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Research Article

Development and Evaluation of Solubility Enhanced Tablets Containing Poorly Soluble Drug Telmisartan

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ABSTRACT

Telmisartan is an oral anti-hypertensive drug and it comes under angiotensin-II receptor blocker. Telmisartan is highly lipophilic and practically insoluble in water and it shows low dissolution profile and poor absorption. The solubility of telmisartan in aqueous solution is strongly pH dependent. In order to improve the solubility and dissolution rate of telmisartan, ten different formulations were prepared by changing the concentration of NaOH and PVP K-30. The solubility enhanced telmisartan tablets were prepared by wet granulation method using NaOH as alkalizer, PVP K-30 as binder (acidic), sodium starch glycolate as super disintegrant and microcrystalline cellulose as diluents. Different formulations were tested for physical inspection, thickness, uniformity of weight, hardness, friability, disintegration time, dissolution, assay, pH. Among them, formulation having concentration of 2.66% NaOH showed the best result (drug release 94.74% in 1 hour) comparing with other formulations. Telmisartan tablet showed high dissolution at high pH and dissolution was decreased with increased in concentration of binder (hardness).

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INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of administration (Nikam SP, 2011). Orally administered drug is completely absorbs only when they show fair solubility in gastric medium and such drugs show good bioavailability. As about 70% of the human body is made up of water, a drug must be soluble and thus possess an acceptable bioavailability level. The drug in the dosage forms is released and dissolves in the surrounding gastrointestinal fluid to form a

solution for easy absorption (Wairkar, S. M*et al.*, 2013).

Tablets are the solid dosage form which contains one or more medicament. They are used for oral administration. Some tablets are swallowed whole or after being chewed. Tablets are generally solid, right circular cylinder, the end surface of which are flat or convex surface which are obtained by compression of uniform volume of powder or granules with the help of die and punches (IP 2010)**.** Conventional tablet has problem of low dissolution. Due to the low dissolution, it directly effect on bioavailability.

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired pharmacological response. It is the property of a solid, liquid, or gaseous chemical substances called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the maximum quantity of solute in a certain quantity of solvent at specified temperature and pressure (Mofizur Rahman, Md *et al*.)**.**

The process of solubilisation contains three steps (Pawar, A R *et al*., 2012)

-The separation of the molecule of the solvent to provide space in the solvent for solute.

- The breaking of intermolecular ionic bonds in the solute.

- The interaction between the solvent and the solute molecule or ion.

Drug absorption from the GI tract can be depended by several of factors most significant contributor being poor aqueous solubility and poor membrane permeability of the drug molecule. When administered an active agent orally it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GIT to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing of solubility and dissolution rate of poorly water soluble drugs. The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability. As for BCS class II & IV drugs have low dissolution, so increasing the solubility in turn increase the bioavailability for BCS class II & IV drugs (Pawar, A. R. *et al*., 2012).

BCS classification (Patel, P.A., *et al*., 2010)

Class I	**Class II**
High permeability High solubility	High permeability Low solubility
Class III	**Class IV**
Low permeability High solubility	Low permeability Low solubility

USP Solubility criteria (USP 2010)

Descriptive term	**Part of solvent required per part of solute**
Very soluble	<1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10000
Practically insoluble	>10000

Hypertension is also known as high blood pressure, is a long term medical condition in which the arteries blood pressures are persistently elevated. High blood pressure is classified as primary (essential) or secondary high blood pressure. Among 90-95% of cases are primary, defined as high blood pressure due to nonspecific lifestyle and genetic factor. Lifestyle factor that increase the risk include excess salt, excess body weight, smoking and alcohol. The remaining is secondary high blood pressure, defined as high blood pressure due to an identifiable cause such as chronic kidney disease, narrowing the kidney arteries, an endocrine disorder or the use of the birth control pill. There are many type of drug used in hypertension. Mainly used drugs are β-blocker, calcium channel blocker, diuretics, angiotensin converting enzyme inhibitor, angiotensin II receptor blocker etc. Telmisartan is Angiotensin

II receptor antagonist used in the treatment of hypertension (Lee M Huang *et al.*, 2002)**.**

Advantages of dissolution enhanced telmisartan tablet (Patel, P.A., *et al*., 2010)

- Rapid onset of drug action
- Better patient compliance
- Reduce the chance of dose dumping
- Enhanced bioavilability
- Reduction or avoidance of adverse side effect
- Reduction in overall healthcare cost

MATERIAL and METHODS

Raw Material

Telmisartan reference standard, API and PVPK-30, MCCP 101 were obtained from Time Pharmaceutical Laboratory Pvt. Ltd. Mukundapur, Nawalparasi, Nepal as a gift sample. Talcum powder (Nike Chemical India), Magnesium Stearate (Loba chemical Pvt. Ltd, Mumbai), Aerosil, Microcrystalline cellulose, Sodium Starch Glycolate, Sodium Hydroxide (Thermo Fisher Scientific India Pvt. Ltd.) and Hydrochloric acid (Thermo fisher scientific India Pvt. Ltd) were purchased from local market. Market product was purchased from local retail pharmacy.

Preparation of Calibration Curve

UV-visible spectrophotometric method of analysis was developed. First of all stock solution of concentration 100µg/ml was prepared in a 0.1N HCl. From this solution, other solutions of concentration (2, 4, 6, 8, and 10) µg/ml were prepared with appropriate dilution. Finally, absorbance of these solutions was determined by UV spectrophotometry at the λmax 253 nm. (Bharathi, A. *et al.*, 2014).

Formulation of tablets

Ten different batches of telmisartan tablets having label strength of 20 mg were prepared by wet granulation technique. The products were coded as F1 to F10. The details of formulations of telmisartan tablets are shown in below**.**

S.N.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1	Telmisartan	20	20	20	20	20	20	20	20	20	20
2	MCCP 101	120	119	118	116	117	116	114	112	112	108
3	PVP K-30	0	0	0	0	1	2	4	6	4	6
4	NaOH	0	1	2	4	2	2	2	2	4	6
5	SSG	8	8	8	8	8	8	8	8	8	8
6	Magnesium state	1	1	1	1	1	1	1	1	1	1
7	Talc	1	1	1	1	1	1	1	1	1	1
8	Water	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
	Total (mg)	150	150	150	150	150	150	150	150	150	150

Finally, the dissolution profile of formulated telmisartan tablets were compared with marketed telmisartan tablet.

Pre-compression evaluation

The assessments involved in the pre-compression studies are moisture, bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

Moisture

Moisture of granules was checked by IR moisture balance. Powder was placed in plate of machine and then heated up to 105 degree and reading was noted (Chauhan, K., *et al*., 2012).

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The

accurately weight powder blend was taken in the funnel. The height of the funnel was adjusted in such way the tip of the funnel just touch the apex of the powder blend. The powder blend should allow to flow through the funnel freely on to the surface. The diameter of powder cone was measured and calculated angle of repose by using the following equation (Sirisha, Y. *et al*., 2013)

Angle of repose, $\tan \theta = h/r$

Bulk density and tapped density

Both loose bulk density (LBD) and tapped bulk density was determined. A powder blend was accurately weighed and shaked to break any agglomerates formed, was introduced in to measuring cylinder. After that the initial volume was noted and then we started the bulk density apparatus machine. After 100 tapping we noted the final volume. We continued Tapping until no further change in volume. LBD and TBD were calculated by using following formula (Sirisha, Y., *et al.,* 2013).

LBD=weight of powder blend/untapped volume of packaging

TBD=weight of powder blend /tapped volume of packaging

Compressibility index

The compressibility index of the powder blend was determined by Carr's index. It is a simplest test to evaluate the LBD and TDB of powder and the rate at which it packed down.

Carr's index= TBD-LBD/TBD*100

Post compression evaluation

The assessments involved in the post compression study are physical inspection, evaluation of uniformity of weight, friability, hardness, disintegration study, dissolution study and pH study.

Visual Inspection

The shape, size and color of different formulation were examined visually. The diameter and thickness of 6 tablets from each formulation was measured using Vernier-caliper and the average was taken and standard deviation was calculated (IP 2010)**.**

Uniformity of Weight

Twenty tablets of each formulation were weighed individually using a digital balance. The average weight was determined and percentage (%) deviation of each individual tablet was calculated using the formula below.

%deviation= [individual weight of tablet-average weight of 20 tablet] / average weight of 20 tablets × 100

Hardness

The strengths of tablets were determined individually with Monsanto hardness tester. Six tablets of each formulation were taken. Each tablet was placed between the anvils until the tablets break and then pressure required to break the tablet was recorded. The average tablet hardness and standard deviation were calculated (Patel, P.A., *et. al*., 2010)**.**

Friability test

Twenty tablets from each batch were examined for friability using Roche friabilator and the equipment was run for 100 revolutions at 25 rpm. The tablet was taken out, deducted and reweight and percentage friability was calculated (Patel, P.A., *et. al*., 2010)**.**

%friability= (loss in weight/initial weight)*100

Assay

For determination of assay, 20 tablets were weighed and powdered. The powder equivalent to 20 mg of telmisartan was weighed and dissolved in 100ml 0.1N HCl and then filtered through the watt man filter paper and withdraw 1.5 ml from filtrate solution and make volume up to 50ml and analyze the drug content by measuring absorbance at 253 nm (Bharathi, A. *et al*., 2014)**.**

Disintegration test

The disintegration test was determined in distilled water at 37 ± 2.0^0c using disintegration test apparatus. Six tablets from each formulation were placed in disintegration apparatus and then noted the time for disintegrate the tablet (Bharathi, A. *et al*., 2014)**.**

Dissolution test

In vitro release profile for each formulation was performed using USP Type II dissolution apparatus. Sample equivalent to 20 mg of Telmisartan was added to 900ml of 0.1 N Hydrochloric acids and stirred at 50 rpm. The absorbance of the samples was measured at λmax 253nm after suitable dilution, using appropriate blank. Results of in vitro drug

release studies obtained from absorbance data were shown graphically as cumulative percentage drug released versus time (Bharathi, A. *et al.,* 2014)**.**

pH study

pH of each formulation was determined by using pH meter.20 tablets were powdered in mortar and pestle. And then it was poured into 60 ml distilled water (5% w/v) and placed pH meter in solution and measured the pH of solution (Al-Sarraf, M. A., *et al.,* 2014)

RESULT & DISCUSSION

Calibration curve

Standard calibration curve was obtained by plotting the values of the concentration versus respective absorbance for each of concentration from 2 to 10µg/ml of telmisartan. The analysis for linearity showed that the solvent used in estimation of telmisartan and in-vitro release are suitable and have no interference while taking absorbance in UV-Visible spectrophotometer. From the calibration curve, the correlation coefficient (R^2) values and regression equation of telmisartan standard in 0.1N HCl was found to be0.996

Pre-compression evaluation

Moisture

Moisture of all formulations was found to be below 1%.

Tapped density

Tapped density of 10 different formulations was determined and it was found that the value was between 0.48 & 0.60. The formulation F2 had minimum tapped value where formulation F5 had maximum value of tapped density.

Angle of repose

The angle of repose of powdered varies with formulation ranging from 25 to 28.67.That indicates that all formulation has good flow property.

Carr's index

Carr's index of 10 different formulations was found to be in the range of 15.56 to 18.85.

Post-compression evaluation

Physical Inspection

The different formulation of telmisartan tablets were examined in their physical aspects, namely, shape and color. On physical inspection, all examined formulated products were found to be white in color and round in shape without any defects.

Thickness test

It was found that the thickness of telmisartn tablets varies with formulations ranging from 3.14 to 4.93.

Uniformity of Weight

The weight variation of ten different formulations of telmisartan tablets were determined and observed result are shown in figure 1. Among the ten formulations it was found that the formulation F1had a minimum weight whereas formulation F7 had a maximum weight. The maximum SD in average weight was seen in formulation F3 (4.91) while formulation F7 (2.56) had a minimum SD value. It was observed that weight variation of all the brands ranged within the limit of ±7.5% of respective average weights.

Hardness Test

The observed value of hardness test is presented in Figure 2. Formulation F1 had a minimum hardness of 5.12 Kg/cm² while formulation F8 had a maximum hardness value of 9.5Kg/cm².

Effect of hardness on dissolution

The relationship between hardness and dissolution was found to be inversely proportional. We used PVP K-30 in increasing concentration the hardness of the tablet was increased but the dissolution was decreased. In formulation F5 hardness was found to be 7 kg/cm² whose dissolution was 82%. But when hardness was increased from 7 to 9.5 kg/cm² in formulation F8, the dissolution value was decreased into 68.85%.

Friability Test

The calculated friability values of all formulations were presented in Figure 3. Friability was observed in the range of 0.18 to 0.34. Formulation F10 had minimum friability value of 0.18 and formulation F1 had a maximum friability value of 0.34. Hence, the friability values of all products met the specification i.e. not more than 1%.

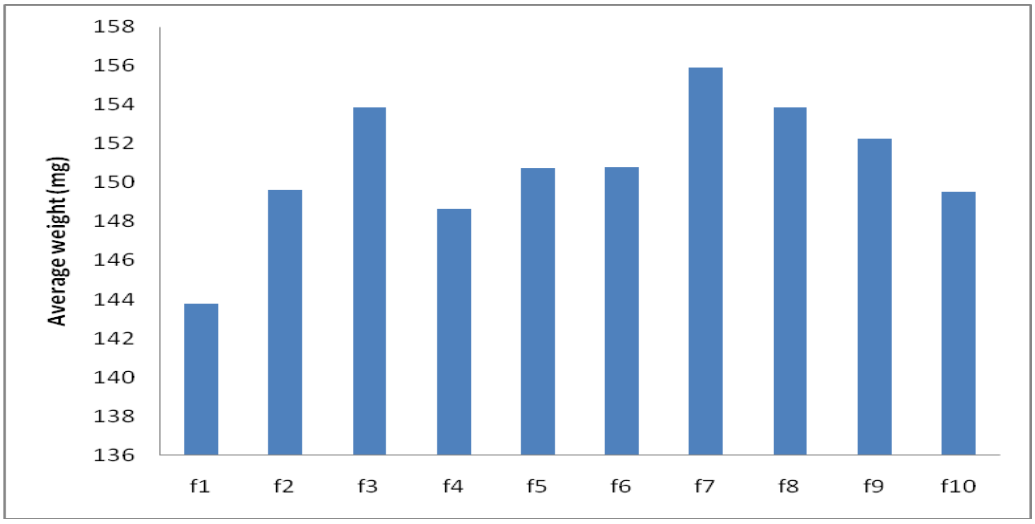

Fig.1: Average Weight of Different Formulations of Telmisartan Tablets.

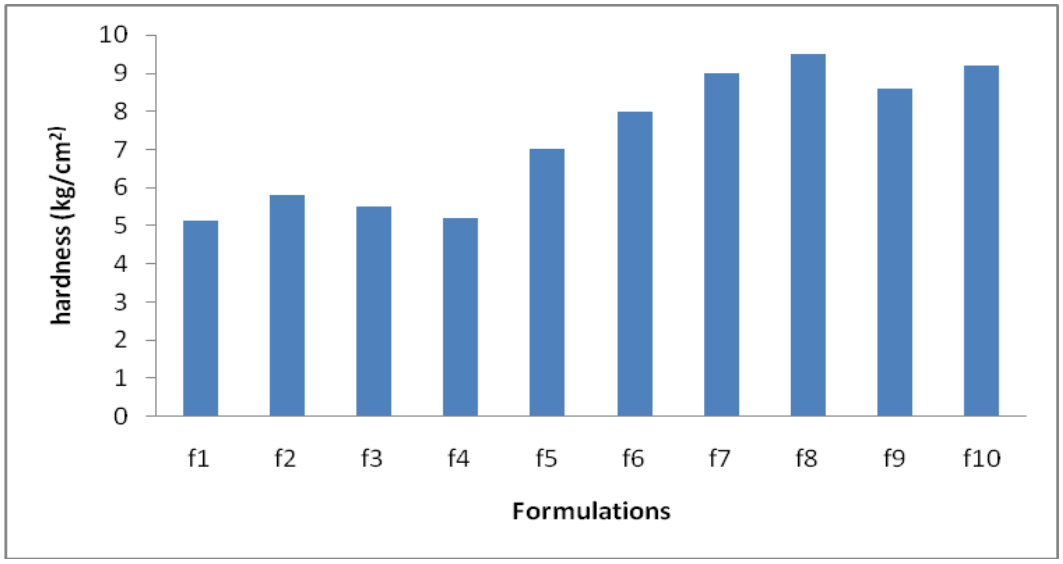

Fig. 2: Hardness of Different Formulations of Telmisartan Tablets.

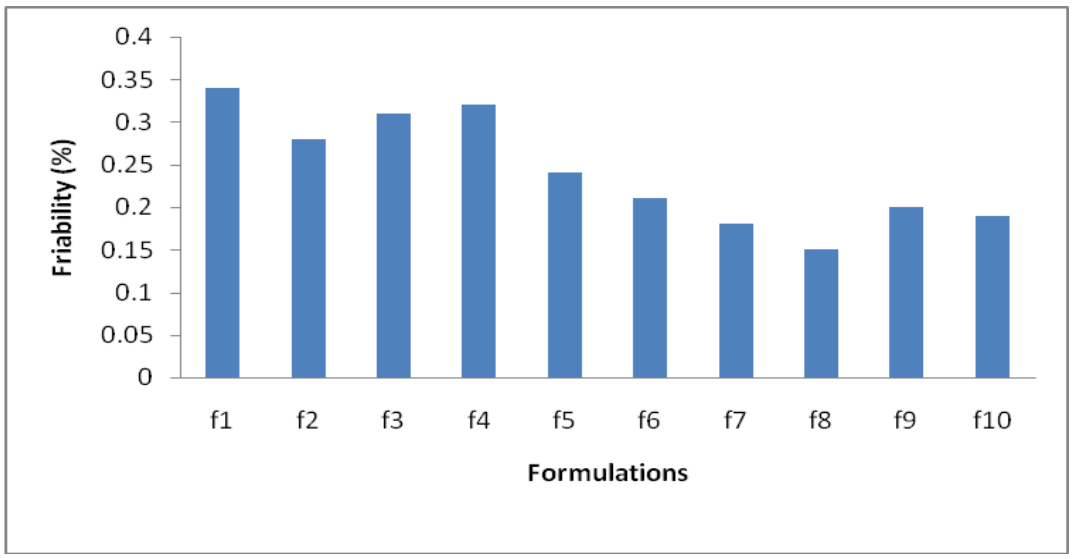

Fig. 3: Friability (%) of Different Formulations of Telmisartan Tablets.

Assay

The results of assay are presented in Figure 4. According to the result, formulation F4 had maximum assay value 103.78% and formulation F1 had a minimum value of 91.34%. The results obtained from the assay of ten formulations of telmisartan tablets showed all Formulation had the value within the IP specification of limit of 90-110%.

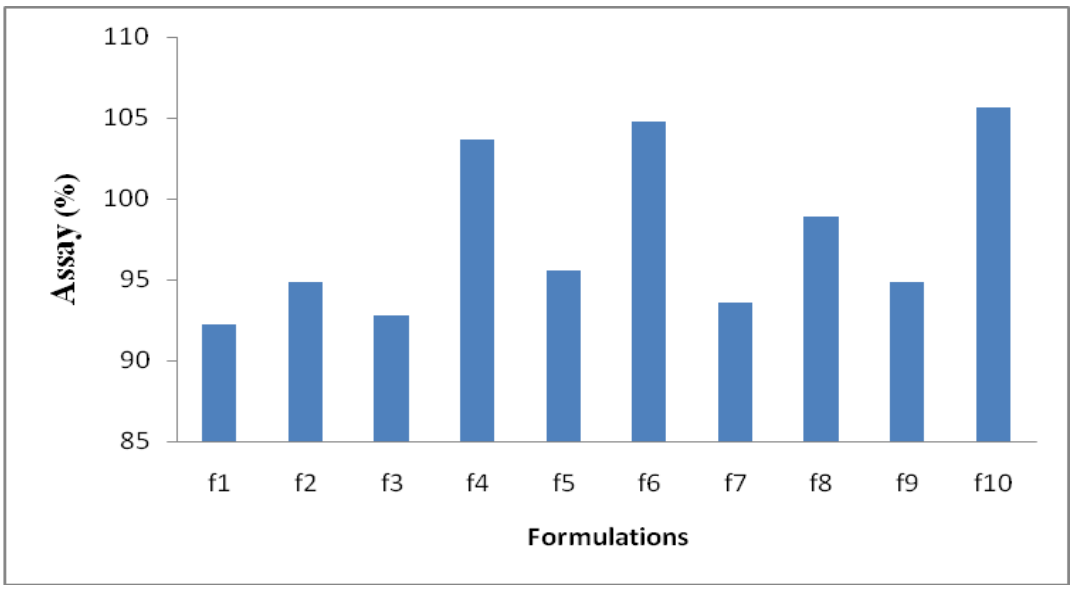

Fig.4: Assay of Different Formulations of Telmisartan Tablets

Dissolution Test

The dissolution value of different formulation of telmisartan tablets are given in Figure 5. The result of the study revealed that drug release % of formulation F1 had a lesser value (39.77%) while formulation F4 had a maximum value (94.74). All the formulation except F1 and F8 passed the limit of 70 to 130 which is given by IP 2010. Due to the low pH, formulation F1 and F8 weren't passing the limit. Formulation F4 showed the better dissolution than marketed product Sartel (Intas pharmaceutical) because formulation F4 had more pH than marketed product.

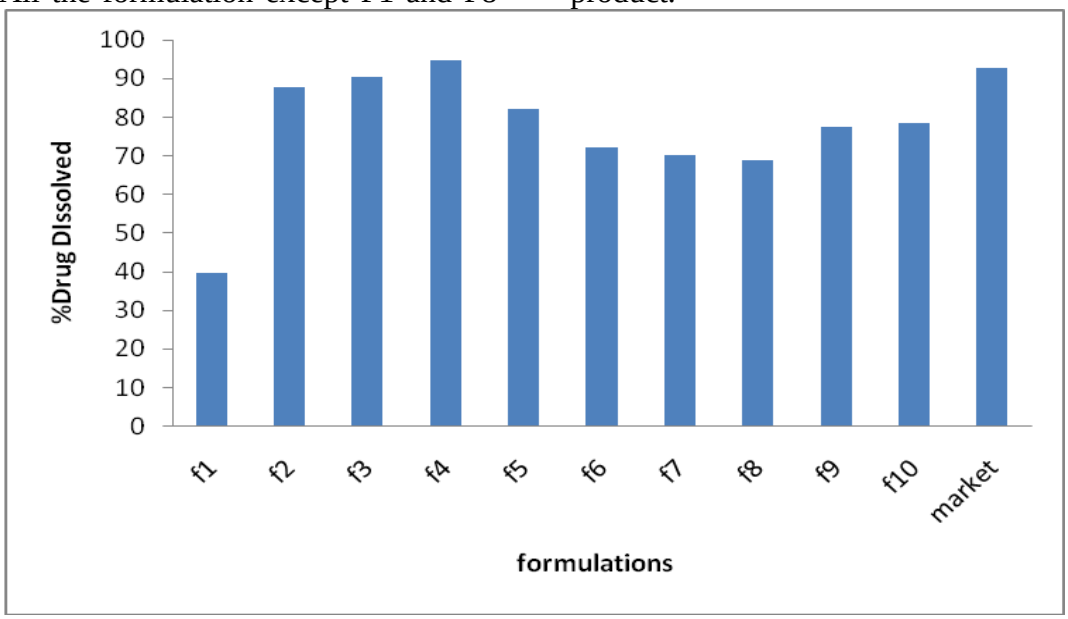

Fig.5: Drug release of Different Formulations of Telmisartan Tablets

Disintegration Test

It was found that disintegration time of telmisartan tablet varies with formulation ranging from 2.16 to 20.25 minutes. The result of DT is given in Figure 6. Formulation F8 had maximum disintegration value where F4 had minimum value. The disintegration time of F8 was out of limit due to the high concentration of binder PVP K-30 in formulation.

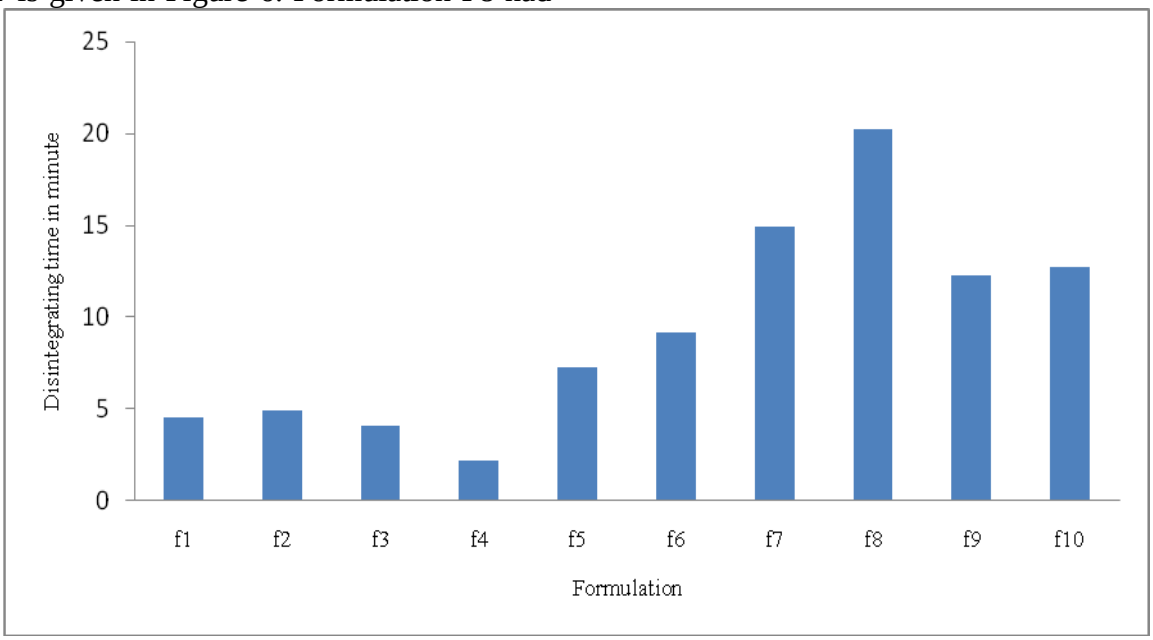

Fig.6: Disintegration time of Different Formulations of Telmisartan Tablets

pH Study

The pH values of all formulated telmisartan were presented in Figure 7. pH values were observed in the range of 7.2 to 11.4. Formulation F1 had minimum pH value while Formulation F4 had maximum pH value. Telmisartan is practically insoluble in pH between 3 to 9. Hence, all formulation except F1 and F8 are in the out of these limit. So they have good dissolution property.

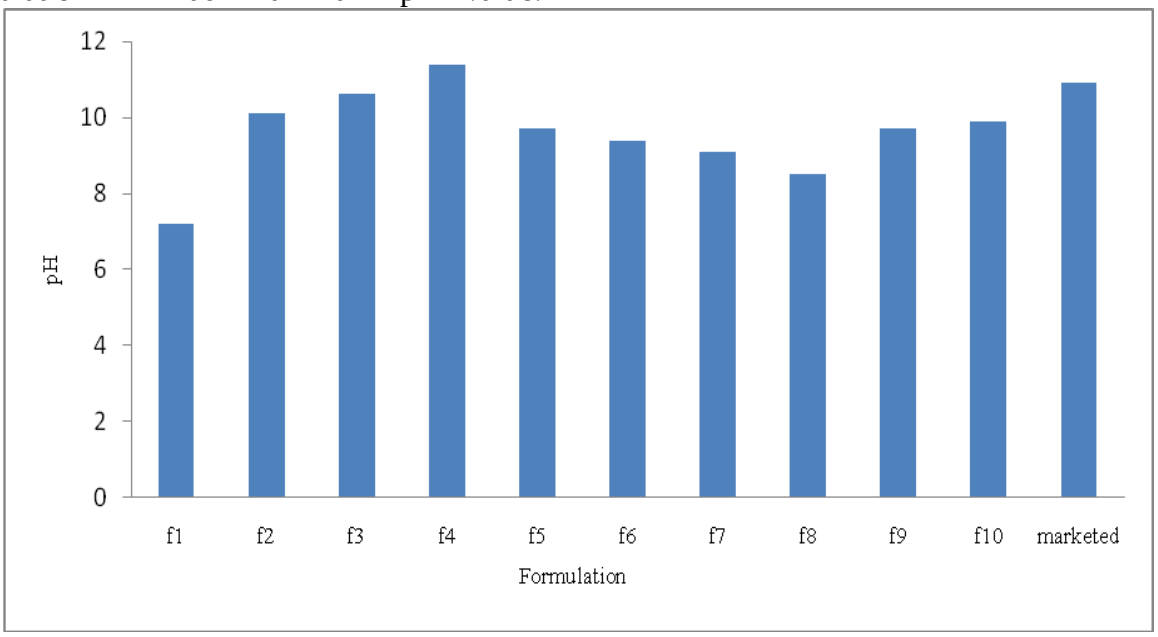

Fig.7: pH of Different Formulations of Telmisartan Tablets

Effect of pH on dissolution

The study clearly showing that, the pH of drug was directly proportional to dissolution. In formulation F1, pH was found to be 7.2 due to this it had very low dissolution. When the concentration of NaOH was increased from formulation F2 to F4, we found dissolution was also increased continuously and found to be maximum at highest pH. But when we added PVP K-30 in formulation F5 to F8, the dissolution value was found to be decreased because PVP K-30 was acidic in nature, hence it reduces the pH.

CONCLUSION

Telmisartan is commonly prescribed antihypertensive drug for the treatment of patient with hypertension. It is practically insoluble in water and pH range 3-9. It falls under the BCS class II that mean it has low solubility and high permeability. So the formulation of telmisartan is very challenging.

The granules of all formulation were found to be having good flow ability and compressibility. All formulation passed friability test, disintegrating test, assay and content uniformity test. Formulation F4 has higher dissolution value where concentration of NaOH is maximum and absence of PVP K-30. Other formulation except F1 and F8 passed the standard dissolution value provided by IP 2010.

Telmisartan tablet is practically insoluble in pH 3 to 9. Formulation F1 and F8 had pH 7.2 and 8.8 respectively. So, they didn't pass the criteria given by IP because they have pH below 9. All other formulations i.e. F2, F3, F4, F5, F6, F7, F9, F10 passed the IP limit and these all had pH above 9. Study also cleared it, when the concentration of NaOH was decreased dissolution value was also increased but when increased the value of PVP K-30 dissolution value was decreased. So, this study clearly said that the dissolution property of telmisartan is depending on the pH. NaOH is basic in nature and it increased the pH above 9 but in other hand PVP has pH (5%W/V) 3 to 7, hence it reduce the pH. In this way, NaOH increased the dissolution where PVP K-30 reduced the dissolution. In other hand, PVP K-30 is binder. Due to its binding property hardness of the tablet was increased with increase in concentration of PVP K-30. Formulation F8 had lower dissolution value not only due to its acidic nature but also due to its higher hardness value. Hence this study concludes that, the dissolution is directly proportional to pH (above 9) and inversely proportional to the hardness of the tablet.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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