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DESIGN, DEVELOPMENT AND OPTIMIZATION OF TELMESARTAN BY USING SOLID DISPERSION TECHNIQUES

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ABSTRACT

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

KEYWORDS: Telmisartan, FTIR and XRD studies.

INTRODUCTION

In the current scenario of the current pharmaceutical industry, 40% of the new chemical entities (NCE) discovered are poorly soluble or lipophilic compounds.[1] The solubility problems that complicate the administration of these new drugs also affect the administration of many current drugs. The ability to supply poorly soluble drugs will grow in importance in the coming years as innovative companies rely on NCEs for a greater share of pharmaceutical market revenue. Similarly, generic drug manufacturers will need to use economically efficient delivery methods, as low solubility drugs are no longer patented, to maintain a competitive advantage and be competitive enough as profit margins decline in the marketplace a price sensitive sector.[2-3]

The bioavailability of low solubility drugs is often intrinsically related to the particle size of the drug. By reducing the particle size, increasing the specific surface area can improve the dissolution properties of the drug to allow for a broader range of formulation methodologies and delivery technologies. Conventional particle size reduction methods, such as grinding and spray drying, rely on mechanical stresses and often impart substantial amounts of physical stress to the drug, which can induce degradation.

Some milling methods have been established to deal specifically with the production of particles at the submicron level, such as micro milling; however, the physical and thermal limitations inherent in fragmentation still present complications related to drug stability. Other methods have been developed to apply less physical stress to drug particles, such as the piston gap homogenizer.[4-6]

1.1. INCLUSION COMPLEXES

Solubilization by drug-cyclodextrin inclusion complexes may be more suitable for drugs where reduction in particle size may not be applicable. Cyclodextrins (CDs), with their ability to form molecular inclusion complexes with pharmacological substances, affect many physicochemical properties of drugs without affecting their intrinsic lipophilicity or pharmacological properties. As a consequence of the inclusion process, many physicochemical properties, such as solubility, dissolution rate, stability, palatability, and bioavailability, can be favorably affected. CDs are thus offering new hope to preparation scientists in their efforts to develop an effective drug delivery system.

The number of applications of CDs in pharmaceutical formulations has been growing in recent years because of their approval by various regulatory agencies. However, the use of CDs in solid oral dosage forms is restricted to low-dose drugs with large stability constants because of the mass limitations of oral dosage units.

Cyclodextrins (CDs) improve solubility significantly, they are still limited in their drug inclusion capacity and retain disadvantageous processing characteristics for oral dosage forms; the volume of CD complexes is often much greater than the volume of drug alone, which may severely limit the types of delivery technologies that may be employed.[7-15]

EXPERIMENTAL

Instrumentation: Spectral and absorbance measurements by using UV –Visible spectrophotometer by using, 1-cm quartz cells. Electronic balance was used for weighing the samples.

Reagent used: Potassium dihydrogen phosphate, Anhydrous disodium hydrogen phosphate (Himedia Lab. Pvt. Ltd.; Mumbai), and Sodium Lauryl Sulphate (reagent grade).

Optimization: Scanning and determination of maximum wavelength (λmax): In order to ascertain the wavelength of maximum absorption (λmax) of the drug, solutions of the drug (10µg/ml) in Phosphate buffer (pH 7.4) Containing Sodium lauryl sulphate (0.02 %) was scanned using spectrophotometer within the wavelength range of 200 – 400 nm against blank. The resulting spectrum is shown in Fig.1 and the absorption curve showed characteristic absorption maximum at 296 nm for Telmisartan.

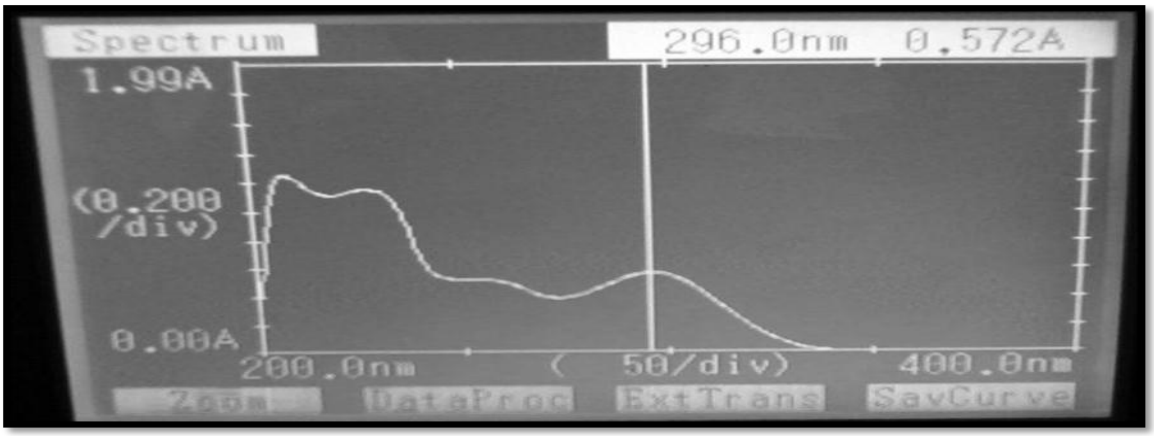

Fig.1.

Sample: Telmisartan (10 µg/ml)

Reference: Phosphate Buffer pH 7.4 containing SLS 0.2%

Preparation of Stock Solution

Standard stock solution of Telmisartan was 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 10 µg/ml.

Preparation of Working Standard Solutions and construction of standard graph

To construct Beer's law plot for Telmisartan, the stock solution was further used to prepare working standard solutions of concentrations ranging from 1 to 10 µg/ml different aliquots of working standard solutions of Telmisartan was transferred separately into a series of 10 ml volumetric flasks and diluted to 10 ml using phosphate buffer. The absorbance was measured at λmax 296 nm against buffer as blank. The results are shown in table 1.

The standard graph for Telmisartan was plotted by taking concentration of drug on x-axis and absorbance on y-axis and is shown in figure 10. The drug has obeyed Beer's law in the concentration range of 1-10 µg/ml.

Table 1.

Concentration (ppm)	Absorbance*
0	0
1	0.050
2	0.103
3	0.156
4	0.209
5	0.259
6	0.312
7	0.365
8	0.425
9	0.485
10	0.565

*Average absorbance values n = 3 of different concentrations of Telmisartan.

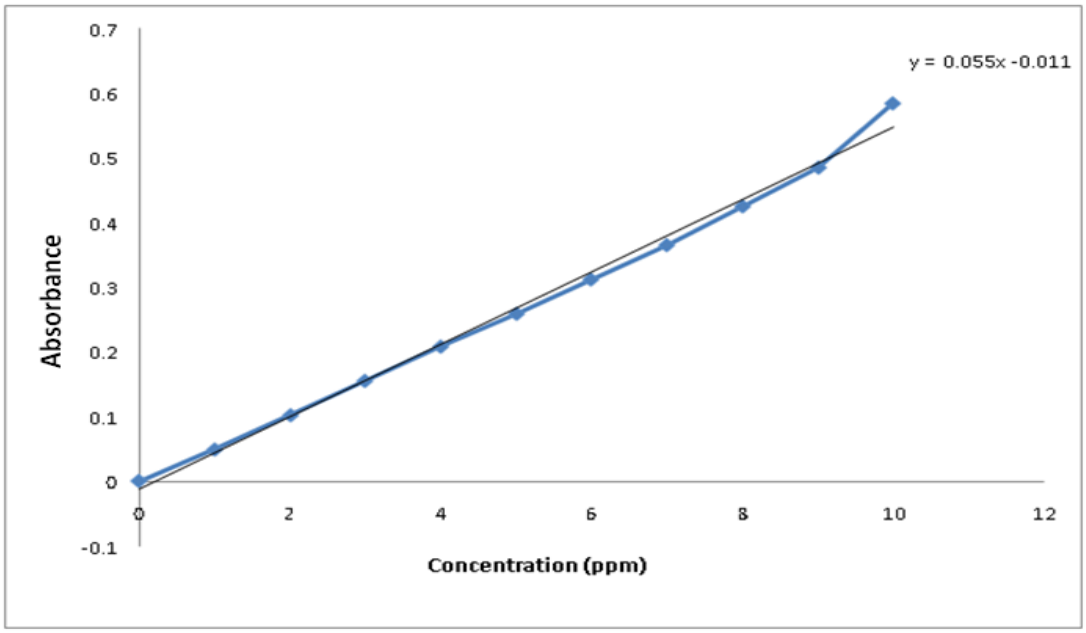

Fig 2: Standard curve for the estimation of Telmisartan in phosphate buffer pH 7.4.

The linear relationship between the concentration of Telmisartan and the corresponding absorbance values was shown by- Y = 0.055 X + 0.011 Where, Y = absorbance, and X = concentration of Telmisartan (µg/ml) A positive correlation between the concentration of Telmisartan and the corresponding absorbance values was observed (correlation coefficient, (r2 = 0.993). The amount of Telmisartan in either the CD complex or the dissolution fluids was calculated using the linear relationship as given above or directly from the standard graph as shown in fig 2.

The precision of the proposed method was ascertained by actual determination of eight replicates of fixed concentration of the drug within the Beer's range and finding out the absorbances by the proposed method. From these absorbances, Mean, Standard deviation, % RSD was calculated. The readings are shown in table 2.

Table 2: Precision readings.

Concentrations (µg/ml)	Absorbances	Statistical analysis
10	0.621	Mean = 0.6234
10	0.621	
10	0.621	
10	0.621	SD = 0.0005
10	0.621	
10	0.620	
10	0.620	
10	0.620	%RSD =0.0801

From the optical characteristics of the proposed method, it was found that Telmisartan obeys linearity within the concentration range of 1-10 µg/ml. From the results shown in Table 2, it was found that the % RSD is less than 2%, which indicates that the method has good reproducibility.

PHASE SOLUBILITY STUDIES OFTELMISARTAN

The phase solubility studies were carried rendering to the method reported by (Higuchi and Connors). An excess of Telmisartan (25mg) was added to 25 ml of distilled water (pH 7.4) containing various concentrations of -CD (3mM–15mM) in a series of conical flask, the flask were sealed and were shaken for 24 hours at room temperature (25 ± 0.5 0C). After 24 hours of shaking to achieve equilibrium, 5 ml of aliquots were withdrawn at 1-hr intervals and filtered instantly through whatmann no.1 filter paper. The filtered samples after appropriate dilution were assayed spectrophotometrically for Telmisartan at 296 nm against blanks prepared in the same concentration of -CD in water so as to cancel out any absorbance that might be revealed by the β-CD molecules. Shaking was continued until 3 consecutive estimations were the same. The phase solubility studies were conducted in triplicate.

When we used -CD & PEG-6000 the concentration of the sample was (5mM–18mM) in a series of conical flask & all process will have applied according t -CD. The phase solubility studies were conducted in triplicate.

Preparation of solid complexes

Complexes of TEL &***β***-CD, TEL with ***β***-CD & PEG-6000 were prepared in the molar ratio of 1:1(on the basis of phase solubility study) by different methods like Physical mixing, Kneading, Solvent evaporation, and Fusion method.).

Physical Mixture

Physical mixture was prepared by triturating TEL &***β*** -CD, TEL with ***β*** -CD & PEG-6000 together for 30 min in a clean and dry glass mortar until a homogeneous mixture was obtained. And then was forced through sieve no 100.

Kneading Method

TEL &***β*** -CD, TEL with ***β*** -CD & PEG-6000 was 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) was then slowly added to the paste and the mixture was

triturated for 1 hr. during the process the water content was empirically adjusted to maintain the consistency of the paste. Methanol was added to assist dissolution of TEL during the process. The paste was dried at room temp., pulverized and forced through sieve no 100.

Fusion Method

TEL and ***β***-CD, TEL with ***β***-CD & PEG-6000 were thoroughly mixed and placed in a sealed container with a small amount of water. The contents are heated to about 100^0C and then removed and dried. The mass was then pulverized and forced through sieve no 100.

Solvent evaporation Method

A solution of Telmisartan in methanol was gradually added to equi-molar concentration of TEL &***β***-CD, TEL with ***β***-CD & PEG-6000 in water and agitated at 50^0C for 30 min and toward the end of addition turbidity developed in the mixture. At the end of this period the solution was filtered, and the moist solid was kept in oven 50^0C for removal of last trace of solvent. The mass was then pulverized and passed through sieve no 100.

Table 3: Composition of solid complexes by using Tel &*β*-CD.

Type of formulation	TEL:- β CD (molar ratio)	Solid dispersion Method	Media
TPM	1:1	Physical Mixing	……..
TKW	1:1	Kneading	Water
TKM	1:1	Kneading	Methanol + Water
TSE	1:1	Solvent Evaporation	Methanol + Water
TFW	1:1	Fusion	Water

Table 4: Composition of solid complexes by using Tel with *β*-CD & PEG-6000.

Type of formulation	TEL: -CD &PEG-6000 (molar ratio)	Solid dispersion Method	Media
TPPM	1:1	Physical Mixing	---------
TPKW	1:1	Kneading	Water
TPKM	1:1	Kneading	Methanol + Water
TPSE	1:1	Solvent Evaporation	Methanol + Water
TPFW	1:1	Fusion	Water

Drug Content

Samples of each solid complex were assayed for drug content by dissolving 100 mg of the complex in 100 ml ethanol. The drug content was determined at 296 nm by UV-Spectrophotometer. The experiment was conducted in triplicate.

Saturation Solubility

To evaluate increase in solubility of Telmisartan after formation of inclusion complexes, saturation solubility measurements were carried out as follows.

Known excess of different formulation of TEL was added to 25 ml of phosphate buffer(pH 7.4). Samples were shaken at room temperature for 24 hr. Samples were then filtered, suitably diluted and analyzed spectrophotometrically at 296 nm. The experiment was conducted in triplicate (n=3).

Fourier transforms infrared (FTIR) spectroscopy

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, range, 500–4000 cm−1. The sample of pure Drug, & β – CD, PEG-6000 was scanned. All the complexes were scanned by FTIR- Lab India.

X –ray Diffractometry

X-ray powder diffraction patterns were recorded on X-ray diffractometer (Rigaku, Japan; Model X-PERT-PRO) with monochromatized Cu radiation, the voltage and current used were 45 kV and 40 mA respectively.

Scanning Parameters

Scan speed: 1 deg/min Sampling width: 0.02 deg.

Scan axis: 2 theta.

Scan angle range: 5 to 40 deg Chart speed: 10mm/deg 2 theta.

CONCLUSION

In the above work, the phase solubility studies suggest a stoichiometry between TEL and β-CD which is not affected by the presence of other chemicals. The disappearance of characteristic drug peaks in both DSC and PXRD studies suggest the complete inclusion of drug into cyclodextrin. The molecular modelling and NMR studies support the hypothesis of stoichiometry between drug and cyclodextrin which is confirmed by solution calorimetric technique. Kane et al. have also used cyclodextrins as the means to improve solubility of telmisartan. The high binding and thermodynamic parameters illustrate that presence of tween 80 facilitates the inclusion. The enhancement in bioavailability of TEL was the result of increased solubility and dissolution profile of TEL complexed with β-CD. Muankaew et al. have prepared a cyclodextrin based formulation of telmisartan using γ-cyclodextrin as binary

component and hydroxyl propyl methylcellulose as the ternary component. The study has also found that there is an increase in solubility and dissolution of telmisartan in the complexed form. An inclusion complex of Telmisartan with β-CD was prepared successfully by the physical mixing, kneading, solvent evaporation and fusion methods. This was confirmed by FTIR and XRD studies. The complex of Telmisartan with β-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. The inclusion complex depicted all the enhanced measures which are confirmed by the spectral as well as experimental analysis. Telmisartan can be used in the form of the complex with the enhanced properties subjected to various conditions.

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