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Solubility and Dissolution Enhancement Profile of Telmisartan using various techniques

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Abstract: Telmisartan is Angiotensin II Receptor Antagonist, which is used in the prevention and treatment of Hypertension.Telmisartan belongs to class II drug in BCS classification i.e. low solubility and high permeability. One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration.Inorder to improve the aqueous solubility and dissolution rate of the telmisartan solid dispersions of drug using different methods were prepared and investigated. Enhancement of solubility of Telmisartan was observed with solid dispersion of drug using carriers such as Poly vinyl pyrrolidone-k30, Poly ethylene glycol-4000 and βeta -Cyclodextrin. The observed results showed the solid dispersion of drug almost three times greater than the pure drug.
Keywords: Telmisartan, Solid dispersion, Aqueous solubility,Bioavailability, Dissolution.

1. Introduction

Telmisartan is Angiotensin II Receptor Antagonist, which is used in the prevention and treatment of Hypertension.Telmisartan belongs to class II drug in BCS classification i.e. low solubility and high permeability.One of the major problems with this drug is its low solubility in biological fluids, which results into poor bioavailability after oral administration.The solubility of Telmisartan in aqueous medium was very low i.e. 0.078 mg/ml in water.Absolute bioavailability of the Telmisartan was 42-58% and biological half-life is only 24 hours that results into poor bioavailability after oral administration. Poor solubility of Telmisartan leads to poor dissolution and hence variation in bioavailability. Thus increasing aqueous solubility and dissolution of Telmisartan is of therapeutic importance[1-7].

A many number of approaches have been developed to improve the drug solubility and dissolution of drugs.The solid dispersion is a technique to achieve this goal particularly the poor aqueous soluble drugs in which the drug is incorporated in to water soluble polymeric matrix .

In this research the solubility and bioavailability of telmisartan in conjugation with various carriers by using various methods were studied.besides this solubility and dissolution study, the various evaluation methods were carried out to determine the physico chemical properties of physical mixture and solid dispersions in comparison to pure drug

2. Materials and Methods

Materials

Telmisartan was obtained from Orchid health care ltd.Chennai.Ethanol, Methol,Sodium lauryl sulphate, Hydrochloric acid, Poly vinyl pyrrolidone-k30, Poly ethylene glycol-4000, and Beta-cyclodextrin were obtained from S.D. fine chemical ltd., Mumbai. All the other materials used in study were of analytical grade

Methods[8-14]

Preparation of physical mixtures

Accurately weighed quantities of drug and carrier were weighed taken in a glass mortar were mixed thoroughly. The resultant mixture was passed through sieve number 100 # and was stored in desiccators for the complete removal of moisture and was tested for the content uniformity. Drug: polymer ratios of 1:1, 1:2 and 1:4 were prepared.

Solvent Evaporation Technique

In this method the drug and carriers are used in different ratios [1:1, 1:2, 1:4]. The respective amount of carrier was dissolved in methanol (20ml) and Telmisartan was added in parts with continuous stirring. The solvent was then removed by evaporation. The prepared dispersions were pulverized and sifted through 100 # and stored in desiccator for further studies[21].

Kneading Method[7,21-23]

In this method the drug and carriers are used in different ratios [1:1, 1:2, 1:4]. Both drug and carrier was triturated by using a small volume of ethanol and water(1:1) to give a thick paste, which was kneaded upto 60 minutes and then kept for air dry. Then the dried mass was scratched and pulverized and sifted through 100# and stored in desiccator for further studies.

Table no: 1 Formula for Telmisartan Physical Mixtures

S.no	Batch code	Composition	Ratio(Drug:Carrier)
1	P1	Telmisartan+PVP-K30	1:1
2	P2	Telmisartan+ PVP-K30	1:2
3	P3	Telmisartan+PVP-K30	1:4
4	P4	Telmisartan+PEG-4000	1:1
5	P5	Telmisartan+ PEG-4000	1:2
6	P6	Telmisartan+PEG-4000	1:4

Table no 2 : Formula for Telmisartan solid dispersions using Solvent Evaporation Technique

S.no	Batch code	Composition	Ratio(Drug:Carrier)
1	S1	Telmisartan+PVP-K30	1:1
2	S2	Telmisartan+ PEG-4000	1:1
3	S3	Telmisartan+PVP-K30	1:2
4	S4	Telmisartan+PEG-4000	1:2
5	S5	Telmisartan+ PVP-K30	1:4
6	S6	Telmisartan+PEG-4000	1:4

Table no 3: Formula forTelmisartan solid dispersions using Kneading Method

S.no	Batch code	Composition	Ratio(Drug:Carrier)
1	D1	Telmisartan+PVP-K30	1:1
2	D2	Telmisartan+ PEG-4000	1:1
3	D3	Telmisartan+PVP-K30	1:2
4	D4	Telmisartan+PEG-4000	1:2
5	D5	Telmisartan+ PVP-K30	1:4
6	D6	Telmisartan+PEG-4000	1:4

Preparation Of Beta Cyclodextrin Inclusion

Complexes and Physical Mixtures Of Telmisartan[15,23,26]

There are several carriers, which have been reported for the preparation of Inclusion complexes by using various methods of preparation described earlier. The following carriers were selected depending upon suitability of carriers like Beta Cyclodextrin. It was selected for their efficiency in increasing the dissolution rate of Telmisartan.

Preparation of physical mixtures

Accurately weighed quantities of drug and carrier were weighed taken in a glass mortar were mixed thoroughly. The resultant mixture was passed through sieve number 100 # and was stored in desiccators for the complete removal of moisture and was tested for the content uniformity. Drug: polymer ratios of 1:1, 1:2 and 1:4 were prepared.

Preparation of inclusion complexes

a. Solvent evaporation technique

b. Kneading method

a. Solvent Evaporation Technique In this method the drug and carriers are used in different ratios [1:1, 1:2, 1:4]. The respective amount of carrier was dissolved in methanol (20ml) and Telmisartan was added in parts with continuous stirring. The solvent was then removed by evaporation. The prepared dispersions were pulverized and sifted through 100 # and stored in desiccators for further studies.

b.Kneading Method

In this method the drug and carriers are used in different ratios [1:1, 1:2, 1:4] Both drug and carrier was triturated by using a small volume of ethanol and water(1:1) to give a thick paste, which was kneaded upto 60 minutes and then kept for air dry. Then the dried mass was scratched and pulverized and sifted through 100# and stored in desiccators for further studies.

Table no:4 Formula for Telmisartan Physical Mixtures

S.no	Batch code	Composition	Ratio(Drug:Carrier)
1	**P7**	Telmisartan+β-cyclodextrin	1:1
2	**P8**	Telmisartan+ β-cyclodextrin	1:2
3	**P9**	Telmisartan+ β-cyclodextrin	1:4

Table no 5: Formula for Telmisartan Inclusion Complexes using Solvent Evaporation Technique

S.no	Batch code	Composition	Ratio(Drug:Carrier)
1	**C1**	Telmisartan+β-cyclodextrin	1:1
2	**C2**	Telmisartan+ β-cyclodextrin	1:2
3	**C3**	Telmisartan+ β-cyclodextrin	1:4

Table no 6 : Formula for Telmisartan Inclusion Complexes using Kneading Method

S.no	Batch code	Composition	Ratio(Drug:Carrier)
1	**C4**	Telmisartan+β-cyclodextrin	1:1
2	**C5**	Telmisartan+ β-cyclodextrin	1:2
3	**C6**	Telmisartan+ β-cyclodextrin	1:4

3. Results and Discussion

3.1 Preformulation Studies

3.1.1 Organoleptic properties

Table No: 7

Tests	Specification	Observation
Color	White colored powder	White powder
Taste	Bitter	Bitter
Odour	Odourless	Odourless

3.1.2 Micromeritic Properties of Telmisartan and Excipients

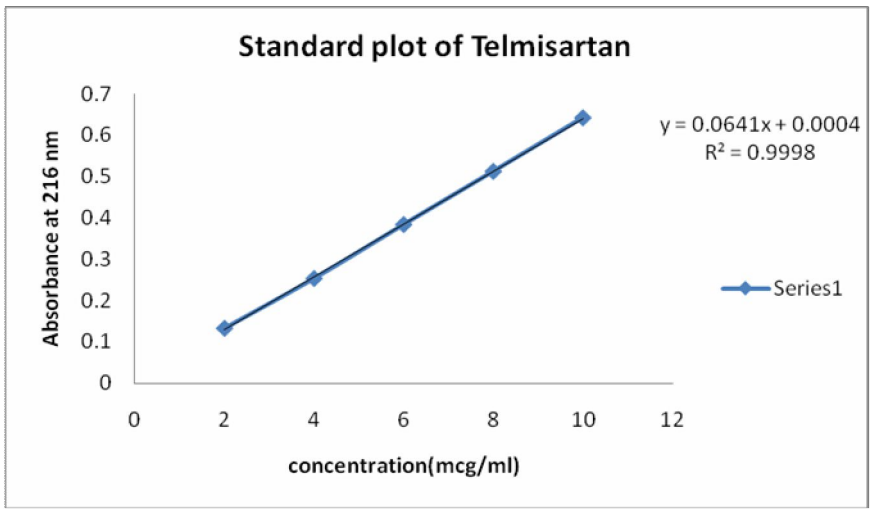
Table No: 8

S.NO	PRARMETERS	TELMISARTAN	PVP-K30	PEG-4000	β-CYCLODEXTRIN
1	Bulk Density(gm/ml)	0.512±0.21	0.571±0.12	0.585±0.21	0.513±0.36
2	Tapped Density(gm/ml)	0.951±0.36	0.606±0.25	0.645±0.14	0.745±0.21
3	Compressibility (%)	44.44±0.12	5.7±0.14	9.30±0.36	21.7±0.12
4	Hausner's ratio	1.8±0.25	1.06±0.36	1.102±0.14	1.35±0.35
5	Angle of repose (θ)	48°54"±0.14	23°16"±0.14	25°54"±.15	28°45"±0.26

3.2 Table No:9 Data for calibration curve of Telmisartan

Concentration (μg/ml)	Absorbance(216 nm)
0	0
2	0.132
4	0.253
6	0.384
8	0.513
10	0.643

Fig.1: calibration curve of Telmisartan



3.3 Fig no 2 FTIR Spectrum of pure Telmisartan

Fig no 3 FTIR Spectrum of PVP K-30

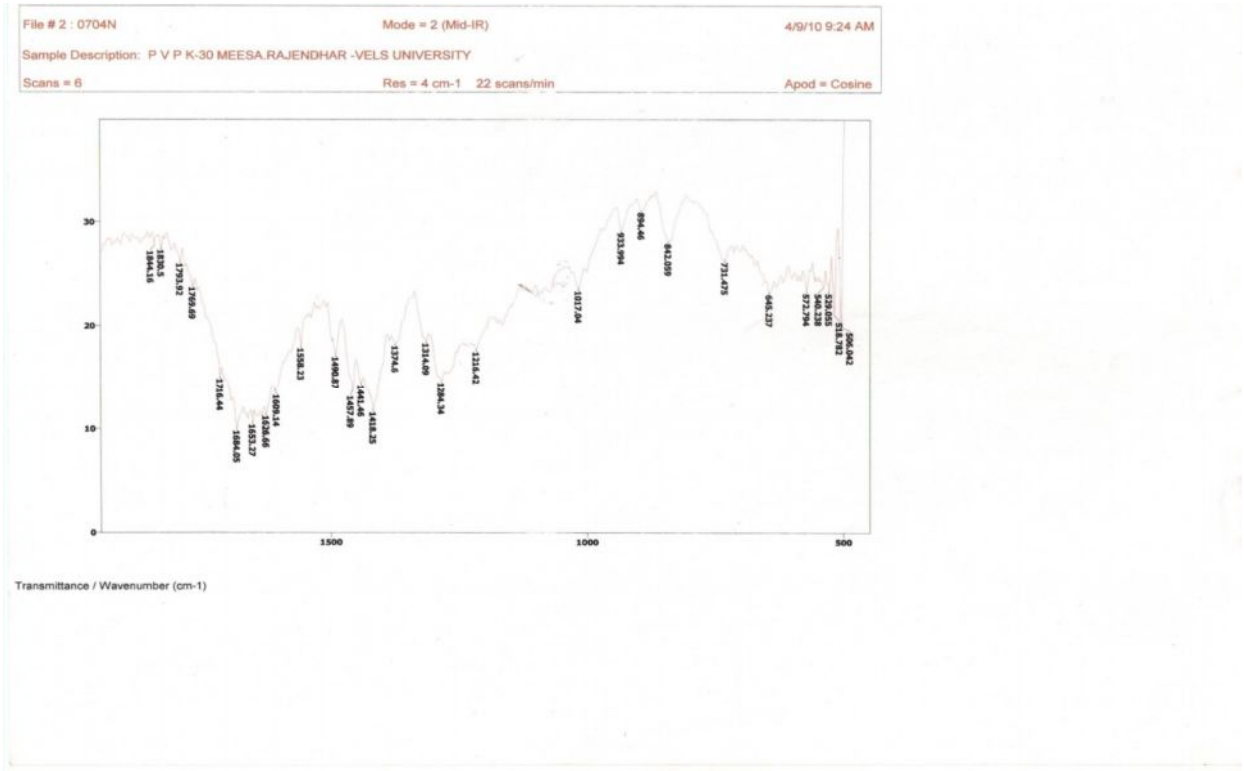


Fig no 4 FTIR Spectrum of PEG-4000

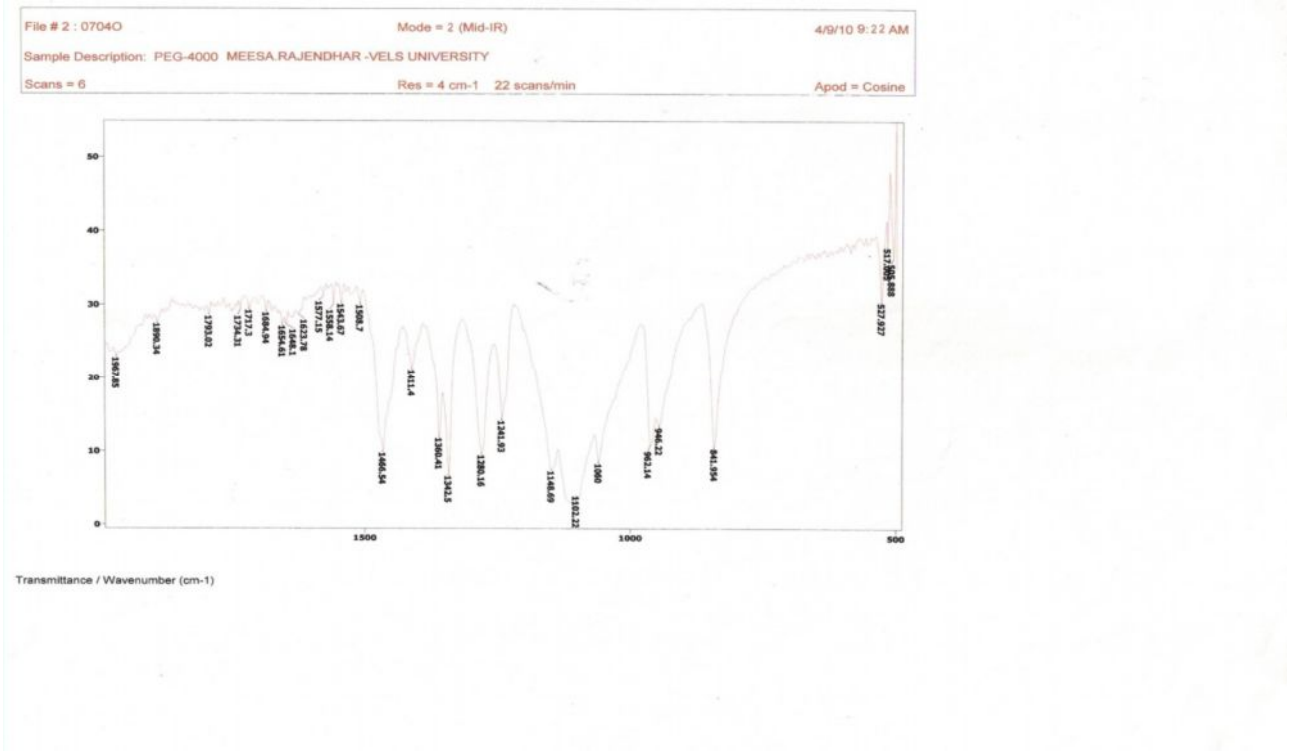


Fig no 5 FTIR Spectrum of B-CD

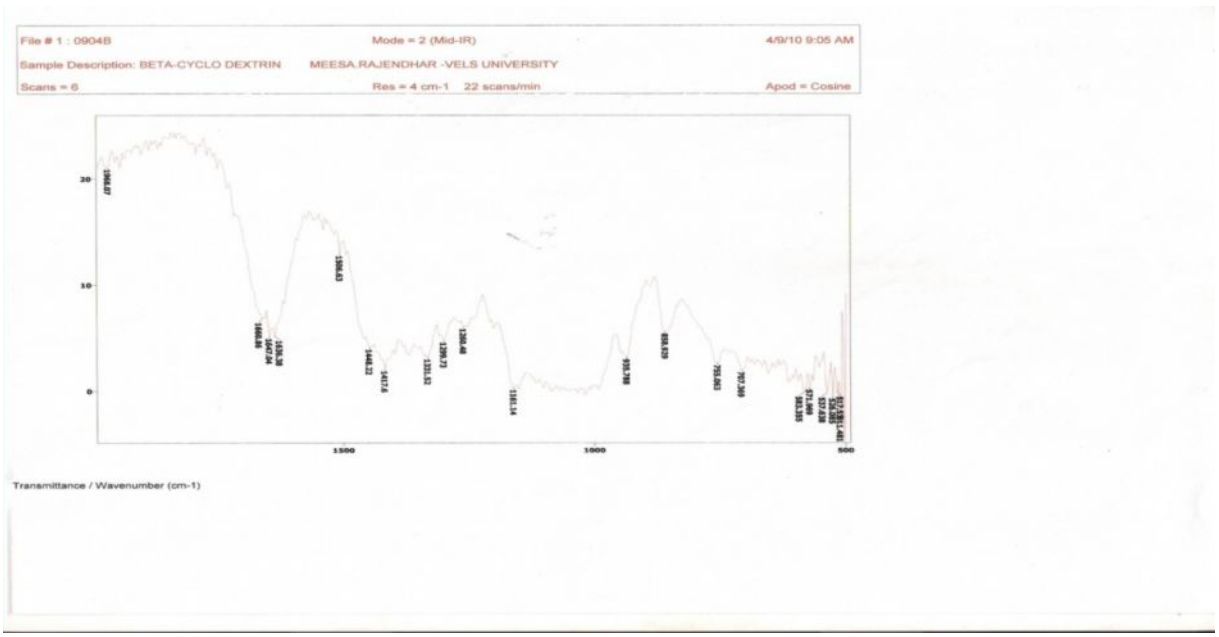


Fig no 6 FTIR Spectrum of Telmisartan+PVP K30

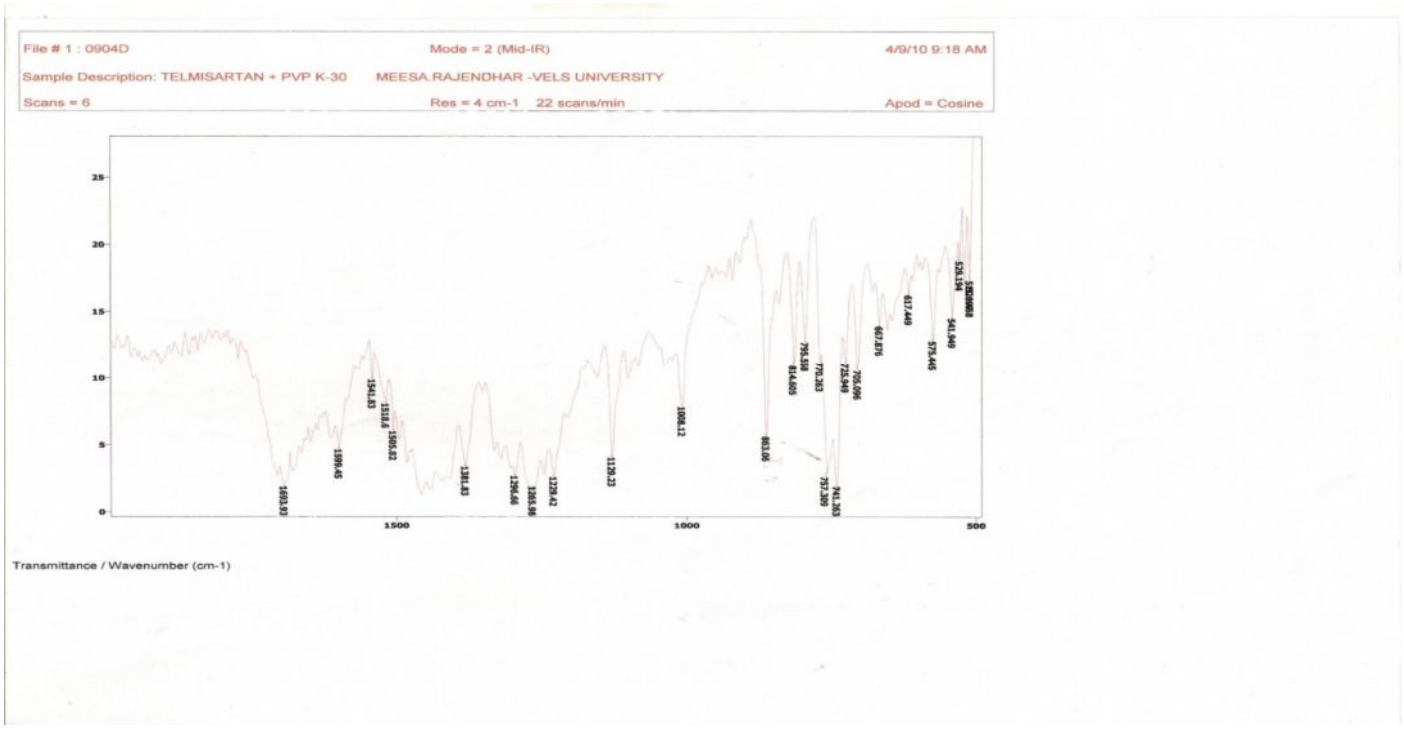


Fig no 7 FTIR Spectrum of Telmisartan+PEG 4000

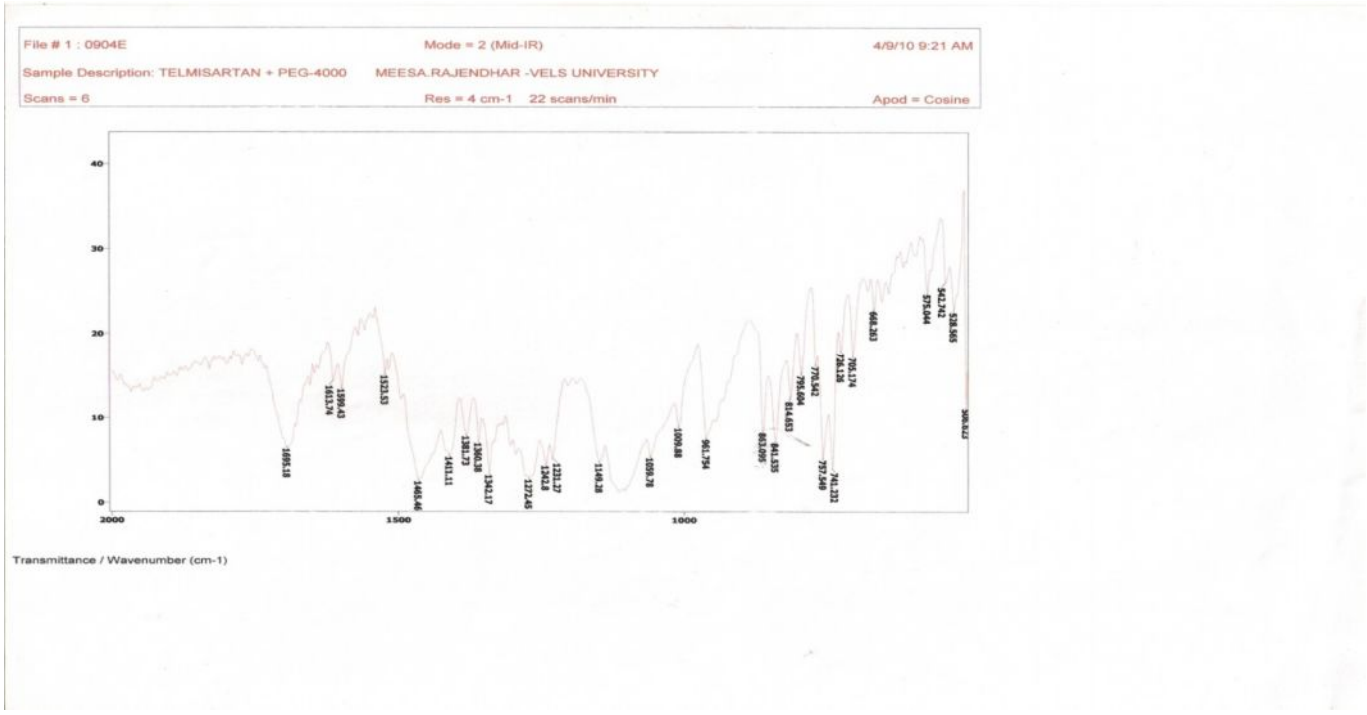
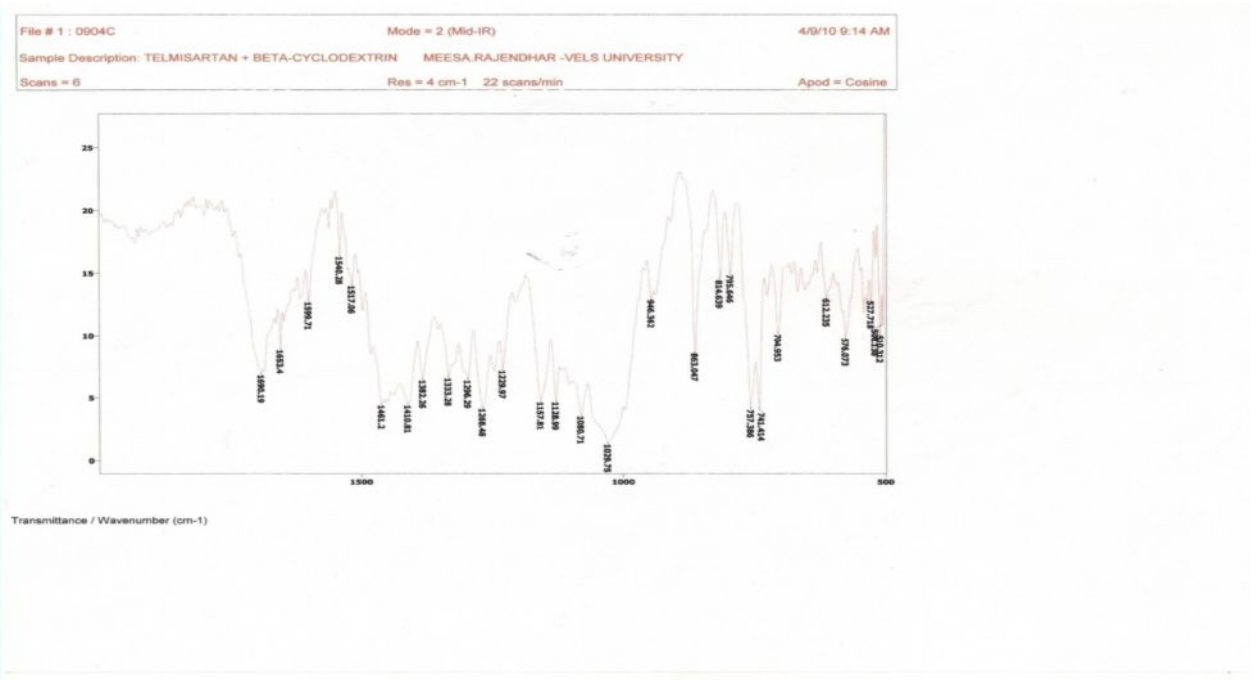


Fig no 8 FTIR Spectrum of Telmisartan+ B-CD



3.4. Micromeritic Properties Of Physical Mixtures

Table no : 10

S. no	Parameter	Formulations								
		P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**
1	Bulk Density(gm/ml)	0.066 ±0.12	0.075 ±0.21	0.071 ±0.21	0.065 ±0.51	0.071 ±0.14	0.070± 0.21	0.066 ±0.25	0.074 ±0.25	0.072 ±0.36
2	Tapped Density(gm/ml)	0.076 ±0.21	0.083 ±0.36	0.075 ±0.36	0.075 ±0.36	0.079 ±0.23	0.074± 0.32	0.076 ±0.14	0.084 ±0.14	0.077 ±0.25
3	Compressibility (%)	13.15 ±0.14	5.6 ±0.52	9.63 ±0.42	13.12 ±0.25	5.4 ±0.32	9.41±0 .63	13.16 ±0.16	6.92 ±0.36	11.90 ±0.35
4	Hausner's ratio	1.15 ±0.11	1.04 ±0.21	1.13 ±0.63	1.12 ±0.36	1.05 ±0.41	1.09±0 .25	1.18 ±0.36	1.03 ±0.25	1.14 ±0.15
5	Angle of repose (θ)	32°11" ±0.52	30°56 "±0.45	28°21" ±0.25	30°12" ±0.25	28°14" ±0.14	29°56 "±0.14	30°12" ±0.25	26°14" ±0.14	27°16" ±0.36

NOTE: P1-P3 : PVP K30 Physical Mixtures
P4-P6 : PEG 4000 Physical Mixtures
P7-P9 : β-CYCLODEXTRIN Physical Mixtures

3.5.Micromeritic Properties Of Solid Dispersions and Inclusion Complexes Prepared By Solvent Evaporaton Method
Table no : 11

S. no	Parameter	Formulations								
		S1	**S2**	**S3**	**S4**	**S5**	**S6**	**C1**	**C2**	**C3**
1	Bulk Density(gm/ml)	0.063±0.14	0.061±0.36	0.076 ±0.56	0.076 ±0.25	0.074 ±0.52	0.074 ±0.25	0.061 ±0.36	0.074 ±0.26	0.071 ±0.62
2	Tapped Density(gm/ml)	0.073±0.32	0.072±0.23	0.085 ±0.25	0.085 ±0.36	0.079 ±0.63	0.078 ±0.36	0.075 ±0.25	0.087 ±0.61	0.081 ±0.14
3	Compressibility (%)	13.6±0.12	13.2±0.36	10.5 ±0.14	6.42 ±0.12	6.32 ±0.41	10.5 ±0.14	13.56 ±0.14	6.12 ±0.15	10.12 ±.36
4	Hausner's ratio	1.15 ±0.25	1.15±0.15	1.06 ±0.36	1.06 ±0.25	1.11 ±0.45	1.11 ±0.36	1.21 ±0.41	1.05 ±0.51	1.12 ±0.25
5	Angle of repose (θ)	26°33"± 0.14	24°65"± 0.36	24°16"± 0.25	20°42" ±0.23	27°15" ±.36	25°24"± 0.25	26°52"± 0.25	22°53"± 0.15	24°54" ±0.14

NOTE: S1,S3,S5 : PVP K30 Solid Dispersions
S2,S4,S6 : PEG 4000 Solid Dispersions

3.6. Micromeritic Properties Of Solid Dispersions and Inclusion Complexes Prepared By Kneading Method
Table no :12

S. no	Parameter	Formulations								
		D1	**D2**	**D3**	**D4**	**D5**	**D6**	**C4**	**C5**	**C6**
1	Bulk Density(gm/ml)	0.070 ±0.12	0.069 ±0.36	0.075 ±0.14	0.075 ±0.25	0.072 ±0.25	0.070± 0.36	0.072±.25	0.075± 0.26	0.073 ±0.62
2	Tapped Density(gm/ml)	0.081 ±0.32	0.080 ±0.14	0..084 ±0.25	0.085 ±0.15	0.077 ±0.36	0.075± 0.25	0.082±0.14	0.086± 0.14	0.083 ±0.15
3	Compressibility (%)	13.5 ±.14	13.3 ±0.36	10.7 ±0.36	6.67 ±0.15	6.49 ±0.25	10.9±0.36	9.99±0.25	5.12±0.36	8.14 ±0.35
4	Hausner's ratio	1.09 ±0.15	1.15 ±0.25	1.02 ±0.56	1.09 ±0.25	1.12 ±0.36	1.12±0.36	1.16±0.36	1.03±0.63	1.13 ±0.45
5	Angle of repose (θ)	24°45" ±0.36	26°15" ±0.23	24°36" ±.41	22°13"± 0.36	23°21" ±.12	25°19" ±0.25	25°67"± 0.15	18°84" ±0.32	23°95" ±0.75

NOTE: D1, D3, D5 : PVP K30 Solid Dispersions
D2, D4, D6 : PEG 4000 Solid Dispersions
C4-C6 : β-Cyclodextrin Inclusion Complexes

The results indicate that the-

1. Formulation (P8) shows excellent flow properties with values ranging from 25-30.
2. Formulation (S4) prepared by solvent evaporation method shows excellent flow properties with values ranging from 20-25.
3. Formulation (D4) prepared by kneading method shows excellent flow properties with values ranging from 20-25.
4. Formulation (C2) prepared by solvent evaporation method shows excellent flow properties with values ranging from 20-25.
5. Formulation (C5)prepared by kneading method shows excellent flow properties with values ranging from 25-30.

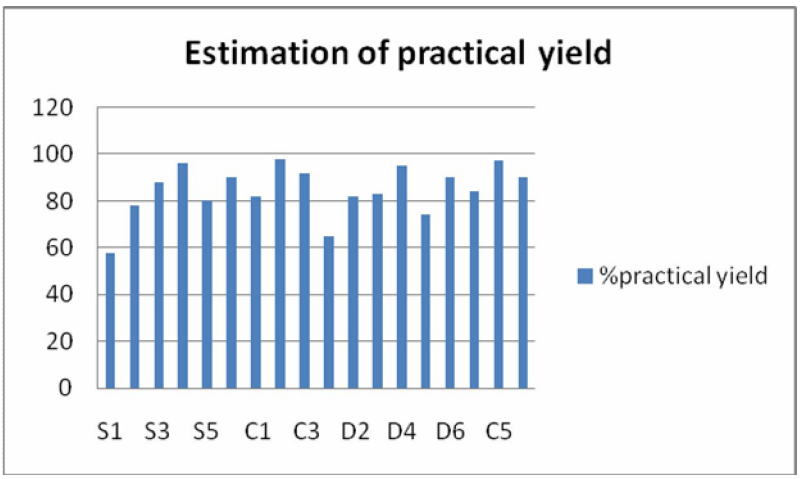
3.7.Estimation Of Practical Yield

Table no:13

S.NO	FORMULATIONS	% PRACTICAL YIELD OF TELMISARTAN
1	S1	58
2	S2	78
3	S3	88
4	S4	96
5	S5	80
6	S6	90
7	C1	82
8	C2	98
9	C3	92
10	D1	65
11	D2	82
12	D3	83
13	D4	95
14	D5	74
15	D6	90
16	C4	84
17	C5	97
18	C6	90

Note : S1-S6 (solid dispersions prepared by solvent evaporation method)
D1-D6 (solid dispersions prepared by kneading method)
C1-C3 (inclusion complexes prepared by solvent evaporation method)
C4-C6(inclusion complexes prepared by kneading method)

Fig no :9 Estimation of Practical Yield



The results indicate that-

1. Formulation (S4) prepared by solvent evaporation method shows better practical yield.
2. Formulation (D4) prepared by kneading method shows better practical yield.
3. Formulation (C2) prepared by solvent evaporation method shows better practical yield.
4. Formulation (C5)prepared by kneading method shows better practical yield.

3.8.Estimation Of Drug Content

Table no:14

S.NO	FORMULATIONS	% OF TELMISARTAN PRESENT
1	P1	97.5
2	P2	98.5
3	P3	98.0
4	P4	97.5
5	P5	99.0
6	P6	98.5
7	P7	97.5
8	P8	98.5
9	P9	98.0
10	S1	97.5
11	S2	97.5
12	S3	98.5
13	S4	99.0
14	S5	98.0
15	S6	98.5
16	C1	98.5
17	C2	99.5
18	C3	99.0
19	D1	98.5
20	D2	98.5
21	D3	99.0
22	D4	99.0
23	D5	98.0
24	D6	98.5
25	C4	98.0
26	C5	99.5
27	C6	98.5

Note : P1-P9(physical mixtures with different ratios of carriers)
S1-S6 (solid dispersions prepared by solvent evaporation method)
D1-D6 (solid dispersions prepared by kneading method)
C1-C3 (inclusion complexes prepared by solvent evaporation method)
C4-C6(inclusion complexes prepared by kneading method)

The results indicate that the

1. Formulation (P8) shows 99.5% of drug content.
2. Formulation (S4) prepared by solvent evaporation method shows 99.0% of drug content.
3. Formulation (D4) prepared by kneading method shows 99.0% of drug content.
   Formulation (C2) prepared by solvent evaporation method shows 99.5% of drug content.
4. Formulation (C5)prepared by kneading method shows 99.5% of drug content.

3.9 *Invitro* Dissolution Profile Of Telmisartan Formulations[16-20,25]

a) Physical Mixtures
Table no:15

S. NO	TIME	PURE DRUG	CUMULATIVE % DRUG RELEASE (X±S.D)								
			P1	P2	P3	P4	P5	P6	P7	P8	P9
0	0	0	0	0	0	0	0	0	0	0	0
1	10	9.25 ±0.33	32.55 ±0.14	35.52 ±0.45	20.45 ±0.33	22.56 ±0.12	31.82 ±0.54	19.95 ±0.36	23.56 ±0.32	25.12 ±0.68	22.65 ±0.14
2	20	13.77 ±0.42	39.58 ±0.16	41.56 ±0.32	26.52 ±0.25	30.35 ±0.25	38.75 ±0.45	24.35 ±0.54	32.45 ±0.45	33.12 ±0.61	34.54 ±0.45
3	30	17.73 ±0.52	45.56 ±0.58	49.52 ±0.26	31.35 ±0.45	40.56 ±0.33	45.15 ±0.54	36.96 ±0.65	42.56 ±0.44	46.14 ±0.51	41.39 ±0.52
4	40	24.45 ±0.12	52.15 ±0.36	55.62 ±0.56	38.65 ±0.65	57.33 ±0.41	59.43 ±0.12	41.12 ±0.45	58.65 ±0.54	59.65 ±0.64	49.26 ±0.65
5	50	29.68 ±0.56	58.65 ±0.56	61.98 ±0.48	42.75 ±0.89	66.57 ±0.51	69.92 ±0.48	44.12 ±0.14	66.45 ±0.33±	67.32 ±0.63	56.21 ±0.56
6	60	35.42 ±0.12	61.66 ±0.44	65.46 ±0.69	46.32 ±0.71	72.45 ±0.56	73.54 ±0.32	48.32 ±0.63	73.52 ±0.25	74.25 ±0.35	64.55 ±0.36

The results indicate that the

- The invitro dissolution study of all formulations were having (P1-P9) shows the cumulative percentage of drug release minimal 46.23 and maximum 74.25 at the end of 60 minutes.
- The invitro dissolution study of all formulations were having (S1-S6) shows the cumulative percentage of drug release minimal 48.50 and maximum 97.39 at the end of 60 minutes.
- The invitro dissolution study of all formulations were having (C1-C3) shows the cumulative percentage of drug release minimal 81.89 and maximum 93.45at the end of 60 minutes.
- The invitro dissolution study of all formulations were having (D1-D6) shows the cumulative percentage of drug release minimal 49.86 and maximum 91.46 at the end of 60 minutes.
- The invitro dissolution study of all formulations were having (C4-C6) shows the cumulative percentage of drug release minimal 83.45 and maximum 99.89 at the end of 60 minutes.

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As compared to other formulations, C5 given 57.45% drug release after first 20 minutes and 99.89% of drug release at the end of 60 minutes.All the formulations complies all evaluatory parameters. Therefore the C5 formulation was chosen as the best formulation from all 27 batches.

Conclusion

From the in vitro drug release profile, it can be seen that formulation containing 1:2 ratio of β-cyclodextrin inclusion complexes by using kneading method showed higher dissolution rates when compared to solid dispersions (1:2) ratio of PEG 4000 by using solvent evaporation method. The significant improvement in dissolution characters of inclusion complexes may be due to formation of readily soluble inclusion complex in the dissolution medium, increased drug particle wettability and reduction of crystallinity degree of the product.

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