Formulation And Characterization Of Telmisartan Using Solid Dispersion Techniques

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Abstract: Telmisartan (TLM) is an angiotensin II receptor antagonist used in the treatment of hypertension. According to BCS (biopharmaceutical classification system) Telmisartan belongs to class II drug, and it is practically insoluble in water and it shows low dissolution profile and poor absorption. The present study is to improve the solubility of Telmisartan by solid dispersion techniques using various methods

More than 1500 different CD derivatives have been described in the literature. Generally, CDs can be divided into naturally occurring and chemically modified CDs (18). Another classification is based on their water solubility (Table 2) (19), so one can distinguish hydrophilic, lipophilic and ionizable derivatives.   -CD, -CD and -CD differ from each other depending on the presence of glucose residue. Complexation of molecules to CDs occurs through a non-covalent interaction between themolecule and the CD cavity. This is a dynamic process whereby the guest molecule continuously associates and dissociates from the host CD. CDs are insoluble inmost organic solvents; they are soluble in some polar, aprotic solvents. Although the solubility of CDs is higher in some organic solvents than in water, complexation may not occur readily in non-aqueous solvents because of the increased affinity of the guest for the solvent compared to its affinity for water.

Key Words: Kneading method; solid dispersion; Telmisartan;   –Cyclodextrine, PEG 6000; dissolution; poorly water-soluble drug; chemometrics.

Introduction

The rate and extent of dissolution of the active ingredient from any solid dosage form determines the rate and extent of absorption of drug. In case of poorly water soluble drug, dissolution is the rate limiting step in the process of drug absorption. Poorly soluble drugs have been shown to be unpredictable and slowly absorbed as compared to the drugs with higher solubility. Several methods have been employed to improve the solubility of poorly water soluble drugs. Acyclovir is a popular anti-Herpes drug among the antiviral category for the treatment of diseases including Herpes simplex (type 1) keratitis, orofacial, cuteneous Herpes, genital herpes, and varicella zoster infections.

Among the Herpes viruses H. simplex (type I) is the most sensitive followed by H. simplex (type II) viruses. Acyclovir is the drug of choice for most of these cases but the problem of using this drug is that it has poor oral bioavailability. The conventional routes and therapies available for the treatment of Herpes, keratitis, includes orally administered tablet but are associated with it is very low bioavailability ranging from 15-30%. Repeated administration of high doses result in infrequent nausea, diarrhoea, rash, and headache. This problem can be resolved by enhancing the solubility and hence dissolution of poorly water soluble drug acyclovir. Consequently, the rationale of this study is to improve the biological performance of Acyclovir through enhancing its solubility and dissolution rate by two systems: solid dispersion and inclusion complexation. In the present work we tried to prepare solid dispersion with polyethylene glycol (PEG 6000), inclusion complexation with -cyclodextrin and hydroxypropyl -cyclodextrin to improve solubility and dissolution rate of acyclovir

which would help to improve bioavailability. The solid dispersion and the inclusion complex techniques seems to pose great potential in significantly enhancing the solubility and dissolution rate of different formulations(1-7).

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

Materials And Methods:

Telmisartan drug sample was obtained from Medley Pharma limited, Daman.   -CD & PEG 600 is purchased from SD Fine Chemicals Mumbai .

Methods Of Preparation:

1. Dry / Physical mixing: Some guests can be complexed by simply adding the guest to the CD and mixing/triturating them together. This works best with oils or liquid guests.

2. Kneading Method: - CD was mixed in glass mortar along with water to obtain a homogeneous paste. The drug 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. The paste formed was dried under vacuum for 24 hours.

Dried powder was passed through specific sieve no. and stored in a dessicator until further evaluation.

3. Solvent Method: Researchers often use hybrid fusion-solvent method if thermal instability and immiscibility between the compound(s) and the carrier are present. In the process, the researchers first dissolve the compound in a small quantity of organic solvent and added to the molten carrier. Researchers then evaporate the solvent to generate the mass. They mill this mass to produce powder at desired particle size ranges.

4. 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, researchers blend the compound and carrier in a suitable mixer. They heat, melt the blend and then cool the molten mixture rapidly to provide a congealed mass. They mill this mass to produce powders at desired particle size ranges.

Experimental Methods:

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 .

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 were measured at   max 296 nm against buffer as blank.

Scanning and determination of maximum wavelength (max):

In order to ascertain the wavelength of maximum absorption (max) 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.
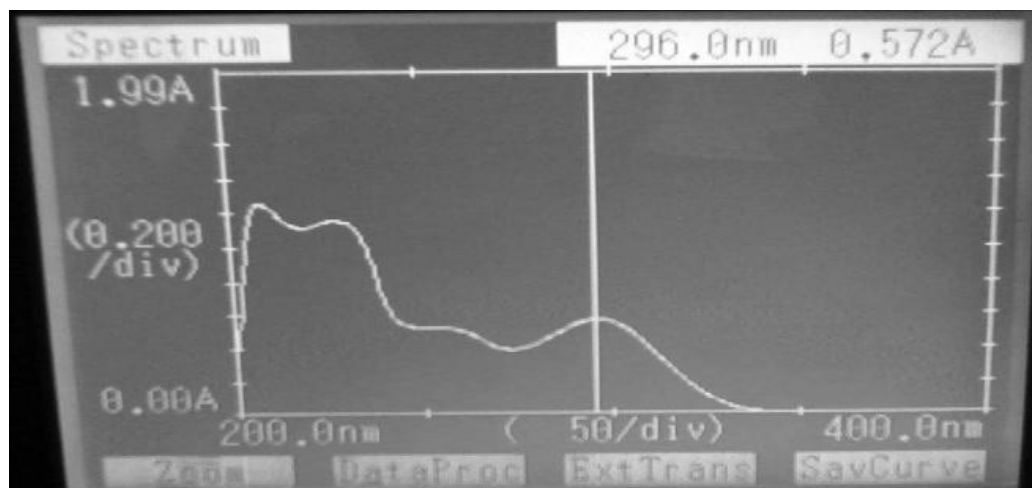
Fig.1. Graph of Telmisartan

Preparation of complexes

All the complexes prepared were of excellent flow property (angle of repose was below 20^0). For further assay or formulation purpose granulometric size fraction of <150 µm was used.

Kneading Method:

TEL & -CD, TEL with -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.

Table 1. Drug content of Tel and -CD complexes (% Drug content)

Formulation	Theoretical drug content in 100mg	Practical drug content in 100mg (mean n=3)	% Drug content
TPM	27.64	27.02	97.75
TKW	27.64	26.93	97.43
TKM	27.64	27.06	97.15
TSE	27.64	27.08	97.98
TFU	27.64	27.11	98.08

Drug Content

First of all, the actual drug content in each formulation was determined. The results are reported in Table 1 & 2. As can be seen, all the formulation showed a good agreement between theoretical and actual drug content. Which correspond to the content uniformity of TEL in its complex formulations.

Table 2. Drug content of Tel with -CD & PEG-6000 complexes (% Drug content)

Formulation	Theoretical drug content in 100mg	Practical drug content in 100mg (mean n=3)	% Drug content
TPPM	27.64	27.02	97.68
TPKW	27.64	26.93	97.10
TPKM	27.64	27.12	98.12
TPSE	27.64	27.08	97.93
TPFU	27.64	27.11	98.08

Powder x-ray diffractromety:

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

Weight variation (Indian Pharmacopoeia 1996)

Each of the twenty tablets from all the formulations was accurately weighed. Average of the twenty values was noted (Table 3). Not more than two of the twenty tablets should differ from the average weight by more than 5% and no tablet should differ by more than 10%.

Table 3. I.P. Specification for weight variation Average weight of tablet Percentage deviation

Average weight of tablet	Percentage deviation
80 mg or less	10
More than 80 mg and less than 250 mg	7.5
250 mg or more	5.0

Table 4. In vitro drug release study.

The dissolution studies were performed using Digital Tablet Dissolution Test	Initial	15 Days	1 Month	3 Months
1. *in-vitro* drug release.	Y	-	-	Y
2. Mean dissolution time	Y	-	-	Y
3. Presence of crystallinity using XRD	-	-	-	Y
4. Compatibility studies using FTIR	-	-	-	Y

Statistical analysis

Similarity factor (f2)

The f2 metric is extensively used because the US FDA endorses it. In a number of recent guidance documents, the FDA has placed more emphasis on the meaningful comparison of dissolution profiles. For example, the FDA Scale–Up and Post Approval Changes Modified Release (SUPAC MR) guidance indicates that similar dissolution profiles for approved and modified formulations are acceptable justification for certain levels of change without prior FDA approval or the need to perform bioequivalence studies Under appropriate test conditions, a dissolution profile can characterize the product more precisely than a single point dissolution test. Among several methods investigated for dissolution profile comparison, f2 is the simplest.

The model independent mathematical approach proposed by moore and Flanner for calculating a similarity factor (f2) was 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 and is defined by the following equation.

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

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.

Values between 50 and 100 indicate that the dissolution profiles are similar, whilst smaller values imply an increase in dissimilarity between release profiles.

Result and Discussion

Phase Solubility Studies

The phase solubility diagrams for the complex formation between Telmisartan and -CD is shown in Figure 3. From this curve, it can be seen that the aqueous solubility of Telmisartan was increased linearly as a function of the concentration of -CD. Solubility of Tel is increased by 7.9 fold at 15 mM concentration of - CD. The phase solubility diagrams of Telmisartan –CD complexes can be classified as type AL according to Higuchi and Connors .

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 - CD and there hence improved dissolution of TEL particle in waterby -CD. The apparent stability constant (KC) at room temperature (30ºC) was calculated from the slope of the linear plot of the phase solubility diagram according to the equation:

Percent dissolution efficiency (%D.E.)

Khan suggested dissolution efficiency (D.E.) as a suitable parameter for the evaluation of in-vitro dissolution data. Dissolution efficiency is defined as the area under dissolution curve up to a certain time "t" expressed as percentage of the area of the rectangle described by 100% dissolution in the same time.

To determine the % dissolution efficiency they obtained dissolution data of pure TEL, its PM, and complexes with CDs were fitted into the following equation.

Table 5. Characterization of prepared tablets of different complexes by using -CD & PEG-6000

Formulation	Average wt (mg)	Thickness (mm)	Hardness (Kg/cm2)	Percentage friability	Disintegration time (sec)
Pure Telmisartan	200 ± 5.24	3.74 ± 0.08	5.56 ± 0.17	0.632	282
TPPM	200 ± 6.12	3.43 ± 0.05	5.67 ± 0.18	0.622	272
TPKW	200 ± 6.13	3.84 ± 0.04	5.38 ± 0.14	0.641	224
TPKM	200 ± 6.52	3.95 ± 0.02	5.32 ± 0.18	0.667	205
TPSE	200 ± 5.72	3.81 ± 0.08	5.28 ± 0.13	0.683	278
TPFW	200 ± 6.53	3.92 ± 0.11	5.21 ± 0.14	0.665	295

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

Invitro Drug Release

Different formulations of TEL were compressed into tablets as per the composition given in table 5 & 5; the tablet thickness and hardness were in the range of 3.6-3.8 mm and 5-6 Kg/cm2, respectively.

Fig.2, show in-vitro drug release profile of different formulations of Telmisartan in tablet form. Pure telmisartan was characterized by only 46% drug release within 100 min in phosphate buffer (pH 7.4) Physical mixtures presented slight improvement in drug release and saturation solubility . this could be attributed to the improved wetability of drug particles by the physical presence of -cyclodextrins. All other complexes on the other hand exhibited dramatical improvement in rate as well as extent of in vitro drug release, the complex formulation of Kneading product employing water and methanol as solvent for complex preparation exhibited highest drug release (~80%) in 50 min,

When we use Telmisartan with -CD & PEG-6000 it will be also improve compare to -CD complexes.its show on fig 3.

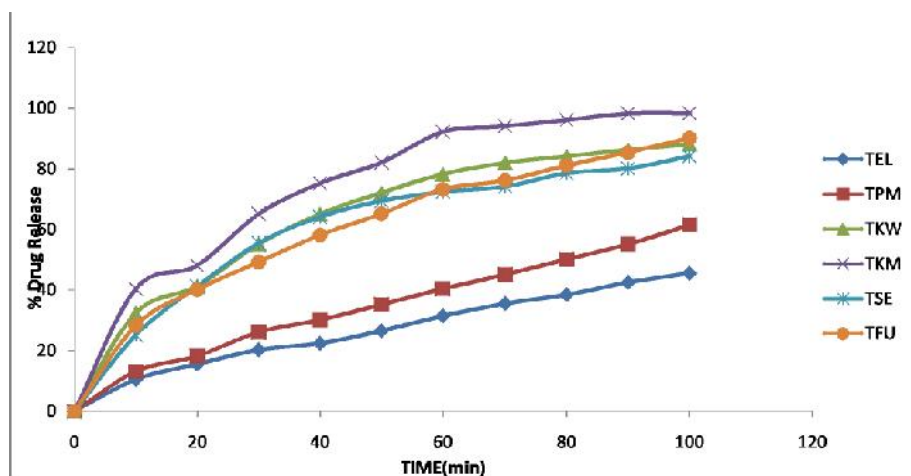**Dissolution profile of different formulation of TEL & -CD in phosphate buffer**

Fig 2, Graph of Dissolution profile of different formulation of TEL & -CD

Table 6, Dissolution profile of different formulation of TEL & -CD in phosphate buffer 7.4

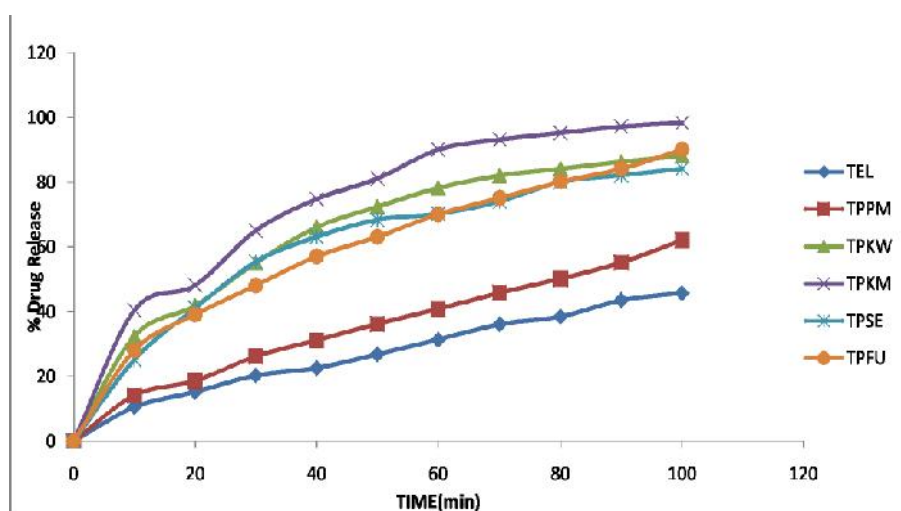| Time (min)	% Drug Release from the formulations (mean; n=3)					
	TEL	TPM	TKW	TKM	TSE	TFU
0	0	0	0	0	0	0
10	10.52	13.17	32.43	40.43	25.17	28.34
20	15.52	18.22	41.23	48.13	41.23	40.13
30	20.27	26.12	55.12	65.14	55.48	49.24
40	22.4	30.1	65.1	75.24	64.12	58.12
50	26.52	35.23	72.13	82.12	69.4	65.15
60	31.43	40.43	78.24	92.21	72.43	73.23
70	35.54	45.15	82.02	94.1	74.13	76.12
80	38.42	50.13	84.13	96.12	78.55	81.13
90	42.53	55.12	86.31	97.13	80.1	85.41
100	45.53	61.44	88.14	97.85	84.15	90.11

Fig 3, Graph of Dissolution profile of different formulation of TEL with -CD & PEG-6000.

Table 7, Dissolution profile of different formulation of TEL with   -CD & PEG-6000 in phosphate buffer 7.4

Time (min)	% Drug Release from the formulations (mean; n=3)					
	TEL	TPPM	TPKW	TPKM	TPSE	TPFU
0	0	0	0	0	0	0
10	10.53	14.12	32.45	40.48	25.17	28.1
20	15.16	18.63	41.84	48.18	41.12	39.12
30	20.28	26.2	55.1	65.12	55.41	48.1
40	22.58	31.15	66.13	74.82	63.13	57.1
50	26.84	36.23	72.42	81.13	68.41	63.12
60	31.34	40.82	78.24	90.1	70.24	70.1
70	36.12	45.84	82.11	93.23	74.12	75.13
80	38.43	50.16	84.14	95.25	80.12	80.15
90	43.52	55.18	86.35	97.25	82.18	84.13
100	45.75	62.1	88.16	98.37	84.18	90.15

Mean dissolution time

In order to calculate mean dissolution time (MDT) of pure telmisartan, its physical mixture, and complexes with T e l &   -CD with PEG-6000 the mean (n=3) of cumulative drug release (µg)

9.3. Percent dissolution efficiency (%DE)

The dissolution efficiency is a suitable parameter for the evaluation of in-vitro dissolution data. Dissolution efficiency is defined as the area under dissolution curve up to a certain time "t" expressed as percentage of the area of the rectangle described by 100% dissolution in the same time. The obtained % DE of different TEL

Stability study

Based on the result of initial characterization the kneaded formulations (TKM, and TPKM) were thought to be the superior formulations and hence were subjected to accelerated stability study. There was insignificant decrease in *in-vitro* drug release between the kneaded formulations containing PEG-6000 over the period of three months while the products formulated without any oxidation showed detoriation from initial release profile (table 8.). Over the period of three months. Also XRD observations (fig. 5 - 6) indicated reduced crystallinity or presence of amorphous form of TEL (Reduced TEL crystalline intensities in different formulations) during stability study.

Table. 8. Dissolution data of TKM & TPKM during stability study at Different time intervals.

Time	% Drug Release from the formulations (mean; n=3)			
	Initial		After 3 months	
	TKM	TPKM	TKM	TPKM
0	0.00	0.00	0.00	0.00
10	40.43	40.48	36.38	46.58
20	48.13	48.18	57.84	52.14
30	65.14	65.12	69.13	68.23
40	75.24	74.82	72.42	77.53
50	82.12	81.13	75.10	85.12
60	92.21	90.1	76.23	89.43
70	94.1	93.23	78.12	90.93
80	96.12	95.25	80.92	92.94
90	97.13	97.25	82.71	94.21
100	97.85	98.37	84.24	95.11

Fourier Transforms Infrared (FTIR) spectroscopy.

FTIR Spectroscopy was performed on Lab India by scanning the sample in zink seleniume (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 were 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. (Figure 4).
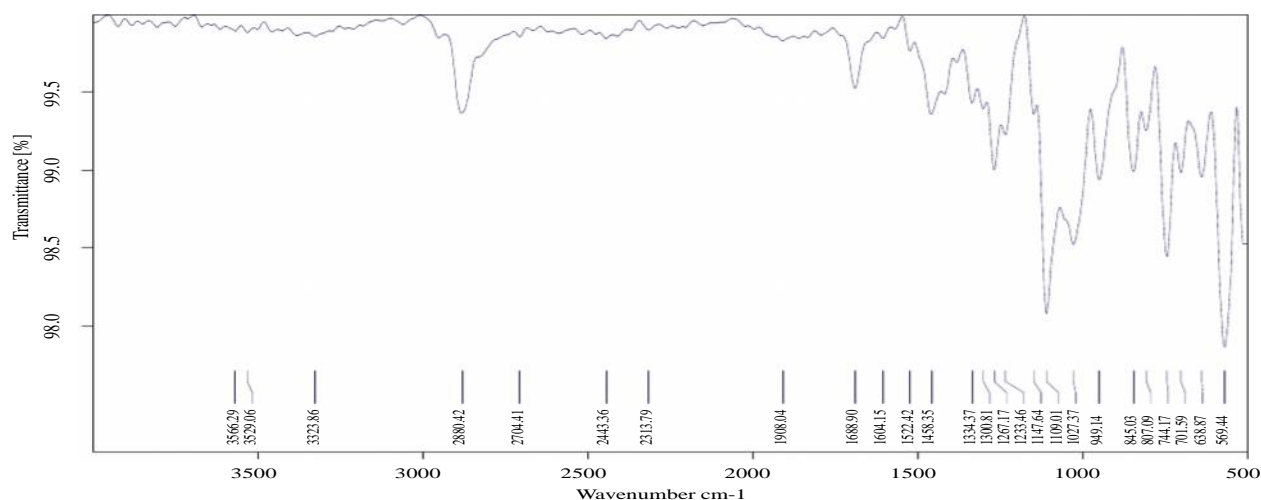

Fig. 4. FTIR spectrum of TPKM (TEL with S--CD & PEG-6000 complex prepares by kneading method employing methanol & water as solvent).
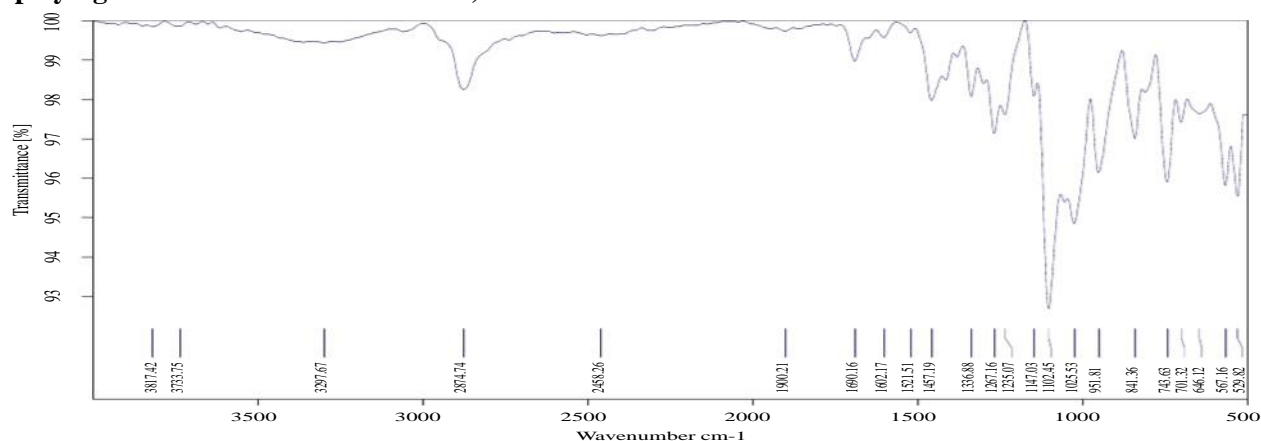

Fig. 5.FTIR spectrum of TPKW (TEL with S--CD & PEG-6000 complex prepares by kneading method employing only water as solvent).

X-ray Diffractoion;

The X-ray diffractometry (XRD) pattern of Telmisartan and its various complexes **with** -CD & **TEL ,** -CD & PEG -6000 are shown in fig. 28 (raw data); (peak search data).
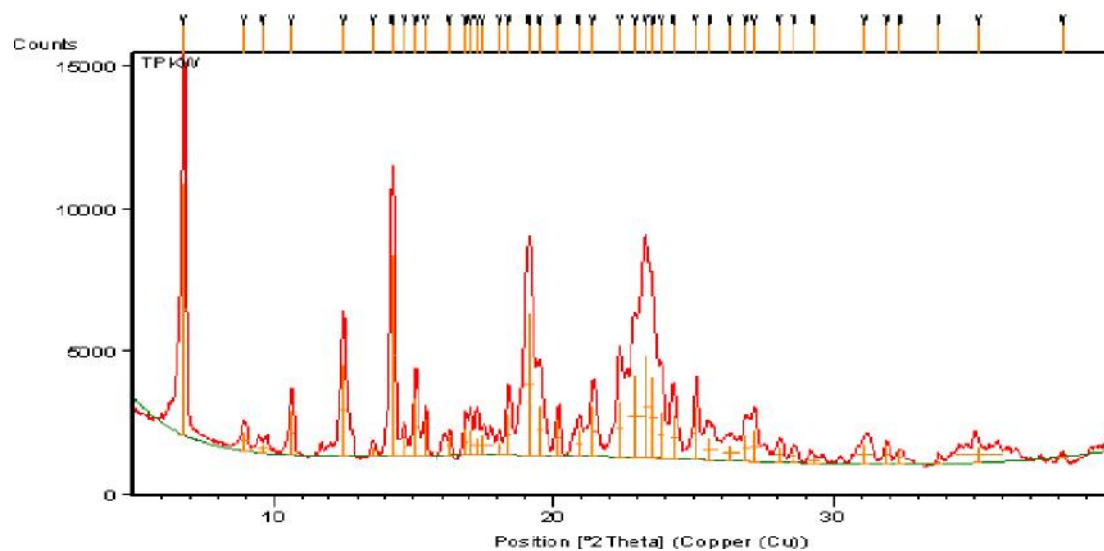
Fig.6.XRD Pattern of TPKW (Tel with -CD & PEG-6000 complex prepared by kneading method employing water as solvent)
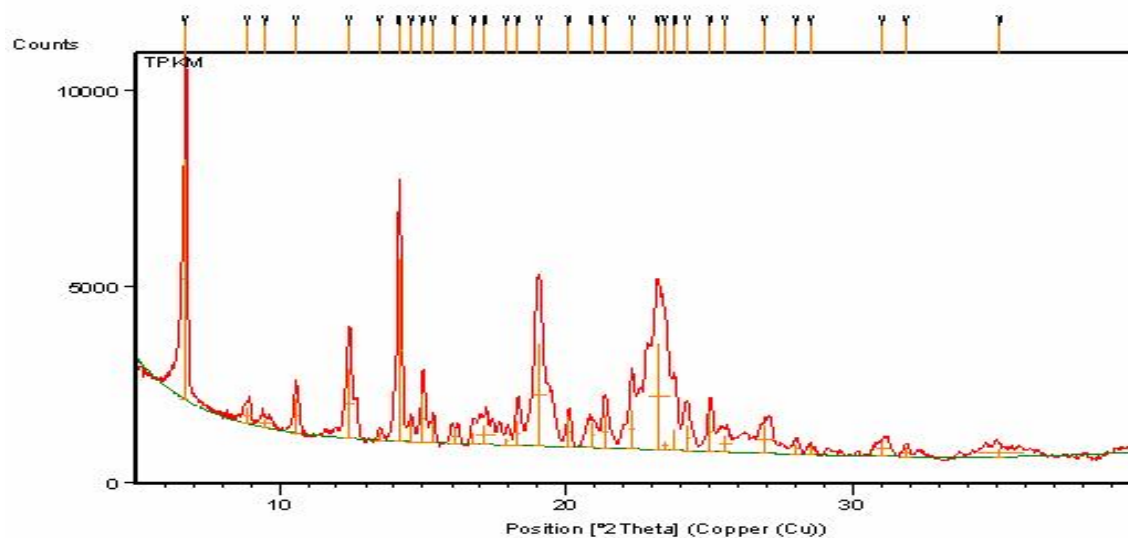

Fig.7. XRD Pattern of TPKM (Tel with -CD & PEG-6000 complex prepared by kneading method employing methanol & water as solvent)

Conclusion

Solubility studies showed a significant, linear increase in the aqueous solubility of the Telmisartan with increasing concentration of -CD um 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 kneading, solvent evaporation and fusion methods in the molar ratio of 1:1. This was confirmed by FTIR and XRD studies.

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 stability.

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