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Formulation and Evaluation of Fast Disintegrating Tablet of Telmisartan

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ABSTRACT

The present research aims to enhance the dissolution profile of Telmisartan through formulation of its fast disintegrating tablets using a super-disintegrant Ac-Di-Sol. The effect of super-disintegrant Ac-Di-Sol was studied mainly on disintegration time and in-vitro drug release. A 2^2 factorial design was employed in formulating the fast disintegrating tablets. The selected independent variables Ac-Di-Sol and microcrystalline cellulose showed significant effect on dependent variables i.e. disintegration time and percent drug dissolved. The disintegration time and percent drug dissolved decreased with increase in the concentration of Ac-Di-Sol and decrease in the concentration of microcrystalline cellulose in the tablet. The optimized formulation was compared with the conventional marketed formulation for the same dependent variables. It showed about 62% increase in dissolution rate. The study concluded that dissolution rate of Telmisartan could be enhanced using Ac-Di-Sol as a super-disintegrant.

Keywords: Fast disintegration tablets; Super-disintegrant; Ac-Di-Sol

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INTRODUCTION

Fast disintegrating 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 [1,2]. The super-disintegrants speed up moisture penetration and dispersion of matrix thereby increasing the disintegration rate of drug delivery system. On contact with water they swell, hydrate, increase volume or form and produce a disruptive change in tablets which results in its fast disintegration. In these cases, the bioavailability and onset of action of drugs from fast disintegrating dosage forms is greater compared to the standard oral dosage forms [3-5].

Hypertension is a chronic clinical condition when the systolic and diastolic blood pressure of the patient increases beyond 140 and 90 mm Hg respectively [6]. It occurs due to sedentary lifestyle, salt rich diets, processed and fat rich diet, excessive alcohol and tobacco intake etc. Sustained hypertension over time is a major risk factor for hypertensive heart disease, coronary artery diseases, stroke, peripheral artery diseases, aortic aneurysm and chronic kidney disease like kidney failure and kidney scarring (glomerulosclerosis). It can even leads to damage to ones brain by temporary disruption of blood supply to brain which is known as Transient ischemic attack (TIA). It can also causes stroke and consequent death of the patient [7,8]. Globally, the overall prevalence of raised blood pressure in adults aged 18 and over was around 22% in 2014 and it has estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths higher in low- income countries compared to middle income and high-income countries [9].

Telmisartan is an antihypertensive drug frequently prescribed to treat conditions like narrowing of blood vessels, potential heart attack, stroke and many other complications associated with hypertension [10]. It inhibits the binding of angiotensin II to the angiotensin II AT1-receptors by binding to them reversibly and selectively in vascular smooth muscle and the adrenal glands resulting in decrease in systemic vascular resistance [11]. Its effective therapeutic dose is 40 -80 mg once daily. It is practically insoluble in water (aqueous solubility is

0.09µg/ml) [12] in pH range of 3 to 9, springily soluble in strong acid and soluble in strong bases [13]. It has varying bioavailability ranging between 42 to 100% [14]. Its half-life is approximately 24 hours.

Although, Telmisartan is a frequently prescribed drug for hypertension, yet it suffers from serious drawbacks like poor aqueous solubility and variable bioavailability. To overcome these shortcomings, enhancement of its solubility and bioavailability has been tried by many ways likepreparation of its inclusion complexes in physical and kneading methods using β cyclodextrins[15], using sodium lauryl sulphate[16,17], using super critical anti-solvent(SAS)process[18], formulation of telmisartan containing cross povidone as super-disintegrant [15], formulation of its fast dissolving tablets using sodium starch glycolate, doshion and crosscarmellose sodium as super-disintegrants[16], formulation of its immediate release tablets using sodium starch glycolate and β cyclodextrin[19],formulation of its liquisolid compacts for improved dissolution[20], enhancement of its dissolution through surface solid dispersions[21], formulation of its fast dissolving films[22], formulation of its self-nanoemulsifying drug delivery system with improved dissolution and bioavailability[23] etc.

Wrzesinski*et. al.* (2010) performed a study on comparison of three super-disintegrants (Ac-Di-Sol, Crospovidone and Sodium Starch Glycolate) in orally disintegrating tablets. It reveals that the Ac-Di-Sol shows a much faster disintegration than crospovidone and sodium starch glycolate at a low level concentration (2%), while crospovidone performed its work at 5% [24].

Desai*et al.* (2014) performed an evaluation of disintegration of Ac-Di-Sol and sodium starch glycolate. The study reveals that sodium starch glycolate absorb the moisture at higher level than Ac-Di-Sol but the disintegration time of sodium starch glycolate was more than that of Ac-Di-Sol [25].

On the basis of above and literature reviews we select Ac-Di-Sol as super-disintegrant for the concerned study. The present study aims to optimize the concentrations of super-disintegrantAc-Di-Sol and bindermicrocrystalline cellulose, to enhance the disintegration and dissolution rate of Telmisartain in a directly compressible, fast disintegrating tablet.

MATERIALS AND METHODS

Materials

Telmisartan was obtained as a gift sample from Monatt Biotech, Bathinda. Ac-Di-Sol was obtained as a gift sample from Ranbaxy, Mohali. Microcrystalline cellulose, magnesium stearate and mannitol were purchased from LobaChemie Pvt. Ltd., Mumbai. The chemicals and reagents used were of analytical grade.

Methods

Determination of drug purity:

Purity of Telmisartan was confirmed by thermal analysis of the pure drug by using (DSC Q10 V 9.9 (300), US). TA system with a differential scanning calorimeter equipped with a computerized data station. Sample (2 mg) was heated in a crimped closed aluminum pan at scanning rate of 10°C/min from 30 to 350 °C in an atmosphere of nitrogen gas by passing it at a flow rate of 80 ml/min (Figure 1)[26]. An empty aluminum pan was used as the reference pan. DSC was calibrated using Indium metal with a melting endotherm at 263°C.

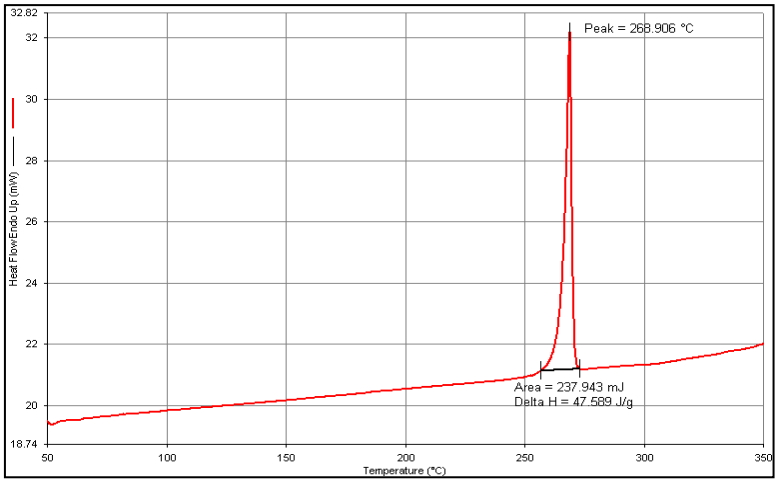

Figure 1: DSC thermograph of Telmisartan

Drug excipient compatibility studies

This study was carried out by comparing the FTIR graphs of Telmisartan and its mixture in Ac-Di-Sol in the ratio of 1:1 using FTIR spectrophotometer (Figure 2) (Alpha Bruker 1206 0280, Germany) employing KBr disc

technique and all samples were scanned from 4000cm^{-1} to 400 cm^{-1} range. The graphs obtained through FTIR spectral analysis of Telmisartan and Telmisartan-Ac-Di-Sol physical mixture were checked for presence of any new peak in the mixture. [26].

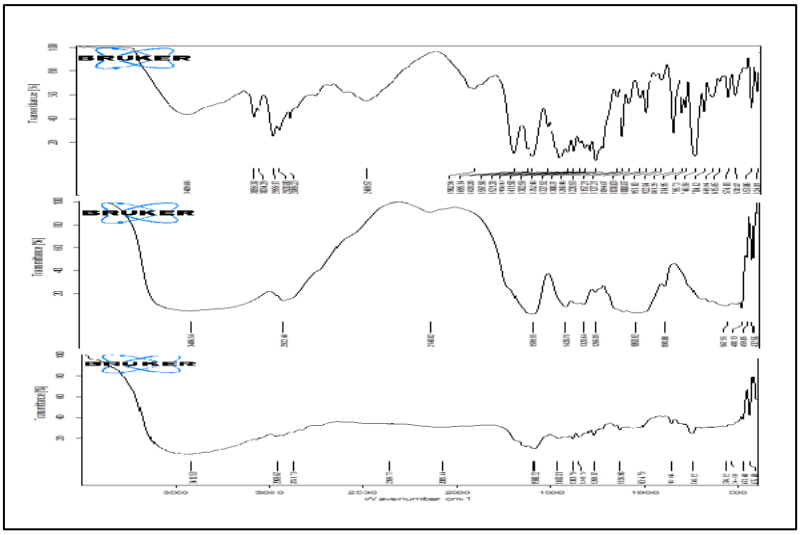

Figure 2: FTIR Spectrum of Pure Drug, Ac-Di-Sol and Drug-Ac-Di-Sol Mixture (1:1)

Formulation and optimization of fast disintegrating tablets of Telmisartan

The optimization process provides not only efficient use of resources, but also a method to obtain a mathematical model which can be used to characterize and optimize a formulation or process. Furthermore, by accurately defining the whole system, optimization techniques are a useful aid to process validation (28).A 2^2 factorial design was selectedto optimize the concentrations of a super disintegrant Ac-Di-Sol and a binder microcrystalline cellulose in a directly compressible, fast disintegrating tablet containing Telmisartan. The concentration of Ac-Di-Sol is optimum between 2-6%. The weight of tablet was 200 mg, so the minimum and maximum amounts ofAc-Di-Sol and microcrystalline cellulose used to formulate the directly compressible tablets, were 2 mg and 12 mg, and 40 mg and 94 mg respectively (Table 1)[16,29,30].The blend so obtained was compressed into tablet using hand operated tablet making machine (Pharmaceutical machinery mfg. works, Indore).

The factor is an assigned variable like concentration, temperature, drug treatment etc. the factorial level are the values assign to the factor. The notation used to denote factorial experiments conveys the following information: When the design is 2^2 factorial, it denotes:

1. Number of factors (2)
2. Level of each factor (2)
3. Experimental conditions present in the design (22 =4)

Table 1: Formulation of fast disintegrating tablet of Telmisartan using 2^2 factorial design

Ingredients	Weight in mg			
	F_1	F_2	F_3	F_4
Telmisartan	40	40	40	40
Ac-Di-Sol	12	2	12	2
MCC	94	94	40	40
Mannitol	49	59	103	113
Magnesium stearate	5	5	5	5
Total	200	200	200	200

Followings are the equations used to calculate the effects of factor A (Equation 1), effect of factor B (Equation 2) and magnitude of interaction of factors (Equation 3):

Effects of factor A = ½ [(ab+a)-(b+1)]…… Equation (1)
Effects of Factor B = ½ [(ab+b)-(a+1)]…….Equation (2)
Magnitude of Interaction = ½ [(1+ab) – (a+b)]....Equation (3)

If the combined effect of two factors had to produce a greater effect than that produce by individual factor, the interaction is said to be synergistic and reverse is said to be antagonistic [31-33].

Table 2: Disintegration time of Four Formulations

Formulation	Drug (mg)	Ac-Di-Sol	MCC	Disintegration Time (Sec)
F1	40	12	94	52±2
F2	40	2	94	65±1
F3	40	12	40	20±3
F4	40	2	40	30±2

*All values are mean ± SD, n=3

Table 3: Effects of Factor and their Interactions

Effect of Factor	Based on Disintegration Time
Effect of Factor A	5.0
Effect of Factor B	-26.75
Magnitude of Interaction	-0.75

The four batches (Table 2) were also evaluated for disintegration time studies and in vitro dissolution studies. The results were obtained (Table 3) clearly showed that effect of Ac-Di-Sol was dominant as compared to microcrystalline cellulose (MCC).These four batches were tested for parameters like weight variation, hardness and friability as per I.P. 2014 [34]. The results were found to be within limits.

Six more batches (Table 4) were formulated by varying concentration of Ac-Di-Sol between its minimum and maximum values i.e. 2 to 12 mg against constant amount of microcrystalline cellulose i.e. 40 mg. According to the Optimization, the concentration of Ac-Di-Sol was found to be effective for formulation prospective and we had to check its concentration to obtain an optimized formulation. The resulting mixtures were compressed into tablets using hand operated tablet making machine (Pharmaceutical machinery mfg. works, Indore).

Table 4: Composition of Different Formulation Batches

Tablet ingredients	Weight in mg					
	F1	F2	F3	F4	F5	F6
Telmisartan	40	40	40	40	40	40
Ac-Di-Sol	2	4	6	8	10	12
MCC	40	40	40	40	40	40
Mannitol	113	111	109	107	105	103
Mag. Stearate	5	5	5	5	5	5
Total	200	200	200	200	200	200

Disintegration Time Studies

The test was carried out on 6 tablets using the disintegration apparatus (Excel Enterprise, Kolkata). Distilled water maintained at 37±2°C was used as disintegration media and the time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds. The test was carried out in triplicate [35].

In-Vitro Dissolution Study

Dissolution study was performed using the USP Apparatus I (Lab India DS 8000, India) in 900 ml at phosphate buffer pH 7.5, maintained at 37±0.5°C with paddle speed at 75 rpm for 30 mins [36]. 10 ml of samples were withdrawn at specified time intervals. The volume of dissolution fluid was adjusted to 900 ml, by replacing each 10 ml aliquot withdrawn with 10 ml of phosphate buffer pH 7.5, pre-warmed at 37±0.5°C. Samples withdrawn were filtered through Whatmann filter paper (no.41), suitably diluted with phosphate buffer pH 7.5, and analyzed at 296 nm, using UV-Visible double beam spectrophotometer (UV-Visible spectrophotometer 3000,Lab India) . The results obtained were listed in table 5and shown in the Figure 4.

Table 5: In-Vitro Dissolution Data of Formulations F1-F6

Time (mins)	Cumulative % drug release ± S.D					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	65±1.95	76±0.59	82±1.47	87±0.81	94±0.063	95±0.56
10	75±0.59	86.80±0.72	87±0.84	89±0.84	99±0.22	99±1.04
15	87.85±0.84	92.325±0.77	95±0.72	95.2±0.56	99.4±1.04	99.4±1.02
20	92.325±0.77	95±0.72	98.8±0.56	99.4±1.04	99.6±1.02	99±0.42
25	95±0.72	98.8±0.56	99.0±0.47	99.4±1.04	99.6±1.02	99.5±0.32
30	98.0±0.56	99.0±0.47	99.02±0.42	99.4±1.04	99.6±1.02	99.5±0.42

*All values are mean ± SD, n=3

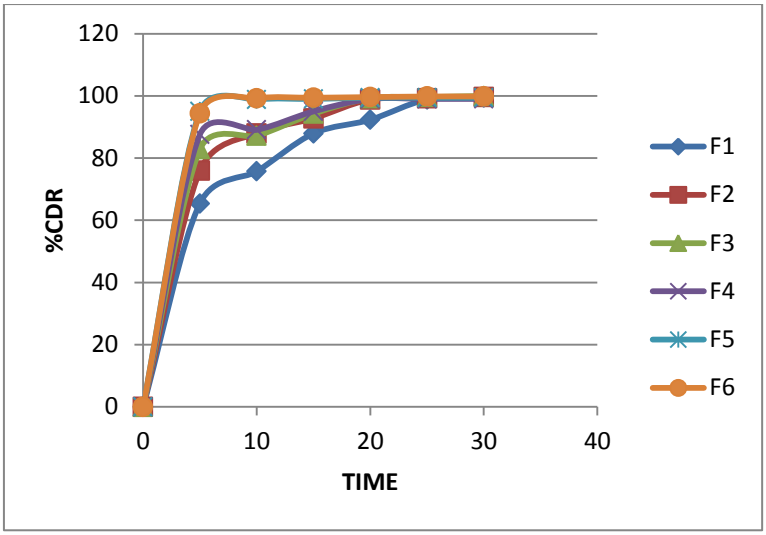

Figure 4: Cumulative Percent Drug Released through Fast Disintegrating Tablets of Telmisartan in pH 7.5 Phosphate Buffer

Again these batches were evaluated for weight variation (± %), hardness (kg/cm^2), friability (%), disintegration timeand *in vitro* dissolution rate. The results are summarized in table.

Table 6: Evaluation of Six Batches of Tablets as per IP-2014

Evaluation parameters*	F1	F2	F3	F4	F5	F6
Weight variation (± %)	3.3±2.539	3.4±2.536	3.3±2.531	3.1±2.510	3.3±2.539	3.1±2.509
Friability (%)	0.5±0.04	0.6±0.06	0.56±0.042	0.55±0.042	0.5±0.04	0.649±0.06
Hardness (kg/cm^2)	3.1±0.15	3.2±0.26	3.6±0.20	3.6±0.20	3.4±0.15	3.18±0.48
Disintegration time (Sec.)	52±0.130	43±0.132	35±0.038	30±0.135	21±0.136	22±0.0240

*All values are mean ± SD, n=4

The results showed that F5 formulation was found to be optimized because of higher in-vitro drug release and good disintegration time as compared to other formulation. This formulation was compared with the marketed formulation for disintegration rate and in vitro dissolution rate studies according to the method described above [34].

RESULTS AND DISCUSSION

The present study was undertaken with an aim to formulate, optimize and evaluate fast disintegrating tablets of Telmisartan using direct compression method with an aid of a super disintegrating agent Ac-Di-Sol.

The drug purity was confirmed by Differential Scanning Calorimetry. DSC Thermogram (Figure 1) showed a sharp endotherm at 268.9°C corresponding to its melting point. No other peak between the temperature rangeof 30 to 350°Cproved that the taken drug sample was pure. The same was confirmed byperforming FTIR analysis of the drug sample. The FTIR spectra (Figure 2) of Telmisartan showed peaks at 3446cm^{-1} (N-H stretching), 3063cm^{-1} (aromatic C-H stretching), 2957cm^{-1} (aliphatic C-H stretch), 1697cm^{-1} (carbonyl group), and 1599cm^{-1} (aromatic C=C bending and stretching)and the peak at 1458cm^{-1} indicating the presence of C=C aromatic group [27].

The FTIR spectra (Figure 2) of Telmisartan were compared with that of FTIR spectra of mixture of Telmisartan and Ac-Di-Sol in the ratio 1:1.No new peak except the characteristic peak of Telmisartan and Ac-Di-Sol was observed in the FTIR spectra of their mixture which confirms that there was no chemical interaction between them (Figure 2). Minor shifting of the characteristic peaks was seen in the spectrum of drug excipients mixture which was probably due to weak van-der-wall interaction between them.

The amount of Ac-Di-Sol was varied between 2 to 12 mg and the formulation was optimized using 2^2 factorial design (Table 4).It was observed that Ac-Di-Sol increased the rate of disintegration and dissolution significantly probability due to its ability to speed up moisture penetration and dispersion of matrix thereby increasing the disintegration rate of the drug delivery system [3,4]. The amount of binder, microcrystalline cellulose which was varied between 40 and 94 mg, did not show marked change in dissolution and disintegration rate in the presence

of Ac-Di-Sol (Table 2). Its increasing concentration however had a small decrease in tablet hardness and increase in tablet friability. All the batches showed the results within the prescribed limit in IP 2014 [34]. As a result six formulations were prepared by varying concentration of Ac-Di-Sol between 2 to 12 mg and keeping the concentration of microcrystalline cellulose minimum(40 mg) (Table 4).

All the batches gave hardness, friability, weight variation , *in vitro* disintegration (Table 6) and dissolution time in accordance to acceptable limits as per I.P. 2014 [34] (Figure 4).Formulation 5 (F5) showed the fastest disintegration and dissolution rate.

Formulation 5 (F5) was compared with a marketed tablet formulation. The optimized formulation F5 dissolved spontaneously showing > 95% release within first 5 minutes while the same value for % CDR inmarketed formulation was achieved in 30 minutes. All the six batches disintegrated fully within 0-52 seconds while the marketed formulation took 4 minutes to disintegrate completely. The disintegration time and *in vitro* dissolution time of optimized formulation was about 90.833% and 62% more than the corresponding values of Telmisartan tablet. The results are summarized in table 7 and table 8.The graphical comparison of %CDR of both the optimized product and marketed formulation was shown in figure 5.

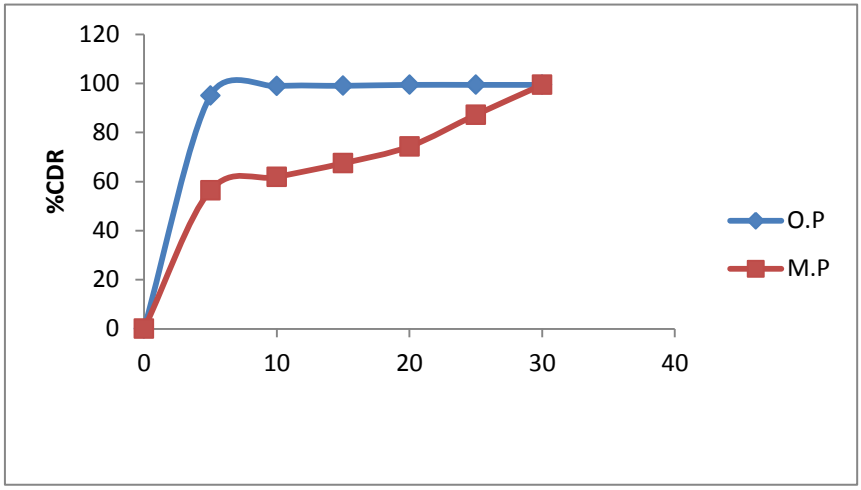

Figure 5: Comparative % CDR of the Optimized Formulation (F5) and Marketed Formulation

Table 7: Comparative Dissolution Profile of Optimized Product (F5) and Marketed Product

Time (mins)	Optimized product (F5)	Marketed product
0	0	0
5	94±0.063	56.42 ± 0.413
10	99±0.22	61.88±0.0852
15	99.4±1.04	67.48±0.413
20	99.6±1.02	74.3±0.188
25	99.6±1.02	87.20±0.432
30	99.6±1.02	99.4±0.075

*All values are mean ± SD, n=3

Table 8: Comparative Evaluation ofOptimized Product (F5) and Marketed Product

Evaluation parameters *	Optimized product (F5)	Marketed product
Weight variation (± %)	3.3±2.539	2.5±1.005
Hardness (kg/cm3)	3.4±1.15	4.13±0.100
Friability (%)	0.59±0.04	0.69±0.014
DT(Sec.)	21±1.2	240±1.5
Disintegration Rate (%)	99.6±1.02	98.6±0.112

*All values are mean ± SD, n=3

CONCLUSION

The present study concludes that Ac-Di-Sol can be a good substitute for conventional disintegrants to increase the onset of action by increasing its dissolution anddisintegration rate. Further *in-vivo* bioavailability studies are required to co-relate the results in the body and confirm the findings.

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