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Formulation and Evaluation of Bio-adhesive Pulsatile Drug Delivery System of Telmisartan

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ABSTRACT

The main objective of this study was to formulate and evaluate of Bio-adhesive pulsatile drug delivery system of Telmisartan, an anti-hypertensive drug in order to achieve better therapeutic efficacy and patient compliance. The approach of combination of bio-adhesive pulsatile formulation is suitable for gastro retention and time specific drug delivery. The study was carried by preparation of fast disintegrating core tablet followed by incorporation of core tablet to design bio-adhesive pulsatile tablet by press coating. The press coated tablet was prepared with the polymersethyl cellulose and carbopol. The formulation was evaluated for precompression and post compression parameters, lag time, drug release and bio-adhesive study. All evaluation parameters were found within limits. The lag time expected for this disease was 8 hours as need of drug release for this disease was more likely to act in early morning. The 8 hour lag time was obtained in optimized formulation which has shown muco-adhesion for the same period. Thus bio-adhesive pulsatile drug delivery system could be the best precautionary alternative for the drugs having maximum absorption in stomach and used for diseases which follows circadian rhythm.

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INTRODUCTION

In the recent era, Novel Drug Delivery System (NDDS) has been growing at a greater rate due to its demand in the pharmaceuticals. The NDDS has changed a lot in the last five to ten years, as it includes technological evolution in the pharmaceutical industry (Liu *et al.*, 2016; Chaudhary *et al.*, 2015). In the area of gastro-retentive drug delivery system, recent approache was bio-adhesive and floating drug delivery system which include gastro-retension by using various bio-degradable polymers for bio-adhesion. These dosage forms are useful for drugs having better absorbtion in stomach or when local delivery required in stomach (Gröning and Heun, 1984; Phanindra *et al.*, 2013). In chronopharmacotherapy, the drug release was designed as per circadian rhythm. Pulsatile drug delivery system is much more dependent on the diseases which following circadian rhythm as it is having specific applicability for those disease like bronchial asthma, myocardial infarction, arthritis, peptic ulcer, diabetes mellitus, lipedemic disease, hypertension (Janugade *et al.*, 2009a; Bahul *et al.*, 2009; Nikalje *et al.*, 2012). In case of pulsatile

drug delivery system drug is released after a predetermined lag time (depends on disease) which is always more than the gastric empting time. Thus, in such drug delivery system, most of the time drug is released in intestine only, which is one of the limitations for drug such as irbesartan, telmisartan etc which have better absorption in stomach (Janugade *et al.*, 2009b). If pulsatile drug delivery system is designed for such drugs, it leads to poor drug absorption in intestine compared with stomch due to its pharmaco-kinetic properties. So to overcome this problem combination of conventional pulsatile drug delivery system with bio-adhesive drug delivery system is much preferred. Dosage form designed by bio-adhesive-pulsatile drug delivery system will release drug only in stomach as required but with predetermined lag time as per disease. In the present work bio-adhesive-pulsatile drug delivery of Telmisartan, an antihypertensive drug was formulated which can be taken before bed time (9 pm) and capable of releasing drug after predetermine time delay (8 h) and can be characterized by proportioning drug concentration in the early morning hours when free cholesterol levels are more prevalent.

MATERIALS AND METHODS

Telmisartan was purchased from Swapnroop Drug and Pharmaceuticals, Aurangabad, India. Sodium starch glycolate, Microcrystalline cellulos, Polyvinylpyrrolidone and Ethyl cellulose were purchased from Molychem, Mumbai India, Magnesium stearate purchased from Hilab chemicals, India. All chemicals used were of analytical grade.

Preparation of Core Tablet (CT)

Core tablet of Telmisartan with dose 40 mg was prepared by direct compression method using ingredients: polyvinylpyrrolidon (10 mg), magnesium stearate (1 mg), sodium starch glycolate (varying quantity of 6/8/10/12/14 mg) and microcrystalline cellulose with adjusting a tablet weight of 200 mg. All ingredients were weighed accurately and mixed well for 15 min. The resultant powder mixture was then compressed into tablets using Rotary Compression Press (Cadmach) with 8 mm standard concave punch. The weight variation of the tablets was determined taking weight of 20 tablets using electronic balance. Hardness, thickness, friability and disintegration time (in water) of tablets were studied by Monsanto hardness tester, vernier caliper, Roche friabilator and disintegration test apparatus, respectively. (Satani *et al.*, 2014)

Formulation of Bio-adhesive Pulsatile Tablet (BPT)

The optimized formulation of core tablet (sodium starch glycolate: 14 mg)was used for the preparation of BPT. The formulation of BPT is as given in Table 1. Bio-adhesive pulsatile tablet was prepared by placing 40% bio-adhesive pulsatile release layer (Polyvinylpyrrolidone, Ethy ellulose, Carbopol) in 12 mm die and core tablet was placed on it. Then, the remaining quantity were added in the die so as to cover core tablet and finally compressed by direct compression method by Rotary compression Machine using 12 mm die and punch set.

Pre-compression evaluation of granules by bulk density, tap density, Carrs index, Hausners ratio and angle of repose

A 50 ml glass cylinder was weighed and filled with 30 ml of granules. The opening was secured with parafilm. The cylinder was gently reversed once and the powder was carefully levelled without compacting. Bulk volume was determined after one mechanical tap on a tap density tester (DolphinTM). Tap volume was measured after 2000 taps. Each analysis was repeated twice. Values of bulk density and tap density were used to calculate Carr's index and Hausners ratio. Angle of repose of the granules was determined by fixed funnel method (Sweetman, 2011).

Post-compression evaluation of tablets

The tablet weight variation and hardness (by Monsanto hardness tester) was obtained as per Indian Pharmacopoeia (Sweetman, 2011) and percent friability (by Roche friabilator) was determined as per United States Pharmacopoeia (Lachman *et al.*, 1986). Thickness of the tablets was determined by using vernier caliper.

Ex-Vivo mucoadhesion test

In the first study a tablet was fixed on glass box. To the upper glass slide mucus membrane was fixed, to it a thread was tied and the thread was passed down through a pulley. The length of the thread from the pulley to the pan was 12 cm. At the end of the thread a pan of weight 17 g was attached into which the weights can be added. The glass slide was placed on the tablet with weight (17 g) for 1 min.

The weight require to detach the tablet from the glass box (muco-adhesive strength) was determined. In the second study, the only change that was made was that the tablet was just placed and not fixed on glass box.

Time required to detach the tablet from the mucus membrane (adhesion time) was recorded (Government of India, Ministry of Health & Family Welfare, 1996; USP, 2006). The force of adhesion was calculated using following formula;

Table 1: Formulation of Bio-adhesive Pulsatile Tablet of telmısartan

Ingredients (mg)	Formulation Codes P1	P2	P3	P4	P5
Core Tablet	200	200	200	200	200
Magnesium Streate	6	6	6	6	6
Polyvinylpyrrolidone	30	30	30	30	30
Ethyl cellulose	282	197	282	282	141
Carbopol	197	282	282	141	282
Microcrystalline cellulose	85	85	_	141	141
Total Weight (mg)	800	800	800	800	800

Table 2: Precompression parameters of BPT

FC	Bulk Density (g / cc)	Tapped density (g / cc)	Compressibility Index (%)	Hausner's Ratio
P1	0.5089± 0.007	0.6694± 0.004	23.98± 1.1	1.32± 0.02
P2	0.5069± 0.006	0.706± 0.005	28.21± 1.3	1.39± 0.03
P3	0.5133± 0.008	0.6673± 0.005	23.08± 1.3	1.30± 0.05
P4	0.5091± 0.004	0.7202± 0.007	29.33± 1.2	1.41± 0.04
P5	0.6032± 0.005	0.8681± 0.008	30.53± 1.1	1.44± 0.06

FC: Formulation Code

Table 3: Post compression parameter of Bio-adhesive Pulsatie Tablet

FC	Weight (mg)	Thickness (mm)	Hardness (kg/cm^3)	Friability (%)	Adhesion Time (h)	Muco-adhesion Strength (g)	Force of Adhesion (N)
P1	800 ± 1.1	7.3 ± 0.02	7.2 ± 0.12	0.053 ± 0.02	8:10± 0.3	29.25± 1.8	2.86± 0.07
P2	801 ± 3.4	7.0 ± 0.02	7.5 ± 0.11	0.065 ± 0.02	8:30± 0.4	34.53± 2.3	3.38± 0.08
P3	800 ± 1.8	7.2 ± 0.20	7.1 ± 0.16	0.054 ± 0.01	8.50± 0.2	36.15± 2.7	3.54± 0.12
P4	802 ± 2.9	7.2 ± 0.10	7.3 ± 0.24	0.062 ± 0.03	9:05± 0.5	30.20± 3.2	2.96± 0.13
P5	801 ± 2.8	7.1 ± 0.11	7.3 ± 0.11	0.067 ± 0.03	9:30± 0.3	32.18± 2.9	3.15± 0.06

FC: Formulation Code

Force of adhesion (N) =

$$\left(\frac{Mucoadhesive\ strength}{100}\right) \times 9.81$$

In-Vitro dissolution study

The dissolution studies of core tablet and BPT were performed by using USP 26 type II dissolution test apparatus (DolphinTM, Mumbai, India) in 900 ml of 1.2 pH 0.1 N HCl. Temperature was maintained at 37±2°C and 75 rpm stirring was provided for each dissolution study.

Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper 41 (pore size 25 μm), concentration of drug was determined spectrophotometrically at 296 nm (UV-Visible spectrophotometer, Jasco V530, Japan).

Stability studies

All BPT of Telmisartan were exposed for the accelerated stability studies (Sweetman, 2011) at 40±2 °C and 75±5% RH) for a period of 6 months in a stability chamber (Thermolab, Mumbai, India). (Tangri *et al.*, 2011; Department of Health and Human Services, 2003) The samples were placed in vials with bromobutyl rubber plugs and sealed with aluminum

Table 4: Stability study data of BPT (n=3)

FC	Time (days)	Weight (mg)	Hardness (Kg/cm^2)	Lag Time (h)	Drug Release (h)	Adhesion Time (h)
P1	0 Day	800 ± 1.1	7.2 ± 0.12	5.2 ± 0.2	96.3 ± 1	8:10± 0.3
	90 Days	800* ± 1.1	7.4* ± 0.17	5.1*± 0.2	97.3* ± 1	8:12*± 0.2
	180 Days	800* ± 1.1	7.5 ± 0.18	5.3*± 0.2	96.3* ± 2	8:17*± 0.4
P2	0 Day	801 ± 3.4	7.5 ± 0.11	6.1 ± 0.2	97.7 ± 1	8:30± 0.4
	90 Days	802* ± 3.4	7.7* ± 0.11	6.3*± 0.4	96.4* ± 1	8:25*± 0.7
	180 Days	804* ± 3.4	7.8* ± 0.11	6.2*± 0.6	97.2* ± 1	8:35*± 0.5
P3	0 Day	800 ± 1.8	7.1 ± 0.16	7.3 ± 0.2	98.6 ± 1	8.50± 0.2
	90 Days	802*± 1.2	7.2* ± 0.22	7.4*± 0.5	98.6 ± 1	8.55*± 0.6
	180 Days	804*± 2.2	7.4* ± 0.32	7.5*± 0.7	98.6 ± 1	8.52*± 0.5
P4	0 Day	802 ± 2.9	7.3 ± 0.24	8.1 ± 0.5	98.3 ± 1	9:05± 0.5
	90 Days	804 ± 3.1	7.3* ± 0.34	8.2*± 0.2	95.3 ± 2	9:10*± 0.4
	180 Days	803* ± 2.2	7.3* ± 0.41	8.1*± 0.4	97.3 ± 1	9:20*± 0.8
P5	0 Day	801 ± 2.8	7.3 ± 0.21	10.2 ± 0.2	96.6 ± 3	9:30± 0.3
	90 Days	801* ± 2.8	7.3* ± 0.21	10.2*± 0.2	96.6 ± 3	9:35*± 0.4
	180 Days	801* ± 2.8	7.3* ± 0.21	10.2*± 0.2	96.6 ± 3	9:32*± 0.6

FC: Formulation Code
Significantly different from the value for raw crystals of PGH at $p < 0.001$ (*), $p < 0.01$ (**) and $p < 0.05$ (***)

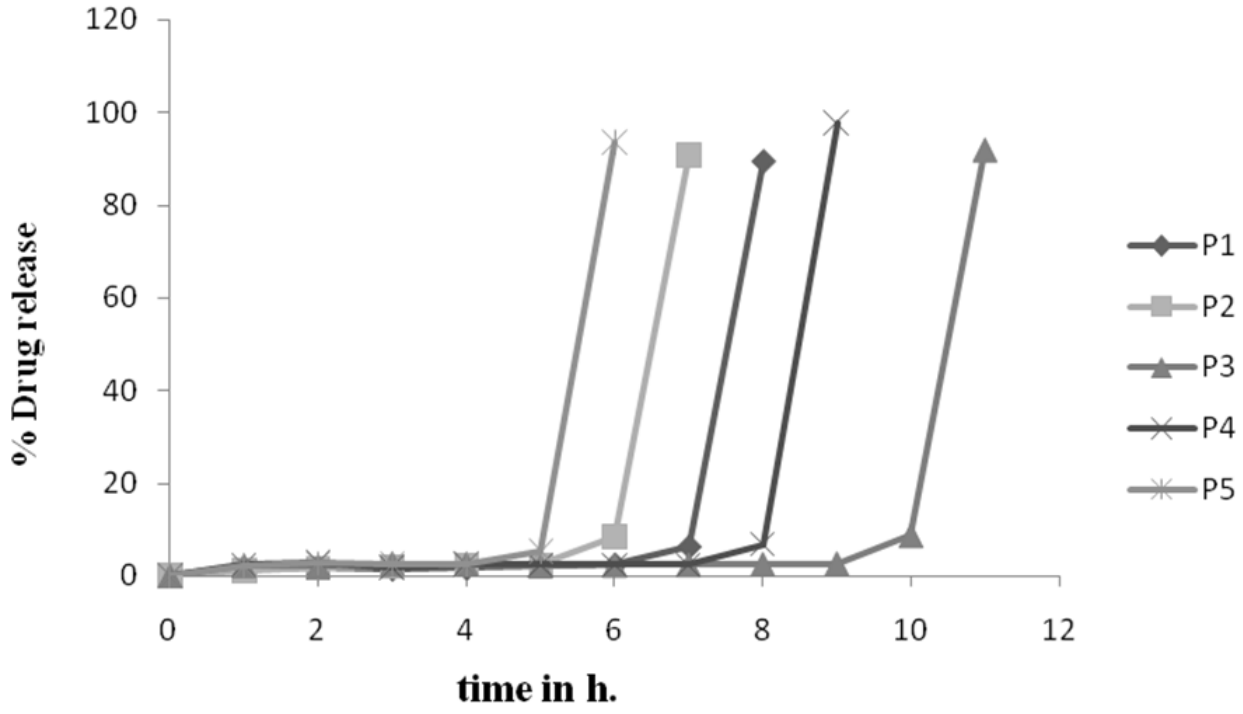

Figure 1: *In-vitro* drug release of all formulations of Bioadesive Pulsatile tablet

caps. The samples were withdrawn at 90 and 180 days and evaluated for the weight, lag time, friability and *In-vitro* drug release and *Ex-vivo* mucoadhesion.

RESULTS AND DISCUSSION

Preparation and Evaluation of Core Tablet (CT)

Core Tablet (CT) of Telmisartan was successfully prepared by direct compression method. Average tablet diameter was 8 mm with thickness 3.2 ± 0.02 mm. The entire formulation passes the weight variation test as the percent weight variation was within the Pharmacopoeial limits (Satani *et al.*, 2014; Sweetman, 2011). The weights of the entire tablets were found to be uniform with low standard deviation. It confirms the suitability of the direct compression method. The percent friability, hardness and disintegration time were well within the Pharmacopoeial limits which revealed that tablets were mechanically stable along with quick disintegration. The *In –Vitro* drug release was found to be between 57.89 ± 0.26 to 95.00±0.09 %. All formulations have shown drug release within 30 minutes. Amongst all the batches the parameters of the batch with sodium starch glycolate 14 mg were found better optimized so that was selected for formulation of the bio-adhesive pulsatile release tablet.

Formulation and Evaluation of the Bio-adhesive Pulsatile Tablet (BPT)

Bio-adhesive Pulsatile tablet (BPT) of Telmisartan was successfully prepared by direct compression method. All precompression parameters were found satisfactory as given in Table 2, indicated good flow and compressibility. The post compression evaluation parameters of the BPT are as given in Table 3. The entire formulation passes the weight variation test as the percent weight variation was within the Pharmacopoeial limits. The weights of the entire tablets were found to be uniform with low standard deviation once again confirms the suitability of the dry granulation method. The percent friability and hardness were well within the Pharmacopoeial limits which revealed that tablets were mechanically stable.

In-Vitro Dissolution study of Bio-adhesive Pulsatile Tablet

In-Vitro release profile of all formulations is as shown in Figure 1. Increase in concentration of Ethyl cellulose and carbapol decreased the drug release which might be due to increased amount of polymers around tablets, which inhibits the release of Telmisartan. (Bahul *et al.*, 2009) For formulation P4 only 6.83 % drug was released up to at 8 hours whereas after that 98.37% drug was release for next hour considered as burst release as expected in pulsatile drug delivery. Also formulation P4 showed distinct lag time of eight hours (Figure 1) as needed in hypertension as per circadian rhythm.

It showed that lag time decreases with increasing concentration of Ethyl cellulose and carbapol.

Muco-adhesion study

Muco-adhesion study done by the weight and pulley method. In this muco-adhesion study force of adhesion was calculated and adhesion time was recorded and it is as shown in Table III. P4 batch showed a satisfactory result with adhesion time 9 h, 15 min, muco-adhesion strength 30.20 g and force of adhesion is 2.96 N. Thus study revealed that the as carbopol concentration increased mucoadhesion was increased and batch P4 has shown satisfactory adhesion up to eight hours.

Stability studies

All BPT did not show any significant change in weight, hardness, lag time, *In-vitro* drug release and muco-adhesion time during stability study as given in Table 4. It has indicated that the prepared tablets were adequately stable as per regulatory requirements.

CONCLUSION

The present study was a first attempt ever in the pharmaceutical field to develop and evaluate Bio-adhesive Pulsatile drug delivery system containing Telmisartan as an active pharmaceutical ingredient for better treatment of hypertension as a precautionary measure in chronic patients. This study investigated that Bio-adhesive Pulsatile tablet of Telmisartan was successfully formulated and batch A4 has given satisfactory results with distinct lag time of eight hours followed by burst release also better muco-adhesion. Bio-adhesive Pulsatile drug delivery system shall be a remarkable method in future by enhancing the patient compliance, providing optimum drug delivery to the target site and minimize the undesired effects.

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