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Formulation and Evaluation of Immediate Release Tablet of Telmisartan

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Abstract
The main objective of this work is to formulate an immediate release oral solid dosage form of Telmisartan which is considered to be stable, robust quality and pharmaceutically equivalent to that of the reference [marketed] product for the treatment of hypertension and also to develop and evaluate immediate release tablets with different compositions of excipients which will meet the standards to that of the reference product with the subsequent achievement of *in vitro* correlation with the reference product. The reference product of the Telmisartan is Micardis manufactured by Boehringer Ingelheim, USA. Telmisartan tablets were formulated by using wet granulation method using microcrystalline cellulose as diluent, MCC as binder, crospovidone as disintegrating agent and magnesium stearate as lubricant The prepared tablets were checked for assay as per USP specifications. All the formulations passed the test and the percentage of active ingredient ranges from 96.9 to 96.8%.
Key words: Immediate release tablet, Telmisartan, hypertension.

Introduction
Medications are only one part of a successful treatment plan. They are appropriate when they provide benefit, improve function and have either no or mild, manageable side effects. Importantly, medications (even if natural) are chemical substances not expected in the body, and as such have side effects. Some of the side effects might be unknown. The use of medications or drugs for any purpose requires patient consent. Pharmacotherapy can be defined as the treatment and prevention of illness and disease by means of drugs of chemical or biological origin. It ranks among the most important methods of medical treatment, together with surgery, physical treatment, radiation and psychotherapy. Drug Delivery System (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. Drug delivery system employed can control the pharmacological action of a drug, influencing its pharmacokinetics and subsequent therapeutic profile. Drug delivery system is an interface between the patient and the drug (Jain *et al*., 2008).

A drug delivery should deliver drug at a rate specified period of time (Williams L, 2006). Two parameters are connected with term delivery: the total amount of drug delivered to the organism and the rate of delivery i.e., amount of drug delivered over a unit time (Krowczynskil, 1987). The drug delivery system employed play a vital role in controlling the pharmacological effect of the drug as it can influence the pharmacokinetic profile of the drug, the rate of drug release, the site and duration of drug action and subsequently the side-effect profile. An optimal drug delivery system ensure that the active drug is available at the site of action for the correct time and duration. The drug concentration at the appropriate site should be above the Minimal Effective Concentration (MEC) and below the Minimal Toxic Concentration (MTC). This concentration interval is known as the therapeutic range and the concept is illustrated in Figure 1.1, showing the drug plasma levels after oral administration of a drug from an immediate release dosage form. Achieving the desired concentration of a drug is dependent on the frequency of dosing, the drug clearance rates, the route of administration and the drug delivery system employed. The therapeutic range is the concentration interval between the Minimal Effective Concentration (MEC) and the Minimal Toxic Concentration (MTC). Oral administration is most popular route for systemic effects due to its ease of ingestion,

versatility and most importantly, patient compliance. Solid oral delivery systems do not require sterile conditions and are therefore, less expensive to manufacture. Patient compliance, high-precision dosing, and manufacturing efficiency make the solid dosage form of choice. Injections generally are not favoured for use by patients unless facilitated by sophisticated auto injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights. However, some factors should be considered when looking to administer drugs via this route.

In particular the transit time in the gastrointestinal tract may vary considerably and between patients and within the same patient, with the gastric residence time being the most variable & with the state of the dosage form (liquid dosage forms are emptied out of the stomach faster than solid dosage forms) & with the fasted or fed state of the patient. The pH conditions in the gastrointestinal tract also vary considerably, from a low pH in the stomach (1.5–2 in the fasted state to around 5 in the fed state) to a higher pH in the small and large intestine. The pH in the small intestine varies from 4 to 7, with an average value of approximately 6.5. This may affect stability and will influence the degree of ionisation of ionisable drugs, which in turn will influence their absorption (unionised forms drugs are usually taken up better than ionised forms of the same drug) and solubility (unionised forms are usually less soluble than ionised forms of the same drug).

Dosage forms can control the rate of release of a drug and/or the location of release, and they can be classified into immediate-release and modified-release dosage forms.

Immediate release – drug release immediately after administration.

Modified release – drug release only occurs some time after the administration or for a prolonged period of time or to a specific target in the body.

Immediate Release Formulation

Many dosage forms are designed to release the drug immediately or at least as quickly as possible after administration. This is useful if a fast onset of action is required for therapeutic reasons. Immediate release allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug. The term “Immediate release” pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. Immediate release delivery systems give a fast onset of action and for a therapeutic action the drug should be in solution, therefore disintegration of the dosage form and dissolution of the drug may have to occur first depending on the dosage form. Immediate release systems usually release the drug in a single action following a first order kinetics profile. The time of action of the drug is limited to the time that the concentration of the drug is above the MEC.

Materials and Methods

Materials

Telmisartan received as a gift sample from Medley Pharmaceuticals Ltd, Daman, India. Magnesium Stearate use as a lubricant and isopropylalcohol and ethanol used as a solvent and PVPK-30 Used as a binding agent received as a gift sample from M/S SD Fine chemicals Mumbai, India. Microcrystalline cellulose used as a diluents and crospovidone used as a super disintegrates received as a gift sample from Loba Chemicals Pvt. Ltd. And Aerosil used as a glident increase the flow properties and purified water used as a vehicle.

Method

Preformulation Studies

Preformulation testing was an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The use of Preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Pre-formulation studies were carried out to serve following purposes:

To Finalize specifications of active pharmaceutical ingredients (API)

To Study the compatibility between active and inactive ingredient

Characterization of reference product

Preformulation study can be divided in to two Subclasses.

1. API characterization
2. Compatibility study

Active pharmaceutical ingredient (API) characterization

Organoleptic Evaluation:-These are preliminary characteristics of any substance which is useful in identification of specific material. Following physical properties of API were studied.

Loss on drying

1.0 gram of Telmisartan was accurately weighed and the powder was kept in a moisture balance apparatus for 3 min. at 105ºC, and the moisture content was calculated.

Bulk density: Bulk density was determined by pouring gently 20 gm of sample (Telmisartan) through a glass funnel into 50 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density = weight of sample in gram / volume occupied by the sample

Tapped density

Tapped density was determined by using Electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%. A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and taped density is calculated using following formula.

Tapped density = wt. of sample in gm / tapped volume

Compressibility Index and Hausner ratio

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the Compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder.

$$\text{Carr's index} = \frac{\text{Tapped desnity} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Angle of Repose: -

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal Plane.

$$\text{Tan } \theta = h / r$$

$$\theta = \text{Tan}^{-1} h / r$$

Where

θ = angle of repose,
h = height,
r = radius.

Wet Granulation Method

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.

Procedure

Step 1: The active ingredient and excipients are weighed and mixed.

Step 2: The wet granulate is prepared by adding the liquid binder–adhesive to the powder blend and mixing thoroughly. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia, cellulose derivatives such as methyl cellulose, gelatin, and povidone.

Step 3: Screening the damp mass through a mesh to form pellets or granules.

Step 4: Drying the granulation. A conventional tray-dryer or fluid-bed dryer are most commonly used.

Step 5: After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size.

Results and Discussions

The present study was undertaken to formulate Telmisartan immediate release tablets. The study involves preformulation studies of drug and excipients, formulation and processing development along with evaluation of tablets made with the optimized formulation. Finally the tablets were evaluated by *in vitro* methods.

Solubility Studies

Table.1: Immediate and Equilibrium Saturation Solubility of Telmisartan

S. No.	Media	Immediate Saturation Solubility (mg/ml)	Equilibrium Solubility 37°C (24 hrs) (mg/250ml)
1.	0.1N HCl	0.0213	5.325
2.	0.1N HCl with 0.5% SLS	1.3089	327.225
3.	0.1N HCl with 1.0% SLS	2.2974	574.35
4.	pH 4.5 acetate buffer	0.8964	224.1
5.	pH 4.5 Phosphate buffer	0.3297	82.425
6.	pH 6.8 phosphate buffer	2.1557	538.925
7.	Purified Water	0.1319	32.975

Telmisartan API has the pH dependent solubility and it increases with increase in pH, solubility in pH 4.5 acetate buffer is slightly more than solubility in pH 4.5 phosphate buffer because of ion effect. As indicated above presence of surfactant amount (0.5 % SLS) also influence the solubility. Telmisartan shows pH dependent solubility and is very poorly soluble drug.

Drug Excipient Compatibility Studies

The compatibility of drug with other excipients was investigated at 40 ^{O}C/ 75 % RH for a period of one month, at a 15 days interval. It was investigated based on their appearance after storage at specific conditions.

Table.2: Drug Excipient Compatibility Studies

S.No.	Drug + Excipient	Ratio	Initial	40 °C/ 75 % RH	
				15 Days	1 Month
1	Telmisartan (API)	-	White	Off White	Off White
2	API + MCC-101	1 : 0.5	White	Off White	Off White
3	API + MCC-102	1 : 0.5	White	Off White	Off White
4	API + MCC-112	1 : 0.5	White	Off White	Off White
5	API + Povidone K-30	1 : 0.2	White	Off White	Off White
6	API + HPC	1:02	White	Off White	Off White
7	API+ Crospovidone	1:04	White	Off White	Off White
8	API + SSG	1:04	White	Off White	Off White
9	API + CCM	1:04	White	Off White	Off White
10	API + Aerosil	1: 0.05	White	Off White	Off White
11	API + Talc	1: 0.05	White	Off White	Off White
12	API + MgStearate	1: 0.05	White	Off White	Off White
13	API+ Stearic acid	1: 0.05	White	Off White	Off White

The results showed not much change in the colour, which indicated the compatibility of drug with other excipients.

Formulation Development

The formulated Telmisartan tablets were investigated for their dissolution profile in 0.1 N HCL and the optimized formulation was finalized using the results.

Dissolution Parameters- Apparatus: USP Type II (Paddle), **Volume:** 900 ml, **RPM:** 75 rpm **Medium:** 0.1 N HCl and **Sampling Interval:** 15, 30 and 60 min.

Table.3: Comparative dissolution profiles for all formulations in 0.1N HCl as Dissolution media

Batch No	R.P	F1	F2	F3	F4	F5	F6	F7	F8
Time(min)	Cumulative% Drug Release								
15	14.9	20.8	25.8	30.9	22.1	21.8	22.8	30.5	20.5
30	23.3	22.8	33.4	38.2	33.9	32.4	31.3	39.6	27.6
60	27.4	30.1	38.8	41.4	37.2	38.7	37.8	42.5	31.8

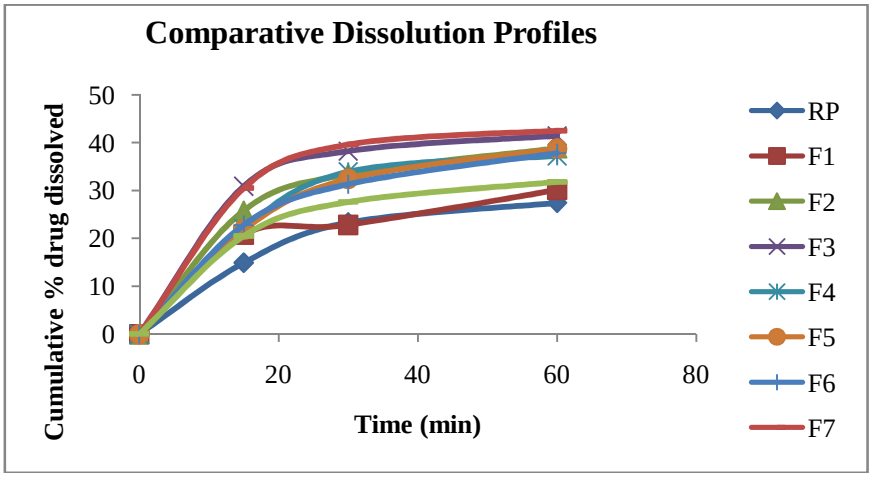

Figure.1: comparative dissolution profiles for all the formulations

Dissolution profile comparison with reference product it can be concluded that the dissolution profile of test product having batch No. F1 is nearest and similar to the reference product when 0.1 N HCl is used as dissolution media. In the table following dissolution profile describes that the reference product drug release for 15 Minutes is 14.9% and 30 min is 23.3% and for 60% is 27.4% compared with the 8 formulations the formulation of F1 is compared is slightly nearest and similar to the reference product.

EVALUATION OF TABLETS

General appearance: The general appearance of tablet, its visual identity and overall elegance essential for consumer acceptance, for control of lot to lot uniformity and general tablet to tablet uniformity and for monitoring trouble – free manufacturing. The control of general appearance of a tablet involves the measurement of a tablets size, shape, color, presence or absence of an odor, taste, surface texture, physical flaws and consistency, and legibility of any identifying markings.

Size and Shape: The size and shape of tablet can be dimensionally described, monitored and controlled. A compressed tablets shape and dimensions are determined by the tooling during compression process. The thickness of a tablet measured with micrometer which provides accurate measurement. The thickness measured with a sliding calliper scale. Tablet thickness should be controlled within a ±5% variation of a standard value.

Unique Identification Markings: Pharmaceutical companies manufacturing tablets often use some type of unique markings on the tablet in addition to color, to aid in the rapid identification of their products. These markings utilize some form of embossing, engraving or printing.

Hardness: Hardness is the crushing strength of tablets, which determines the ease of handling and rigors of the transportation. The hardness of the tablets are measured using hardness tester.

Weight variation test: Weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average. The tablets passes the EP test if no more than 2 of the individual masses deviate from the average mass by more than the percentage deviation shown in table and none deviates by more than twice that percent.

Friability: Friability test is performed to assess the effect of friction and shocks, which may often cause tablets to chip or break. For tablets with a unit weight equal to or less than 650 mg, take a sample of whole tablet corresponding as near as possible to 6.5 g. For tablets with a unit weight of more than 650 mg, take a sample of 10 whole tablets. The tablets should be carefully dedusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum for 100 times, and remove the tablets. Remove any loose dust from the tablets as before, and accurately weigh. A maximum mean weight loss from the three samples of not more than 1.0% is considered acceptable for most products. The percentage friability was measured using the formula.

Table.4: Evaluation of tablets

S. No	Physical parameter	F1	F2	F3	F4	F5	F6	F7	F8
1	Weight variation	1.65± 0.2	.57± 0.11	1.42± 0.08	1.54± 0.09	1.18± 0.26	1.35± 0.22	1.44± 0.04	1.23± 0.18
2	Hardness(kg/square inch)	4	5	4	4	5	4	5	4
3.	Thickness(mm)	4.5	4.7	4.6	4.8	4.7	4.6	4.5	4.6
4.	Friability	0.5%	0.62%	0.55%	0.57%	0.65%	0.6%	0.52%	00.62%
5.	Assay	98%	97%	96%	93%	92%	95%	93%	98%

Conclusion

Telmisartan tablets were prepared by using wet granulation technique. Different trials were taken by making use of various specialized, solvents, disintegrants, diluents and non micronized drug. The physical parameters such as weight uniformity, hardness, thickness, friability, disintegration time, dissolution and drug content (assay) were evaluated for the tablets. The optimized formulation of Telmisartan tablets **F8** was patent non infringing and innovative as well as its analysis profile matched with that of reference sample. Dissolution profile of **F8** was observed to be better than the reference sample meeting the requirements of the specific market. Tablets of successful wet granulation trial batch has been charged in the stability chambers for stability study as per **ICH** guidelines to find the effect of storage condition and time on dissolution.

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