INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACY, BIOLOGY AND CHEMISTRY

Research Article

Design and Evaluation of Sustained Release Capsule of Telmisartan

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ABSTRACT

Telmisartan is an Anti-hypertensive drug which is insoluble in water; hence the drug may be slowly or incompletely dissolves in the gastro-intestinal tract. So the rate of Dissolution and therefore its bioavailability is less (bioavailability 42%). In the present Study an attempt has been made to prepare Fast Dissolving Capsules of Telmisartan by Using Super disintegrants–Crosspovidone, Ac-de-sol, and sodium starch glycolate, level of addition to increase the rate of drug release from dosage form to increase the dissolution rate and hence its bioavailability. The capsules were prepared by Dissolution methods and the prepared blend and capsules were evaluated for their physicochemical properties and *In-Vitro* dissolution study. The evaluation studies were performed such as Weight Variation, Thickness, Disintegrating Time, and *In-Vitro* Drug Release and Stability Study. The Disintegration time of Dissolving Capsules were increased by the addition of concentration of Superdisintegrants.

Keywords: Telmisartan, UV Spectroscopy, Sustained Release Capsule, Croscarmellose sodium.

INTRODUCTION

Telmisartan is used to treat high blood pressure (hypertension) by blocking the Hormone angiotensin thereby relaxing blood vessels, causing them to widen. High blood pressure reduction helps prevent strokes, heart attacks, and kidney problems. Telmisartan is an Angiotensin Receptor Blocker (ARB) shows high affinity for the angiotensin II type1 (AT1) receptors, has a long duration of action, and has the longest half-life of any ARB (24 hours)[1-3]. It is indicated for the treatment of hypertension but Telmisartan's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD)[4]. It is practically insoluble in water and in the p^H range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloricacid), and soluble in strong base. Numerous studies have been carried out in order to modify the dissolution kinetics of poorly soluble drugs to improve their bioavailability. A common method used to improve the dissolution rate of a poorly water soluble drug is by formation of a solid dispersion (SD) with hydrophilic polymer polyvinyl pyrrolidone and other diverse carriers[5-7]. Briefly, an SD is defined as a molecular mixture of drug in carriers. The changes of drug crystallinity to an amorphous form and the reduced particle size for better wettability are the main mechanisms whereby SD enhances drug dissolution[8-10]. The Bioavailability of Telmisartan is Poor About 45%, which due to Extensive First Pass hepatic metabolism; The Bioavailability can be increase by Fast Dissolving Formulation. Conventional Telmisartan tablets available in market are not suitable where quick onset of action is required[11]. Hence, the objective of the present study was to develop Telmisartan (SR) immediate release capsules using Lactose DCL 11, MCC and Magnesiun sterate the release the main objective of the presents study was to develop Sustained release Capsules of Telmisartan by simple and cost effective direct compression methods.

Protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD).

MATERIALS AND METHODS

Telmisartan is procured by Lupin Drugs pvt. Ltd. Pune, CrosscaromelloseSodium, Crosspovidone are gifted by Signet Chemical Corporation, Mumbai, Lactose,HPMC, PVG 6000, MCC p^H 102, CCS ,PVP K 30 were procured by Debjit Bhowmik Etal, Colorcon Asia Pvt. Ltd. Mumbai.

MagnesiumStearate, is procured by Nice Chemicals Pvt. Ltd., Cochin.

Preparation of sustained released Telmisartan Capsule by Dissolution Methods using Superdisintegrants

CCS = Cros Carmellose Sodium
MCC=Micro Crystalline Cellulose
Average wt. of Telmisartan part: 140 mg

PROCEDURE[12,13]

Telmisartan Sustained release Capsule was prepared by dissolving the Capsules in disintegration method using various Disintegrants used like Lactose Talc. Weighed the Telmisartan, PEG 6000, HPMC, MCC pH 102 according to the formula. Dissolve PEG 6000 & CCS in Ethanol by slow addition. Avoid lump formation during addition of PEG 6000 & CCS, stir to dissolve and to form a homogenous clear solution. Loaded the sifted material into the main bowl of Rapid Mixture and fill in the capsule Add the materials as showed in the given below table

Table 1: Formulation Table 1:1 Ratio

Drug + Polymer	200 mg
HPMC	188 mg
Talc	4 mg
Magnesium sterate	4mg
Aspertine	4 mg

Table 2: Formulation Table 1:1.5 Ratio

Drug + Polymer	250 mg
HPMC	138 mg
Talc	4 mg
Magnesium sterate	4 mg
Aspertine	4 mg

Table 3: Formulation Table 1:2 Ratio

Drug + Polymer	300 mg
HPMC	88 mg
Talc	4 mg
Magnesium sterate	4mg
Aspertine	4mg

Table 4: Formulation Table 1:2.5 Ratio

Drug + Polymer	350 mg
HPMC	38 mg
Talc	4mg
Magnesium sterate	4 mg
Aspertine	4 mg

binder to the dry mix and continue the granulation at high speed till a coherent mass is obtained. Transferred the wet granules into the FBD main bowl. Dried the granules at room temperature till the solvent was completely evaporated. Sifted the semi dried granules to the multi mill fitted with 1.5 mm screen using knives forward medium speed. Transferred the semi dried sifted and milled granules into FBD bowl. Dried the semi sifted granules at 45˚C till the required LOD was achieved. Checked the LOD of the granules. Sifted the dried granules through the 16 #Limit: Not more than 2.5% W/W for LOD of the granules [14-16]. Loaded it into the Capsules. Loaded the dried granules along with the above sifted materials into the material and blend it for 10min. Sifted the SSF through 40# mesh and load it into the blender and mix it for 5 mts. The formulations were shown in shown in table no.1.

***IN-VITRO* DISSOLUTION STUDIES**

Dissolution studies were carried out as per the USP 26 specifications, using USP dissolution apparatus type 2 at pH conditions i.e. 6.8 Phosphate Buffer for 1 hr followed by the pH 6.8 for remaining hrs. Analysis Telmisartan was estimated by U.V.spectrophotometer at 223nm. Best formulation was subjected to HPLC analysis as per the specifications given (Column used - Kromasil C 18 ODS column, Mobile Phase – Buffer : Acetonitrile – 75: 25 , pH of the mobile phase 3.0 (Adjusted with Orthophosporic acid, Flow Rate - 1ml/min., Injection volume- 100µl, Wavelength – 215 nm, HPLC system – Waters). The prepared mobile phase was filtered through 0.45 µmmicro pore filter and degassed by sonication for 10 minutes.

BUFFER

50 ml of 1 M monobasic sodium phosphate and 8.0 ml. of 1 M phosphoric acid and dilute with water to 1000ml adjust with 1 M phosphoric acid to pH 3.0.

STANDARD PREPARATION

Weigh accurately about 100 mg of Telmisartan working standard in a 50ml Volumetric flask dissolves in a dissolution medium makeup the volume with same. Dilute 5 ml from the above solution to 50 ml with dissolution medium.

PROCEDURE

Inject 20 µl sample preparation (one injection) and standard preparation into the Liquid chromatography and record the chromatogram. Measure the responses for the major peaks. Calculate the dissolved quantity of Telmisartan in percentage form the peak areas of standard and sample preparation and percentage of potency of working standards used.

ASSAY

Preparation of Standard Telmisartan (HPLC method)

Weigh accurately about 50 mg of Telmisartan working standard in a 50ml volumetric flask dissolves in a dissolution medium makeup the volume with same. Dilute 5 ml from the above solution to 50 ml with dissolution medium.

Chromatographic condition

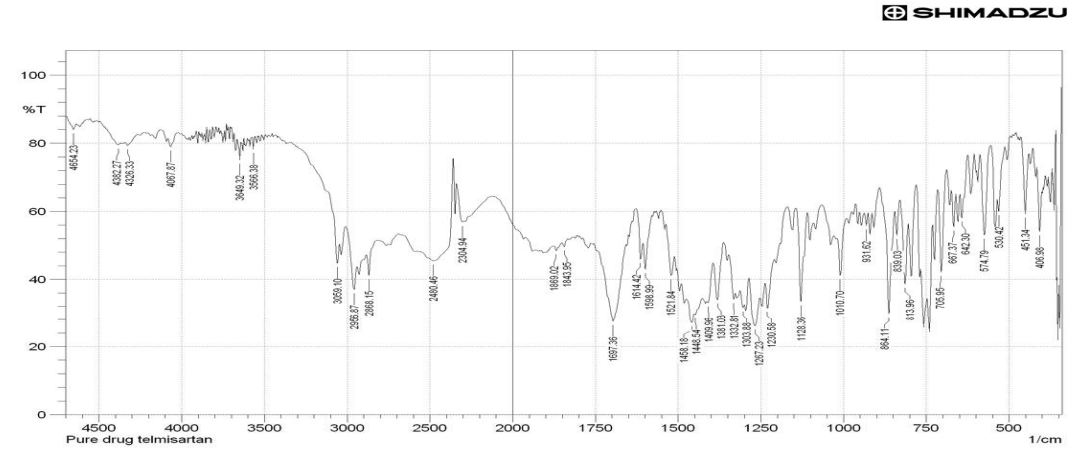
Mobile phase used for the analysis consist of Buffer: Acetonitrile aqueous solution in the ratio of 75:25 v/v. They were filtered before use through a 0.45 µm membrane filter and pumped through the column RP C18 (250 x 4.6 i.d) mm, 5µm, in isocratic mode at a flow rate of 1 mL/min. Prior to the injection of the drug solution, the column was equilibrated for at least 30 min with the mobile phase flowing through the system. The analysis was performed at ambient temperature and the run time was set at 10 min. The eluents were monitored at 223 nm and retention of Telmisartan was found to be 7.7 min.

Sample preparation

Weighed about 50mg equivalent of Telmisartan in a 100 ml volumetric flask and 5 ml of water, to disperse and 70 ml of methanol warm 10 minutes dilute to volume with methanol. Filter the supernatant liquid with 0.45 micron membrane filter. Dilute 5ml from the solution to the 50 ml with mobile phase.

Fourier transform infrared (FT-IR)

Fourier transform infrared (FT-IR) spectral studies were conducted on FTIR Spectrophotometer (Shimadzu Instrument Corporation Inc., Japan) instrument using KBr pellets to investigate possible interactions between the respective polymers in the release media. All samples were crushed with potassium bromide. The weight ratio of a sample and potassium bromide was 2 mg to 300 mg. Crushed powders were compressed using a hydraulic compactor at approximately 20,000 pounds under vacuum for 3 min. FT-IR measurements were performed under nitrogen atmosphere at a flow rate of 50 standard cubic feet per hour. Spectral scanning was conducted from 4000 to 400 cm−1 at a resolution of 4 cm−1.



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	406.98	53.997	14.452	416.62	401.19	3.178	0.717
2	451.34	59.23	19.96	464.84	439.77	3.697	1.177
3	530.42	60.05	7.403	536.21	513.07	3.706	0.25
4	574.79	53.086	24.782	588.29	555.5	5.697	2.176
5	642.3	58.116	9.832	648.08	624.94	4.251	0.75
6	667.37	55.413	10.149	675.09	661.58	2.952	0.483
7	705.95	42.125	26.406	715.59	688.59	6.506	2.204
8	813.96	38.564	20.456	829.39	804.32	7.509	1.895
9	839.03	52.976	8.225	844.82	829.39	3.627	0.379
10	864.11	29.882	33.009	891.11	844.82	13.475	4.307
11	931.62	55.817	3.732	937.4	925.83	2.75	0.145
12	1010.7	41.161	12.862	1020.34	991.41	8.662	1.134
13	1128.36	33.471	26.942	1143.79	1109.07	10.959	3.342
14	1230.58	31.521	8.839	1236.37	1209.37	11.22	1.115
15	1267.23	26.104	10.891	1286.52	1253.73	16.822	2.815
16	1303.88	31.609	2.127	1313.52	1300.02	6.409	0.183
17	1332.81	34.074	4.969	1348.24	1327.03	8.484	0.317
18	1381.03	34.026	13.491	1394.53	1363.67	11.895	2.003
19	1409.96	33.119	2.687	1413.82	1394.53	8.199	0.265
20	1448.54	29.513	1.023	1452.4	1427.32	12.544	0.152
21	1458.18	27.07	3.874	1475.54	1452.4	12.051	0.593
22	1521.84	41.173	9.289	1537.27	1512.19	8.309	1.048
23	1598.99	42.918	10.1	1606.7	1579.7	7.979	0.881
24	1614.42	45.93	8.829	1625.99	1606.7	5.419	0.492
25	1697.36	27.408	21.941	1741.72	1656.85	35.931	9.86
26	1843.95	49.613	1.675	1851.66	1834.3	5.126	0.101
27	1869.02	48.458	1.612	1874.81	1851.66	7.057	0.149
28	2304.94	56.802	3.105	2339.65	2293.36	10.07	0.596
29	2480.46	45.45	0.083	2513.25	2478.53	11.729	0.003
30	2868.15	41.182	7.084	2883.58	2818	20.883	0.765
31	2956.87	37.032	9.709	3008.95	2939.52	23.749	2.437
32	3059.1	44.782	8.415	3120.82	3045.6	18.71	0.722
33	3566.38	78.285	3.629	3576.02	3556.74	1.8	0.129

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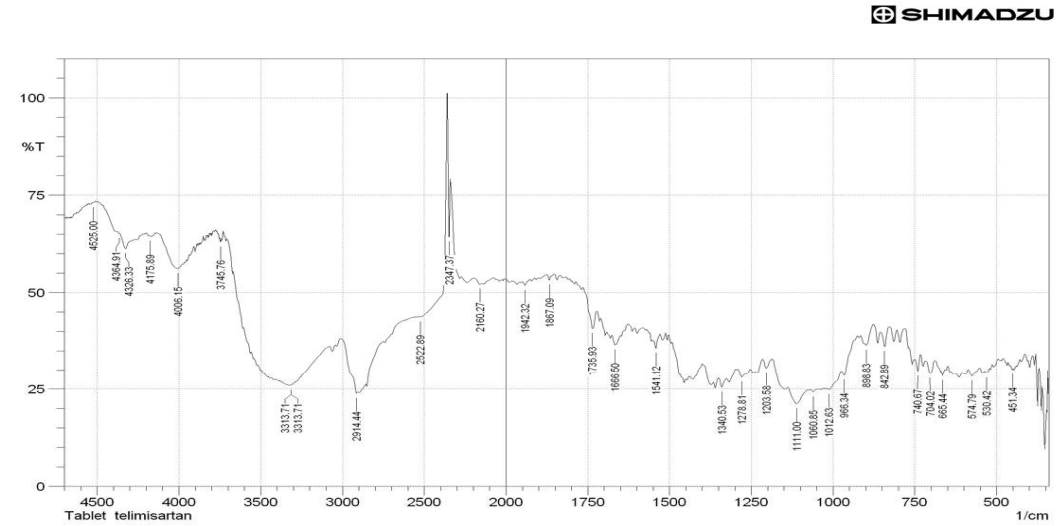
Graph. 1: Telmisartan + PEG 6000 Estimated by FTIR



No.	Peak	Intensity	Corr. Intensity	Base (H)	Base (L)	Area	Corr. Area
1	451.34	30.082	0.622	457.13	449.41	3.974	0.033
2	530.42	29.229	0.798	536.21	520.78	8.141	0.098
3	574.79	28.369	1.529	586.36	563.21	12.41	0.273
4	665.44	28.507	1.374	669.3	657.73	6.156	0.099
5	704.02	29.093	3.368	719.45	688.59	15.736	0.657
6	740.67	29.683	3.743	748.38	732.95	7.692	0.347
7	842.89	36.163	4.367	856.39	829.39	11.121	0.528
8	898.83	36.465	3.799	916.19	877.61	16.052	0.861
9	966.34	28.638	2.53	974.05	925.83	22.823	0.221
10	1012.63	24.839	1.023	1020.34	974.05	26.639	0.537
11	1060.85	24.211	0.694	1068.56	1045.42	14.065	0.104
12	1111	21.233	4.001	1138	1068.56	43.995	2.383
13	1203.58	30.541	2.287	1215.15	1190.08	12.527	0.395
14	1278.81	28.149	1.463	1290.38	1267.23	12.482	0.247
15	1340.53	25.474	2.38	1350.17	1327.03	13.26	0.406
16	1541.12	35.704	2.937	1552.7	1529.55	9.853	0.293
17	1666.5	36.513	2.499	1676.14	1651.07	10.663	0.408
18	1735.93	40.726	6.42	1764.87	1722.43	14.543	1.078
19	1867.09	53.282	1.123	1874.81	1861.31	3.619	0.052
20	1942.32	51.826	1.162	1950.03	1926.89	6.45	0.086
21	2160.27	52.114	0.562	2194.99	2148.7	12.828	0.071
22	2347.37	64.283	22.273	2358.94	2341.58	2.027	1.196
23	2522.89	43.785	1.341	2526.75	2358.94	51.969	22.349
24	2914.44	23.828	1.733	3010.88	2904.8	54.28	-0.475
25	3313.71	25.985	0.416	3321.42	3078.39	124.271	-0.296
26	3313.71	25.985	0.416	3321.42	3078.39	124.271	-0.296
27	3745.76	62.974	1.222	3749.62	3743.83	1.143	0.028
28	4006.15	56.127	0.16	4008.08	3979.15	7.138	0.022
29	4175.89	64.429	0.097	4185.53	4173.96	2.202	0.005
30	4326.33	61.238	2.541	4362.98	4305.12	11.678	0.488
31	4364.91	65.152	0.101	4376.48	4362.98	2.488	0.002
32	4525	73.014	0.161	4528.86	4509.57	2.617	0.012

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Graph. 2: Telmisartan + Capsule Estimated by FTIR

STABILITY STUDY ON CAPSULES

The batch F1 are selected as an optimum batch and the stability study was carried out at accelerated condition of 40°C/75%RH condition for a period of three months.

Method

The capsules were individually wrapped using Aluminium foil and packed in ambered color screw cap bottle and put at above specified condition in incubator for 3 months. After three months capsules were evaluated for content uniformity and *In-vitro* drug release.

Observation

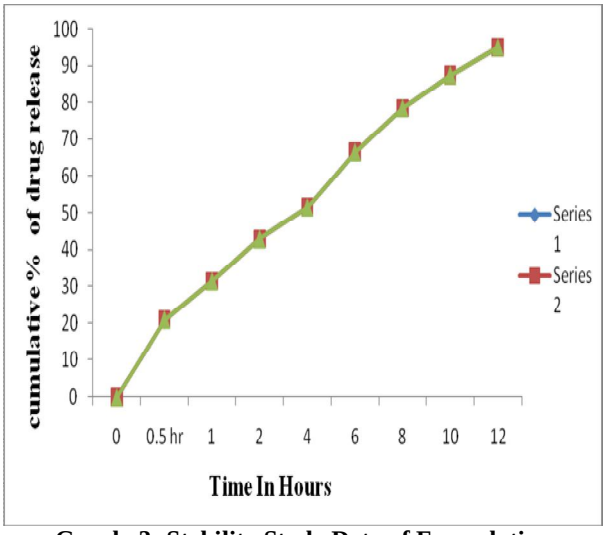
- The results of stability study after 3 months.
- The plot of cumulative % Drug release v/s Time.

Drug content

Comparative content uniformity of the Capsule after 3 months stability

Table 5: Stability Study Data of Formulation after Each Month at $40^0C \pm 2^0C$, 75% RH

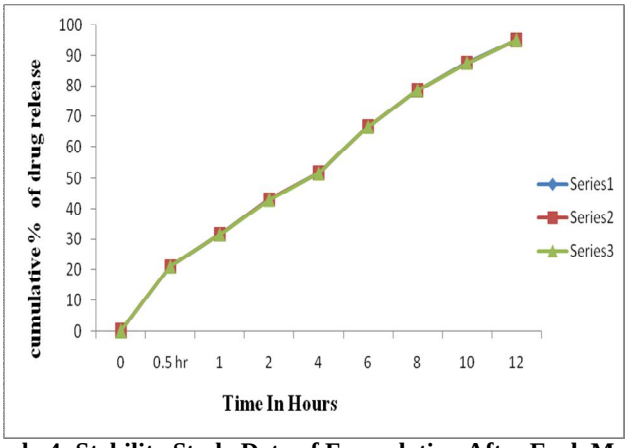
SL.NO	Time	Zero month	First month	Second month
1	0	0	0	0
2	0.5 hr	21.05	21.04	21.03
3	1	31.57	31.55	31.53
4	2	42.97	42.96	42.94
5	4	51.59	51.57	51.55
6	6	66.57	66.55	66.53
7	8	78.58	78.56	78.54
8	10	87.57	87.56	87.53
9	12	95.04	95.03	95.01



Graph. 3: Stability Study Data of Formulation after Each Month at $40^0C \pm 2^0C$, 75% RH

Table 5: Stability Study Data of Formulation After Each Month at $40^0C \pm 5^0C$, 75%RH

S.NO	Time	Zero Month	After First Month	After Second Month
1	0	0	0	0
2	0.5 hr	21.05	21.01	20.99
3	1	31.57	31.51	31.48
4	2	42.97	42.92	42.89
5	4	51.59	51.53	51.50
6	6	66.57	66.51	66.49
7	8	78.58	78.52	78.50
8	10	87.57	87.51	87.48
9	12	95.04	95.00	94.99



Graph. 4: Stability Study Data of Formulation After Each Month at $40^0C \pm 5^0C$, $75^{\%}RH$

RESULTS AND DISCUSSION

The procured sample of Telmisartan was tested for its identification by FTIR. The manufacturer was also conformed of quality and purity of the sample. The drug and excipients compatibility was done physical and instrumental method at room temperature and refrigerator condition in opened and closed vial methods were used. The result does not show any physical or chemical change to the mixture after 14 days. This fact concluded that the drug and excipient are compatible with each other.

Therefore the drug formulation of batch F1 was selected further encapsulated the granules into hard gelatin capsules in process evaluation and stability studies.

The F1 batch drug granules were encapsulated in hard gelatin capsules by using rotatory die process. They were evaluative for weight variation, disintegration, dissolution study.

No significant difference was observed in the weight of individual hard gelatin capsules from the average weight. Hard gelatin capsules weights of all batches were found within recommended pharmacopeia limit. The data of unifomatity of the content indicated that hard gelatin capsules add drug content with in pharmacopeia limits.

The data of disintegration of the hard gelatin capsules shows within the pharmacopeia limits.

The *in vitro* drug release of the hard gelatin capsules was done by using the type –ii USP paddle type operators and the *in vitro %* drug release of the drug was acceptable.

STABILITY STUDIES

The results of stability studies of the hard gelatin capsules showed in the table. Indicated significant changes in tablet and hard gelatin capsules formulation with time. The stability of the capsules was acceptable.

CONCLUSION

The study was under taken with an aim to formulate, develop and evaluate the Solid dispersed granules of Telmisartan 100mg in hard gelatin capsules. Preformulation study of Telmisartan was done initially and results directed further course of formulation. Based on preformulation studies different batches of Telmisartan were prepared using selected polymers. The prepared drug was evaluated for identification appearance and drug content, before being capsulated has hard gelatin capsules. Hard gelatin capsules tested for weight variation, disintegration and content uniformity as per official procedure. Dissolution of hard gelatin capsules are prepared F1 batch was carried out in 0.1 N HCl media and percentage drug release profile shows 95.4% was satisfactorily performed.

Based on stability testing of hard gelatin capsules, it was concluded that Telmisartan capsules were stable satisfactorily.

From the above results and discussion it is concluded that formulation of Telmisartan capsule F1 can be taken as an ideal or optimized formulation. Our study encourages further clinical trials on this formulation

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