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Accelerated Stability Testing and Evaluation of Telmisartan Brands: A Comparative Study

Ankita D Bankhele*, Dhanraj A Gaikwad, Dr. Rajesh Oswal
Assistant Professor- Department of Pharmaceutics, Genba Sopanrao Moze College of Pharmacy Wagholi, Pune. 412207 Maharashtra, Quality Control Executive- Serum Institute of India- Hadapsar, Principal- Genba Sopanrao Moze College of Pharmacy Wagholi, Pune.

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ABSTRACT:
Introduction: Telmisartan is angiotensin II receptor antagonist (ARB) used in the treatment of hypertension and diabetics nephropathy at dose 300mg/day. As per ICH guideline, stress testing is an essential part of the formulation development strategy. Accelerated stability studies provides data to establish inherent stability characteristics of drug, with detection of degradation, if any. Two marketed brands of Telmisartan (Sartel-20 and Telmisartan TM-20) were tested for accelerated stability and compared. **Method**: The Brands were kept in humidity chamber, the samples were taken for accelerated stability testing at 0, 15, 30, 60, 90, 120, 150 and 180 days. Brands were evaluated for friability, hardness, disintegration and drug content. The dissolution was carried out on the Dissolution apparatus II (Electrolab TDL 06L) with the phosphate buffer at pH 7.5, Rpm 70 and temperature 37± 0.5. **Results:** The comparative study of both the brands conclude that both the products are stable as the accelerated stability testing was carried out for six months. **Conclusion:** The Accelerated stability testing concludes that the Sartel 20 was found to be more efficient than the Telsartan TM 20 brand.

Keywords: Telmisartan, Accelerated stability testing, Comparative study.

I. INTRODUCTION

Telmisartan (TELM) in Figure 1 is chemically nominated as 4'-[(1,4'-dimethyl-2-propyl [2,6'-bi-1H-benzimidazole]-1'-yl) methyl] [1,1'-biphenyl]-2-carboxylic acid.[1] Its molecular formula is $C_{33}H_{30}N_4O_2$ and molecular weight is 514.62 g/mol.[2,3,4] TELM is an angiotensin II receptor antagonist (ARB) used in the treatment of hypertension and diabetic nephropathy with elevated levels of serum creatinine and proteinuria (>300 mg/day) in type-2 diabetes and hypertensive patients.[5] Following oral administration, peak concentration (C_{max}) of Telmisartan are achieved in the 1st hour. Over the broad dose range of TELM viz 20-160mg it shows non-linear pharmacokinetics, when administered orally it shows greater than proportional increase of plasma concentrations (C_{max} and AUC) with increasing doses.[6,7,8]

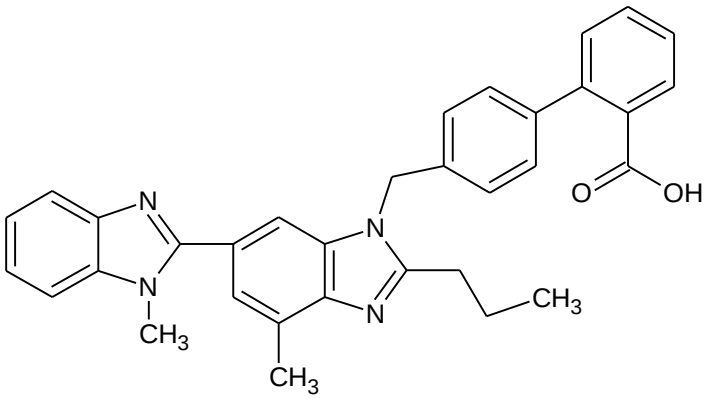

Figure 1: Structure of Telmisartan Drug

International Journal of Pharmaceutical Research and Applications
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The stability of a drug in climates with extreme temperature is a primary concern.[9] International Conference on Harmonization (ICH) issued a parent drug stability test guideline Q1A (R2) suggests that accelerated stability testing is an essential part of formulation development strategy.[1,10] Therefore the active pharmaceutical ingredient(TELM) is subjected to various stress degradation conditions temperature and humidity.[11] Accelerated stability studies provide information to establish inherent stability characteristics of drug, leading to identification of degradation products.[1,12]

Formulations of different brands may have different types excipients like diluents, disintegrates, lubricants that may affect the disintegration and dissolution rates of a formulation.[3] This also may be the result of different compression forces to which it is subjected. Many research attempts are being conducted to compare the generic brands of TELM, but they lack the accelerated stability study aspect. Apart from this, feedback from physicians revealed that some TELM brands need to be given in higher doses than the recommended one to produce the desired clinical effect. This imposed accelerated stability studies of TELM brands.

II. MATERIALS AND METHODS

Marketed formulation

SARTEL 20 (Intas Pharmaceuticals Ltd.) and TELSARTAN TM 20 (Dr. Reddy's Laboratories Ltd.) contains TELM IP 20 mg which was procured from open market for this study.

Table 1: Details of marketed formulation

Parameters	**Sartel – 20**	**Telsartan TM 20**
Batch Number	KW1605	GH70704
Manufacturing Month	June 2017	July 2017
Expiry Month	May 2020	June 2019
Manufactured by	Intas Pharmaceuticals Ltd.	Dr. Reddy's Laboratories Ltd.

Reagent and chemicals

Methanol was used as a solvent, Phosphate buffer (pH 7.5) were used as dissolution medium and all the chemicals and reagents used in the study were of analytical grade.

Calibration curve

Stock solution: Exact 10 mg of TELM was weighed on electronic balance (Shimadzu – AX200) and transferred to 100ml volumetric flask. About 50 ml methanol was added and then sonicated for 15 minutes. Volume was made up to 100 ml with methanol (TELM standard stock solution 100 µg/ml). Preparation of working standard: It was prepared from the stock solution of 100 µg/ml. It was scanned to entire UV range to determine $\lambda_{max.}$ Aliquots of TELM such as 4, 6, 8, 10, 12, 14 and 16µg/ml were prepared to obtain linear relationship. Absorbance of the aliquots was recorded at 296nm using UV visible spectrophotometer (Jasco -V 730).[1,13] The calibration curve was plotted for TELM by considering concentration of drug on X- axis and absorbance on the Y- axis as shown in figure 1 and 2.

Drug content determination (assay)

About 20 tablets were weighed and then crushed in mortar and pestle to form a powder. The quantity of tablet powder corresponding to 10 mg of TELM was weighed and was added in a volumetric flask containing 50 ml of methanol. This mixture was then sonicated for 15 min and further its volume was made up to 100 ml with methanol. Then the solution obtained was filtered by Whatmann filter paper (Grade 1). The filtrate was then diluted to obtain 10 µg/ml concentration. The absorbance was determined in UV visible spectrophotometer (Jasco -V 730) against blank at 296nm.[13] The drug content was determined by using calibration curve and it was expressed in percentage. Assay was conducted separately using this method for each formulation.

Dissolution Testing

About six tablets were selected randomly from each formulation and they were taken in dissolution vessels, simultaneously. USP apparatus II (Electrolab – TDL 06L) along with paddles was used. Instrument was set to 75 rpm and 37 ± 0.5°C temperature as per IP monograph of TELM tablet. Phosphate buffer (pH7.5) was used as dissolution medium.[3,13] Dissolution was conducted for 30 minutes and 5ml samples were pipetted out and 5ml fresh medium were added in vessel to maintained sink condition at the interval of 5, 10, 15 & 30 minutes. All six tablets were tested at each time point.

International Journal of Pharmaceutical Research and Applications
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Mean Dissolution Time (MDT) Determination
MDT was determined by using PCP dissoV3 software. Theoretically MDT can be calculated using following formula,

$$MDT = \sum_{j=1}^{n} \frac{tj \Delta Mj}{\Delta Mj}$$

Where, n is the number of dissolution sample; j is the sample number, t is time at midpoint between t and tj-1 and ∆M is additional amount of drug dissolved between tj and tj-1.[14]
Significance of MDT: Drug's MDT depends on dose/solubility ratio, even when the model measured is the simplest possible[15]. This fact plays a significant role in drug absorption when absorption is dissolution limited. It gives information about the drug release strategy. It is helpful in IVIVC of Level B. It tends to increase with time. It is a function of polymer loading as well as solubility of drug.[16]

Mathematical Release Model
The mathematical release models were determined by using PCP Disso V3 software. Mathematical models are used to study release phenomenon of drug from dosage forms.[15,17]

Dissolution Efficiency
Dissolution efficiency (DE) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.[15]

$$D.E. = \int_0^t (y \times dt)/y100 \times t \times 100\%$$

Where y is the drug percent dissolved at time t
Significance of DE: It helps in monitoring the variations in batches.[18]

Accelerated Stability studies
The tablets of both brands were kept for 6 months at controlled temperature and Humidity (40 °C ± 2 °C and 75 ± 5 % RH) and evaluated for at the intervals of 0 day, 15 days. 30 days, 60days, 90days, 120 days, 150 days and 180 days.[9,11]
Weight variation, disintegration, friability, hardness, assay and dissolution test were performed at all intervals.

Disintegration
Disintegration test were performed using disintegration test apparatus (Veego Instrument Corporation VTD-4AVP) The 6 individual tablets of each brands were disintegrated using disintegration apparatus. Water as a solvent was used for this test. According to IP limit, the disintegration time required for uncoated tablets is not more than 15 minutes.[8,18,19]

Hardness test
The hardness test was performed on 6 individual tablets of both brands using Monsanto hardness tester (ORCHID SCIENTIFICS).[8,20]

Friability test
Ten tablets are weighed initially and then they are rotated in Roche type friability test apparatus (Veego Instrument Corporation). After 100 rotations at a speed of 25 rpm the tablets are weighed again to calculate percent friability.[18,20]
% friability = Initial weight – final weight / Initial weight * 100
Percent friability of tablets less than 1 % is considered acceptable.

III. RESULTS AND DISCUSSION

Calibration curve determination
Standard curves and equations of Telsartan-20 and Sartel-20 tablets were plotted as shown in figure 1 and 2 respectively. It consisted of TELM 20 mg relating concentration and absorbance. The calibration curve was found to be linear in the range of 4 –16 µg/ml with a regression coefficient close to 0.9978 and 0.9963 respectively.

International Journal of Pharmaceutical Research and Applications
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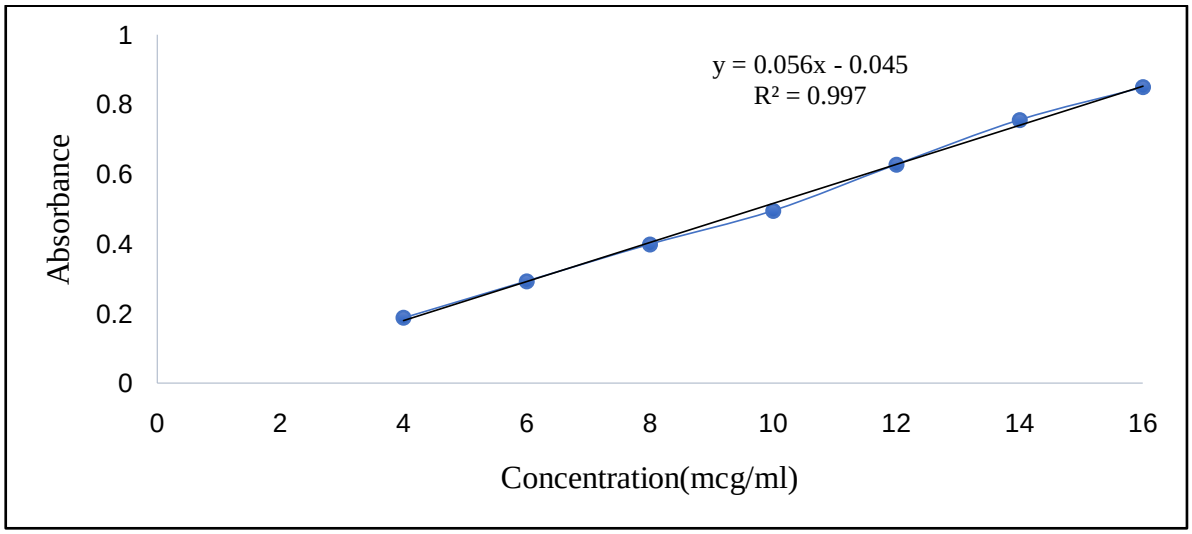

Figure 1: Calibration curve of Telsartan TM-20 in Methanol

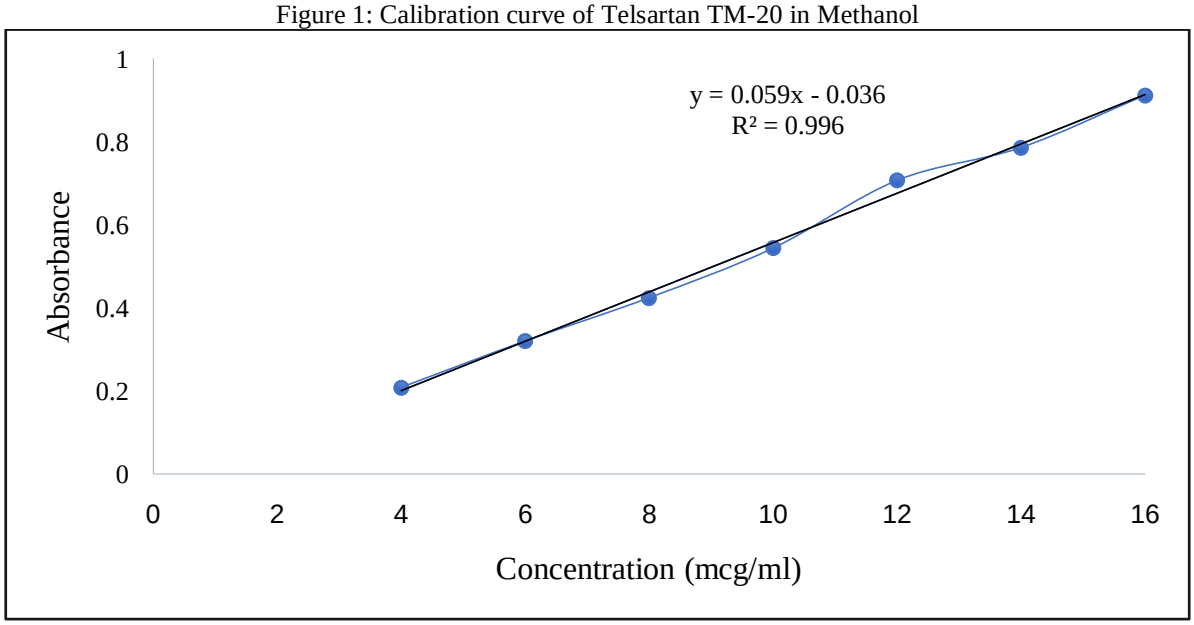

Figure 2: Calibration Curve of Sartel 20 in methanol

Assay

The content of Telmisartan in Sartel-20 tablet was found to be 99.26% initially. After accelerated stability testing for 6 months it was degraded up to 8% and found 91.60%. Whereas, Telsartan TM-20 showed 98.97% content of drug initially, and after the accelerated stability testing for 6 months it was degraded up to 7% and found 91.12% as shown in table 2. From the obtained result it can be noted that both formulations are stable for accelerated stability testing of 6 months.

Table 2: Assay

Brands	Percent drug content during accelerated stability testing							
	0days	15days	30days	60days	90days	120days	150days	180days
Sartel-20	99.26± 0.96	98.86± 0.69	98.28± 0.89	97.78± 0.88	96.31± 1.21	94.92± 0.71	93.11± 0.68	91.60± 0.68
Telsartan TM-20	98.97± 1.51	97.96± 1.14	96.64± 1.38	96.14± 0.90	94.89± 1.32	93.87± 1.22	93.09± 1.18	91.12± 0.90

Data is expressed as mean ± S.D., (n = 6)

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1010-1019 www.ijprajournal.com ISSN: 2456-4494

Dissolution studies

Throughout the accelerated stability testing study Sartel – 20 showed more than 50% drug release within 5 min. and more than 80% of drug release in 10 min. Whereas Telsartan TM 20 showed slow drug release compared to sartel-20 but both the brands release its content i.e. more than 90% within 30 min. It may be because of difference in formulation contents between Sartel-20 and Telsartan TM-20.

Table 3: Average % Release

Days	Brands	Percentage CDR* at time intervals in min			
		5	10	15	30
Initial day	Sartel – 20	67.542	92.749	97.478	98.966
Initial day	Telsartan TM 20	20.060	29.792	40.355	98.01
15 days	Sartel – 20	61.024	85.476	94.834	98.068
15 days	Telsartan TM 20	23.384	36.799	56.054	97.054
30 days	Sartel – 20	54.684	79.298	85.091	97.16
30 days	Telsartan TM 20	21.894	28.919	47.787	96.02
60 days	Sartel – 20	55.743	83.076	92.961	96.747
60 days	Telsartan TM 20	22.954	40.056	57.551	95.738
90 days	Sartel – 20	61.781	81.278	88.914	95.825
90 days	Telsartan TM 20	23.226	41.198	58.048	94.084
120 days	Sartel – 20	58.770	80.547	88.164	94.07
120 days	Telsartan TM 20	22.723	40.394	57.280	93.002
150 days	Sartel – 20	58.925	80.021	87.433	92.99
150 days	Telsartan TM 20	22.193	39.481	56.634	92.84
180 days	Sartel – 20	58.335	78.946	86.818	90.78
180 days	Telsartan TM 20	21.773	38.949	55.583	90.238

At the initial days both brands showed almost 98% of drug release within 30 minutes. However, it decreased up to 90% within 6 months of accelerated stability testing (Table 3).

Mean Dissolution Time

Mean dissolution time of Sartel-20 is 4.64 minute for around 98% drug release whereas Telsartan TM-20 required 15.76 minute for the same amount of drug release as shown in table 4. The difference in MDT between Sartel-20 and Telsartan TM-20 was because of difference in polymer features loaded in tablets of both the brands. During the accelerated stability testing study MDT of Telsartan TM-20 (figure 3) was decreased up to 11.79 min it indicates that polymer slightly lost its property. However, in Sartel-20 (figure 4) no significant difference in MDT was observed.

Table 4: Mean dissolution time

Days	Brands	Time(min)			
		5	10	15	30
Initial day	Sartel – 20	2.50	3.86	4.28	4.64
Initial day	Telsartan TM 20	2.50	4.13	6.32	15.76
15 days	Sartel – 20	2.50	3.93	4.34	5.10
15 days	Telsartan TM 20	2.50	4.32	7.13	13.58
30 days	Sartel – 20	2.50	4.05	4.63	5.75

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1010-1019 www.ijprajournal.com ISSN: 2456-4494

30 days	Telsartan TM 20	2.50	3.71	7.18	14.21
60 days	Sartel – 20	2.50	4.15	5.08	4.97
60 days	Telsartan TM 20	2.50	4.63	7.03	11.86
90 days	Sartel – 20	2.50	3.70	4.46	5.03
90 days	Telsartan TM 20	2.50	4.68	6.95	11.52
120 days	Sartel – 20	2.50	3.85	4.60	5.15
120 days	Telsartan TM 20	2.50	4.69	6.99	11.64
150 days	Sartel – 20	2.50	3.82	4.55	5.15
150 days	Telsartan TM 20	2.50	4.69	7.05	11.78
180 days	Sartel – 20	2.50	3.81	4.59	5.04
180 days	Telsartan TM 20	2.50	4.71	7.04	11.79

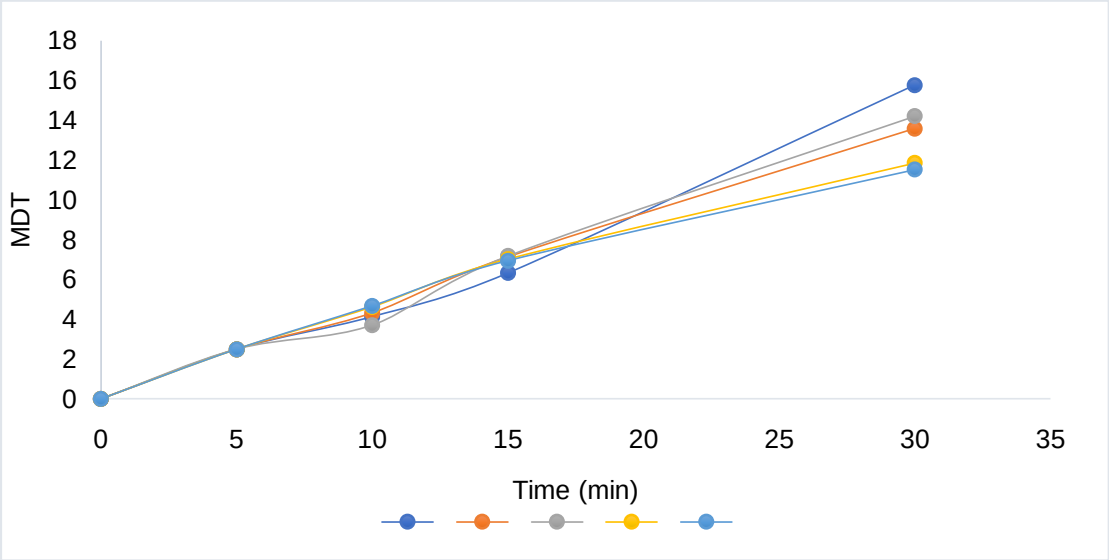

Figure 3: Mean Dissolution time for Telsartan 20mg

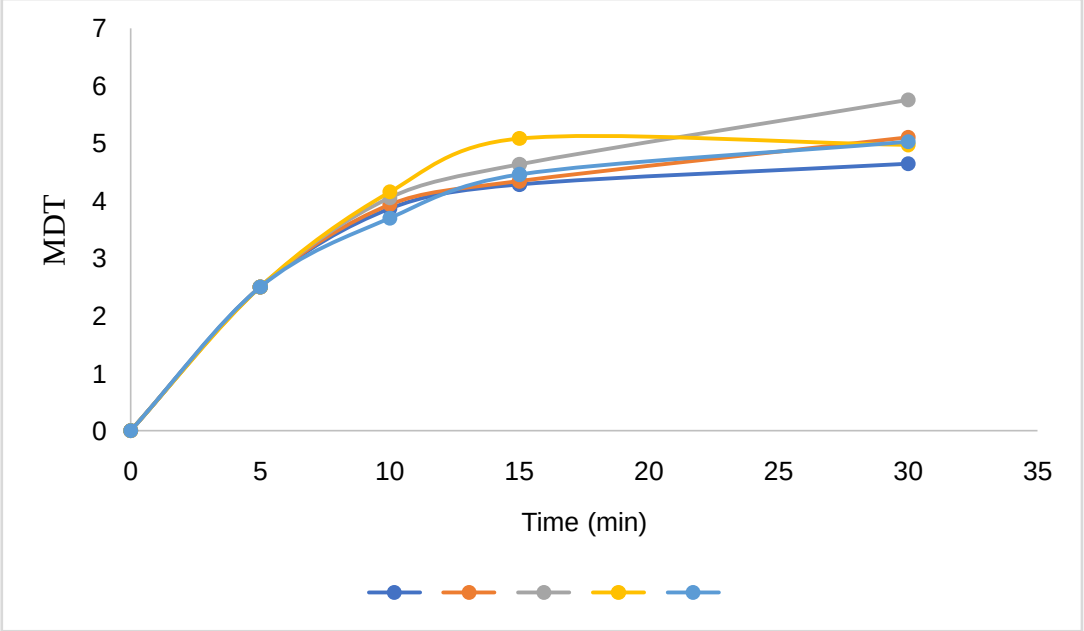

Figure 4: Mean Dissolution time for Sartel-20mg

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1010-1019 www.ijprajournal.com ISSN: 2456-4494

Mathematical release model

Table 5: Kinetic release profile

Parameters	Telsartan TM 20	R values	K values	Sartel- 20	R values	K values
0 day	Zero Order Model	0.9885	3.1910	Matrix Model	0.8849	22.7775
15 days	Zero Order Model	0.9719	3.3779	Matrix Model	0.9013	21.8247
30 days	Zero Order Model	0.9840	2.9893	Matrix Model	0.9258	20.0003
60 days	Hixson Crowell Model	0.9983	-0.0155	Matrix Model	0.9169	20.9805
90 days	First Order Model	0.9988	-0.0572	Korsemeyer - Peppas Model	n= 0.2212	45.9787
120 days	First Order Model	0.9987	-0.0563	Matrix Model	0.9133	20.4315
150 days	First Order Model	0.9985	-0.0557	Korsemeyer - Peppas Model	n=0.2380	43.0538
180 days	First Order Model	0.9990	-0.0536	Korsemeyer- Peppas Model	n=0.2359	42.7755

Initially Telsartan TM-20 showed zero order drug released kinetic. It reveals that drug release was independent of drug dose loaded in tablet. After 90 days of accelerated stability testing, it showed first order drug release which may be because of polymers used in the formulation that loses its property of controlling drug release. Therefore, drug is released by concentration gradient mechanism i.e. by first order. During 60 days of accelerated stability testing, Telsartan TM-20 followed Hixson Crowell model which implies dissolution occur in planes that are parallel to the drug surface. However, Sartel-20 followed matrix model drug release kinetic till 2 months of accelerated stability testing as shown in table 5. It reveals that no efforts were taken in formulation development for manipulation of drug release.

Percent Dissolution Efficiency

Table 6: Percent Dissolution efficiency

Days	Brands	Time(min)			
		5	10	15	30
Initial Day	Sartel – 20	33.77	56.96	69.68	84.07
Initial Day	Telsartan TM 20	10.03	17.48	23.34	45.99
15 Days	Sartel – 20	30.51	51.88	65.33	81.11
15 Days	Telsartan TM 20	11.69	20.89	29.40	52.85
30 Days	Sartel – 20	27.34	47.17	58.84	73.40
30 Days	Telsartan TM 20	10.95	18.18	24.90	46.24
60 Days	Sartel – 20	27.87	48.64	61.86	77.56
60 Days	Telsartan TM 20	11.48	21.49	30.60	50.62
90 Days	Sartel – 20	30.89	51.21	62.51	76.44
90 Days	Telsartan TM 20	11.61	29.91	31.15	50.64
120 Days	Sartel – 20	29.38	49.52	61.13	75.35
120 Days	Telsartan TM 20	11.36	21.46	30.59	50.06
150 Days	Sartel – 20	29.46	49.47	60.89	74.91
150 Days	Telsartan TM 20	11.10	20.97	30.00	49.55
180 Days	Sartel – 20	29.17	48.90	60.23	74.08

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1010-1019 www.ijprajournal.com ISSN: 2456-4494

180 Days	Telsartan TM 20	10.89	20.62	29.50	48.71

D for issolution efficiency (DE) helps in monitoring the variations in the batches. Due to variation in compression force, hardness varies and therefore affects dissolution profile. Percent dissolution efficiency of Sartel 20 was found to be 84.07% at 30-minute while, Telsartan TM 20 showed 45.99% at the same time (Table 6). It reveals that Sartel 20 is more efficient in dissolution. Dissolution efficiency varied on accelerated stability testing both the brands. In case of Sartel 20 DE decreased about 10% of initial value after the 6 months of accelerated stability testing but there is slight increase in DE of Telsartan TM 20. This variation in DE confirmed the changes in the properties of polymers incorporated in tablet formulation of both the. However, the change is not significant and passes the accelerated stability testing test.

Disintegration studies

Table 7: Disintegration Studies

Brands	Average Disintegration time(min)							
	0days	15days	30days	60days	90days	120days	150days	180days
Sartel – 20	4.98± 1.03	4.86± 0.92	4.63± 0.76	4.51± 0.90	4.5± 0.76	4.45± 1.07	4.21± 0.97	4.03± 1.0
Telsartan TM 20	16.17± 1.94	14.38± 1.23	14.23± 0.74	14.25± 0.76	14.15± 0.76	14.13± 1.01	14.06± 1.17	13.9± 0.73

Data is expressed as mean ± S.D., (n = 6)

The disintegration time of both brands were within the limits of the Indian pharmacopeia for conventional tablet. Telsartan TM 20 tablets showed longer disintegration time as compared to Sartel-20 tablets (table 6) even though the hardness of Sartel-20 tablets was more (Table 7). This may be due to presence of excipients in Sartel-20 tablets. Disintegration time of Sartel 20 was not considerably change during 6 months' accelerated stability testing whereas DT for Telsartan TM 20 was significantly change. It reveals that Telsartan TM 20 was more susceptible to accelerated stability testing.

Determination of hardness

Table 8: Average Hardness

Brands	Average Hardness (Kg/cm^2)							
	0days	15days	30days	60days	90days	120days	150days	180days
Sartel– 20	7.08± 0.37	7± 0.44	7± 0.54	6.91± 0.20	6.83± 0.25	6.66± 0.25	6.41± 0.20	6.25± 0.27
Telsartan TM 20	5.16± 0.40	5.08± 0.20	4.91± 0.20	4.91± 0.37	4.33± 0.25	4.25± 0.27	4.16± 0.25	4.08± 0.20

Data is expressed as mean ± S.D., (n = 6)

Hardness of commercial tablets were within the limits of pharmacopoeia (Table 8). Generally, the tablets which had low hardness value disintegrates fast and have more friability value. But the brand of Sartel 20 tablet disintegrates faster than Telsartan TM 20 tablets although the hardness of Telsartan TM 20 tablets is less than that of Sartel 20 tablets. It is known that excipients and compression force during a tableting process plays an essential role on the overall properties of the products, such as tablet disintegration rate, friability, and hardness. It is therefore reveals that hardness of Sartel 20 was kept higher without hampering disintegration time by manipulating formulation ingredients and compression force.

Friability test

Table 9: Friability

Brands	Friability (%)							
	0days	15days	30days	60days	90days	120days	150days	180days
Sartel –	0.088	0.120	0.230	0.431	0.503	0.533	0.589	0.602

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 4 July-Aug 2022, pp: 1010-1019 www.ijprajournal.com ISSN: 2456-4494

20								
Telsartan TM 20	0.092	0.165	0.240	0.332*	0.451	0.516	0.611	0.651

The friability was found to be within the limits of pharmacopoeia i.e. less than 1%(Table 9). Friability of both brands increases during 6 months of accelerated stability testing but within the limits of pharmacopoeia. Increase in friability of both brand during accelerated stability testing may be because of decrease in binding forces in excipients it confirmed by results of hardness.

IV. CONCLUSION

Accelerated stability testing is the key procedural component in development of pharmaceuticals such as new drugs and/or new formulation. Stability tests are carried out so as to find shelf life of the product and it can be included on the label. Various studies for instance assay, dissolution studies, disintegration test etc. were conducted to find out the stability of the product. After accelerated stability testing drug content (assay)of both the brands were in the range as specified in official compendia. From this we can conclude that the chosen brands are stable up to their shelf life. There was slight effect of accelerated stability studies on the assayed formulation. Dissolution study of both brands conclude that there is no significant change in dissolution parameters like MDT, DE and average drug released. However, drug release kinetic model gets change during the accelerated stability testing for both brands. It reveals that formulation ingredient responded slightly for accelerated stability testing. As no significant change was observed in other parameters of both brands therefore it can be concluded that they are stable for six months at accelerated conditions. From the accelerated stability testing data, authors conclude that the Sartel 20 was found to be more efficient than the Telsartan TM 20 brand.

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