ORIGINAL RESEARCH PAPER

Pharmacy

"ENHANCING TELMESARTAN BY USING SOLID DISPERSION TECHNIQUES"

KEY WORDS: Telmesartan, cyclodextrins, complexation, Solid Dispersion.

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ABSTRACT

Telmisartan (TLM) is an angiotensin II receptor antagonist used in the treatment of hypertension. Telmesartan (TLM) is an orally active direct-acting Angiotensin1 receptor antagonist and possess therapeutic potential in the pharmacotherapy of hypertension. Telmisartan is classified as a class II medicine by the BCS (biopharmaceutical categorization system), and it is nearly insoluble in water, with a low solubility profile and poor absorption. Drugs with poor aqueous solubility are still an ongoing challenge in the successful formulation of therapeutic products due to their low oral bioavailability. Solid dispersions are a dispersion mixture of one or more active ingredients in an inert carrier at the solid state prepared by melting, solvent, solvent-melting or other methods. Cyclodextrins(CDs) with their cylinder-shaped cavities are capable to form inclusion complexes with a wide range of commonly used drugs. Complexation of molecules to CDs occurs through a non-covalent interaction between the molecule and the CD cavity. This is a dynamic process whereby the guest molecule continuously associates and dissociates from the host CD. The present study is to improve the solubility of Telmisartan by solid dispersion techniques using various methods and proved to be effective for further pharmaceutical usage.

1.INTRODUCTION

Telmesartan (TLM) is an orally active direct-acting Angiotensin1 receptor antagonist and possess therapeutic potential in the pharmacotherapy of hypertension. Its molecular formula is C33H30N4O2, and molecular weight is 514.6[1]. The results have indicated that TLM exerts potent and sustained antagonism of AII mediated presser responses *in vivo* and effectively lowers blood pressure in animal models of hypertension as well as in humans. The hypotensive effects are of long duration and have potential superiority over other similar type of drugs like losartan. TLM also acts as a selective modulator of insulin and glucose metabolism[2].

It is believed that TLM's dual mode of action may provide protective benefits against the vascular and renal damage caused by diabetes and cardiovascular disease (CVD). TLM is practically insoluble in water; its aqueous solubility is strongly pH-dependent with maximum solubility observed at high and low pH. Due to its hydrophobic nature TLM shows low dissolution profile in gastrointestinal fluid resulting poor absorption [3], distribution and consequently poor target organ delivery. Improvement of aqueous solubility in such cases shall lead to improved therapeutic efficacy of the drug. Drugs with poor aqueous solubility are still an ongoing challenge in the successful formulation of therapeutic products due to their low oral bioavailability[4]. It is a hard nut to crack that has discouraged pharmaceutical practitioners for many years. In the 1990s; the biopharmaceutical classification system (BCS) was introduced to characterize various drugs according to their solubility and permeability.

It reports that over 70% of drugs and active entities are poorly water-soluble compounds (BCS II or BCS IV) due to the considerable involvement of high throughput screening and combinatorial chemistry [5,6]. These active pharmaceutical ingredients (APIs) often suffer from formulation challenges because of limited dissolution and/or low permeability.

Accordingly; applicable formulation techniques are highly aspired to improve the apparent solubility or dissolution of poorly soluble drugs and thus enable them become bioavailable. A variety of formulation strategies have been explored to overcome the poor aqueous solubility of drugs, including micronization, nanocrystalization , salification , cyclodextrin inclusion , cocrystallization , micelle solubilization , solid dispersion , liquisolid technique , and encapsulation in nanoparticles[7,8,9,10]. The bottom-up technique, dispersion starting from molecules, almost can maximize the dispersion of a drug and lead to more stable dispersion systems (amorphous, molecular or colloidal). Therefore, the bottom-up dispersion technique represents the most promising approach for pharmaceutical processing. Solid dispersions are a dispersion mixture of one or more active ingredients in an inert carrier at the solid state prepared by melting, solvent, solvent-melting or other methods[11].

The approaches used for preparing SDs are referred as solid dispersion techniques. According to Noyes–Whitney equation, the dissolution rate of a drug in a given medium depends on the concentration difference between the dissolving interface and the bulk solution. For poorly water-soluble drugs, the dissolving rate on the interface is positively associated with the particle size of drug, especially above 100 nm [12]. SDs can maximize the reduction of a drug 's size by dispersing it in a large quantity of carrier excipient, thus increasing the absorption area, hence the bioavailability. In SDs, the drug can be in presence as molecular, amorphous, microcrystal or colloidal state, which is dependent on the formulation and preparative process thereof. The high-energy or metastable state of drug in SDs makes it tend to dissolve in a medium, as opposed to the bulk drug [13]. Apart from drug solubilisation, SDs can also improve the gastrointestinal absorption of poorly soluble drugs by affecting the absorptive epithelia, in particular those surfactant-based and absorption enhancer-containing SDs. Currently, the scale-up manufacturing of SDs has no longer been a limitation factor that hinders their success to the clinical application.

SDs can either serve as a pharmaceutical intermediate used for preparation of various dosage forms such as tablets, capsules and granules, or as a final pharmaceutical product, e.g., pellets produced by one-step granulation in fluidized bed.

Cyclodextrins(CDs) with their cylinder-shaped cavities are capable to form inclusion complexes with a wide range of commonly used drugs by taking the whole molecule or part of it into the cavity and are known to improve the aqueous solubility of drugs [14]. Many drugs such as valsartan, Lovastatin, Praziquantel, etc have been complexed with CDs and formulated for enhancing solubility and therapeutic activity. β-cyclodextrin and its more hydrophilic derivative

hydroxypropyl-β-cyclodextrin (HP-β-CD) have been selected for the complexation study of TLM. In the present study inclusion complexes of TLM with β-CD and HP-β-CD will be prepared by kneading, co-evaporation, and physical mixing, and characterized by FTIR spectroscopy, differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD) with the aim of improving the aqueous solubility and dissolution profile of the TLM.

2.MATERIALS AND METHODS

Telmisartan drug sample and all the excipients required will be obtained from the Sri Venkateshwara University.

S.NO.	DRUGS/CHEMICALS	CATEGORY
1.	**TELMESARTAN**	Anti-Hypertensive drug
2.	**PHOSPHATE BUFFER (pH7.4)**	Maintains pH
3.	**SODIUM LAURYLSULPHATE**	Detergent, wetting gent, and emulsifying agent
4.	**β-CYCLODEXTRIN**	Stabilizing agent, solubilizing agent.
5.	**MICROCRYSTALLINE CELLULOSE**	Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.
6.	**LACTOSE**	Tablet and capsule diluents
7.	**CROSPOVIDONE**	Tablet disintegrant
8.	**MAGNESIUM STEARATE**	Tablet & capsule lubricant.
9.	**SODIUM HYDROXIDE**	Base

3.Drug Profile

3.1.TELMISARTAN- It is a benzimidazole derivative and a non-peptide angiotensin II receptor antagonist with antihypertensive property. Telmisartan selectively antagonizes angiotensin II binding to the AT1 subtype receptor, located in vascular smooth muscle and adrenal gland. The antagonism results in vasodilation and inhibits the angiotensin II-mediated aldosterone production, which in turn leading to a decrease in sodium and water as well as an increase in potassium excretion leading to a subsequent reduction in blood pressure.

Telmisartan is an angiotensin II receptor blocker used in the therapy of hypertension. Telmisartan is associated with a low rate of transient serum aminotransferase elevations, but has yet to be linked to instances of acute liver injury. Telmisartan is a member of the class of benzimidazoles used widely in the treatment of hypertension (24).

It has a role as an antihypertensive agent, an angiotensin receptor antagonist, (peptidyl-dipeptidase A) inhibitor, a xenobiotic and an environmental contaminant. It is a member of biphenyls, a member of benzimidazoles and a carboxybiphenyl.

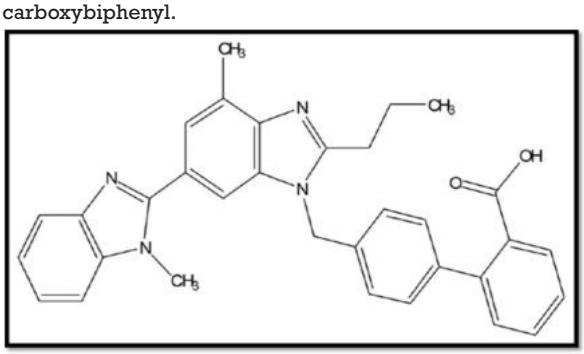


Fig- Structure of Telmesartan.

3.2. CYCLODEXTRINS-They are a group of structurally related natural products formed during bacterial digestion of cellulose. These cyclic oligosaccharides consist of (α-1,4)-linked α-D-glucopyranose units and contain a somewhat lipophilic central cavity and a hydrophilic outer surface. Due to the chair conformation of the glucopyranose units, the cyclodextrins are shaped like a truncated cone rather than perfect cylinders [6]. The hydroxyl functions are orientated to the cone exterior with the primary hydroxyl groups of the sugar residues at the narrow edge of the cone and the secondary hydroxyl groups at the wider edge. The central cavity is lined by the skeletal carbons and ethereal oxygens of the glucose residues, which gives it a lipophilic character. The polarity of the cavity has been estimated to be similar to that of an aqueous ethanolic solution. The natural α-,β-and γ-cyclodextrin consist of six, seven, and eight glucopyranose units, respectively[4].

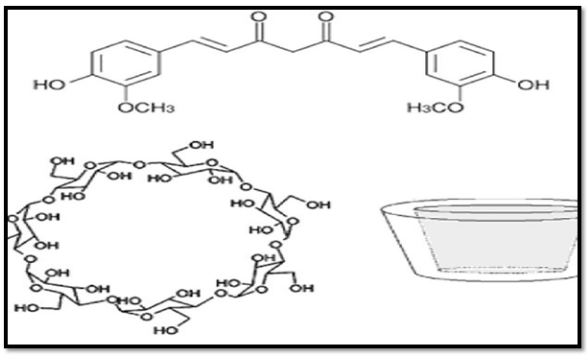


Fig -The chemical structure and the molecular shape of β-cyclodextrin.

3.3. POLYETHYLENE GLYCOL 6000

The USPNF 23 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures. Solid grades (PEG>1000) are white or off-white in colour, and range in consistency from pastes to waxy flakes. They have a faint, sweet odour. Grades of PEG 6000 and above are available as free-flowing milled powders. PEG, PEO or POE refers to an oligomer or polymer of ethylene oxide. The three names are chemically synonymous, but historically PEG has tended to refer to oligomers and polymers with a molecular mass below 20,000 g/mol, PEO to polymers with a molecular mass above 20,000 g/mol, and POE to a polymer of any molecular mass. Polyethylene glycol is produced by the interaction of ethylene oxide with water, ethylene glycol, or ethylene glycol oligomers. All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels. Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%) and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

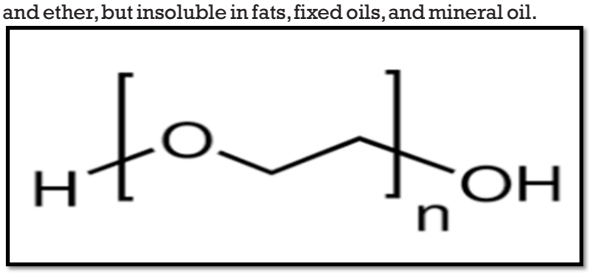


Fig- Polyethylene Glycol chemical structure

4.1METHODS OF PREPARATION:-

The following methods is to be employed for the complex formation [23]-

a) Dry / Physical mixing: The compounds will be complexed by simply adding the compound to the CD and mixing/triturating them together. This mechanism works best with oils or liquid compounds.

b) Kneading Method: - CD will be mixed in glass mortar

along with water to obtain a homogeneous paste. The drug will be then slowly added to the paste and the mixture will be triturated for 1 hr during the process the water content will empirically be adjusted to maintain the consistency of the paste. The paste formed will be dried under vacuum for 24 hours. Dried powder will be passed through specific sieve no. and stored in a desiccator until further evaluation.

c) Solvent Method: In the process, we will first dissolve the compound in a small quantity of organic solvent and add to the molten carrier. Then will evaporate the solvent to generate the mass. We will mill this mass to produce powder at desired particle size ranges.

d) Fusion-melt Method: The fusion-melt involves melting the compound(s) and the carrier components together at temperatures at or above the melting point of all components. In the fusion process, we blend the compound and carrier in a suitable mixer. Then will heat, melt the blend and then cool the molten mixture rapidly to provide a congealed mass. We will mill this mass to produce powders at desired particle size ranges.

5. EXPERIMENTAL METHODS

a) Preparation of Stock Solution

Standard stock solution of Telmisartan will be prepared by dissolving 10 mg of drug in 100 ml of Phosphate buffer (pH 7.4) containing Sodium lauryl sulphate (0.2%) in 100 ml of volumetric flask to get a concentration of 10g/ml[24].

b) Preparation of Working Standard Solutions

To construct Beer's law plot for Telmisartan, the stock solution will further be used to prepare working standard solutions of concentrations ranging from 1 to 10 g/ml. Different aliquots of working standard solutions of Telmisartan will be transferred separately into a series of 10 ml volumetric flasks and diluted to 10 ml using phosphate buffer [24]. The absorbance will be measured at max 296 nm against buffer as blank.

c)Scanning and determination of maximum wavelength (max)

In order to ascertain the wavelength of maximum absorption (max) of the drug, solutions of the drug (10g/ml) in Phosphate buffer (pH 7.4) Containing Sodium lauryl sulphate (0.02 %) will be scanned using spectrophotometer within the wavelength range of 200 – 400 nm against blank[24].

5.1 PREPARATION OF COMPLEXES

The following method is employed for the preparation of the complexes-

KNEADING METHOD: -

TEL & -CD, TEL with -CD & PEG-6000 will be mixed separately in glass mortar along with water to obtain a homogeneous paste. The drug (either in powder form or as solution with minimum quantity of methanol) will then slowly added to the paste and the mixture will be triturated for 1 hr. during the process the water content will be empirically adjusted to maintain the consistency of the paste.

Methanol was added to assist dissolution of TEL during the process. The paste will be dried at room temperature, pulverized and passed through sieve no. 100[23].

5.2 Dissolution study

The dissolution profiles of the TEL, its complexes will be obtained using USP dissolution rate type II apparatus at 37±0.5 °C. Dissolution media will consist of 900 ml of phosphate buffer (pH 7.4), previously filtered, degassed, and maintained at 37±0.5 °C. The stirring speed will be set at 50 rpm.

The amount of inclusion complexes added will be equivalent to 40 mg of TEL. The aliquots of 5 ml will be withdrawn at regular time intervals and analysed till the absorbance of the solution attains a constant value. At each sampling time, an equal volume of fresh medium will be added and the correction for the cumulative dilution will be calculated [25]. Each dissolution study was performed on duplicate batches.

5.3Powder X-ray diffractromety:

Powder x-ray diffraction patterns were recorded on X-Ray diffraction instrument (Philips Analytical X'PertPRO) with Cu radiation, at a voltage of 45kV and current of 40mA. The scanning speed was Gonio between 5and 40theta. diffraction angle (2) range.

5.4Fourier transform infrared spectroscopy (FT-IR)

The FT-IR spectra of TEL and its complexes will be recorded with the instrument.

FTIR spectra of the drug, the drug and carriers and the drug carriers and the additives were all carried out. Each formula (5 mg) was mixed with about 100 mg. potassium bromide and compressed into discs under pressure of 10,000 to 15,000 pounds per square inch. The IR spectra were recorded using Infra-Red Spectrophotometer (IR435-U-04, Shimadzu and Kyoto, Japan).

6.STATISTICAL ANALYSIS

a) Similarity factor (f2) -The model independent mathematical approach proposed by Moore and Flanner for calculating a similarity factor (f2) will be used for comparison between dissolution profiles of different samples. The similarity factor is a measure of similarity in the percent dissolution between the two dissolution curves.It is defined by the following equation-

$$f2 = 50\ log\left[\left\{1 + \left(\frac{1}{n}\right)\sum_{i=1}^{n} \mathrm{Wt}(Rt - TE\ \ )2\right\} - 0.5\ X100\right]$$

Where, f2 is similarity factor, n is the number of observations, Wt is optional weight factor, Rt is percentage drug dissolved from reference formulation, and Tt is percentage drug dissolved from test formulation at a particular time t. A value of 100% for the similarity factor (f2) suggests that the test and reference profile are identical[25].

7.RESULTS

7.1. Phase Solubility Studies

The phase solubility diagrams for the complex formation between Telmisartan and β-CD is shown in Figure 1.

From this curve, it can be seen that the aqueous solubility of Telmisartan was increased linearly as a function of the concentration of β -CD. Solubility of Telmisartan is increased by 7.9 fold at 15 mM concentration of β - CD. The phase solubility diagrams of Telmisartan β –CD complexes can be classified as type AL according to Higuchi and Connors.

The phase solubility study was useful in determination of inclusion complexation of the drug with HP β-CD in aqueous media. From the phase solubility studies, it was observed that a linear increase in solubility was observed with increasing concentration of HP β-CDs. The slope values obtained were less than 1 (i.e. 0.8), which indicated that the 1:1 molar ratio of drugcd complex was stable. The stability constant (K) was found to be 615m indicating the formation of 1:1 stable complex.

Because the straight line had a slope 0.080 (<1), the increase in solubility was due to the formation of a 1:1 M complex in solution with β - CD and there hence improved dissolution of TEL particle in water by β -CD.

The apparent stability constant (KC) at room temperature (30°C) was calculated from the slope of the linear plot of the phase solubility diagram. The apparent stability constants were calculated from the phase solubility diagrams and according to the following equation:

Kc = Slope / Intercept (1 - Slope)

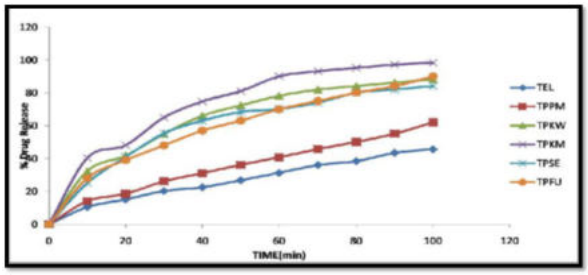


Fig 1, Graph of Dissolution profile of different formulation of TEL with β-CD & PEG-6000.

Table 1. Characterization of prepared tablets of different complexes by using β-CD & PEG-6000

Formulation	Average wt (mg)	Thickness (mm)	Hardness (Kg/cm2)	Percentage friability	Disintegration time (sec)
Pure Telmisartan	200± 6.42	2.89 ± 0.06	5.45 ± 0.15	0.512	285
TPPM	200 ± 6.12	3.43 ± 0.05	5.67 ± 0.18	0.622	276
TPKW	200 ± 6.13	3.84 ± 0.04	5.38 ± 0.14	0.646	222
TPKM	200 ± 6.52	3.95 ± 0.02	5.32 ± 0.18	0.667	201
TPSE	200 ± 5.72	3.81 ± 0.08	5.28 ± 0.13	0.681	273
TPFW	200 ± 6.53	3.92 ± 0.11	5.21 ± 0.14	0.656	293

Mean± S.D.; (n=20) (n=10) (n=10) (n=10) (n=10)

7.2. Dissolution profile of different formulation of TEL & β-CD in phosphate buffer

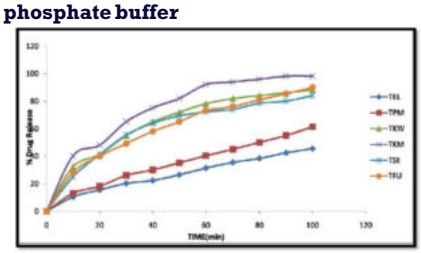
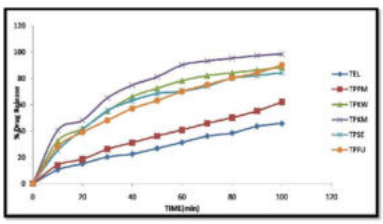


Table 2 , Dissolution profile of different formulation of TEL & □-CD in phosphate buffer 7.

Time (min)	% Drug Release from the formulations (mean; n=3)					
	TEL	TPM	TKW	TKM	TSE	TFU
0	0	0	0	0	0	0
10	10.53	12.17	33.43	40.34	27.17	26.34
20	15.49	18.25	41.23	48.16	41.26	40.11
30	20.27	26.12	55.12	65.14	55.48	49.24
40	22.4	30.1	65.1	75.24	64.12	58.12
50	26.52	35.23	72.13	82.12	69.4	65.15
60	31.43	40.43	78.24	92.21	72.43	73.23
70	35.57	45.15	82.02	94.1	74.13	76.12
80	38.42	50.13	84.14	96.12	78.55	81.13
90	42.53	55.12	86.31	97.13	80.1	85.41
100	45.53	61.44	89.14	97.82	84.15	90.11

7.3. Graph of Dissolution profile of different formulation of TEL with □-CD & PEG-6000.



FTIR

FTIR Spectroscopy was performed on Lab India by scanning the sample in zinc selenium (Znse). Before taking the spectrum of the sample, a blank spectrum of air background was taken. Number of scans, 24; resolution, 4 cm□1; range, 500–4000 cm□1 The sample of Pure Drug, PEG-6000 was scanned. The complexes of PEG-6000 with TEL prepared by different methods were scanned by FTIR ranges from 500-4000, There is no interaction between drug PEG-6000.

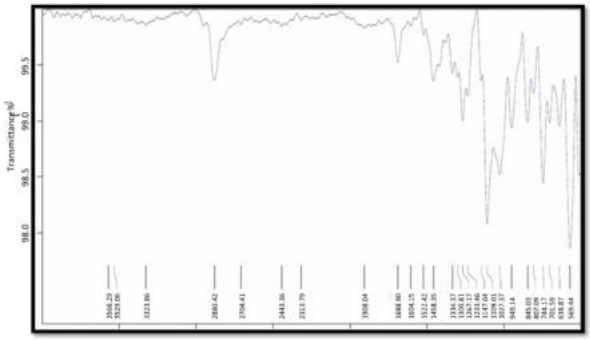


Fig. 4. FTIR spectrum of TPKM (TEL with □--CD & PEG-6000 complex prepares by kneading method employing methanol & water as solvent).

8.CONCLUSION

Solubility studies showed a significant, linear increase in the aqueous solubility of the Telmisartan with increasing concentration of □-CD, maximum concentration of □-CD (15mM/L) so improvements in the saturation solubility of Telmisartan.

An inclusion complex of Telmisartan with □-CD was prepared successfully by the physical mixing, kneading, solvent evaporation and fusion methods in the molar ratio of 1:1. This was confirmed by FTIR and XRD studies.

The complex of Telmisartan with □-CD & PEG-6000 prepared successfully by the physical mixing, kneading, solvent evaporation and fusion methods in the molar ratio of 1:1. This was confirmed by FTIR and XRD studies.

With the present investigations it can be concluded that solubility of poorly soluble drug Telmisartan can be enhanced effectively using solubility enhancement approaches such as solid dispersion. The results obtained proved that *in vitro* dissolution of both the drugs was improved after solubility enhancement as compared to pure drug and marketed tablet. Pharmacokinetic data proved the hypothesis of improvement in bioavailability proving that developed formulations have better oral absorption than the conventional dosage form and pure drug. Hence the developed formulations have scope of better patient compliance and therapeutic efficacy.

These in all five method employing kneading method using methanol-water as solvent employing exhibited the fastest and highest in vitro dissolution rate when compared to the tablet of pure telmisartan, and during stability study there was very slight decrease in its dissolution profile.

These findings are extremely important from a commercial point of view as the prepared complexes removes drawback of a poor dissolution profile of Telmisartan and its stability.

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