



FORMULATION AND EVALUATION OF BIOADHESIVE PULSATILE DRUG DELIVERY SYSTEM OF AN ANTILIPIDEMIC DRUG

Snehal U. Shinde^{*1}, Pallavi M. Sangave², Kajal B. Chougule², Sachinkumar V. Patil³
Shitalkumar S. Patil¹ and Dipak Bhingardev

¹Ashokrao Mane College of Pharmacy Peth-Vadgaon, Kolhapur, Maharashtra, India.

²Womens College of Pharmacy, Peth-Vadgaon, Kolhapur, MS, India.

³Shree Santkrupa College of Pharmacy, Ghogaon, Karad, Satara, MS, India.

Article Received on
25 May 2018,

Revised on 15 June 2018,
Accepted on 05 July 2018

DOI: 10.20959/wjpps20188-12066

*Corresponding Author

Snehal U. Shinde

Ashokrao Mane College of
Pharmacy Peth-Vadgaon,
Kolhapur, Maharashtra,
India.

ABSTRACT

The main objective of this study is to formulate and evaluate of Bioadhesive pulsatile drug delivery system of an antilipidemic drug. In order to achieve an improved therapeutic efficacy. The present research work describes the combination of Bioadhesive pulsatile principles are very suitable for site and time specific. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. several gastroretentive drug delivery approaches being designed and developed, including high density (sinking) systems that is retained in the bottom of the stomach,

low density (floating) systems that causes buoyancy in gastric fluid, mucoadhesive systems that causes bioadhesion to stomach mucosa, unfoldable, extendible, or swellable systems. The bioadhesive pulsatile tablet was prepared satisfactorily with no weight variation and hardness within official limit. In drug release study lag time up to 7 h. Thus bioadhesivepulsatile drug delivery system is best option for anhyperlipidemic patients.

KEYWORDS: Bioadhesive, gastrointestinal tract, pulsatile, lag time, therapeutic efficacy.

INTRODUCTION

The term bioadhesion commonly defined as adhesion between two materials where atleast one of the materials is of biologicalorigin. In thecase of bioadhesivedrug delivery system, bioadhesion often refers to the adhesion between the excipients and biological tissue. When Adhesion is restricted to mucous layer lining of the mucosal surface layer known as

mucoadhesion. This delivery recently been of greater interest in pharmaceutical field to achieved improved therapeutic efficacy. For the purpose of drug delivery, the term bioadhesion is defined as the ability of the drug carrier system or the material to adhere to a biological tissue for extended period of time, leadstoan increased drug concentration gradient at the absorptionsite and therefore improved bioavailability of systemically delivered drugs.^[1] Bioadhesive dosageforms have been used to target local disorders at the mucosal surface(e.g. mouth ulcer)to reduce the over all required and minimize sideeffect that may becaused bysystemic administration of drugs.^[2]

The exact mechanism of mucoadhesion is not known, an accepted theory states that a close contact between the mucoadhesive polymer and mucin occurs which is followed by the interpenetration of polymer and mucin. The adhesion is prolonged due to the formation of Vander vaals forces, hydrogen bonds and electrostatic bonds.^[3]

Concept of chrono pharmaceuticals has emerged, where in, research devoted to the design and evaluation of drug delivery system tha trelease is a the rapeuticagentata rhythm that ideally matches the biological requirement of a givendisease therapy. “Chronopharmaceutics” consist of two words chronobiology and pharmaceuticals.^[4,5]

Apulsatile drug delivery of fenofibrate was formulated which can be taken before bed time (9 pm) and capable of releasing drug after predetermine time delay (7h) and can characterized by proportioning drug concentration in the early morning hours when free cholesterollevels are more prevalent.^[6]

Bioadhesive drug delivery system is a strategy to prolong the residence time of various drugson gastrointestinal surfaceand bioadhesiondefined as ability of material (synthetic or bioadhesive) to adhere the biological tissue for an extended period of time. The pulsatile drugdelivery system is the rapidand transient release of certain amount of molecule within a hort time period immediately after a predetermined release period that is lag time. Drugs having maximum absorption in stomach or unstable in intestine are preferred for bioadhesive drug delivery system. Bioadhesive pulsatile drug delivery will be more beneficial for drugs which need pulsatile release in stomach. Disease like hyper lipidaemia pulsatile drug delivery system is desired but if it will be combined with bioadhesive action it will be more beneficial for targeting drugs in stomach with time dependent release. Hepatic cholesterol synthesis which ishigher during the night than daylightand diurnal synthesis represent upto30-40 % of

daily cholesterol synthesis. However the maximal production occurs in the morning. So there is a constant need for new delivery system that can provide increased therapeutic benefits to the patients by delivering antilipidemic drug at the right time, right place and in right amounts to coincide with circadian rhythm of body and avoid gastric emptying time of antilipidemic drug. So it is necessary to use bioadhesive pulsatile drug delivery system.

MATERIALS AND METHODS

Materials

Fenofibrate was obtained from Smruthiorganics Pvt. Ltd. Solapur, Maharashtra, India. Carbopol was obtained from L03 A- chemical pvt. ltd. (Mumbai), Maharashtra, India. HPMC K4M was purchased from Marksman's Pharma, Verna Goa, Magnesium Stearate was obtained from Hilabchemicals (Srirampur), Maharashtra, India. Talc and Mannitol were obtained from Molychem (Mumbai), Maharashtra, and India. All the chemicals used were of analytical grade.

Experimental Methods Preparation of core tablet (CT)

Tablets of fenofibrate were made by direct compression method. All ingredients were weighed accurately and mixed well for 15 min. Sodium starch glycolate (SSG) used as disintegrating and magnesium stearate (Mg. St.) were used as lubricant and Dicalcium Phosphate (DCP) used as diluents.

The resulting powder mixtures were then compressed into tablets (average tablet weight mg) using KBR machine (Diameter 8mm).^[7,8,9]

Formulation of the Bioadhesive Pulsatile Release Tablet by direct compression (BPRT)

The optimized c5 was used for preparation of BPRT. Dry coating using concentration of HPMC K-4m LR. Also magnesium stearate, talc, and mannitol used for coating of core tablet. Which were mixed for 10 minutes. Dry coated bioadhesive pulsatile tablet was prepared by placing 50% bioadhesive pulsatile release layer in 13 mm die and core tablet was placed on it. Then, the remaining quantity of bioadhesive pulsatile release layer was added in the die so as to cover BPRCT and finally compressed by using KBR tablet machine. (Diameter 13 mm).

Preformulation Study

Compatibility study- FTIR of Drug and Excipients

Drug Excipient Compatibility Study was carried out by Fourier transform infrared spectroscopy (FT-IR spectrophotometer, Agilent Technologies, carry 630 FTIR). The sample was analyzed in the region of 4000 and 400 cm^{-1} . The procedure consisting of dispersing mixture of drug and polymer (1:1), mixed well and then this solid mixture kept onto sample holding surface for analysis. The initial spectrum of drug and polymer mixture was taken then the same mixture of drug and polymer was kept in stability chamber at 400 C and 75 RH for one month. After one month sample mixture were analyzed by Fourier Transform infrared spectroscopy (FT-IR spectrophotometer, Agilent Technologies, carry 630 FTIR). The drug and Excipients compatibility study was done by comparing initial and after one month spectra of mixture sample weather the drug and Excipients compatible or not.

Pre-compression evaluation of granules

Bulk density, Tap density, Carrsindex, Hausner's ratio and Angle of repose

A 50 ml glass cylinder was weighed and filled with 30ml of granules. The cylinder was gently reversed once and the powder was carefully leveled with out 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 used to calculate Carr's index and Hausners ratio, Carr's index and Hausners ratio^[10] The angle of repose of the granules was determined by fixed funnel method.^[11]

Post Compression Evaluation of t ablets

The tablet weight variation and hardness (by Monsanto hardness tester) was obtained as per IP^[12] and percent friability (by Roche friabilator) was determined as per USP.^[13]

Thickness of the tablets was determined by using Vernier calliper.

***In Vitro* mucoadhesion test**

In first study a tablet was fixed on glass box. To the upper glass slide mucus membrane was fixed and 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 17g was attached into which the weights can be added. The glass slide was placed on the tablet with weight (17g) for 1 min. The weight required to detach the tablet from the glass box (muco-adhesive strength) was determined. In second study only change was made that tablet was just placed and not fixed on glass box. Time required to detach the tablet from the mucus

membrane (adhesion time) was recorded.^[14,15]

The force of adhesion was calculated using following formula;

$$\text{Force of adhesion (N)} = \text{Mucoadhesive strength} / 100 \times 9.81$$

***In-Vitro* dissolution study**

The dissolution studies of core tablet and Bioadhesive pulsatile release tablet (BPRT) of Fenofibrate were performed by using USP paddle type 2 dissolution test apparatus (Veego VDA- 8DR, USP), in 900 ml of 0.1N HCL with 0.075 % SLS. Temperature was maintained at 37 ± 2 °C and 75 rpm stirring was provided for each dissolution study. Core tablet 100 mg and BPRT equivalent to 600 mg of fenofibrate were used 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 fenofibrate was determined by UV visible spectroscopy (Agilent Cary 60) as specified in yield and drug content.^[16,17,18]

RESULTS AND DISCUSSION

Preformulation Study

Compatibility study- FTIR of Drug and Excipients

Spectrum of pure drug and physical mixture was as given in fig. It was observed that there were no changes in IR spectra of mixture of drug and polymers. This indicates no physical interactions, because of some bond formation between drug and polymers. This indicates that the drug was compatible with the formulation components.

Bulk density, Tap density, Carr's index, Hausner's ratio and Angle of repose

Preparation and Evaluation of Core Tablet (CT)

Core Tablet (CT) of Fenofibrate was successfully prepared by direct compression method. Average tablet diameter was 8 mm with thickness 0.19 ± 0.02 mm. The entire formulation passes the weight variation test as the percent weight variation was within the Pharmacopoeial limits.^[12,13] 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 68.89 ± 0.65 to $97.21 \pm 0.42\%$. All the formulations gave release within 30 minutes. Amongst all the batches the parameters of the batch CT6 were

found better optimized so that was selected for formulation of the bioadhesive pulsatile release tablet.

Formulation and Evaluation of the Bioadhesive Pulsatile Release Tablet (BPRT)

Bioadhesive Pulsatile release tablet (BPRT) of fenofibrate was successfully prepared by direct compression method. The evaluation parameters of the BPRT 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.

Mucoadhesion study

Mucoadhesion study done by the weight and pulley method. In this mucoadhesion study force of adhesion was calculated and adhesion time was recorded and it is as shown in Table 4. A5 batch shown satisfactory results that is adhesion time was 7h 30 min, mucoadhesion strength was 38.61 g and force of adhesion is 3.72N.

In-Vitro Dissolution of Bioadhesive Pulsatile Release Tablet

In-Vitro release profile so all formulations are as given in figure 1 and 2. It was in order of A5>A6>A2>A3>A1>A4. Increase in concentration of HPMC decreased the drug release which might be due to increased amount of polymer around tablets, which inhibits the release of Fenofibrate. For formulation A4 only 90.12% drug was released at 8 h where as up to 98.37% drug was release for formulation A5. Bioadhesive Pulsatile Release tablets A1- A6 formulations show ed distinct lag time. It show ed that lag time decreases with in creasing concentration of HPMC, during dissolution studies, formulations A1 to A4 contains less amount of HPMC due to this it shows less lag time. A5 Batch show ed the greater drug release that is 98.37 ± 0.012 %, hence A5 Batch was considered as optimized batch.

Table 1: Formulation of core tablet of fenofibrate.

Ingredients	CT1	CT2	CT3	CT4	CT5	CT6
Drug	40	40	40	40	40	40
DCP	57	55	53	51	49	47
SSG	02	04	06	08	10	12
Mg St	1	1	1	1	1	1
Total	100	100	100	100	100	100

Table 2. Composition of Bprt of Fenofibrate.

Ingredients (Mg)	A1	A2	A3	A4	A5	A6
Core	100	100	100	100	100	100
Carbopol	70	70	70	70	70	70
HPMC	374	379	384	389	394	399
Mg.stearate	06	06	06	06	06	06
Talc	10	10	10	10	10	10
Mannitol	40	35	30	25	20	15
Total Weight	600	600	600	600	600	600

Table 3: Evaluation parameter of bprt.

Batch Code	Weight Variation (mg)	Thickness (mm)	Hardness	Friability
A1	585±2	2.71±0.01	4.71±0.01	0.64±0.03
A2	594±2.08	3.71±0.01	5.76±0.07	0.64±0.02
A3	588.5±1	3.76±0.10	6.65±0.02	0.43±0.02
A4	589±2.51	3.73±0.01	4.31±0.01	0.61±0.01
A5	597±1.52	2.41±0.005	4.52±0.02	0.53±0.02
A6	591±6.08	3.63±0.46	6.69±0.03	0.52±0.01

Table 4: Mucoadhesion study.

Batch Code	Adhesion Time (In h)	Mucoadhesion Strength (In g)	Force of Adhesion (N)
A1	5 h	29.38	2.84
A2	5.15 h	30.5	9.81
A3	6.15 h	33.69	3.23
A4	6 h	34.95	3.33
A5	7.30 h	38.61	3.72
A6	7.15 h	35.45	3.43

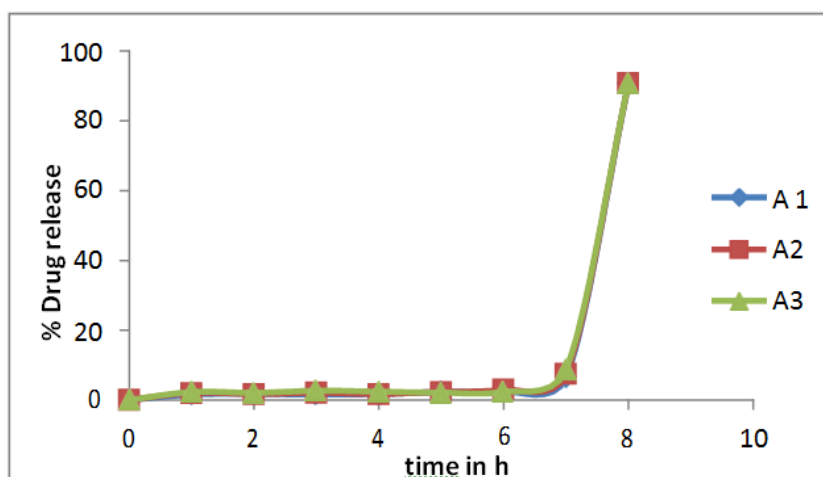


Fig. 1: % Drug release of A1 to A3 Batch.

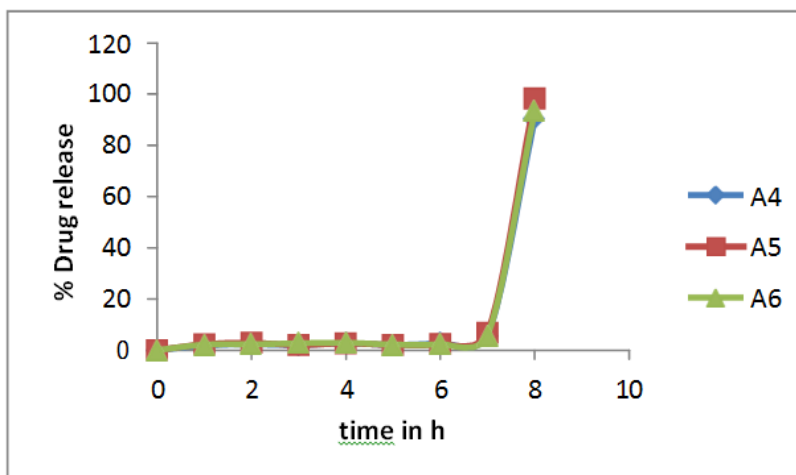


Fig. 2: % Drug release of A4 to A6 Batch.

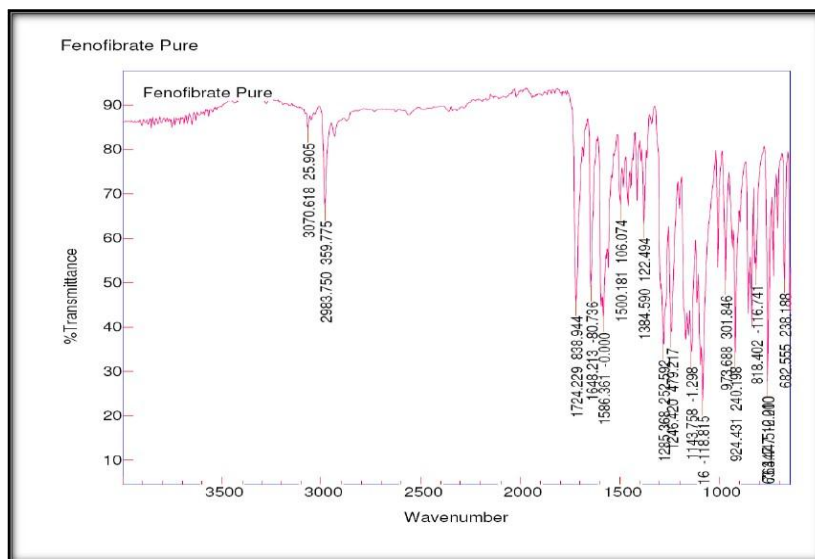


Fig. 3: FTIR spectra of pure fenofibrate.

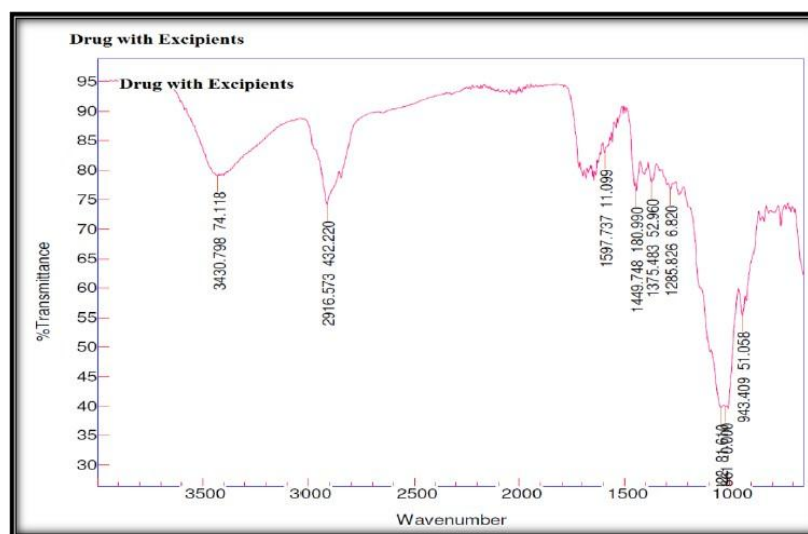


Fig 4: FTIR Spectra Drug with Excipients.

CONCLUSION

The present study was made to develop and evaluate Bioadhesive Pulsatile drug delivery system containing fenofibrate as active ingredient for better treatment of Hyper lipidaemia. This study investigated that optimization of fenofibrate was successfully done and batch A5 was given satisfactory results. Bioadhesive Pulsatile drug delivery system shall be remarkable method in future by enhancing the patient compliance, providing optimum drug delivery to the target site and minimize the undesired effects.

ACKNOWLEDGMENT

Author is thankful to Smruthi Organics Ltd, Solapur, Maharashtra, India for providing the Fenofibrate as gift sample.

REFERENCES

1. M. Rajput, R. Sharma, Sunil Kumar, F. Jamil, N. Sissodia and S. Sharma. Pulsatile Drug Delivery System: A Review, International Journal of Research in Pharmaceutical and Biomedical Sciences, Jan-March, 2012; 3(1): 118-124.
2. Carvalho CF, Bruschi ML, Evangelista RC, Gremião MPD. Mucoadhesive Drug Delivery Systems. Brazilian Journal of Pharmaceutical Sciences, 2010; 46(1): 1-17.
3. Malik A, Parvez N, Sharma PK. Novel Polymers for Mucoadhesive Drug Delivery. International Journal of Pharmacy, 2014; 4(3): 212-220.
4. Reddy JRK, Jyothsna MV, Mohamed Saleem TS, Chetty CMS. Pulsatile Drug Delivery Systems. Journal of Pharmaceutical Science and Research, 2009; 1(4): 109-115.
5. Rasve G, Borade G, Deshmukh S, Tagalpallewar A. Pulsatile Drug Delivery System: Current Scenario. International Journal of Pharma And Bio Sciences, 2011; 2(3): 332-343.
6. Safiullah GS, Rizwan Khan MA, Alam KE, Hussain AA. Evaluation of Antihyperlipidemic Activity of Ethanolic Extract of *Glycosmis pentaphyllain* Hyperlipidaemia wistar Rats. International Journal of Pharma Sciences and Research, 2015; 6(2): 282-292.
7. Banerjee ND, Singh SR. Formulation and Evaluation of Compression Coated Tablets of Cefpodoxime Proxetil, International Journal of Pharmaceutical Science and Research, 2013; 4(7): 104-112.
8. Salunkhe AK, Dias RJ, Mali KK, Mahajan NS, Ghorpade VS. Formulation and Evaluation of Floating Pulsatile Drug delivery System of Metoprolol Tartrate. Scholars Research Library, 2011; 3(3): 147-160.

9. Rajendra TM, Upendra CG, Chaudhari PD. Floating Pulsatile Drug Delivery of Ranitidine Hydrochloride For Nocturnal Acid Breakthrough: Design, Optimization, *In-Vitro* and *In-Vivo* Evaluation. International Journal of Pharmaceutical science. 2013; 5(3): 723-727.
10. Dasandi B, Shah S, Shivprakash. Determination of Quinapril and Quinapril at In Human Plasma By Ultra Performance Liquid Chromatography-Electrospray Ionization Mass Spectrometry. Biomed Chroma, 2009; 23(5): 492-498.
11. Thalberg K, Lindholm D, Axelsson A. Comparison of Different Flowability Tests for Powders for Inhalation. Science Direct Powder Technology, 2004; 146: 206-213
12. Indian Pharmacopoeia. New Delhi: Publications and information directorate, 1996.
13. United States Pharmacopoeia. 2006. Rockville MD: US Pharmacopoeial Convention.
14. Bagul U, Gujar K, Dhat S, Aphale S, Bhavsar M. *In Vitro* Study of Mucoadhesive Strength of Polymers For Mucoadhesive Drug Delivery Systems. International Journal of Current Pharma Research, 2009; 1(1): 42-46.
15. Nikalje AP, Tiwari S, Kamble S. Mucoadhesive As Oral Controlled Gastroretentive Drug Delivery System. International journal of Research in Pharmacy and Science, 2012; 2(3): 32-59.
16. Aulton E. Pharmceutics, the Science of Dosage Form. 2nd Edition, Churchill Livingstone, 2002; 397-439.
17. USFDA: Dissolution Methods for Drug Products.
18. Brahmaiah B, Nama S, Nuthakki S, Katta Vamshi K, Pasumarthi P. Enhancement of Dissolution Rate of Fenofibrate By Using Various Solid Dispersion Techniques. World Journal Pharma Sci., 3(3): 914-932.