Research Article

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Design and Evaluation of Chronotropic Systems for Colon Targeted Drug Delivery

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ABSTRACT
Targeting of drugs to colon via oral route can be achieved by different approaches controlled by pH conditions, gastrointestinal transit time and colonic microbial flora. Modified Pulsincaps and compression coated tablets of aceclofenac, a non steroidal anti-inflammatory drug used for the treatment of rheumatoid arthritis were developed to target drug release in the colon. Pulsincaps were formulated by treating bodies of hard gelatin capsules with formaldehyde and caps were untreated. Aceclofenac was incorporated into these specialized capsule bodies which were plugged with hydrogels like guar gum, acacia, gelatin and sodium alginate separately and in combination. Pulsincaps were evaluated for lag time, qualitative test for free formaldehyde and in *vitro* drug release studies. Compression coated tablets of aceclofenac were developed using Guar gum to deliver drug to colon due to its release retarding property and susceptibility to microbial degradation by colonic bacteria like *Bacteroides species*. These tablets were evaluated for various parameters like hardness, friability, drug content, *in vitro* drug release studies in simulated colonic fluid containing Male Wistar Rats colonic contents.The findings of the present study conclusively state that developed dosage forms are promising for colon targeting of aceclofenac to synchronize the chronobiological symptoms for effective treatment of rheumatoid arthritis.

Key words: Chronobiological, Compression coated, Guar gum, Hydrogel, Pulsincaps, Rheumatoid arthritis

INTRODUCTION

Therapeutic advantages of controlled drug delivery are recognized and hence greater attention has been focused on the development of controlled release site specific drug delivery systems. There is a requirement of an appropriate technology to deliver the drug at specific time and site which results into novel type of drug delivery systems, "chronotropic or pulsatile drug delivery systems". The principle rationale behind designing these delivery systems is to release the drug at desired time as per the pathophysiological need of disease, resulting in improved patient therapeutic efficacy and compliance. Pulsatile drug delivery systems are designed to release certain amount of drug within a short period of time, immediately after a predetermined lag time. These systems are developed when zero order drug release is not desired[1]. Rheumatoid arthritis (RA) is traditionally considered as a chronic, inflammatory autoimmune disorder that causes the immune system to attack the joints. The symptoms of rheumatoid arthritis are severe in early morning hours, so an attempt has been made to overcome the problem by delaying drug release by colon targeting to maintain peak plasma concentrations in early morning hours [2]

Rheumatoid arthritis is a disease condition wherein chronotropic systems are promising. Colon targeting is useful for delivery of those drug where a delay in drug absorption is required from a therapeutic point of view e.g. in case of nocturnal asthma, arthritis, angina.[3] Aceclofenac is non-steroidal anti-inflammatory drug used extensively in the treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis also it has short biological half-life 4 h, and dosing frequency is 50-100 mg twice daily which make it an ideal candidate for modified release oral, Colon Targeted drug delivery system[4] The present research work is based on the concept that the formulations that are pulsincaps and compression coated tablets are designed in such a manner that on leaving the stomach & intestine they reach colon and release aceclofenac thus showing chronopharmaceutical approach for the better treatment of rheumatoid arthritis.

pH-dependent, time-dependent, or enzymatically controlled delivery systems are three major approaches of colon targeting. However, a disadvantage of the pH-dependent system is that a substantial amount of drug may be released in small intestine because the pH-difference between the small intestine and the large intestine not being very pronounced. The timed-release systems release their load after a predetermined time period of administration. In humans, studies have shown that, after leaving the stomach, a formulation arrives at the ileocaecal junction in about 6hr after administration. Thus once gastric emptying has occurred; a time-based system can be employed for the targeted release. Based on this concept, a pulsincap dosage form was developed. The rationale of this study was to design aceclofenac loaded pulsincap dosage form that can be targeted to the colon in a time-dependent manner. Colonic delivery of aceclofenac could prevent degradation in upper gastro-intestinal tract and provide maximum dose at site of action.

Natural polysaccharides such as xanthan gum, xylan and guar gum are not digested in the human stomach or small intestine, but are degraded in the colon by resident bacteria[5] .Colon targeted tablets of aceclofenac containing guar gum were developed and evaluated. Guar gum was being used to deliver drug to colon due to its drug release retarding property and susceptibility to microbial degradation in the large intestine.

Hence in the present study, time dependent release that is Pulsincaps and enzymatically controlled (microflora-assisted delivery) release that is compression coated tablets

are formulated for colon targeted release of aceclofenac for treatment of arthritis.

MATERIALS AND METHODS

Materials

Aceclofenac was obtained as gift sample from Aarti Drugs, Mumbai, India. Empty Hard gelatin capsules(size 00) for Pulsincaps were obtained as gift sample from Associated capsules, Mumbai, India. Guar gum, Sodium alginate, Acacia, Magnesium stearate and Talc were procured from S D Fine Chemical Ltd, Mumbai, India. Hydroxypropyl methylcellulose (HPMC) was obtained from Lupin Research Park, Pune, India. All other chemicals and reagents used were either of analytical or pharmaceutical grades.

Methods

A). Preparation of pulsincaps of aceclofenac

1. Preparation of formaldehyde-exposed hard gelatin capsule bodies

Hard gelatin capsules of 00 size were taken. The bodies of hard gelatin capsules were placed on a wire mesh. Formaldehyde (10%) was taken into a desiccator and potassium permanganate was added to it until vapor was produced. The reaction was carried out for 12 h after which bodies were removed and dried at 50 °C for 30 min. to ensure completion of the reaction between gelatin and formaldehyde vapor. [6] The capsule bodies were then dried at room temperature to ensure removal of residual formaldehyde. The collected samples were assayed for the residual formaldehyde content.

2. Estimation of residual formaldehyde content in treated gelatin capsule bodies

The residual formaldehyde content in treated bodies was determined as per the method described by William. Vapor hardened capsule body samples collected at 20-, 30-, 40-, 50-, and 60-min interval were cut into small pieces. Pieces of capsule samples were added separately to a mixture of 1 ml of 10% chromotropic acid solution and 10 ml of concentrated sulfuric acid in different test tubes. All test tubes were placed in a beaker filled with water for boiling. After cooling to room temperature, contents of test tubes were quantitatively transferred to a 100 ml volumetric flask and diluted up to the mark with distilled water. A blank was prepared in the similar way using 1 ml distilled water in place of pieces of body. Absorbance of sample was measured by colorimetry at 569 nm.[7,8,9]

3. Method of plug formation

Plugs of different polymers like guar gum, sodium alginate and acacia individually and in combination using different concentrations (Table 1) were prepared by accurately weighing the polymer and mixing with quantity sufficient water to form mass by molding method. Formaldehyde treated bodies of capsule containing accurately weighed Aceclofenac (100mg) were plugged with these prepared plugs and were capped with water soluble un-treated caps.

4. Evaluation of Pulsincaps

***In-vitro* drug release profile**

Dissolution studies were carried out for 8 hrs for Pulsincap dosage form according to USP dissolution test apparatus II(Paddle) method. The dissolution media used were: Acidic buffer pH 1.2 for 2 hrs (since the average gastric emptying time is 2 hrs), Phosphate buffer pH 7.4 for 3 hrs (since the average small intestinal transit time is 3hrs), and Phosphate buffer pH 6.8 for subsequent hours. The dissolution media was rotated at 50 rpm. Samples (10ml) were withdrawn at specific time intervals and equal volume of media was replaced immediately to maintain sink conditions. Withdrawn samples were then filtered, and amount of aceclofenac was determined by UV absorption at 276nm. The cumulative amount drug released was calculated.

Table 1 Formulation optimization of pulsincaps by varying polymer and amount of polymer plug

Batch No	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Drug (mg)	100	100	100	100	100	100
Plugging composition of Pulsincap (Concentration of polymer plug (mg))						
Guar gum	70		80	10		
Gelatin		80			10	
Sodium alginate				70	80	
Acacia			10			90

B). Preparation of compression coated tablets of aceclofenac

Preparation of core tablets of Aceclofenac

Core tablets (average weight 120 mg) were prepared by direct compression technique. A weighed quantity of drug, cross PVP, Spray dried lactose, talc and magnesium stearate were thoroughly mixed and passed through the mesh (# 250) to ensure complete mixing. The powder weighing 120 mg was taken and compressed into tablets using 8 mm round, flat and plain punches on a on a multi station tablet punching machine (Lab press, India). The composition of core tablets is given in Table 2.

Table 2 Composition of core tablets

Ingredient	**Quantity (mg)**
Aceclofenac	100
Spray dried Lactose	09
Cross PVP	8.5
Magnesium stearate	1
Talc	1.5

Preparation of compression-coated tablets

The formulated core tablets were compression-coated with Guar Gum and Hydroxy propyl methyl cellulose (HPMC) in different ratios with a coat weight of 330 mg. For compression coating, about (130 mg) of coat material was first placed in the die cavity. Then, the core tablet was carefully positioned at the centre manually, which was then filled with the remaining (200 mg) of coat material. The coating material was then compressed around the core tablet by using 10 mm round, flat and plain punches. The composition of compression-coating material is shown in Table 3.

Evaluation of compression coated tablets of aceclofenac

1. Evaluation of core and compression coated tablets

The prepared core and compression-coated tablets were studied for their physical properties like weight variation, hardness, friability and drug content uniformity using reported procedure.

For estimating weight variation, 20 tablets of each formulation were weighed using a single pan electronic balance. The thickness of the tablet was measured by using a micrometer screw gauge. The hardness of five tablets was measured using Monsanto hardness tester. Friability was determined on 10 tablets using Roche friability testing apparatus for 4 min at 25 rpm.

Table 3 Composition of compression coatings

Ingredient	Batch No				
	A	B	C	D	E
Guar gum	100	150	200	250	300
HPMC	224	174	124	74	24
Magnesium stearate	2	2	2	2	2
Talc	4	4	4	4	4

2. Assay:
Three tablets of each type of formulation were weighed and crushed in mortar and was dissolved in 100ml methanol. This was the stock solution from which l ml sample was withdrawn and diluted to 100 ml with 6.8 phosphate buffer. The absorbance was measured at wavelength 276 nm using double beam UV-Visible spectrophotometer.

3. *In-vitro* drug release profile[10,11]:
Dissolution studies were carried out for 12 hrs for tablet dosage form according to USP dissolution test apparatus I (Basket) method. The dissolution media used were: Simulated gastric fluid (SGF) that is Acidic buffer pH 1.2 for 2 hrs (since the average gastric emptying time is 2 hrs), Simulated intestinal fluid (SIF) Phosphate buffer pH 7.4 for 3 hrs (since the average small intestinal transit time is 3hrs), and Simulated colonic fluid (SCF) Phosphate buffer pH 6.8 for subsequent hours. The dissolution media was rotated at 100 rpm. Samples (10ml) were withdrawn at specific time intervals and equal volume of media was replaced immediately to maintain sink conditions. Withdrawn samples were then filtered, and analyzed spectroscopically.

4. Modified Dissolution Studies[12]
Guar gum is a naturally occurring galactomannan polysaccharide; consists of chiefly high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycosidic linkages and shows degradation in colon due the presence of microbial enzymes. Hence a modified dissolution test was carried out to mimic colonic environment. The *in vitro* drug release studies were carried out using dissolution tester (100 rpm, 37 ^{o}C) with slight modifications. Dissolution medium was 150 ml of 4% rat cecal content maintained in dissolution vessel. The swollen formulation after completing the dissolution in 0.1M HCl (2 hrs) and phosphate buffer pH 7.4 (3 hrs) were placed in the basket and immersed in the rat cecal content medium. As the cecum is naturally anaerobic, the experiment was carried out with continuous supply of carbon dioxide. At different time intervals, 2 ml sample was taken and analyzed for drug content using UV-spectrophotometer.

RESULTS AND DISCUSSION

A). Colon Targeted Pulsincap of Aceclofenac

Estimation of residual formaldehyde content in treated gelatin capsule bodies

Orally tolerated limit of formaldehyde is 0.1%. The residual formaldehyde was 0.0092% after heat exposure for 50 min. After 50 min, the residual formaldehyde level was constant. Since 50 min reaction time was optimum, the residual amount of formaldehyde remained in the capsule was safe for oral intake.

The effect of 0.1 N hydrochloric acid was performed on treated and untreated capsule bodies. The treated bodies were unaffected for 24 hrs. while untreated bodies collapsed within 15 min. This proves that these formulations would be unaffected in gastric environment.

***Invitro* drug release studies**

From the Figure 1 it can be seen that in formulations F1, F2, F3, F4 the hydrogel plug was out of the capsule before 4-5 hrs releasing the drug before time where as formulation F5 , the hydrogel plug did not come out from the capsule within desired time period , hence formulation F6 where the drug release started after 5 hrs and the hydrogel plug was out in 6hrs, is suitable for colonic delivery of aceclofenac as it could minimize drug release in the simulated small intestinal fluid and release major portion of the drug in the simulated colonic fluid, when compared to the other formulations. Therefore, the study proves that aceclofenac can be successfully colon targeted by the use of a time-dependent modified Pulsincap formulation F6.

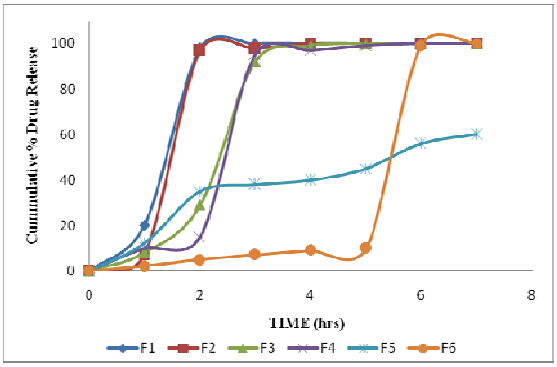

Figure 1 Graph for Release of aceclofenac (Pulsincap)

B). Colon Targeted Compression Coated Tablets of Aceclofenac

Evaluation of core tablets

The core tablets were prepared by direct compression technique using crosslinked PVP as binder and water soluble spray dried lactose as a direct compression aid. Average weight of the core tablet was fixed at the lowest possible level (120 mg) to accommodate maximum amount of coat material over the core tablet and the average percentage deviation of core tablet was within the official limit. The core tablets were found to disintegrate within 3 min showing required fast disintegration characteristics. The core tablet formulations passed the test for friability with 0.6 % and they showed hardness of 2.6 kg/cm^2 thickness of 1.9mm and 100.09 % of labeled amount of drug, indicating uniformity of drug content (Table 4).

Evaluation of compression-coated tablets

The prepared tablets were evaluated for various parameters and the results in Table 4 show that all the formulations were within the limits. All the formulation

showed uniform thickness, weight, drug content (99.90 % to 99.99 %), hardness (4.8 to 5.2 kg/cm^2). When HPMC in polymer mixture increased the crushing strength of coated tablets increased. HPMC provides mechanical strength to the tablets. The percentage friability of all the batches was below 1%, indicating that the friability is within the limits. All tablets complied with the pharmaceutical quality control standards.

Table 4 Evaluation of core and compression coated tablets of Aceclofenac

Formulation code	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug content (%)	Weight variation (mg)
Core tablet	2.6	0.6	1.9±0.2	100.09%	120±0.8
A	4.8	0.7	3±0.2	99.90%	450±0.5
B	4.9	0.5	3±0.4	99.99%	450±0.8
C	5.0	0.5	3±0.3	99.92%	450±0.7
D	5.2	0.5	3±0.2	99.95%	450±0.8
E	5	0.5	3±0.3	99.92%	450±0.6

Invitro Drug Release form Compression coated tablets of Aceclofenac

Figure 2 shows the results of *in vitro* drug release studies without rat caecal contents. The drug release from the formulations A, B, C, D, E takes place at a highly retarded rate. The amount of drug released from the formulations in simulated gastric (2hrs) and intestinal fluid (3 hrs) was very less and the tablets remained intact and drug released at the end of 12 hrs was 20-45 %. The decreased drug release in the colonic area from the formulations might be due to swelling of the polymer HPMC and Guar gum forming a thick viscous stiff gel layer around the core tablets on being exposed to the dissolution fluids. This viscous gel layer will retard penetration of dissolution fluids into core tablets and reduce the diffusion of drug from the core tablets. On the other hand, the formulations fail to release drug in physiological environment of stomach & small intestine and drug release was incomplete in physiological environment of colon, this might be due to high proportion of guar gum present in the coat and absence of rat caecal content in the dissolution fluid. The percent of drug released at the end of 12 hrs from formulation A, B, C, D, E was 20.22%, 25.67%, 34.43%, 40.76% and 45.29% respectively. This indicates that until the coat is degraded by the colonic microbial flora, the gum will not permit the release of the remaining drug present in the core.

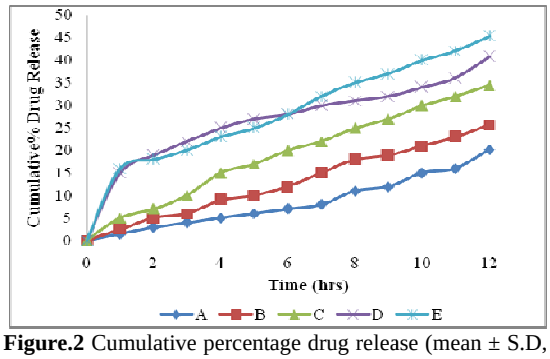

Figure.2 Cumulative percentage drug release (mean ± S.D, n=3) versus time profile for compression coated aceclofenac tablets in SGF (2 h), SIF (pH 7.4) (3 h), and SCF (pH 6.8 without rat caecal contents) (upto12 h)

The drug delivery systems targeted to colon should not only protect the drug being released in the stomach and small intestine, but they also should release and sustain the drug release in the colon. Hence, *in vitro* drug release studies were carried out in phosphate buffer containing rat caecal contents. **Figure 3** represents the drug release profiles of tablets in the presence of of rat ceacal content medium. Drug released from formulations A,B,C,D was about 100% within 6,7 ,9 and 12hrs respectively indicating that as the proportion of Guar gum increased, time taken for degradation of guar gum by colonic bacteria increased and thus drug release decreased. Formulation E released only 80% drug in 12 hrs indicating that as the proportion of guar gum increased further, the drug release decreased and aceclofenac was incompletely released at the end of 12 hrs. Thus Formulation D was found to be optimum. Thus it is evident that unless the coat is completely degraded by colonic bacteria, drug release may not increase.

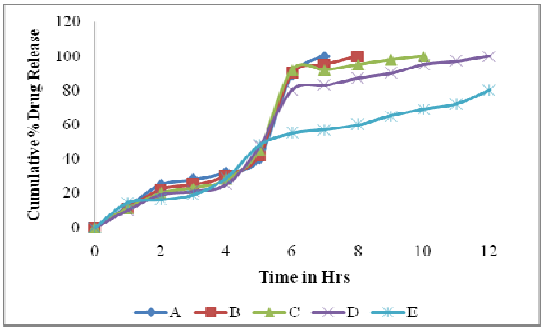

Figure 3 Cumulative percentage drug release (mean ± S.D, n=3) versus time profile for compression coated aceclofenac tablets in SGF (2 h), SIF (pH 7.4) (3 h), and SCF (pH 6.8 containing 4% rat caecal contents) (upto12 h)

CONCLUSION

The overall goal for optimum therapy is to match the needs of the patient while improving the efficiency and safety of the administered drugs. Thus, chronotropic systems for pulsed release of aceclofenac from Pulsincaps after a lag time after 5hrs and complete release after 6 hrs which is equivalent to gastric emptying time and the presence of Guar gum in the coat of compression coated tablets reduces the initial premature drug release in the upper part of GIT and ensures complete release of drug in the colon due to increased susceptibility of guar gum to degradation by bacterial enzymes present in dissolution fluids.

Thus both the formulations were successfully developed for colon targeting of Aceclofenac for treatment of Rheumatoid arthritis.

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