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Use of Combined Techniques of Solubilization for Improving Solubility and Dissolution of Immediate Release Tablet Containing Telmisartan

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ABSTRACT

Telmisartan is Angiotensin II (AT_1) receptor antagonist used in the treatment of hypertension. The drug is practically insoluble in water and insoluble in pH range 3-9, so the rate of dissolution and therefore its bioavailability is less. In this investigation an attempt was made to develop Novel Immediate release solid oral formulations of Telmisartan using Combined Techniques of Solubilization, so Tablet can be prepared using less complicated, less expensive excipients and processes as well as to fulfill all prerequisites for pharmaceutical use. In the study the approach of Combined Techniques of Solubilization used was solid dispersion (SD) based approach were polymers like PVP K 25 and PEG 4000 were used and kneading method was applied For dispersion Preparation and Fluidized Bed Processing was used to prepare Highly Porous and High soluble Granules of Mannitol Coated with Solid Dispersion of Drug and by Using this Granules immediate release tablets were formulated. The experimental batches were designed using fractional factorial design and ANOVA was used for optimization. All the batches were evaluated for Hardness, Friability and *In-vitro* Disintegration and dissolution time. The Dissolution pattern of optimized formulation were compared with innovator's product and it was found to be superior to innovator's product; also they showed pH independent and higher solubility then marketed Product.

KEYWORDS

Combined Techniques of Solubilization, Fluidized Bed Processing, Solid dispersion.

INTRODUCTION

An oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. Telmisartan is a nonpeptide Angiotensin Receptor II (Type-ATI) Antagonist, That Cause Inhibition of the action of Angiotensin II on Vascular Smooth Muscle in the Symptomatic Treatment of Hypertension.

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Telmisartan is a poorly water soluble antihypertensive drug which shows large inconsistency in onset of action and Bioavaibility, so require very high dose due to its very less absorption in GIT. As the patients with sudden increase Blood pressure, have markedly reduced function ability and extremely restless, in such cases rapid onset of action is of prime importance which can be provided by immediate release tablets. It is a drug of choice when the other antihypertensive drugs like ACE inhibitors and β-blockers are unable to control the blood pressure. And also due to its long circulating half-life of about 22-24 hrs and high protein binding capacity (99.5%) of Telmisartan, its immediate release dosage form can also provides advantage of

both quick as well as prolonged blood pressure lowering effect. The aim of the study is to develop and evaluate the Immediate Release tablets of Telmisartan and to enhance the aqueous solubility of Telmisartan.[1] Immediate release tablet is intended to be swallowed and to disintegrate and release their medicaments rapidly in the GIT or in dissolution medium for better bioavailability and rapid onset of action.[2] Ideally Immediate release tablet releases the drug within 10 to 20 minutes after its oral administration. So this type of tablet can be valuable to provide rapid action in such an emergency conditions. As the patients with sudden increase blood pressure, have markedly reduced function ability and extremely restless, in such cases rapid onset of action is of prime importance.[3] so the patients would be benefited from acute treatment by using immediate drug delivery system. This may help to return the blood pressure to normal state and resume patients' functional activities before the high blood pressure damage the vital system of the body. As we know Conventional Solubilization techniques available are sometimes not capable to improve the solubility of some drug to the extent which is desired. Telmisartan is the example of such drug that has shown a little success while using the conventional Solubilization techniques.[4] so there is a need to try some different techniques for improving the solubility and dissolution of immediate release tablet of Telmisartan. Combined techniques of Solubilization (CTS) can be used for this purpose. In the Solid dispersion based approach of CTS the techniques that were combined "preparation of Solid dispersion of drug + Microenvironmental pH alteration + Incorporation of Surface active agent + Incorporation of Superdisintegrant". The 2^{4-1} Fractional Factorial Design was used to conduct the experimental trial and ANOVA was used to optimize the best formulation.[5]

MATERIALS AND METHODS

MATERIALS

Telmisartan was obtained from Morepen Laboratories Ltd. And other polymers like Poloxamer 188 and SLS were purchased FMC Biopolymer, China. While Meglumine and Sodium hydroxide were obtained from Easter Holding group co, Ltd. and Anhui Suntran Chemicals co., Ltd. Respectively. And all the other ingredients that were used in the study were of analytical grade.

METHODS

Drug-Excipients compatibility study by FT-IR

Fourier-transform infrared **(**FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The samples (Telmisartan and Excipients) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. [6]

Drug-Excipients compatibility study by DSC

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The samples (drug and excipients) were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference.[7]

Preliminary trials to determine the Phase Solubility of Solid Dispersion

Phase Solubility measurements were performed according to the method of Higuchi and Connors. Various aqueous solutions of PVP K-25 and PEG 4000 were prepared, and 20 mL of each solution was taken into separate glass vials. An excess amount of drug was added to these vials. The vials containing drug–hydrophilic polymer carrier mixtures were shaken at 37 ± 0.1 °C for 48 h in a water bath shaker. After 48 h, samples were filtered through 0.45-µm filter paper. The filtrate was suitably diluted with corresponding polymer carrier solution (0.25%, 0.5%, 0.75%, or 1% w/v) and analyzed Spectrophotometrically.[8, 9]

Table 1: Phase Solubility

Sr. No	Batch code	Composition	Ratio (Drug: Carrier)
1	SD1	Telmisartan +PVP K-25	1:1
2	SD2	Telmisartan + PEG-4000	1:1
3	SD3	Telmisartan +PVP K-25	1:2
4	SD4	Telmisartan +PEG-4000	1:2
5	SD5	Telmisartan +PVP K-25	1:1
6	SD6	Telmisartan +PEG-4000	1:3

Procedure for Tablet preparation by Solid Dispersion Based approach

In this approach of combined technique of Solubilization the solubility enhancement was achieved by combining "Solid dispersion + Micro environmental pH alteration + Incorporation of Surface Active agents + Incorporation of Superdisintegrant"[10, 11]

Solid dispersion preparation (Kneading Method)

In this method the drug and carriers are used in ratio of (1:2). 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 up to 60 minutes. In the above paste Meglumine was added and again starred for 30 min and finally non aqueous solution of PVP K 25 was added in the paste and again stirred for another half an hour to prepare a thick yellowish paste.[12]

Coating solution preparation

The prepared dispersion was mixed with aqueous solution of NaOH and stirred for 30 min after addition of extra water. The solution was allowed to stir till clear solution was formed. [13]

Granule preparation in FBP

Powdered Layering (Pelletization) of the above solution containing drug complex Using FBP (Top Spray). Mannitol (Pearlitol 200) was used as inert carriers for layering. Mannitol and povidone were placed into a fluid-bed granulator (Electrocraft Pvt. Ltd.) and sprayed with granulation liquid. Then is sprayed with purified water; followed by a drying step and a screening step.[14, 15]

Process data granulation

- Inlet air temperature: 80-100 °C
- Spraying rate: 500-900 mL/min
- Process data drying step
- Inlet air temperature: 80 -100 °C
- End of drying: Gut temperature more than 70 °C

Evaluation of Granules and Tablets

The prepared granules were evaluated for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. And the prepared tablets (F1-F8) were evaluated for weight variation, friability, hardness and disintegration time.[16, 17]

Drug content

Twenty tablets were taken randomly and individual tablet were crushed, an amount of the powder equivalent to 80mg of Telmisartan was dissolved in the 50 ml of Ethanol Water mixture (1:1). The solution was Shaken for 30 min and added sufficient 0.1 M Ethanolic SLS to produce 100 ml and filtered, diluted suitably and analyzed for drug content at265 nm using UV-Visible spectrophotometer (UV 1601-Shimadzu, Japan).[18]

In-vitro Dissolution Study

In-vitro drug release was determined using USP (United States Pharmacopeia) dissolution apparatus II of paddle type (TDT-08L, Electrolab) at 100 rpm maintained at 37+ 0.5 °C in 900 ml of 0.1 N HCl (pH 1.2) dissolution media. Percent drug released should be determined by taking an aliquot of 10 ml at different time intervals. An equal volume of fresh dissolution medium was replaced to maintain the original volume. The samples were diluted for estimating percent released by UV-Visible Spectrophotometer.[19, 20]

Experimental trials

Fractional factorial design

The 2^{4-1} Fractional factorial design was applied for conducting experimental trials.

Optimization

The dissolution efficiencies observed from the dissolution data of complexes prepared with different methods and ratios was analyzed using a one-way analysis of variance (ANOVA) followed by Dunnett's test and T-Test by using the software prism graph pad.

Table 2: Coding for different Factors

Factor	Name	Units	Mini.	Max.	Coded	Values	Mean	Std. Dev.
A	Meglumine	mg	15	40	-1.000 =15.00	1.000 =40.00	27.5	12.5
B	Poloxamer 188	mg	5.5	18.5	-1.000 =5.50	1.000 =18.50	12	6.5
C	Polyplasdon Xl 10	mg	8	18	-1.000 =8.00	1.000 =18.00	13	5
D	SSG	mg	5	20	-1.000 =5.00	1.000 =20.00	12.5	7.5

Table: 3 Experimental Batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Coating Solution								
Telmisartan	40	40	40	40	40	40	40	40
NaOH	3.0	3.0	3.0	3.0	3.0	3.0	3.0	30
Meglumine	15	40	15	40	15	40	15	40
PVP K-25	80	80	80	80	80	80	80	80
P. Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Poloxamer 188	5.5	5.5	18.5	18.5	5.5	5.5	18.5	18.5
Base/Core Material								
Mannitol	176	176	176	176	168	168	168	168
Extra Granular								
Polyplasdone XL 10	8	8	8	8	18	18	18	18
SSG	5	20	20	5	20	5	5	20
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Table: 4 Optimized Batches

Ingredients	F9	F10	F11	F12
Telmisartan	40	40	40	40
Meglumine	31.5	29.8	25	19.8
Poloxamer 188	8.0	15.5	7.5	13.7
PVP K-25	20	20	20	20
IPA : ACETONE (60:40)	Q.S	Q.S	Q.S	Q.S
Base Material				
Mannitol	176	176	176	176
Polyplasdone XL 10	10.6	8.8	13.6	10.6
SSG	18	13	18	15
Magnesium stearate	2.5	2.5	2.5	2.5

Stability study of optimized batch

The optimized formulation was subjected to real time (25±2 °C, 60±5% RH) and accelerated stability (40±2 °C, 75±5% RH) test. After specified period of time (1, 2, 3 months) samples were withdrawn and Physiological Parameters, Drug Content and *in-vitro* dissolution study were conducted on all the samples.

RESULT AND DISCUSSION

Drug-Excipients compatibility study by FT-IR

Compatibility studies were performed using FTIR spectrophotometer. The characteristic absorption peaks of Telmisartan were obtained at different wave numbers in different samples.

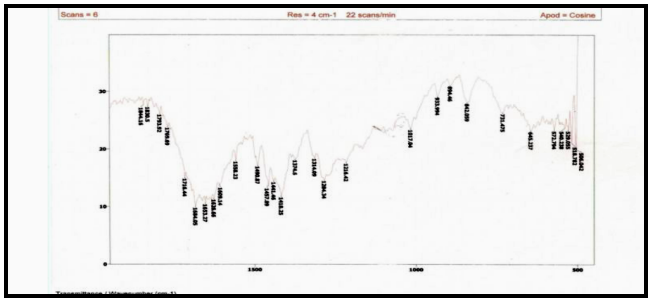


Figure: 1 FTIR Spectrum of PVP K-25

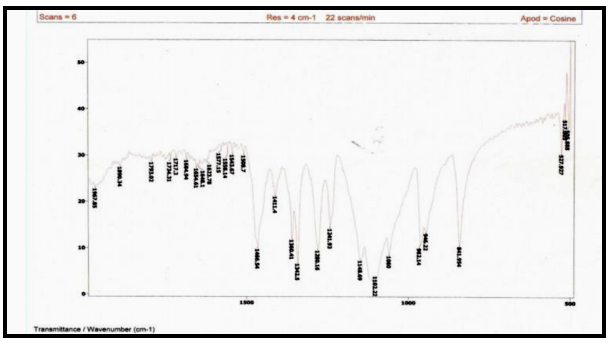


Figure: 2 FTIR Spectrum of PEG - 4000

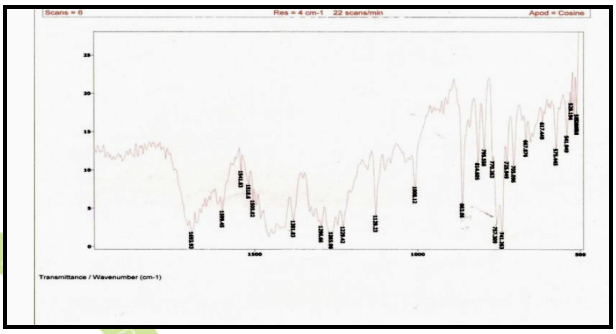


Figure: 3 FTIR Spectrum of Telmisartan + PVP K 25

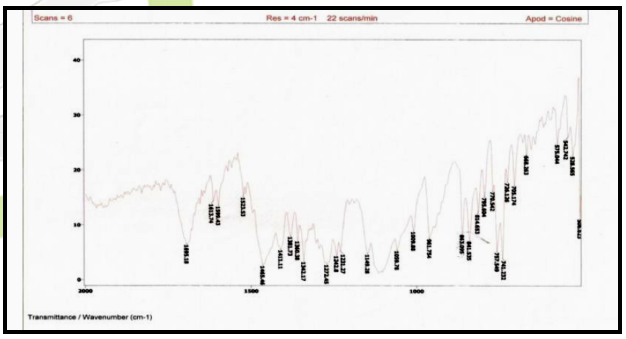


Figure: 4 FTIR Spectrum of Telmisartan + PEG 4000

FT-IR spectroscopic studies conducted for possible drug: carrier interactions. FT-IR spectra of pure drug Telmisartan, and solid dispersions which are as shown in Fig indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion aromatic (C-H) 30519.12 cm^{-1} band disappeared and aliphatic (C-H) band increased to 2926.61 cm^{-1}, and acid (-COOH) band decreased to 1650.58 cm^{-1}, aromatic (C=C) functional group is disappeared at1599.79 cm^{-1}, aromatic (C-H) band decreased to 1416.07 cm^{-1}.

Drug-Excipients compatibility study by DSC

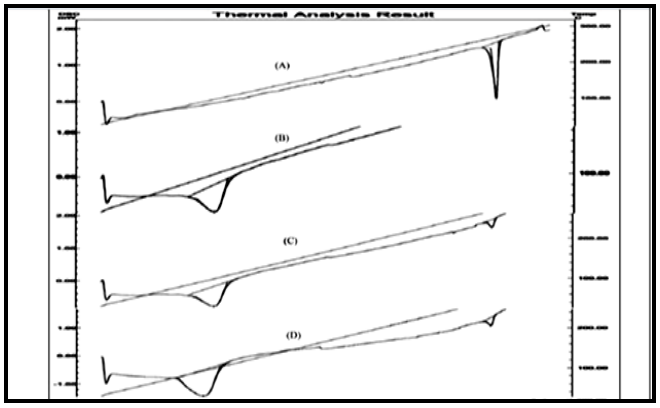


Figure No: 5 DSC Graph of (A) TLM, (B) PEG 4000 , (C) PMB, (D) KNB

TLM = Telmisartan; **PMB** = Physical mixture of TLM and PEG 4000; **KNB** = Kneaded Dispersion of TLM and PEG 4000

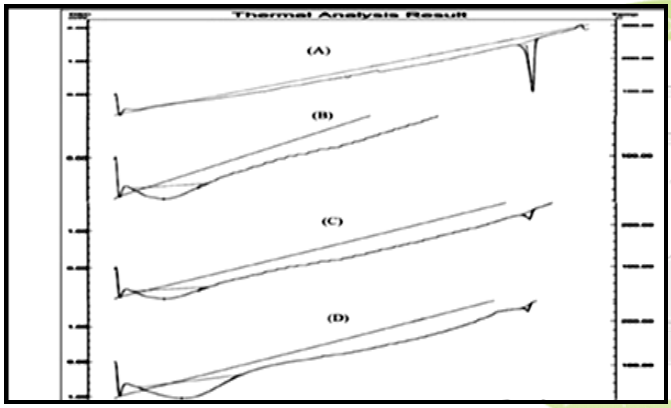


Figure: 6 DSC Graph of (A) TLM, (B) PVP K 25, (C) PMB, (D) KNB

TLM = Telmisartan; **PMB** = Physical mixture of TLM and PVP K 25; **KNB** = Kneaded Dispersion of TLM and PVP K 25

Table: 5 Preliminary trials to determine the Phase Solubility of Solid Dispersion

Batch code	% Drug Content*
SD1	88.9 ± 1.84
SD5	90.6 ± 0.02
SD3	96.5 ± 0.03
SD4	94.1 ± 0.04
SD1	93.8 ± 0.01
SD6	92.7 ± 2.85

*All values are expressed as mean ±SD, n=10

Form the % Drug Content it was found that the formulation SD 3 (Telmisartan : PVP K 25 = 1:2) shows maximum drug loading so it was selected for the further experiments.

Evaluation

Micromeritic Properties of Solid Dispersions Granules

The Granules of all nine formulations were evaluated for Bulk Density, Tapped Density, Compressibility index (%), Angle of Repose (θ), Hausner's ratio those are shown in table.

The Granules for all formulations were evaluated for bulk density which ranged from 0.502±0.21 to 0.543±0.32, Carr's index ranged from 14.98±0.21 to 16.69±0.18, Hausner's ratio from 1.711±0.33 to 1.212±0.32 and angle of repose ranged from 27.14±0.29 to 32.12±0.15. It indicates that, the Granules possess good Flowability and compressibility.

Table: 6 Micromeritic Properties of Solid Dispersions Granules

Batch code	Bulk Density* (gm/ml)	Tapped Density* (gm/ml)	Angle of Repose (θ)**	Compressibility index (%) **	Hausner's ratio**
F1	0.502±0.21	0.645±0.14	30.24±0.33	16.69±0.18	1.212±0.32
F2	0.525±0.33	0.612±0.32	31.25±0.18	15.52±0.14	1.184±0.14
F3	0.511±0.21	0.611±0.26	30.75±0.32	15.88±0.26	1.189±0.21
F4	0.509±0.18	0.621±0.32	32.12±0.15	15.62±±0.27	1.185±0.18
F5	0.550±0.25	0.623±0.14	31.07±0.32	15.45±0.21	1.183±0.14
F6	0.521±0.25	0.619±0.13	33.14±0.26	16.16±0.32	1.193±0.26
F7	0.543±0.32	0.612±0.33	28.52±0.14	15.2±0.32	1.179±0.21
F8	0.526±0.21	0.61±0.14	27.14±0.29	14.98±0.21	1.711±0.33

*All values are expressed as mean ±SD, n=5; **All values are expressed as mean ±SD, n=20

Table: 7 Physical parameters of Tablets of Telmisartan prepared by Solid Dispersion

Batch code	Wight variation(mg)**	Thickness (mm)*	Hardness (Kg/cm^2)**	Friability (%) **	In-vitro disintegration time (sec)***	Assay (%)*
F1	351.1±0.36	4.35±0.23	4.25±0.16	0.56±0.11	56±0.17	98.14±0.21
F2	353.5±0.39	4.33±0.15	4.27±0.31	0.54±0.12	55±0.22	99.02±0.33
F3	352.2±0.15	4.36±0.34	4.25±0.33	0.52±0.21	50±0.32	100.5±0.12
F4	353.4±0.30	4.34±0.22	4.30±0.30	0.61±0.18	58±0.35	98.91±0.27
F5	354.2±0.25	4.37±0.18	4.28±0.21	0.58±0.25	54±0.25	99.25±0.33
F6	350.1±0.14	4.34±0.13	4.26±0.17	0.55±0.19	48±0.30	100.9±0.26
F7	352.6±0.26	4.38±0.23	42.31±0.19	0.63±0.14	63±0.27	98.92±0.39
F8	351.7±0.32	4.36±0.16	4.29±0.13	0.60±0.13	61±0.13	101.05±0.11

*All values are expressed as mean ±SD, n=5; **All values are expressed as mean ±SD, n=20; ***All values are expressed as mean ±SD, n=10.

Physical parameters for all the Tablets formulation of Telmisartan were found to be within the accepted limits and batch no F6 and F8 have superior flow property and compressibility then other formulations.

Drug Release Profile of Telmisartan in 0.1N HCl

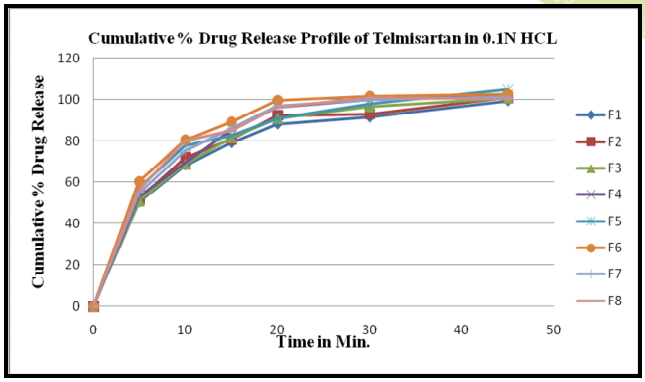


Figure: 7 Drug Release Profile of Telmisartan in 0.1N HCl

Statistical Analysis

As Described earlier there are 4 Factors: A, B, C, D and Reduced 2FI Model was applied for Statistical analysis and Cumulative % Drug dissolution after 20 min in both the medium was selected as constrain for statistical analysis.

Table: 8 Different Batches and respective Cumulative % Drug Dissolution after 20 min

Batch	A = Meglumine (mg)	B = Poloxamer 188 (mg)	C = Polyplasdone XL 10 (mg)	D = SSG (mg)	Response 1*
F1	15	5.5	8	5	85.35±0.13
F2	40	5.5	8	20	94.35±0.13
F3	15	18.5	8	20	91.7±0.12
F4	40	18.5	8	5	92.98±0.26
F5	15	5.5	18	20	87.78±0.17
F6	40	5.5	18	5	93.97±0.34
F7	15	18.5	18	5	89.43±0.15
F8	40	18.5	18	20	96.91±0.3

* n = 12; Response 1 = % Drug Release in 20 min in 0.1N HCl

Response 1 = % Drug Release in 20 min in 0.1N HCl

Transform: Power **Lambda:** 2.22

Constant: 0

Final Equation in Terms of Actual Factors:

(% Drug Release in 20 min in 0.1N HCl) 2.22 =

+15978.18004

+139.1979773 * Meglumine

+238.154388 * Poloxamer 188

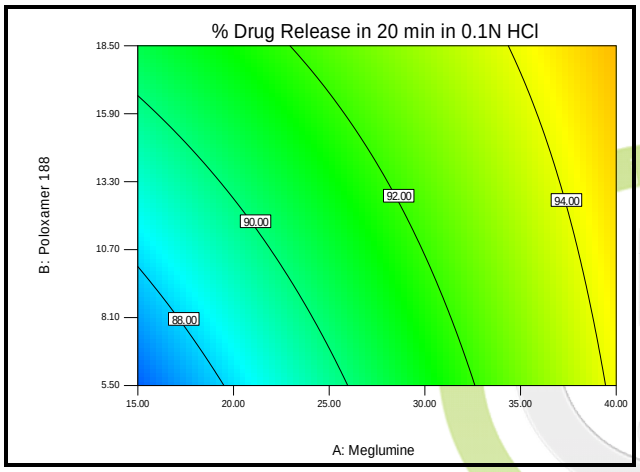
-59.90442357 * Polyplasdon Xl 10

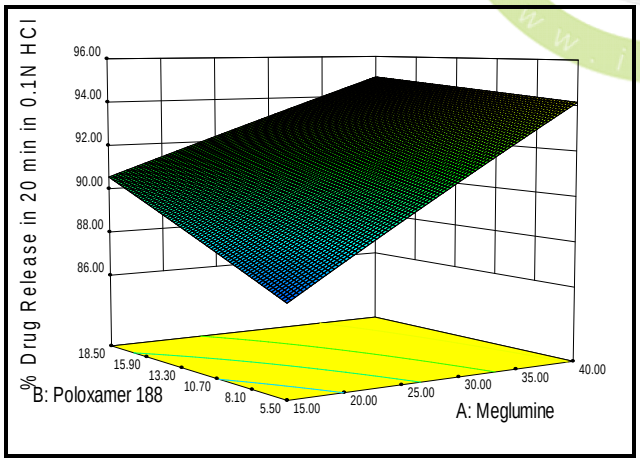
+82.4576495 * SSG

-5.064668082 * Meglumine * Poloxamer 188

+4.047285047 * Meglumine * Polyplasdon Xl 10

Contour plot and 3D Surface graph of % Drug Release in 20 min in 0.1N HCl





Optimization

The goal was to select the formulation which require minimun amount of Meglumine as well as Poloxamer 188 and gives maximum drug release. Among N number of formulations the following 3 is best suited for our purpose.

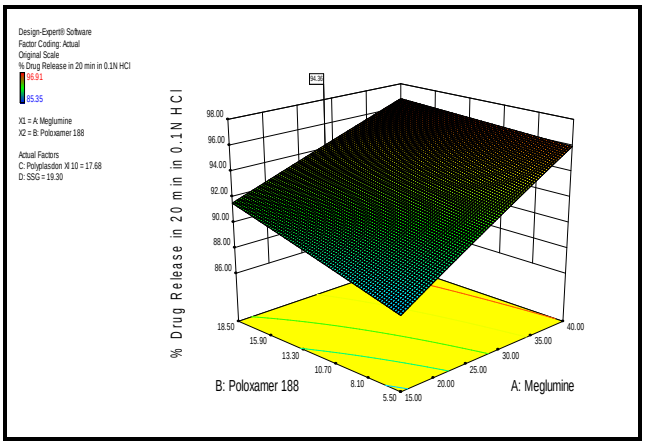


Table: 9 Optimized batch

Solid Dispersion based Approach	F9	F10	F11	F12
Meglumine	30.00	30.00	28.15	27.04
Poloxamer 188	18.50	17.50	15.50	17.50
Polyplasdon Xl 10	17.97	15.73	16.68	18.97
SSG	20.00	20.00	19.30	18.50
% Drug Release in 20 min in 0.1N HCl (predicted)	94.17	94.03	94.36	95.57
% Drug Release in 20 min in 0.1N HCl (Obtained)	94.87 ±0.30	93.83 ±0.19	95.36 ±0.26	95.82 ±0.30
Desirability	0.82352	0.77924	0.82042	0.89352

Among these the third formulation was found to be appropreate because it contain less amount of Meglumine to give maximum drug release in 20 min.

Release rates of F9, F10, F11 and F12 were statistically compared to those obtained from marketed product. With reference to marketed product release rates, F9 and F11 showed insignificant difference (P>0.05), suggested that systems provided comparable Telmisartan release rate with marketed product. The Results also indicates that F10 and F12 systems provide better Telmisartan release profile compared to marketed product.

Table: 10 Comparison of the Drug release profile of Innovator's and optimized Formulations

Sr. No.	Time (min)	% Cumulative Drug Release				
		Innovator	**F 9**	**F 10**	**F 11**	**F 12**
1	0	0	0	0	0	0
2	5	54.18±0.05	65.18±1.62	64.18±1.31	64.82±1.62	59.68±2.62
3	10	69.45±0.83	69.45±1.93	70.45±1.31	79.45±2.36	72.45±1.83
4	15	80.79±0.05	82.73±2.84	80.35±3.28	82.74±1.62	83.38±3.28
5	20	98.67±2.83	98.73±1.62	94.48±3.28	96.63±2.83	98.34±3.28
6	30	98.55±1.62	99.96±2.83	95.53±0.05	97.23.28	99.89±2.83
7	45	100.36±1.69	101.54±1.31	103.54±1.62	103.89±1.82	100.59±2.62

*Values are mean ±S.D of n=10

Table: 11 f_2 and f_1-values from drug release data of Test formulations vs. reference

Sr. No.	Comparison	f_2-value	f_1-value	Similarity of Ref. & Test
1	Reference vs. F9	58.36	4.49	Accept
2	Reference vs. F10	67.28	7.43	Accept
3	Reference vs. F11	61.62	4.55	Accept
4	Reference vs. F12	68.79	2.47	Accept

STABILITY TESTING OF OPTIMIZED BATCH

Table: 12 Results of Accelerated stability testing (3 month)

Results of Accelerated stability testing (3 month)					
Condition (1)		40ºC±2ºC/75%RH±5%RH			
Batch No.		F 9, F 10, F 11, F12			
	Initially	F 9	F 10	F11	F 12
Physiological Parameter*					
Morphology	+++	+++	++	+++	+++
Hardness (kg/cm^2)	4.6	4.2	4.1	4.1	4.3
Disintegration time(sec)	19	18	22	19	20
Drug Content					
% Potency	99.75	98.57	98.48	98.26	99.02
In Vitro drug release					
Time in min	**Initially**	**F 9**	**F 10**	**F11**	**F 12**
0	0	0	0	0	0
15	93.25±1.63	92.73±1.39	90.38±3.28	92.73±0.05	93.38±3.28
20	98.36±1.62	99.73±0.03	94.38±1.62	96.73±2.83	94.38±1.39
30	101.23±1.52	99.96±2.83	100.53±0.05	102.23.28	99.89±2.83

*+++ = No Change, ++ = Slight change + = moderate Change

Results of Accelerated stability testing at 40ºC±2ºC/75%RH±5%RH for 3 month showed that all the Optimized Batches showed good Physiological Property, Morphology, adequate Drug content, and similar Drug Release approximately same as of zero day even after 3 months.

CONCLUSION

The present study was undertaken with an aim to formulate and evaluate immediate release tablets of Telmisartan using Combined Technique of Solubilization for increasing the dissolution rate of poorly soluble drug, by using Meglumine, Poloxamer 188, PVP K 25, PolyplasdoneXL-10 and Sodium Starch Glycolate in different concentration. From the results of Preformulation study Dug: Polymer ratio of 1:2 was selected for solid dispersion preparation. The granules of all the Formulations were found to be having good flowability and compressibility. The tablets were having proper Hardness, uniform weight and *In-vitro* Disintegration time was between 40 to 70 second. The Dissolution pattern of optimized formulations F9, F10, F11, F12 were compared with innovator's product and F9, and F11 have similar release profile as marketed product while F10, F12 have shown better drug release profile and both of them were found to be superior to innovator's product; also they showed pH independent solubility and were found to be more stable then marketed Product.

REFERENCES

1. Chang RK, Guo XF, Burnside BV, and Couch YR, "Fast dissolving tablets." Pharmaceutical Technologies, 2000, 24(6), 52-58.
2. European Pharmacopoeia. Ed. 4, Defination of Immediate release tablet. Supplement 4.2; 2002. pp. 2435.
3. Debjit BA, Jayaka KB, Sampatk. NV, "Design And Characterization of Fast Dissolving Tablet of Telmisartan", International Journal of Pharmaceutical Research. 2009, 1(1), 31-40.
4. Pharmaeurope, "European Directorate for the quality of medicine", 1998, 10(4), 547. www.pheur.org.
5. European Pharmacopoeia. Ed. 2, Dissolution media for Telmisartan Tablet. Supplement 4.2; 2002. pp. 243
6. Indian Pharmacopoeia. Dissolution media for Immediate release tablet of Telmisartan Tablet. Supplement 5.3; 2010. pp. 368
7. Liberman HA, and Lachman L, Pharmaceutical Dosage Forms-Tablet, Volume I, Marcel Dekker Inc., New York, 1989, pp. 11-14, 136, 198-199, 210- 212, 99-101, 159-160, 387-391.
8. Rai VK, Pathak NS, Bhaskar R, Nandi BC, "Optimization of Immediate release tablet of Raloxifene hydrochloride by wet granulation method" International Journal of Drug Research, 2009, 1(1), 51-54
9. Pani NR, Nath LK, "Optimization and Formulation of Immediate Release Tablet of Nateglinide by Using 3^2 Factorial Design" International Journal of pharmaceutical Technology, 2010, 2 (3), 1978-1984.
10. Suresh KM, Kausalya JR, Padmapriya SR, Anusha RN, Senthilnathan CB, "Solubility and dissolution enhancement of Telmisartan using various techniques." International Journal of Pharmaceutical Technology and Research. 2011 3(3), 1737-1749.
11. Ping Li A., Luwei Zhao B, "Cosolubilization of non-polar drugs in Polysorbate 80 Solutions" International Journal of Pharmaceutics, 2002, 24 (4), 211-217.
12. Kausalya JM, Sekar AV, Chellan KG, "Immediate release tablets of Telmisartan using superdisintigrants-formulation, evaluation and stability studies" Chemical Bulletin, 2008; 26(4), 375-379.
13. Phuong Ha LT, Lagoviyer YD, "Enhanced solubility study of Telmisartan using different Solubilization techniques" International Journal of Pharmaceutical Science, 2010, 2(2), 46-48.
14. Kurade VN, Bogner RH, Wilkosz MF "Solubility enhancement of Nimesulide and

Telmisartan by solid dispersion technique" US Pharmacist. 2002, 27(1), 34-43.
15. Melgardt MG, Acarturk HF, "The effect of some natural polymers on the solubility and dissolution characteristics of Telmisartan" International Journal of Pharmaceutics, 2005, 2(1), 18-26.
16. Shukla AM, Masuda YS, Kajiyama AG, "Improved solubility study of Telmisartan using different solubilization techniques", International Journal of Pharmaceutics, 2010, 2(2), 46-48.
17. Pratikh N, Sekar V, and Raghavan A, "Immediate Release Tablets of Telmisartan Using Superdisintegrant-Formulation, Evaluation and Stability Studies" International Journal of Pharmaceutics. 2007, 25(2), 175-177.
18. Maria AR, Silva PI, Robson AS, and Ruben DS, "Hydrochlorothiazide Complexation Preparation by Three Different Methods" Journal of Molecules 2011, 11(6), 482-499.
19. Vasanthakumar SR, Vijaya RD, "Immediate Release Tablets of Telmisartan Using Superdisintegrant" Pharmaceutical Bulletin, 2008, 56(4), 575-577.
20. Jogani PD, Bhowmik DS, and Balapatel AL, "Fast Dissolving Tablet of Telmisartan by using Superdisintegrants- Crosspovidone, Ac-de-sol, and sodium starch glycolate" International Journal of Pharmaceutical Science, 2010, 15 (3) 98-102.

