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

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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 pharmaceutics 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 pharmaceutics.[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 themorning. So there isaconstant need for new delivery system that can provid eincreased therapeutic benefits to the patientsby delivering antilipidemic drug at the right time, right place and in rightamounts to coincidewith circadian rhythm of bodyandavoid gastricemptying timeof antilipidemic drug soitis necessary tousebioadhesivepulsatile drug delivery system.

MATERIALS AND METHODS

Materials

Fenofibrate was obtained fromSmruthiorganics Pvt. Ltd. Solapur, Maharashtra, India. Carbopol was obtained from L03 A- chemical pvt. ltd. (Mumbai), Maharashtra, India. HPMC K4M waspurchased 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 ofcoretablet (CT)

Tablets of fenofibrate were made by direct compression method. All ingredients were weighted accurately and mix 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 cylinderwasgently reversed once and the powder was carefully leveled with out compacting. Bulk volume was determined after one mechanical tap ona tap density tester (DolphinTM).Tap volume was measured after2000 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 thetablets was determined by using Verniercalliper.

***In Vitro* mucoadhesion test**

In firststudy a tablet was fixed on glassbox. To the upper glassslide mucus membrane was fixed and to it athread was tied and the thread was passed down through a pulley, the length of the thread from the pulley tothepan was 12 cm. At the end of the threadapan of weight17g 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 require 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) wasrecorded.[14,15]

The force of adhesion was calculated using following formula;

Force of adhesion (N)=Mucoadhesive strength/100 × 9.81

***In-Vitro* dissolution study**

The dissolution studies of core tablet and Bioadhesivepulsatile release tablet (BPRT) of Fenofibrate were performed by using USP paddle type 2 dissolution test apparatus (Veego VDA- 8DR, USP), in 900 ml of0.1N HCLwith0.075 %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 offen of ibrate were used for each dissolutionstudy. Sample swerecollected periodicallyand replaced with a freshdissolutionmedium. After filtrationthrough What man filter paper 41 (poresize 25µm), concentrationoffenofibrate was determined by UV visible spectroscopy (AgilentCary60) as specified in yieldand 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 compressionmethod. Average tablet diameter was8 mmwiththickness0.19 ±0.02 mm. The entire formulation passes the weight variation test as the percent weight variation was with in the Pharma copoeial limits.[12,13] The weights of the entire tablets were found to be uniform withlow standard deviation. Itconfirmsthe suitability of the direct compression method. The percentfriability, hardness and disintegration time were well within the Pharmacopoeial limits which revealed that tablets were mechanically stablea long with quick disintegration. The*In – Vitro*drug release was found to be between 68.89±0.65 to 97.21±0.42%. All the formulations gaverelease with in 30 minutes. Amongstall the batches the parameters of the batch CT6 were

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

Formulationand Evaluation of the Bioadhesive Pulsatile Release Tablet (BPRT)

Bioadhesive Pulsatile release tablet (BPRT) off enofibrate was successfully prepared by direct compression method. The evaluation parameters of the BPRT are as given in Table 3.Theentireformulationpasses 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 drygranulation method. The percentfriability and hardness were well within the Pharmacopoeial limits which revealed that tablets weremechanically stable.

Mucoadhesion study

Mucoadhesion study done by the weight and pulley method. In this mucoadhesion study force ofadhesion was calculated and adhesion time was recordedand 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 BioadhesivePulsatile Release Tablet**

In-Vitro release profile so fall 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 formulationA4only 90.12% drug was releasedat8 h where asup to 98.37% drug was release for formulation A5. Bioadhesive Pulsatile Release tablets A1- A6 formulations show eddistinct lag time. It show edthatlag time decreases with in creasingconcentration of HPMC, during dissolution studies, formulationsA1 toA4 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 coretablet 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: Evalution 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

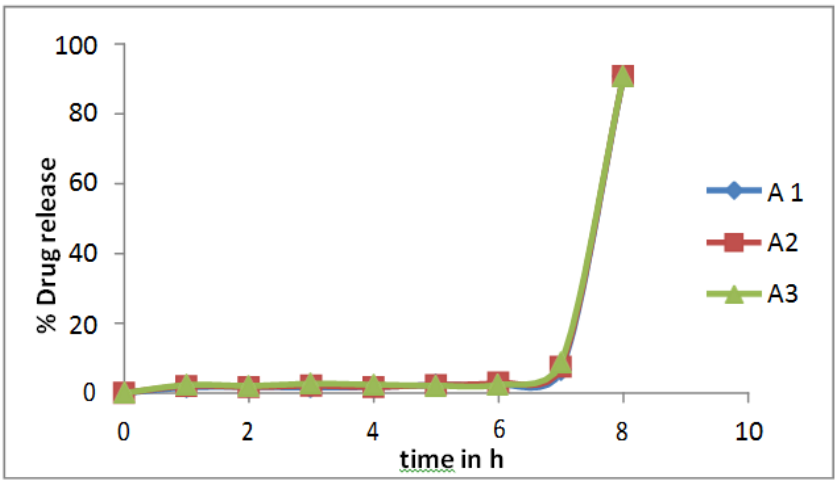

Fig. 1: % Drug release of A1 to A3 Batch.

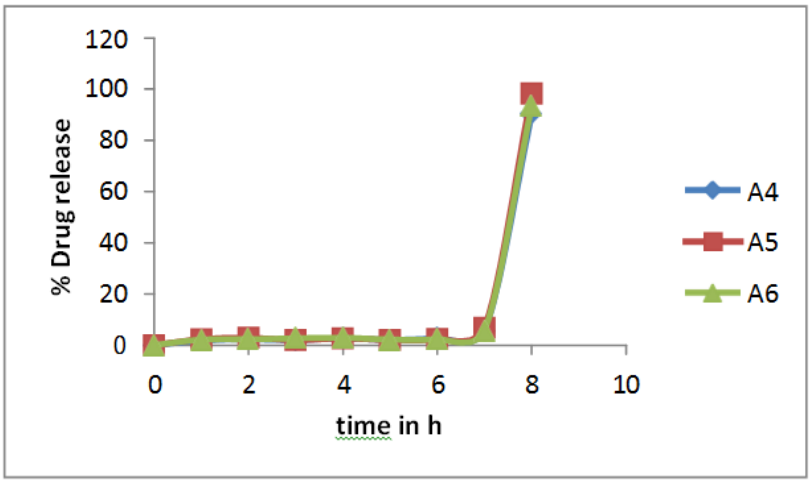

Fig. 2: % Drug release of A4 to A6 Batch.

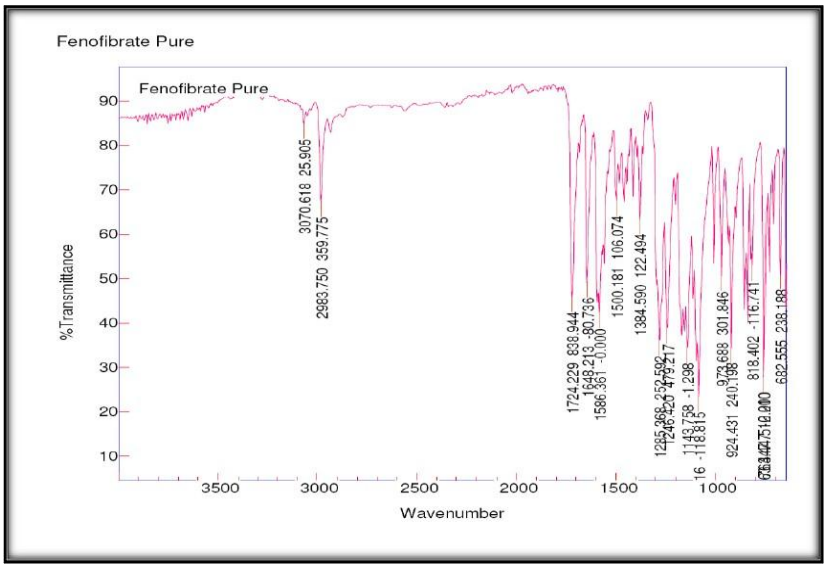

Fig. 3: FTIR spectra of pure fenofibrate.

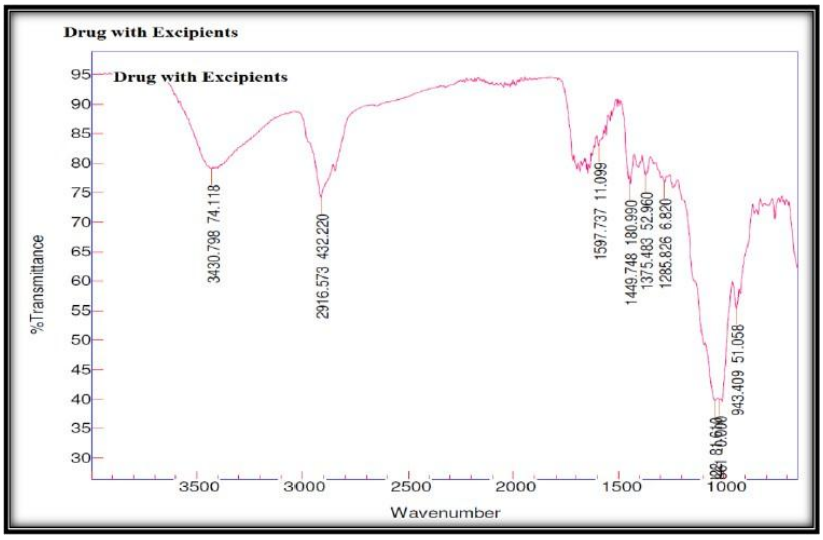

Fig 4: FTIR Spectra Drug with Excipients.

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 satis factory results. Bioadhesive Pulsatile drug delivery system shall beremarkable 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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