegration (ODT) F7 tablets through an oral feeding needle by dispersing the required dose into carboxy methyl cellulose solution (the best formulations that showed the best dissolution and disintegration behavior) (Prashanthievangelin *et al.*, 2020).

Collection of Blood samples after administering Telmisartan ODT

Blood samples (approximately 1 mL) were drawn from the sinus orbital into heparinized tubes at 0, 5, 15, 30, 45 and 60 minutes after the dosage form was administered. The blood samples were centrifuged at 5000rpm for 15 minutes to obtain the plasma measurements, then stored at 20°C for HPLC analysis (Zwieten, 1994).

Each 0.2 mL plasma test sample was extracted with 1 mL acetonitrile, followed by 10 minutes of centrifugation at 3000 rpm. After that, the supernatant (100 litres) was mixed with 500 litres of acetonitrile-water-acetic acid (15/85/0.1). Finally, a 20-liter aliquot was injected into the chromatographic system.

On an HPLC (Schimadzu, Japan) instrument, the HPLC investigation of Telmisartan was carried out by the mobile phase 60:40 v/v mixture of buffer and methanol. A 250 x 4.6 mm (i.d.) 5m ODS section was used for division and quantitation. The mobile process was infused into the framework at a rate of 0.7 mL/min using paired pumping mode. The infusion volume and run time for all samples were determined to be 20 L/1.2ml/min flow rate and 10 minutes run time, detection wavelength 230nm, respectively (Amidon *et al.*, 1995).

The pharmacokinetic parameters calculated were maximum plasma concentration (Cmax), maximum plasma concentration duration (Tmax), an area under the plasma concentration versus time curve from zero to 60 minutes (AUC0–t), area under the plasma concentration versus time curve from zero to infinity (AUC0–α), mean residence time (MRT), Tmax, and relative bioavailability (RB). A one-way ANOVA test was used to analyze the data, and the results were presented as mean, standard deviation (SD). All statistical studies were carried out using the Prism programmed version 7.0. Statisti-

cal significance was described as a P-value of or less 0.05 (Badhan, 2015).

RESULTS AND DISCUSSION

Drug solubility study

To prepare a dosage form, the assortment of excipients is significant criteria should be pharmaceutically suitable, ideal and compatible to the formulation. Telmisartan is highly soluble in water, 0.1 N HCl, Acetate buffer, Phosphate buffer. All these excipients are pharmaceutically acceptable and non-irritant, non-sensitizing and suitable for the preparation of tablets. The results are shown in Tables 1 and 3.

C ompatibility studies by DSC analysis – Telmisartan and its Mixture of excipients formulation

DSC analysis for pure drug (Telmisartan) and with ODT excipients were analyzed and reported to determine the compatibility of drug and excipients in the formulation. Figures 1 and 2 follows,

The Preformulation studies of both Telmisartan ODT granules as shown in Table 4. Angle of Repose of Telmisartan ODT granules shows the values ranges from 26.32 $\pm$ 0.067 to 29.69 $\pm$ 0.056. Since the Angle of repose shows that the flow property for both the granules was good and it is within the acceptable limits, less than 35°. Bulk density of both the granules, i.e., Telmisartan ODT granules, indicates good packaging character. Telmisartan ODT granules show Bulk density values ranges from 0.38 $\pm$ 0.90 to 0.55 $\pm$ 0.41. Telmisartan ODT granules shows tapped density values ranges from 0.48 $\pm$ 0.54 to 0.64 $\pm$ 0.67. Telmisartan ODT granules shows Carr's Index values ranges from 13.26 $\pm$ 0.693 to 17.93 $\pm$ 1.465. Telmisartan ODT granules shows Hausner's ratio values ranges from 1.1529 $\pm$ 0.032 to 1.2185 $\pm$ 0.016. The Carr's index for all the formulation was found to be less than 15%, which indicate acceptable flow properties. The Hausner's ratio for all the granules was less than 2% Figure 3.

Evaluation of ODT tablets

The results of ODT were shown in Table 5. The thickness of the Telmisartan ODT tablets was found to be optimum for all the formulations, i.e., from 4.069$\pm$0.002mm to 5.046$\pm$0.002 mm. The thickness of the Telmisartan ODT tablets was found to be optimum for all the formulations, i.e., from 4.50$\pm$0.002mm to 4.58$\pm$0.002mm. The thickness of all tablets was between the desired ranges. The weight variation of the Telmisartan ODT tablets was found to be optimum for all the formulations, i.e., from 104.24$\pm$ 1.84 to 112.82 $\pm$ 2.82%. The pharmacopoeial limits for weight variation deviation for tablet formulations of 100 mg tablet were $\pm$7.5%. The average % deviation for all the tablet formulations was found to be within specified limits. All the tablet formulations complied with the weight variation test. All tablet formulations showed hardness values between 4-6 kg/ cm^2, i.e., from 5-6 kg/ cm^2. The hardness of the Telmisartan ODT tablets was found to be optimum for all the formulations. Tablet hardness is not an absolute indicator of the strength of tablet since some formulations tend to cap when compressed into hard tablets. The friability of the Telmisartan ODT tablets was found to be optimum for all the formulations. Therefore another measure of tablet's strength want to measure, i.e., Friability is measured. In friability testing, the tablets are subjected to combined effects of abrasion and shock. The pharmacopoeial limit for friability is less than 1%. All formulations were complied with the friability test, i.e., 0.222 to 0.291. This shows that the ODT of all batches possess good tableting strength and are suitable for packaging and transportation. Good content uniformity was found in all the tablet formulations. The values are ranged from 96.38$\pm$0.5 to 100.56$\pm$0.2%. Among all the formulations, the F7 formulation shows more drug content, i.e., 100.56$\pm$0.2%. The disintegration time for all the formulation shows very fast, i.e., less than 45 seconds. Among all the Telmisartan ODT 9 formulations, the F7 formulation shows very less disintegration time of about 5 min. The dissolution studies shows that F7 formulation possess an expected release pattern, i.e., 101.8 $\pm$ 2.72% of drug release in the 5^{th} min time interval itself.

Optimization of Telmisartan ODT

The CP: CSS for Telmisartan ODT were selected as the suitable disintegrating agent, which selected from preoptimization screening formulation results shown in table 5.11 to 5.16. The 2^3 factorial optimization design and its result are shown in table 5.17-5.18 and Figures 5.15 - 5.18 revealed about the effect of an independent variable on a dependent variable during the preparation of Telmisartan. From the data, it was concluded that there was a strong correlation between Disintegration time, Dissolution rate and super disintegration concentration. From figure 5.15, 5, 16. it was confirmed that there was a decrease in disintegration time of ODT by increasing the superdisintegrants concentration like crosscarmellose sodium and CCS: CP concentration ratio. On executing the superdisintegrants vs disintegration time in min, with ANOVA, the 'P' value was found to be <0.05, i.e. P-value 0.00873 for Telmisartan ODT (Table 5.19-5.21), which indicates a significant difference in Disintegration time on increasing the concentration of Super disintegra-

tion. Among all 8 formulations of Telmisartan ODT, F7 formulation of Telmisartan ODT showed desired disintegration time of about 5min and 12 min at a high +1 level of super disintegration time (i.e. 2.5:2.5 proportion of CP: CCS and 5 mg of CCS). An increase in disintegrants concentration in the preparation of ODT showed a simultaneous increase in the percentage amount of drug release, i.e., dissolution rate, with the decrease in disintegration time of ODT, which confirmed the good and fastest release pattern of ODT in GI fluid. By establishing it in ANOVA, the 'p' value was found to be < 0.05 .e. P-value 0.00495 for Telmisartan ODT (Table 5.22-5.24), which confirmed that there was a significant change in percentage amount of drug release by increasing the concentration of super disintegrants. F7 Telmisartan ODT formulation showed the required percentage amount of drug release of about 102.1± 2.2% at 5min time interval in high +1 level of super disintegration concentration. An increase in superdisintegrants concentration showed a simultaneous increase in the %amount of drug release at a short time (Table 6). From the optimization data, it was concluded that, among all the formulations, F7 Telmisartan ODT shows good desired results like disintegration time and dissolution rate. The polynomial equations were derived from the coefficient values from 2^3 factorial designs was produced by the changes in the independent variable based on the dependent variable are as follows:

$$DT\ of\ Telmisar\tan\ ODT = 22.5 - 12.75X1$$

$$\%\ amount\ drug\ release\ of\ Telmisar\tan\ ODT = 79.6 + 17.85\ X1$$

Pharmacokinetic studies of various Telmisartan formulations

***In-vivo* pharmacokinetic studies**

To determine the unknown plasma drug concentration, a calibration curve was designed by using different concentration of Telmisartan, as shown in Table 7 and Figure 4. The linearity for the calibration curve was determined by plotting the peak area and nominal concentration of Telmisartan. For linearity study eight different concentration of Telmisartan were analyzed (0.02, 0.04, 0.06, 0.08, 0.1, 0.12, 0.14, 0.16 μg/ml). The peak area response was found to be linear over the concentration range studied. The coefficient of correlation 'r^2' was found to be 0.999.

The HPLC method by interpolation technique has been successfully used to determine the pharmacokinetic data from the unknown plasma drug concentration followed by single-dose administration of Telmisartan (Temla) and Telmisartan ODT (F7). From the peak area of the injected sample, the unknown concentration was determined. The mean plasma concentration of Telmisartan as a function of time has been plotted as shown in Figure 4, and the comparative studies on *In-vivo* plasma drug concentration profile between marketed Telmisartan marketed tablet (Telma); Telmisartan ODT (F7). It was observed that Telmisartan (F7) fastens the release as well as the pharmacokinetic parameters when compared to the Telmisartan marketed formulation. There was a significant difference in 'p' value as < 0.05 between the pharmacokinetic parameters of marketed Telmisartan, Telmisartan ODT (F7) with T_{max} of 5 and 10min; and the maximum peak plasma concentration (C_{max}) of 0.141 μg/ml and 0.152 μg/ml respectively. The area under Curve ($AUC_{0-\alpha}$) was found to be 4.682μg/ml/h and 12.920μg/ml/h, respectively. From the *in-vivo* pharmacokinetic data, it was concluded that an Increase in $AUC_{0-\infty}$; decrease in T_{max}; increase in C_{max} in Telmisartan ODT shows better bioavailability and faster duration of therapeutic action than other marketed Telma® dosage forms. On calculating the relative bioavailability by keeping marketed formulation to be standard, it has been confirmed that the Telmisartan ODT (F7) formulation showed the enhancement of bioavailability of about 2.49 % than marketed Telma tablet.

SUMMARY

ODT is a novel tableting technology which is formulated, and it overcomes the difficulties that are faced in other multicompressed tablets. From the preformulation studies (DSC studies), it was confirmed the Telmisartan and excipients used in the formulation are compatible to each other, as shown in DSC in which the melting point of the drug, i.e., predicted by the endothermic peak, is reproducible as seen in physical mixture thermogram Telmisartan loaded ODT was formulated by wet granulation technique and evaluated as follows. About 9 formulations was formulated, and all the formulation obeys a good powder flow characteristic from the angle of repose carr's index and Hausner's ratio. All the experimental formulation batches have been subjected to various evaluations viz, average weight, friability, disintegration, thickness, hardness, dissolution, content uniformity. Among all Telmisartan ODT formulations, F7 possess an expected release pattern and disintegration time in a short time period (i.e., 102.1± 2.2% at in 5^{th} min and disintegration time at 5± 1 seconds). The optimized ODT not only improved the bioavailability of the drug by decreasing the drug extraction at the liver site, as evident

from in-vivo pharmacokinetic studies, and may also offered a substantial reduction in the systolic blood pressure in antihypertensive studies in Wistar rats. The in-vivo performance of the selected ODT was far more improved than that of the available marketed product as well as the plain drug, advocating the superiority of the developed system over the marketed one. The pharmacokinetic pharmacological evidences coupled with the results from the in-vitro parameters like wetting time, disintegration time and drug release profile provide a ray of hope for a commercially viable ODT product for Telmisartan to manage the hypertension-related problems. The formulation F7 (Telmisartan ODT) has achieved the objective of ODT drug delivery with desired release characteristics, cost-effective, decrease dose, effective administration, and hence improved patient compliance. The invivo pharmacokinetic studies reveals that an Increase in $AUC_{0-\infty}$; decrease in Tmax; increase in Cmax in Telmisartan ODT shows better bioavailability and faster duration of therapeutic action than other marketed Telma® dosage form. The invivo pharmacodynamic studies revealed based upon the results obtained, it was confirmed that Telmisartan ODT (F7) can control hypertension very faster and immediately than the marketed Telma® treated group, i.e. at 5 minutes itself. From the results of stability studies, it was confirmed that the Telmisartan ODT were stable at various temperature, humidity conditions, and there was no drastic change in evaluation parameters of both Telmisartan ODT.

CONCLUSION

Thus it was concluded that the Oral dispersible table (ODT) was a suitable dosage form to enhance the solubility at the same time the bioavailability of BCS class II drugs like Telmisartan. The formulation Telmisartan ODT (F7) has achieved the objective of ODT drug delivery with desired release characteristics, cost-effective, decrease dose and effective administration and hence improved patient compliance.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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