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Research Article

Formulation Development and in vitro Evaluation of Sustained Release Tablets of Telmisartan by Solid Dispersion Technology

Ganesh R. Godge* Varsha D. Palwe, Pratap Y. Pawar

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Corresponding Author:

*** Mr. Godge G.R.**
Asst. Professor,
Dept. of Pharmaceutics,
P.D.V.V.P.F's College of Pharmacy,
Vilad Ghat,M.I.D.C,
Ahmednagar-414111.
Contact No.09028757508.

e-mail: palwevarsha25@Gmail.Com

ABSTRACT

In the present work ,an attempt was made to formulate sustained release tablets of Telmisartan by solid dispersion technique for improving solubility Telmisartan using PEG 4000 and PVP K30.The Telmisartan tablets were prepared by wet granulation method using HPMC K4M as sustained release polymer in different concentrations .The prepared tablets were evaluated for various physiochemical parameters, *In vitro* Drug release study was carried out in phosphate Buffer PH 6.8using USP TYPE II paddle apparatus. Increase in HPMC concentrations resulted in a significant decrease in Telmisartan release .tablets containing 75 mg of HPMC K4M (f1and f4) shows 78% and 70% drug release upto 9 hr. Tablet containing 90 mg of HPMC K4M (f2and f5) shows 80 % and 81%drug release upto 9 hr. and tablet containing 105 mg HPMC K 4M (f3 and f6)shows highest drug release 91%and83% compared to other formulations. the in vitro data is fitted in to different kinetic models like zero order ,first order, korsmeyer and matrix plot. From this study, it was clarified that solid dispersion technique was one of the promising sustained release system applying for the poorly water soluble drugs

Key-words: Telmisartan, sustained release, HPMC K4M ,PVP K30.

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Introduction

Traditional drug delivery system has been characterized by immediate release and repeated dosing of the drug which might lead to the risk of dose fluctuation, this arises the need of a formulation with control release that maintain a near-constant or uniform blood level .sustain release with the introduction of extended release matrix tablet have proved to be an effective tool to control the release of drug without involving the complex production procedures by the sustained release method therapeutically effective concentrations can be achieved in the systemic circulation over an extended period of time ,thus achieving better compliance of patients numerous sustain release oral dosage forms such as membrane controlled system ,matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed intense research has recently focused on the designation of sustain release systems for poorly water soluble drugs. However generating such a systems requires certain consideration of which the half life and the pharmacological action of the drug form an essential part .but making a considerations of the drawbacks seen with the the conventional drug delivery system (repeated dosing and dose fluctuation) the sustain release helps to achieve the following goals: i)uniform release of drug over prolong period of time ii)reduced dosing frequency . iii)less fluctuating blood levels.in many instances, conventional method is more preferred to deliver the drug ,but some drugs are unstable and toxic by frequently dosing .these kinds of drug have narrow therapeutic range and face solubility Difficulties.in such cases ,sustained drug delivery system is used,which maintain the drug plasma level in the therapeutic index.

Materials

Telmisartan was provided as gift sample by Cipla lab, Mumbai. HPMC K4M and pvpk30 was provides gift sample by Svizera laboratory, Mumbai, magnesium stearate, talc of analytical grade was purchased from Vishal chemicals. Mumbai.

Methods

Preparation of telmisartan solid dispersion(SDs)

The solid dispersions of telmisartan were prepared by physical mixing method.the weighed quantities of drug and polymer PEG4000and pvp k30 taken in glass mortar were mixed thoroughly .the resultant mixture was passed through sieve no.100# and was stored in dessicators for the complete removal of moisture.drug :polymer ratios of 1:1, 1:2and 1:4 were prepared.

Invitro dissolution studies of solid dispersion

The quantity of solid dispersions equivalent to 40 mg of Telmisartan was placed in dissolution medium.the dissolution study of solid dispersions was conducted using dissolution testing apparatus II (paddle method)in 900ml of phosphate buffer solution of ph 6.8 at 37 °C and at a speed 50 rpm aliquots of 5ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling& analysed spectrophotometrically at 295nm against suitable blank using uv-visible spectrophotometer(shimadzu)

Formulation of sustained relase tablets of telmisartan solid dispersion by wet granulation method

Wet granulation is the most widely used to prepare tablets.formulation with different binders was compressed into tablets.the required quantities of Telmisartan ,starch ,lactose monohydrate ,HPMC K4M, were weighed accurately using analytical balance and were mixed well using laboratoryconditions.The aqueous binder solution was added and mixed thoroughly to form dough mass .The mass was passed through Mesh no.12 to obtain wet granules .The wet Granules were dried in a hot air oven at 40^0 c temperatures.then the dried granules were passed through mesh no.16 to break aggregates. Talc & mag state were passed through mesh no.100 on to dry granules and blended in a polyethylene bag .The Tablet granules were then compressed using compression machine.

Evaluation of tablets

The matrix tablet of Telmisartan ,prepared with and without solid dispersions by wet granulation method ,were evaluated for pre-compression and post compression parameters such as angle of repose,compressibility,

hausnerratio and hardness ,friability,weight variation ,thickness,drugcontent,the obtained result were tabulated in table2 and 3respectively.

Drug content

Five tablets of each type of formulation were weighed and crushed in mortar & powder equivalent to 40 mg of Telmisartan was weighed and dissolved in 100 ml of phosphate buffer PH(6.8).this was the stock solution from which 1ml withdrawn and diluted to 10 ml with phosphate buffer PH(6.8).the absorbance was measured at wavelength 295 nm using uv-visible spectrophometer.

Drug polymer interaction study(FTIR study)

The FTIR spectra of Telmisartan alone and it's combination with polymer are shown in figure.the FTIR spectra of pure Telmisartan showed the peaks 1349 cm-1 (C-N strechning),3311 cm-1 (N-H strechning) 2807 cm-1(-CO strchning in carboxylic acid)and carboxylic acid 1762 cm-1.these peaks considered as characteristic peaks of Telmisartan and were not affected and prominently observed in IRspectra of Telmisartan along with polymers (pvpk30,PEG4000, HPMCK4M)As shown in figure,indicated no interaction between Telmisartan and polymers .

In-vitro dissolution study

The in- vitro dissolution studies of all formulations(f1-f7) were carried out using USP II (paddle method),in phosphate buffer PH6.8 at 37 ± 0.5 °C,50 Rpm.sample withdrawn at regular intervals .the volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of dissolution medium .the filtered samples were analyzed spectrophotometrically at 295 nm.the amount of drug released was determined using respective calibration curves .

Drug relase kinetic study

To describe kinetics of drug release from the sustained release tablets of ,mathematical models,such as zero order, first order and matrix ,korsmeyerpeppas,hixoncrowell model were used.the criteria for selecting most appropriate model were based on goodness of fit test .the zero order kinetics describes system in which drug release rate is independent of its concentrations ,the first order kinetics describes the systems in which drug release rate in concentration dependent.

Data analysis

To analyze the mechanism of the drug release rate kinetics of the formulations ,the data obtained were plotted as

1.cumulative % drug relaseVs.Time (zero order plot)
2.cumulative %drug relasedVs square root of time (higuchi plot)
3.log cumulative % drug remaining Vs.Time(first order plot)
4.log %drug relased Vs.log time (korsmeyer plot)

Results and Discussion

A simple technique of sustained relase solid dispersion tablets was used in the present investigation.solid dispersions were prepared using polymers like (pvpk30,PEG4000).sustained relase solid dispersion were prepared using HPMC K4M polymer.standard graph of telmisartan in phosphate buffer PH 6.8 showed good linearity.its 'R2' value is 0.996 and hence obeyed beer lambert's law. The FTIR spectra of Telmisartan with the polymers pvp k30,PEG 4000 and HPMC K4M revealed the major functional groups of Telmisartan were same or nearly same ,hence there was no probable interaction between drug and polymers .the sustained release of tablets of solid dispersion were prepared as described in methodology .the solid dispersion prepared in the ratio of drug :polymer(1:1 of drug and PEG 4000,1:1drug :pvpk30)and also of without solid dispersion Telmisartan tablets.the formulations were evaluated for hardness,friability,weight variation drug content, in-vitro dissolution study. The hardness of tablets found to be 5.4 to 5.4 kg/cm^2.All the tablets shows % friability in the range 0.65-0.85% which is within the limit.All the formulations passes weight variation test as all tablets within the range

limit for weight variation.Assay for the prepared formulations was performed to determine Drug content uniformity and it was found between 97.10% to 99.50%.

Table 1.formulae of sustained release tablets of Telmisartan solid dispersion

No.	Ingredients(mg)	PVPK30 solid dispersion			PEG4000 solid dispersion			Plain Drug
		F1	F2	F3	F4	F5	F6	F7
1.	Telmisartan	-	-	-	-	-	-	40
2.	Telmisartan SD equivalent to 40 mg	80	80	80	80	80	80	-
3.	HPMC K4M	75	90	105	75	90	105	105
4.	Starch	85	70	55	85	70	55	85
5.	Lactose(monohydrate)	154	154	154	154	154	154	164
6.	Magnesium Stearate	3	3	3	3	3	3	3
7.	Talc	3	3	3	3	3	3	3
8.	P. Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2: Evaluation of Pre-Compression Parameters

Batch Code	Angle of repose (Θ)	Bulk density (mg/ml)	Tapped Density (mg/ml)	Carr's index (%)	Hausner Ratio HR
F1	27.59	0.68	0.74	8.82	1.08
F2	25.74	0.71	0.78	9.85	1.09
F3	25.31	0.74	0.80	8.10	1.08
F4	25.85	0.70	0.75	7.14	1.07
F5	27.59	0.73	0.79	8.21	1.08
F6	26.71	0.74	0.80	8.10	1.08
F7	26.31	0.73	0.79	8.21	1.08

Table 3: Evaluation of post -compression parameters

Batch code	Hardness(kg/cm²)	Thickness(mm)	Friability(%)	Weight variation (%)	%Drug content(mg)
F1	5.1	3.62	0.80	312	97.10
F2	5.0	3.63	0.85	313	98.30
F3	5.2	3.54	0.72	314	98.75
F4	5.4	3.37	0.65	312	98.00
F5	5.3	3.43	0.79	311.5	95.80
F6	5	3.64	0.66	314	99.50
F7	5.2	3.52	0.72	313.5	97.50

Table 4: Values of constants (K) and correlations of coefficients (R) for release from Telmisartan solid dispersion tablets .

Batch Code	Zero Order(R)	First order (R)	Matrix(R)	Hix crow (R)	peppas (n)	Best fit model
F1	0.9813	0.9291	0.8701	0.9537	0.47	zero order
F2	0.9790	0.9405	0.8689	0.9591	0.46	zero order
F3	0.9919	0.9409	0.9103	0.9736	0.47	zero order
F4	0.9455	0.8882	0.8020	0.9096	0.47	zero order
F5	0.9878	0.9878	0.8877	0.9878	0.45	zero order
F6	0.9661	0.9660	0.8493	0.9660	0.46	zero order
F7	0.9661	0.6416	0.9396	0.6416	0.46	zero order

Table no5: Dissolution profile of TEL-PVPK30 & PEG 4000 solid dispersions

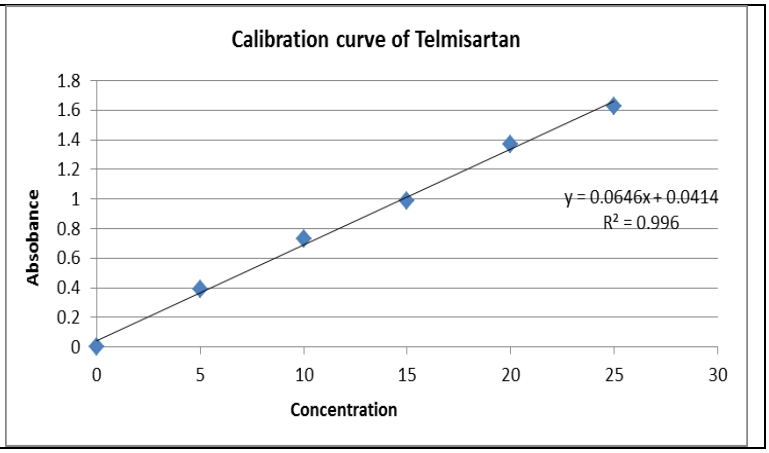
CUMULATIVE % DRUG RELEASE							
Time (min)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**Pure drug Telmisartan**
5	**60.82**	**40.01**	**55.13**	**58.78**	**59.33**	**58.13**	**34.45**
15	**67.00**	**48.35**	**60.19**	**64.11**	**64.00**	**60.11**	**48.16**
30	**71.36**	**58.11**	**64.44**	**73.23**	**72.11**	**68.45**	**58**
60	**82.15**	**61.34**	**69.24**	**76.11**	**74.09**	**71.39**	**60.11**
120	**86.00**	**70.11**	**76.36**	**81.19**	**78.38**	**72.19**	**68.97**

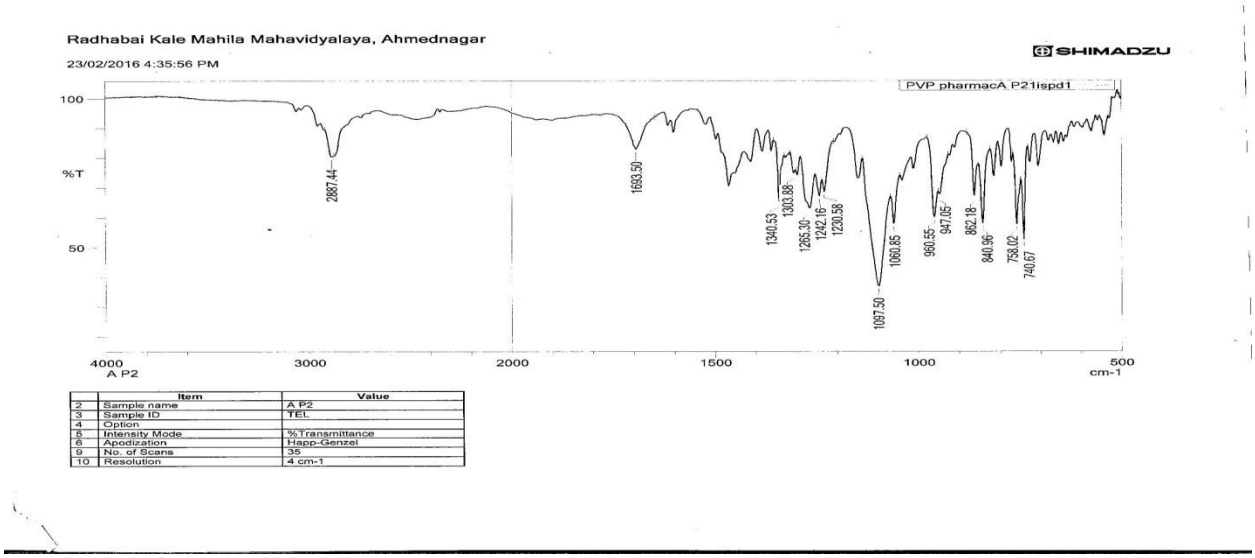
Table no6: Dissolution profile F1-F7 Formulations

CUMULATIVE % DRUG RELEASE							
Time(min)	**f1**	**f2**	**f3**	**f4**	**f5**	**f6**	**f7**
0	0	0	0	0	0	0	0
30	0.87	0.5	1.75	1.3	4	1	66
60	1.4	1.3	4.265	1.6	5	6	80
90	1.6	1.5	16.44	3.5	15	15	86
120	10.7	10.6	17.33	4.7	17	16	96
150	16.5	16.5	23.41	12.7	20	19	
180	24.5	25.1	31	12.8	27	25	
210	30.6	30.4	39	17.3	28	26	
240	40.2	40.2	47	18.8	33	27	
270	40.7	47.9	57	23.3	42	31	
300	41.1	48.4	59	27.6	49	31	
330	47.8	54.6	69	32.9	50	38	
360	53.4	62	72	43.9	56	43	
390	54.3	71	75	45	70	45	
420	62.5	79	77	59	78	54	
450	76.3	79.12	84	67	80	55	
480	77.7	80	90	69	80	68	
510	78.8	80.85	91	70	81	83	

Table no7: Standard Curve of Telmisartan in Phosphate Buffer PH 6.8 &Fig.1 Calibration curve of Telmisartan in phos buffer PH 6.8

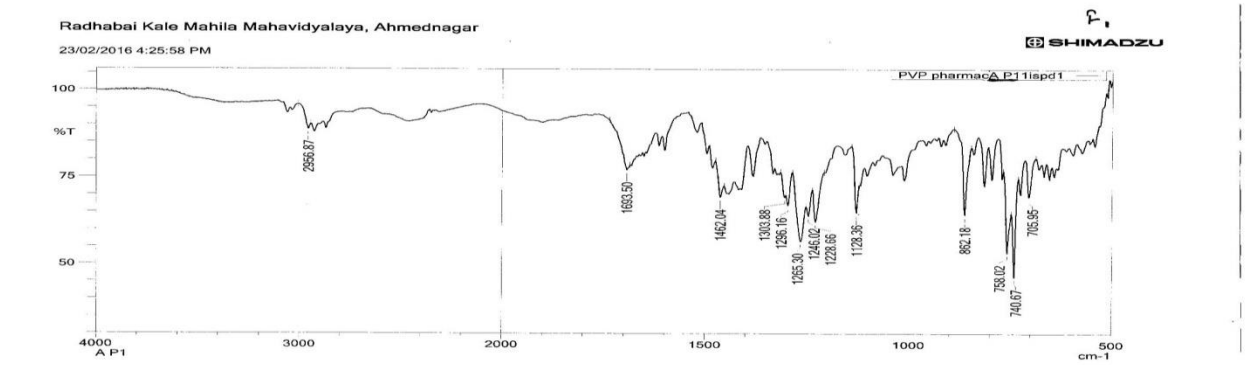
CONC(µg/ml)	ABSORBANCE
0	0
5	0.3875
10	0.7324
15	0.9824
20	1.3683
25	1.6231





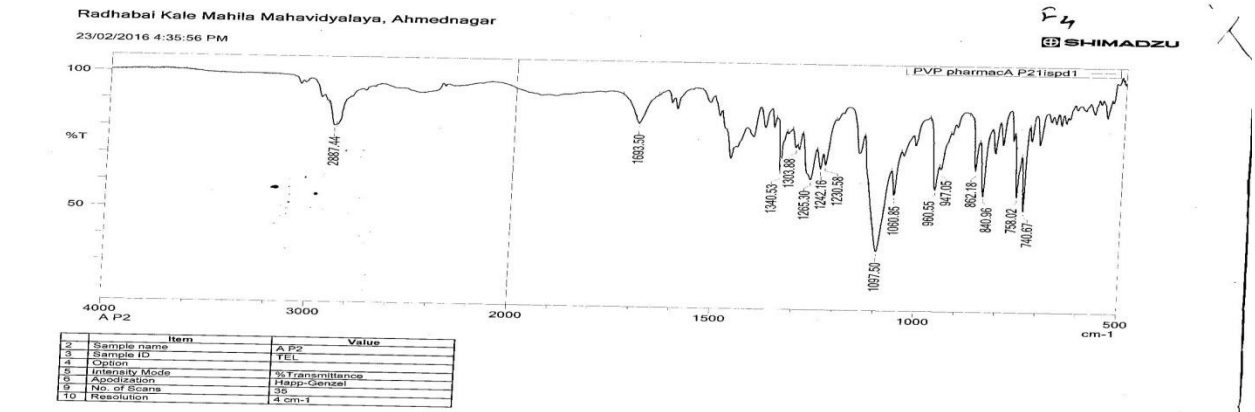
	Item	Value
2	Sample name	A P2
3	Sample ID	TEL
4	Option	
5	Intensity Mode	%Transmittance
6	Apodization	Happ-Genzel
9	No. of Scans	35
10	Resolution	4 cm-1

Fig 2:FTIR spectra of Telmisartan drug



	Item	Value
2	Sample name	A P1
3	Sample ID	TEL
4	Option	
5	Intensity Mode	%Transmittance
6	Apodization	Happ-Genzel
9	No. of Scans	35
10	Resolution	4 cm-1

Fig3. FTIR spectra of Telmisartan and pvp k30



	Item	Value
2	Sample name	A P2
3	Sample ID	TEL
4	Option	
5	Intensity Mode	%Transmittance
6	Apodization	Happ-Genzel
9	No. of Scans	35
10	Resolution	4 cm-1

Fig 4:FTIR spectra of Telmisartan and PEG 4000

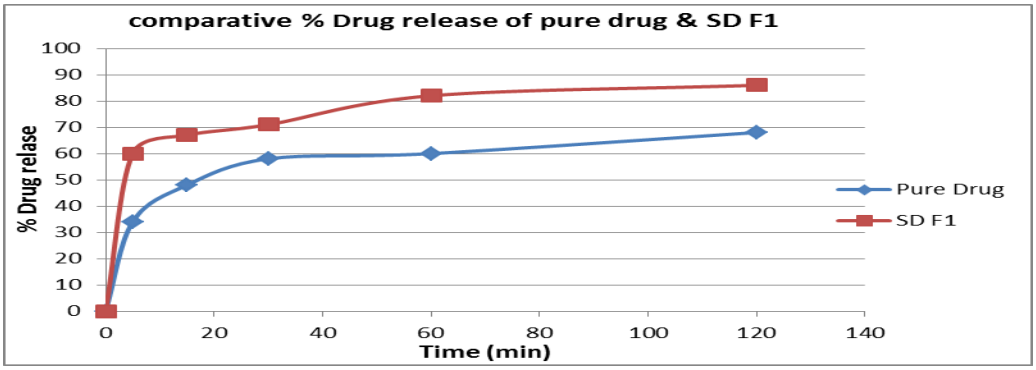


Fig no.5 Dissolution profile of pure drug & Solid dispersions of TEL-PVPK30(f1)

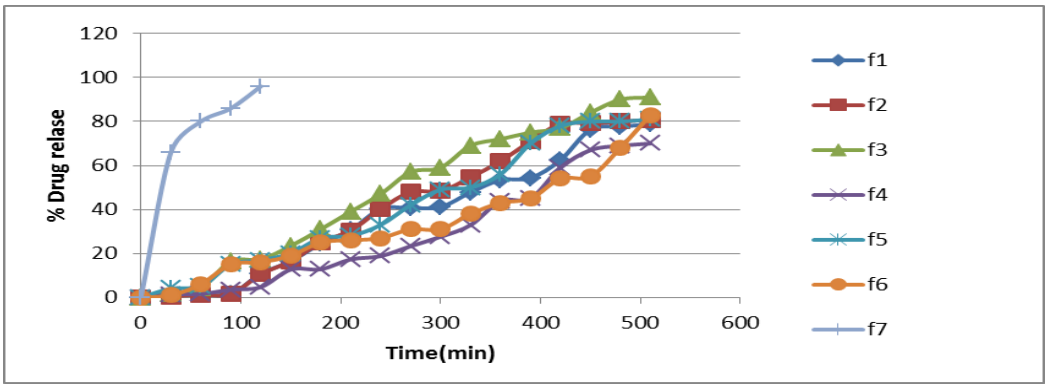


Fig no.6 Dissolution profile of f1-f7 Tablet formulations

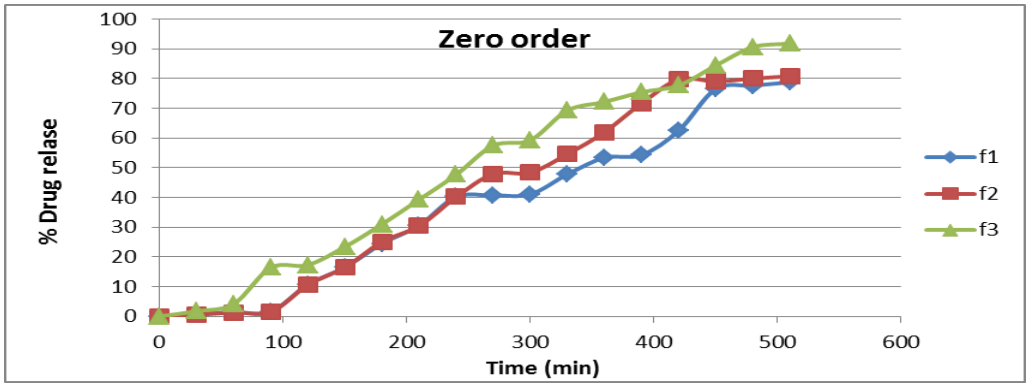


Fig no7:cumulative % drug release *VS* Time(zero order kinetics)of F1-F3

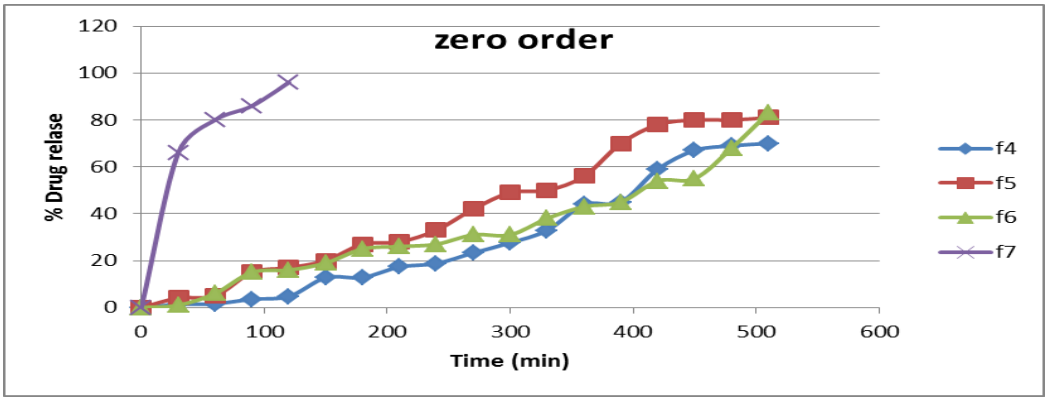


Fig No8:Cumulative % Drug Release *VS* Time(Zero Order Kinetics)Of F4-F7

Conclusion

A Satisfactory attempt was made to develop a novel sustained release tablets using HPMC polymer and evaluated for invitro characterization studies Telmisartan tablets containing solid dispersion of pvpk30 Peg 4000 exhibited increase in solubility and improved drug dissolution as compared to the plane Telmisartan tablets.In sustained –release solid dispersion tablets , the release rate of Telmisartan decreased with increasing HPMC K 4M concentration.sustained release tablets prepared using solid dispersions(f3 and f6)were shown early $t_{50\%}$ than it's plane drug tablet formulation(f7).In vitro drug release study formulations indicated that Telmisartan was released in sustained release manner up to 12 hours and it shows the zero order drug release.mechanism of drug release observed was korsmeyer-peppas with 'n' value 0.45 to 0.47 i.e fickian diffusion and polymer relaxation.from the studies on Telmisartan solid dispersion , we can conclude that sustained release tablets of pvp k30 and PEG 4000 solid dispersion of Telmisartan provides more satisfactory sustain release than pure Telmisartan sustain release tablets.

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