Research Article CODEN: IJPRNK IMPACT FACTOR: 1.862 ISSN: 2277-8713
D Patel, IJPRBS, 2014; Volume 3(2): 716-725 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

FORMULATION AND EVALUATION OF COLON TARGETED SYSTEM OF ACECLOFENAC BY PH AND MICROBIAL TRIGGERED COMBINED APPROACH

D. PATEL[1], K. PATEL[1], H. GOHEL[1], H. JAIN[1], U. UPADHYAY[1]
Sigma Institute of Pharmacy, Vadodara 390019.

Accepted Date: 19/04/2014; Published Date: 27/04/2014

Abstract: The objective of present study is to develop chronopharmaceutical drug delivery system for treatment of rheumatoid arthritis, which are influenced by circadian rhythm and develop pH and microbial triggered formulation to reduce risk of systemic toxicity, reduced risk of local irritation. Arthritis pain mainly take place in the early morning. Chronopharmaceutical drug delivery system is capable of delivering drug when and where it required most. Time-delayed formulation, designed to release drug after a predictable lag time, are intended for oral chronotherapy. Microbial matrix tablets were prepared using different natural polymers. From those optimized batch of each polymer is further going for coating. Coating was carried out by Eudargit S 100. From all natural polymers, xanthan gum and guar gum combination showed better drug release than other natural polymers. Coating of Eudragit S100 showed better release in controlled manner. The programmable chronopharmaceutical drug release has been achieved from xanthan gum and guar gum combination microbial matrix tablet coated with Eudragit S-100 over a 12 hrs period, consistent with the demands of chronotherapeutic drug delivery for rheumatoid arthritis.

Keywords: Aceclofenac, Eudragit S 100, Xanthan gum, Guar gum, Rhematoid arthritis.

PAPER-QR CODE

Corresponding Author: MS. D. PATEL

Access Online On:

www.ijprbs.com

How to Cite This Article:

D Patel, IJPRBS, 2014; Volume 3(2): 716-725

INTRODUCTION

Controlled drug delivery systems for constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern is known as "pulsatile release" [1-3]. For this mode of delivery, it is assumed that constant plasma drug levels are not preferred and that an optimal therapeutic effect comes from a periodically fluctuating drug concentration. Two different methodologies have been broadly investigated as possible solutions to this challenge. One is the fabrication of a delivery system that releases its payload after a predetermined time delay or in pulses of predetermined sequences. The other is to develop a system that can respond to changes in the local environment. Treatment of diabetes with insulin is an example where this type of delivery system is expected to be beneficial.[4] Chronotherapy coordinates drug delivery with human biological rhythms and holds huge promise in areas of pain management and treatment of asthma, heart disease and cancer. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed chronotherapy. [5]

Rheumatoid arthritis (RA) is a chronic inflammatory disorder which affects the joints and is associated with swelling, stiffness and pain. The onset of RA arises usually between the age of 30 and 50, but may also occur at any other age. About Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology and a chronic progressive disease that reduces the quality of life of individuals that suffer from the condition. Although many requirements must be met to establish a diagnosis of RA, morning stiffness is a characteristic feature of RA21. Tumor necrosis factor-α (TNF-α), interleukin-1β (IL1β), and interleukin-6 (IL-6), which are inflammatory cytokines, show high concentrations in human blood and synovial fluid, and excess production of these cytokines plays a central role in the pathogenesis of RA[6-7].

Aceclofenac, phenyl acetic acid derivative, is a novel NSAID used to treat symptomatic pain and inflammation. Aceclofenac is known to have reduced side-effect, especially related to the gastrointestinal tract (GIT) when ingested as 200 mg single daily or in divided doses. The success of arthritis treatment depends on the maintenance of consistent therapeutically effective drug concentration in the body over a period of time. Aceclofenac has a shorter mean plasma elimination half-life of 4 h. Therefore, it is imperative to design prolong releasing dosage form in order to reduce the frequency of dosing and adverse effects, especially since duration of treatment is typically longer for NSAIDS.

Colon-targeted drug delivery have been proposed to target orally administered drugs to the colon, including prodrugs, pH-sensitive polymer, time dependent systems, and microflora-activated systems. Several natural polysaccharides have been investigated for their potential as colon drug carrier systems, and, among them, alginate and chitosan are considered particularly attractive due to their nontoxicity, biocompatibility, mucoadhesion properties, and biodegradability by colonic micro flora. [8]

pH dependent multiparticulate colon specific delivery system is to formulate enteric coated granules. Enteric coating has traditionally been used to prevent drug release in the upper GI tract. Enteric coating polymers are reported to have been used as both binders and as coating materials for granules. [9] The influence of incorporating organic acids in granule matrices on drug release has also been studied[10] most commonly used pH-dependent coating polymers for peroral delivery are methacrylic acid copolymers, Eudragit L100 and Eudragit S100, which dissolve at pH 6.0 and 7.0 respectively. The combination of these two polymers in various ratios makes it possible to manipulate drug release within 6.0-7.0 pH range. It has been reported earlier that the use of Eudragit S alone is not suitable for colonic delivery. [11]

Microbially controlled delivery system is the most appealing as it relies on the unique enzymatic ability of the colonic micro flora and enables a more specific targeting, independent of pH variations along the GI tract. amylose- Eudragit RS/RL coating system even at high coating thickness did not provide sufficient resistance to degradation in acidic and neutral media. The susceptibility of these films to colonic micro flora was also tested in the batch fermentor where the films were found to degrade and there by exhibit colon specificity. [12]

MATERIALS AND METHODS

Materials

Aceclofenac was obtained as a gift sample from Intas Pharmaceuticals, Ahmedabad and all other ingredients and reagents were of analytical grade and were used as received.

Method[13]

Aceclofenac tablets were prepared by wet granulation technique using different polymers as shown in Table no. 1. Formulations were blended and granulated with PVP K 30 using isopropyl alcohol as a solvent .The wet mass was passed through a mesh (1000 µm) sieve and the granules were dried at 50 °C for 30-45 min. and dried granules are sieved (650 µm), lubricated with magnesium stearate and talc mixture and compressed. The optimized batches of polymeric matrix tablet were coated with coating solution of Edragit S in a pan coater apparatus. In-process samples at coating level 10% w/w (% polymeric weight gain) is taken to check the morphology of coating to do dissolution studies in simulated fluids of stomach and

small intestine. A 10% w/w increase in the coating level was selected as an optimum coating percentage level for all the tablets. Then the pH dependent polymeric coated tablets were tested for drug release studies in the simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and simulated colonic fluid separately.

Table 1: Formulation of Aceclofenac colon tablets

INGREDIENT	F1 mg	F2 mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg	F8 mg	F9 mg	F10 mg	F11 mg	F12 mg	F13 mg
Aceclofenac	100	100	100	100	100	100	100	100	100	100	100	100	100
Guargum	30	60	90	-	-	-	-	-	-	-	-	-	30
Xanthan gum	-	-	-	30	60	90	-	-	-	-	-	-	60
Pectin	-	-	-	-	-	-	30	60	90	-	-	-	-
Karaya gum	-	-	-	-	-	-	-	-	-	30	60	90	-
MCC	160	130	100	160	130	100	160	130	100	160	130	100	100
Talc	6	6	6	6	6	6	6	6	6	6	6	6	6
Mg. stearate	4	4	4	4	4	4	4	4	4	4	4	4	4
PVP K30	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
TOTAL	300	300	300	300	300	300	300	300	300	300	300	300	300

Coating solution:

Table 2: Composition of coating solution for F14 – F18 batches

Sr. no.	Ingredients	Quantity
1	Eudratgit S 100	5%
2	Castor oil	0.10%
3	Acetone	100ml

Evaluation parameters

1) Physical appearance

All the controlled release tablets were visually inspected for any tablet defects like capping, lamination, presence of any colored particle.

2) Hardness

The resistance of tablet to breakage under the conditions of storage, transportation and handling before usage depends on its hardness. Hardness of tablet was determined by using Monsanto hardness tester.

3) Friability

Friability was measured by Roche friability tester. 10 tablets are kept in the friability and it is rotated at 25 rpm for 4 minutes. Initial and final weights are then recorded and friability is calculated by following formula.

$$\text{Friability} = \left[\frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \right] * 100$$

4) Weight variation test

Weight variation test were done as per the Indian Pharmacopoeia. 20 tablets were generally taken and were weighed individually and the weight variation was calculated with the use of standard deviation.

5*) In Vitro* drug release studies in presence of rat caecal material: (IAEC/SIP/ 11 /2012-13)

Two wistar rats of body weight (150-200g) with no prior drug treatment were used for all the present ex vivo studies and maintained on normal diet and administered 1ml of 2% dispersion of pectin in water and this treatment was continue for 7 days in order to include the enzyme that specifically act on pectin or xanthan gum or guar gum, 30minutes before starting the study, each rat was sacrificed and abdomen was opened. The caecum was traced, legated at both ends, dissected and immediately transferred in to phosphate buffered saline (PBS) pH 6.8, which was previously bubbled with CO_2. The caecal bag was opened, the contents were weighed homogenized and then suspended in simulated colonic fluid of pH 7.4 to give desired concentration of 2% caecal content. The experiment was carried out with a continuous supply of CO_2 in to the dissolution media. Drug release studies for first 5 hrs were performed as described under section describing *In vitro* drug release studies in simulated gastro intestinal

fluid. After 5 hrs release studies were carried out in simulated colonic fluid containing rat caecal material. Aliquots of samples were withdrawn periodically and replaced with fresh buffer bubbled with CO_2 and analyzed by UV spectrophotometer at λ_{max} 275

6) Coating of pH dependent polymer

Coating of pH dependent polymer was carried out on optimized batch. The composition of coating solution is as shown in table no. 3. Eudragit S 100 as a polymer and castor oil as a plasticizer were used.

7) Kinetic modeling of drug release

The dissolution profile of optimized batch was fitted to zero order, first order, Higuchi to ascertain the kinetic modeling of drug release and the model with the highest correlation coefficient is then considered to be the best model.

8) Stability Studies

The stability study was performed as per ICH guidelines at temperature of 40º C / 75% RH for 3 months. The optimized formulation is then analyzed for drug content and % drug release.

Results and discussion

1) **Hardness, Friability, Weight variation Data:**

Table 3: Evaluation parameters for different formulations

Batch	Hardness (kg cm-2± %S.D) n=3	Friability (%)	Weight variation Avg weight (mg) (%S.D < 10%)
F1	6.22+0.01	0.32	1.93
F2	5.72+0.36	0.76	1.22
F3	6.02+ 0.32	0.52	1.71
F4	5.24+ 0.35	0.49	2.13
F5	6.52+ 0.36	0.39	1.98
F6	6.29+ 0.48	0.59	2.39
F7	6.53+ 0.36	0.66	2.45
F8	5.55+ 0.35	0.42	2.19
F9	6.76+ 0.46	0.59	1.83
F10	6.23+0.35	0.62	2.36
F11	6.67+0.34	0.73	2.59
F12	5.06+0.38	0.79	2.76
F13	5.59+0.36	0.89	2.74

2) ***In Vitro* drug release studies in presence of rat caecal material: (IAEC/SIP/ 11 /2012-13)**

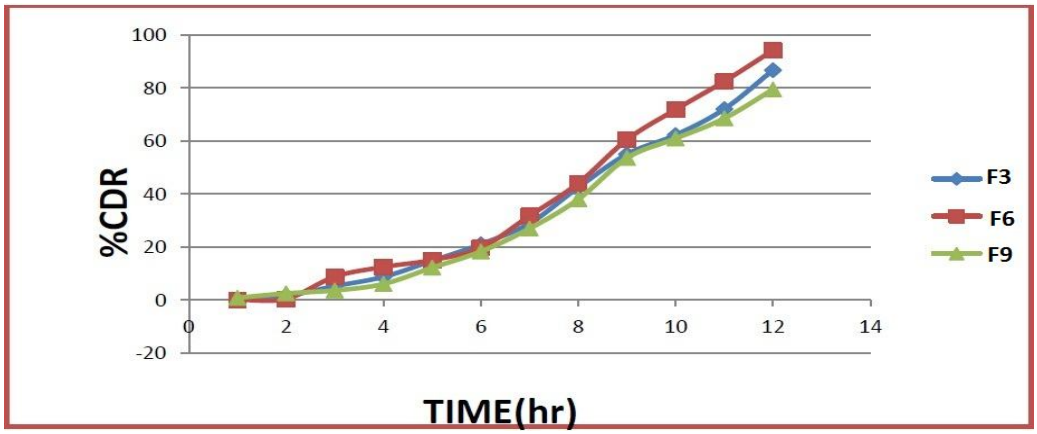

Figure 1*: In-vitro* drug release in presence of rat ceacal for F3, F6, F9 Batches

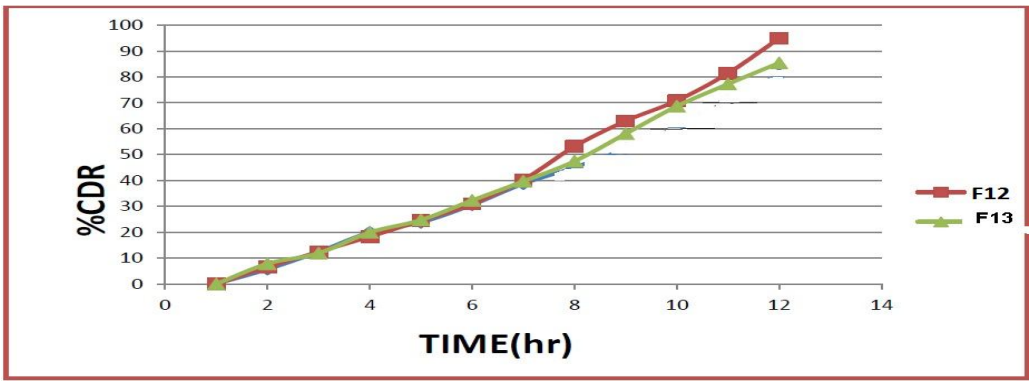

Figure 2*: In-vitro* drug release in presence of rat ceacal for F12, F13 Batches

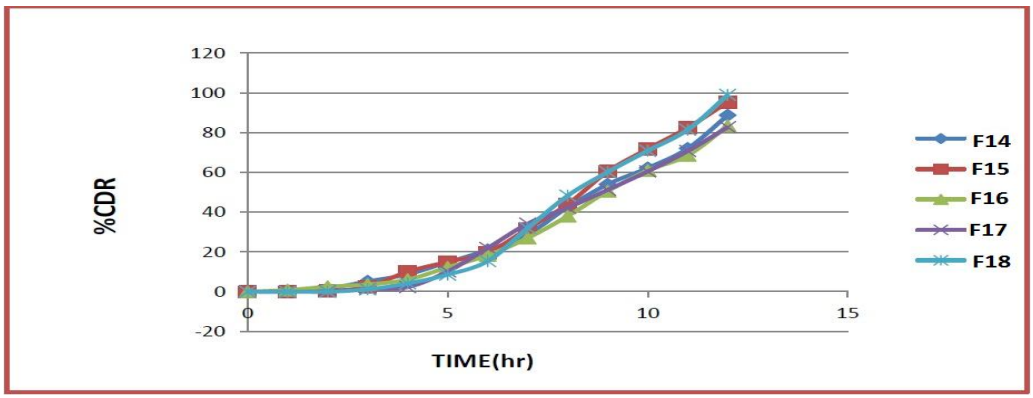

Figure 3: *In-vitro* drug release in presence of rat ceacal for F14 to F18

3) **Kinetic modeling of drug release**

Figure 4: Zero order release for F18 batch

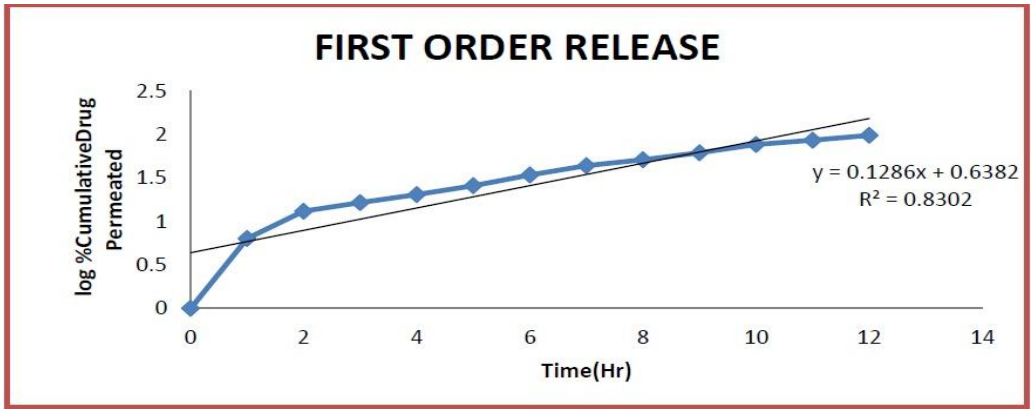

Figure 5: First order release for F18 batch

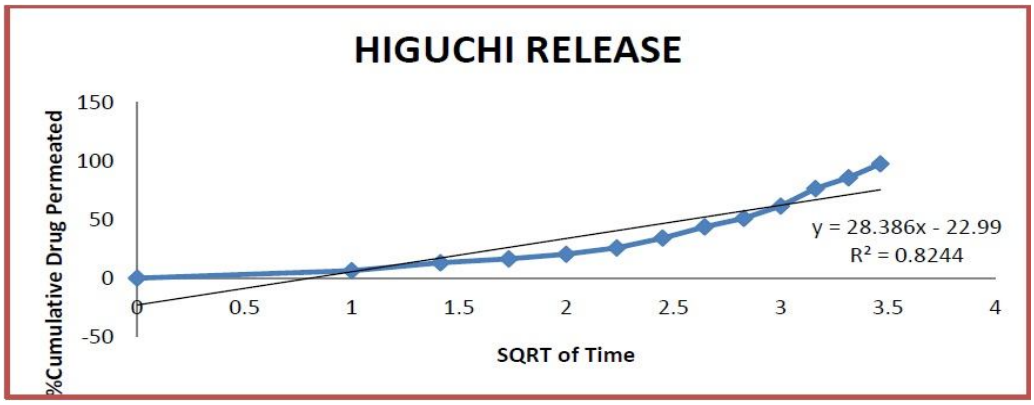

Figure 6: Higuchi release for F18 batch

4) **Stability Studies**

Formulation showing optimum release was selected for stability studies According to ICH guidelines, selected formulation (F18) was stored at 40 ºCtemperature and 75 % relative

humidity (RH) for a period of 3 months. Formulation was evaluated at periodical intervals of one month for drug content. Evaluation parameters do not show any major difference and all are in acceptable limits.

Table 4: Stability study of F18 batch

Formulation code	Parameters	Storage time			
F18	Drug content (%)	Initial	1 month	2 month	3 month
		99.34	99.27	99.08	98.92

Comparison of dissolution of optimized multiparticulate (F18) before and after the tablet was charged to the stability study.

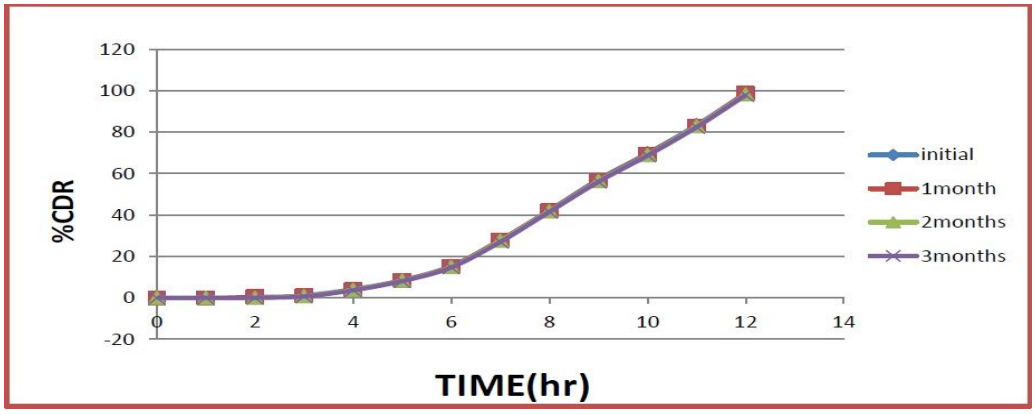

Figure 7: *In-vitro* drug release in presence of rat ceacal for F18 batch at 0, 1, and 3 months

Conclusion

The results obtained indicate that xanthan gum and guar gum combination could be useful as matrix system for sustained drug delivery and passed in different physical evaluation test, and *in vitro* drug release study. Batch F18 with coating of Eudragit S100 shows better release in controlled manner and drug release profile in simulated gastric, intestinal and colonic fluid. The matrix tablet containing Xanthan gum and Guar gum combination as a carrier, PVP K 30 as binder and Eudragit S 100 as a pH dependent polymeric coat suitable for targeting Aceclofenac for local action in the colon.

REFERENCES

1. Bi CY. Chronopharmaceutics: Gimmick or clinically relevant approach to drug delivery- A Review. Journal for Control Release 2004; 98 (3): 337-353.

2. Jain NK Controlled and novel drug delivery. 1st Ed. CBS Publishers; New Delhi, 2002 p-340.

3. Khan MS, Sridhar BK and Srinatha A. Development and evaluation of pH dependent microbed for colon targeting .International Journal of Pharmaceutical Reserch . 2010; 72(1): 18-23.

4. Sarasija S , Stutie P. Chronotherapeutics: Emerging role of biorhythms in optimizing drug therapy. Indian Journal of Pharmaceutical Science. 2005; 67(2): 135-140.

5. Gaikwad M, Belgamwar V, Tekade A, Gattani S and Surana S. Formulation and evaluation of floating, pulsatile, multiparticulates using pH-dependent swellable polymers. Pharmaceutical Development and Technology. 2010; 15(2): 209–216.

6. Watts PJ, Barrow L, Steed KP, Wilson CG, Spiller RC, Melia CD , Davies MC. The transit rate of different–sized model dosage forms through the human colon and the effects of a lactulose induced catharsis. International .Journal of Pharmacology. 1992; 87: 215-221.

7. Marvola M, Nykanen P, Rautio S, Isonen N and Autere AM. Enteric polymers as binders and coating materials in multiple-unit site-specific drug delivery systems. Europian Journal of Pharmaceutical Science, 1999; 7: 259-267.

8. Chambin O, Dupuis G, Championb D, Voilley A and Pourcelot Y . Colon-specific drug delivery: Influence of solution reticulation properties upon pectin beads Performance. International Journal of Pharmaceutics. 2006; 321: 86–93.

9. Saraf S, Aceclofenac: A potent non steroidal anti inflammatory drug. << http://www.pharmainfo.net/review/aceclofenac-potent- nonsteroidal- anti inflammatory drug>>. (accessed on 12 January 2013).

10. Krishnaiah YSR, Satyanarayana V, Kumar BD, Karthikeyan RS and Bhaskar P, In vivo pharmacokinetics in human volunteers: oral administered guar gumbased colon- targeted 5-fluorouracil tablets. *European Journal of Pharmaceutical Science.*2003; 19: 355-362.

11. Lamprecht A, Scaffer U and Lehr CM. A Size dependent targeting of micro- and nano-particulate carriers to the inflamed colonic mucosa. Pharmaceutical Research. 2001; 18: 788-793.

12. Saffran M, Pansky B and Budd GC , Williams FE. Insulin and the gastrointestinal tract. *Journal of Controlled Release* 1997;46: 89-98.

13. Jose S, Prema MT, Chacko AJ, Cinu Thomas A and Souto EB, "Colon specific chitosan microspheres for chronotherapy of chronic stable angina." *Colloids and Surfaces B: Biointerfaces.* 2011; 83: 277–283.