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Formulation and Evaluation of Telmisartan with Hydrochlorothiazide Conventional Release Tablets

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ABSTRACT

The Telmisartan and Hydrochlorothiazide Tablets are prepared by using low substituted HPC as a disintegrant. The addition of Diuretics to angiotensin II receptor blockers will potentiate the action of angiotensin receptor blockers. The tablets are prepared by using wet granulation technology and purified water is used as a granulating fluid.

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INTRODUCTION:

The oral route of drug administration is the most important route of administering drugs for systemic effect. About 90% of drugs used to produce systemic effects are administered by oral route. Tablet is unit dosage form in which one usual dose of the drug has been accurately placed by compression. Liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions, and elixirs are usually designed to contain one dose of medication in 5 to 30 ml and the patient is then asked to measure his or her own medication using teaspoons, a tablespoon or another measuring device. Such dosage measurements are typically in error by a factor ranging from 20 to 50% when the drug is self-administered by the patient.

MATERIALS AND METHODS:

MATERIALS:

Table 1: List of Materials

Sr. No.	RAW MATERIALS	MANUFACTURER
1	Telmisartan	AurobindopharmaLtd., Hyderabad
2	Hydrochlorothiazide	AurobindopharmaLtd., Hyderabad
3	Aerosil 200 pharma	Signet Chemicals, Mumbai
4	Lactose Monohydrate	Colorcon, Mumbai
5	Avicel 102	Signet Chemicals, Mumbai
6	HPMC	Aurolab, Madurai
7	Starch 1500	Signet Chemicals, Mumbai
8	Avicel 101	Signet Chemicals, Mumbai
9	Low substituted hydroxyl propyl cellulose	Colorcon Verna Industrial estate area, Goa
10	Magnesium stearate	SD Fine Chemicals Limited, Mumbai

METHODS:

Method of preparation of tablet:

Wet granulation method:

Wet granulation forms the granules by binding the powders together with an adhesive, instead of by compaction. The wet granulation technique employs a solution, however, the binder may be incorporated dry into the powder mix, and the liquid may be added by itself. The method of introducing the binder depends on its solubility and on the components of the mixture. The binder is blended in with the dry powders initially; when a large quantity is required, the binder is usually dissolved in the liquid. The solubility of the binder also has an influence on the choice of methods, since the solution should be fluid enough to disperse readily in the mass. The liquid plays a key role in the granulation process. The main objective of granulation is to improve flow properties and compression characteristics of the mixture to prevent segregation of the constituents. Though this technique is old for the product of compressed tablet, this method is being used because of the content uniformity.

Preparation of Telmisartan/HCTZ tablets by wet granulation method [39]

Table 2: Formulation of Telmisartan with HCTZ

Sr. No.	Chemicals	F1	F2	F3	F4	F5	F6	F7
1	Telmisartan	80	80	80	80	80	80	80
2	HCTZ	12.5	12.5	12.5	12.5	12.5	12.5	12.5
3	Avicel 101	70	70	60	50	40	30	30
4	L- HPC	-	-	-	-	12.5	15.0	15.0
5	Avicel 200	-	-	-	10	20	30	30
6	Starch 1500	10.0	12.5	15.0	20.0	25.0	25.0	30.0
7	HPMC	10	10	10	12.5	-	-	-
8	Aerosil-200 Pharma	70	70	70	-	-	-	-
9	Pharmatose DCL 11	-	-	-	60	60	60	60
10	MagnesiumSterate	1.8	1.8	1.8	1.8	1.8	1.8	1.8

Sifting: Microcrystalline Cellulose (Avicel PH 101) and Lactose Monohydrate (Pharmatose 200M) sifted separately through # 40 mesh (ASTM, 425 µm) in both batches.

Dry Mixing: Sifted materials were loaded into Rapid Mixer Granulator and dry mixing was carried out for 5+5+5 minutes in 1st batch and in 2nd batch for 10 min with Impeller at slow speed. Unit dose samples were collected and submitted for analysis. The results found to be satisfactory within the acceptable limits.

Granulation: Granulation fluid (Purified water-fluid uptake-10%) was added over a period of 5-6 min with the impeller at slow speed in 1st batch and in 2nd batch, the fluid was added in 3min10sec.Kneading was done for 2 min in 1st batch and in 2nd batch to have better granules Kneading was done for 30 sec with the impeller at slow speed in both batches.

Drying: Drying was carried out in Fluidized Bed Dryer at an inlet temperature of 55±5°c in 1st batch and in 2nd batch drying was carried out with an inlet temperature of 60±5°c to have a better control of drying. Loss on Drying of the granules at the end of drying was found to be 3.98%w/w (the lot I) and 3.81%w/w (Lot II) in 1st batch and in 2nd batch 3.85%w/w against a limit of 3.0-5.0%w/w.

Sifting & Milling: Dried granules were sifted through #30 mesh(ASTM,600µm) & retentions milled through 1.0mm screen at medium speed, knives forward configuration. Milled granules were sifted through #30 mesh (ASTM<600µm). The retentions were milled through 1.0mm screen at fast speed, knives forward. Ensured all the material passed through 30 mesh (ASTM<600µm) in both batches.

Extra granular Materials Sifting: Microcrystalline Cellulose(Avicel PH 200)sifted through #30 sieve(ASTM 600µm), Pregelatinized Starch(stach 1500) and low Substituted HYDROXYPROPYL Cellulose(L-HPC(LH-11)) sifted through #40 sieve(ASTM 425µm) Magnesium stearate was sifted through #60 mesh(ASTM,25.0µm) in both batches.

Pre-lubrication: Sifted Extra granular material was added into Octagonal Blender and mixed for 5+5+5 min in 1st batch and in 2nd batch for 10 min in which unit dose samples were collected and submitted for analysis. The results found to be satisfactory within the acceptable limits.

Lubrication: Sifted magnesium stearate was added into the Octagonal blender and mixed for 3 min in both batches. Unit dose samples were collected and submitted for analysis. The results found to be satisfactory within the acceptable limits. In the process, blend analysis is

complying with the proposed specifications. Compression was done on 16-station compression machine. All physical parameters were found consistent.

Evaluation of Tablets:

To design tablets and later monitor tablet production quality, quantitative evaluation and assessment of tablet chemical, physical and bioavailability properties must be made. The important parameters in the evaluation of tablets can be divided into physical and chemical parameters.

Physical appearance: The general appearance of tablets, its visual identity, and overall elegance is essential for consumer acceptance. The control of the general appearance of tablet involves measurement of the number of attributes such as tablet size, shape, colour, presence or absence of odour, taste, surface texture and consistency of any identification marks.

Hardness test: This is the force required to break a tablet in a diametric compression. The hardness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moves along the gauze in the barrel fracture. The tablet hardness of 5 kg is considered suitable for handling the tablet.

Tablet size and Thickness: Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depending on the die and punches selected for making the tablets. The thickness of a tablet is measured by Vernier Callipers scale. The thickness of the tablet related to the tablet hardness and can be used as an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition, the thickness must be controlled to facilitate packaging. (Values are given in Table No:15)

Friability: This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. The initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as a percentage. It should be preferably between 0.5 to 1.0%. (Values are given in Table No: 05)

The average weight of Tablets: It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits:±10% for tablets weighing 300mg or less.

±7.5% for tablets weighing 300mg to 315mg ±5% for tablets weighing more than 315mgTwentytablets were taken randomly and weighed accurately. The average weight is calculated by -Average weight = weight of 20 Tablets / 20.

Disintegration test: For most tablets, the first important step toward a solution is breaking down of a tablet into smaller particles or granules, a process is known as disintegration. This is one of the important quality control tests for disintegrating type tablets. Six tablets are tested for disintegration time using USP XXII apparatus. Disintegration type conventional release tablets are tested for disintegrating time.

Construction of Calibration curve of Telmisartan:

Accurately weighed 100 mg of Telmisartan and transferred into 100 ml of volumetric flask and dissolved in the small quantity of methanol and diluted with 6.8 phosphate buffer up to the mark to give stock solution 1 mg/ml. 1 ml was taken from the stock solution in another volumetric flask and diluted up to 100 ml to give a stock solution of 10 µg/ml. Further dilutions were made from 2-40 µg/ml with 6.8 phosphate buffer and absorbance was measured at 235 nm.

***In vitro* Dissolution Studies of Tablets[45]:**

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP XXVII paddle method and 900ml of pH 6.8 phosphate buffers as the dissolution medium. The medium was allowed to equilibrate to the temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 1 hr in pH 6.8 phosphate buffer at 50 rpm. At definite time intervals of 5 ml of the aliquot of the sample was withdrawn periodically and the volume replaced with the equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 235 nm using UV-spectrophotometer.

Dissolution parameters:

Apparatus--USP-II, Dissolution Medium--pH 6.8 phosphate buffer RPM--50Sampling intervals --5, 10, 15, 20, 30 and 45. Temperature--37°C ± 0.5°C**.**

RESULTS AND DISCUSSION:

The pre-formulation studies for API and blends for various formulations are given in the following table:[3,4,5].

Table 3: Results of Pre-formulation study of API:

Bulk Density gm/ml	Tapped Density gm/ml	Carr's Index (%)	Hausner's Ratio	Angle of Repose (Θ)
0.362	0.612	42	1.64	30.1

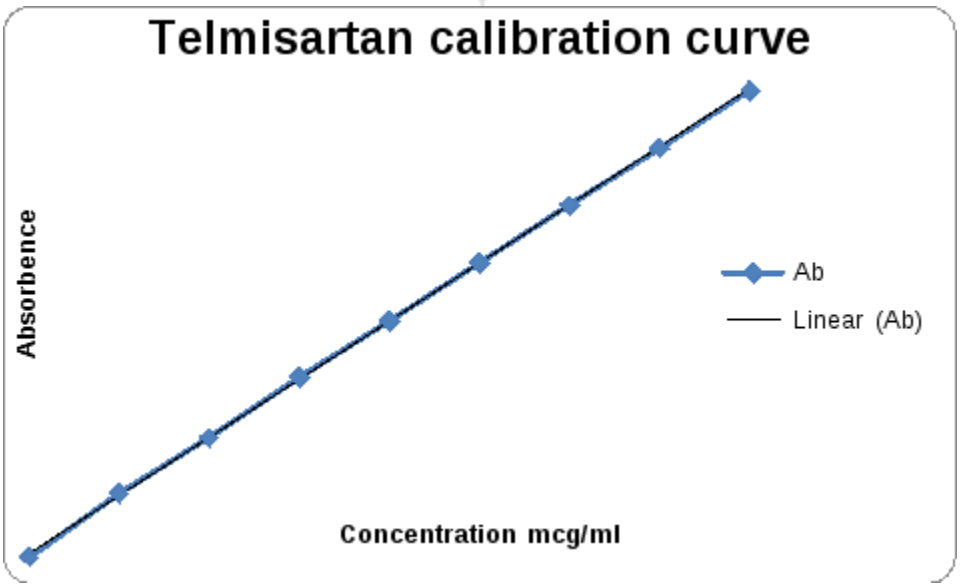

Figure 1: Calibration curve of Telmisartan

Pre-Compression Parameters:

Table 4: telmisartan/HCTZ blend

Sr. No.	Formulation code	Bulk Density(g/ml)		Compressibility index (%)	Hausner's ratio	Angle of repose (Ɵ)
		Untapped	Tapped			
1	F_1	0.382	0.439	34.46	1.56	25.0
2	F_2	0.410	0.461	36.39	1.59	28.6
3	F_3	0.428	0.486	38.43	1.62	29.3
4	F_4	0.431	0.457	44.6	1.72	28.6
5	F_5	0.426	0.460	40.35	1.65	30.5
6	F_6	0.412	0.491	41.8	1.67	32.6
7	F_7	0.391	0.445	40.17	1.65	29.1

Table 5: Evaluation of Telmisartan with Hydrochlorothiazide for different formulations

Sr. No.	Formulation code	Hardness of Tablets	Thickness of Tablets	Friability of Tablets	Disintegration time for Tablets	Dissolution Profile for Tablets
1	F1	4.18	4.45	0.400	314.0	89.18
2	F2	4.28	4.43	0.286	313.5	95.40
3	F3	4.35	4.40	0.467	302.6	102.14
4	F4	4.42	4.41	0.466	309.6	96.19
5	F5	4.90	4.43	0.525	308.6	94.14
6	F6	5.76	4.41	0.458	306.2	95.16
7	F7	6.48	4 .42	0.393	311.	97.41

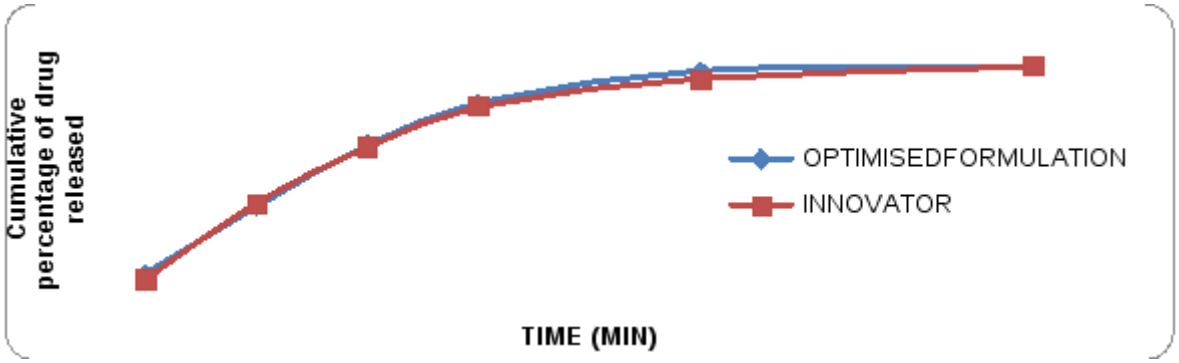

Figure 2: Comparison of *in-vitro* dissolution profile of innovator Vs optimised formulation

SUMMARY:

For the treatment of hypertension telmisartan and hydrochlorothiazide, conventional tablets are formulated. The hydrochlorothiazide added to the formulation to potentiate the activity of the telmisartan. The drugs are found to be stable and there is no any interaction between these two drugs and are producing synergistic activity. Also confirmed that there is no interaction between the drug and the excipients as a result of incompatibility results in different ratios. The resulted tablets are evaluated for their hardness, weight variation, thickness, friability, disintegration, dissolution etc.., In F1 batch the granules are cohesive even after drying for about 20 min. the loss on drying greater than 3%. The compressed tablets are evaluated for disintegration, the disintegration time in deviating from specifications. In F2 batch to overcome these problems, the binder concentration increased so that the agglomerates are decreased than the F1 trial. In F3 further concentration of binder is increased to decrease the moisture content present in the final blend. In F4 the microcrystalline cellulose 101 and 200 are added in various concentrations and the amount of starch is further increased to avoid problems like cohesive mass and to obtain LOD less than 3%.In F5 the disintegrant is changed to low substituted hydroxypropyl cellulose as it is found to be better than the previous and even the binder is increased. In F6 the microcrystalline cellulose 101 and 200 are added in equal concentration to overcome the cohesive mass. The results are found satisfactory. Even though the results are satisfactory in F6 the concentration of binder is further increased in F7 to obtain the better results and the results are good. The tablets from F7 complies with all the specifications for the evaluation tests. The dissolution profile of F7 batch was complied with the innovator and found to be equal with that of an innovator. Then

the F7 batch samples are kept for stability studies and are found to be good after three months.

CONCLUSION:

The stable robust qualities of telmisartan and hydrochlorothiazide conventional tablets are formulated. The formulated tablets are compared with the specifications of the innovator and the optimized formulation complies with the specifications. The disintegrant used in the formulation is low substituted hydroxypropyl cellulose which is different from that of the innovator and even the binder differs from the innovator even though the specifications of the evaluation are compiled as per the specifications. The optimized formulation (F7) is kept for stability studies and the results are good and acceptable I.P. limits.

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