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Design and Characterisation of Aceclofenac Multiparticulate Colon Targeted Drug Delivery

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A B S T R A C T

Present work was design and develop sconsistent and optimized formulations of aceclofenac multiparticulate targeted drug delivery to colon with the following objectives. The first purpose of the study was developing multiparticulate CDDS by means of swelling and time dependent polymers such as hydroxypropyl cellulose (HPC) and ethyl cellulose (ec) embedded on aceclofenac to let loose the drug at colon in a sustained manner.

Keywords: aceclofenac, pellets, CDDS

A R T I C L E I N F O

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1. Introduction

Disease Conditions

Rheumatoid arthritis (**RA**): RA is a malformed and painful joints, it may be persistent or inflammatory disorder that primarily affects joints. This can lead to loss of function and affects the underlying bone and cartilage. The root of diseaseis not completely unstated; develop inflammatory response around the joints secondary to engorgement of synovial cells, fibrous tissue in the synovium and excess synovial fluid.

Types of Irritable bowel syndrome (IBS)

IBS can be grouped as either constipation-predominant (IBS-C), with alternating stool pattern (IBS-A) and diarrhoea-predominant (IBS-D).IBS-D is categorized by bloating, persistent abdominal pain and modification of bowel habits. It was initiated with infectious unhealthiest fever, diarrhoea, and affirmative stool culture or vomiting. Later one has subsequently been termed "post-infectious IBS (IBS-PI)[68-69].

Multiparticulate Pellets Technology

Multiunit particulate systems (MUPS) are a novel technique for controlled and customized drug delivery. Each discrete unit with a diameter of 0.5 – 2 mm has its own release uniqueness and further contributes to the product's effectiveness. Multiple–unit dispersion after administration would be consistent, and each sub-units act as individual modified release entity. Hence variability is reduced by gastric emptying, local accumulation of drug in GI-tract avoided, enhanced residence time and lower inter and intra subject variability on absorption drug to systemic circulation. Pellets are manufactured by both bottom-spray coating (Wurster technology). This process is an automated, well-recognized for providing exceptional coating uniformity and effectiveness. The spray drying minimized by reducing the distance between core pellets and coating material and contributes uniform spherical shape. Convectional pan coating technique that helps in the preparation of pellets by layering. The core pellets encrusted by active drug and binder suspensions by spray application of layering substance. The active substance can be absorbed on core pellets either in powder form or by solution form; layers are densely and quickly applied to core pellets during process[90].

Key factors in developing modified release pellets

Irrespective of the type polymer used for coating the key parameters for the success of pellet coating are as follows[92]. Rate of release should beaccomplished in a repeatable manner for indented formulation.

- The small changes in coating recipe or process conditions should not impact the discharge pattern. Coating Processes should friendly and easy toscale-up from the bench scale to production.
- Finished dosagemust be firm and meticulous; changes in drug release uniqueness should devoid of significant time-dependent.
- Coating ingredient and method must be cost-effective.
- Science base process should selected, so as to endure the authoritarian challenge that leads preface of any pharmaceutical product.

2. Materials and Methods

Materials: Aceclofenac, sugar sphere 30-35#, hpmc (methocel e5), hpc (klucel lf), ethyl cellulose 7 cps, peg 6000, acetone.

Formulation Manufacturing Procedure

Preparation of Aceclofenac colon targeted delayed release pellets: The Aceclofenac colon targeted release pellets formulation involves three different steps which includes drug absorption to sugar spheres by dissolving Aceclofenac and HPMC E5 in acetone. Hydroxypropyl Cellulose was used in swelling polymer covering of drug pellets and functional coating with ethyl cellulose 7cps at different concentrations as mentioned in the composition of formulation's are as described

Chemical evaluation of Aceclofenac CDDS DR pellets

Aceclofenac Drug content by HPLC method: Weigh and remove pellets from 20 caps from that remove pellets containing 50 mg of Aceclofenac. Pre-weighed amount of pellets corresponding to 250 mg of pellets was correctly weighed and poured to 100 ml flasks containing approximately 50 ml of buffer pH 6.8 after lightly powdered. Then shacked to dissolve the drug and volume was made up with buffer pH 6.8 and mixed methodically. Extracted solutionriddle through a 0.22 mm filter and analyzed for drug substance.

3. Results and discussion

In-Vitro Dissolution Studies

Dissolution conditions for Aceclofenac formulation

Polymer coated pellets

Medium: 0.1N HCl for 2 hrs

PH 7.4 Phosphate buffer for 3 hrs

PH 6.8 Phosphate buffer for 12 hrs

Test Preparation procedure

Dissolution medium filled in bowls 900 ml and temp kept at 38±0.5 °C. Capsule doped to each glass beaker and test started. Withdrawn 10 ml of aliquot were at definite time interval with a magnitude of fresh media was replaced. Solution was filtered through 0.45 µ (Millipore) nylon filters. Reject the little quantity of filtrate and 5ml of solution was diluted to 10 ml with same solution.

Compatibility Studies Aceclofenac along with Excipients

The physical mixture of active ingredient (API) and raw materials at various ratios were exposed to different environmental stress conditions as mentioned in table 4.5. The physical responses derived from the study illustrated in table 5.8 and interaction at molecular level and/physical transformation such as phase transition changes of API and along with physical mixtures were illustrated in figures 5.15 and 5.16 measured by DSC. The FTIR spectrum depicted at figure 5.17 and frequencies corresponding to functional groups explained in table 5.9 & 5.10.

***In-Vitro* Profiles**

Aceclofenac: The dissolution studies of finished dosage forms were evaluated by the conditions mentioned in subsection 4.7.1. The rate of drug dissolved at 0.1 N HCl, phosphate buffer pH 7.4 and pH 6.8 were performed individually and continues manner by changing the media one after other. The cumulative % drug release was illustrated in table 5.30, 5.31 and 5.32. The Graphical layout of dissolution profile of individual media portrayed at figure 5.33, 5.34 and 5.35. The cumulative percentage drug release of Aceclofenac colon targeted optimum formulation carried out at continues medium, results were depicted in table 5.33 and graphically at figure 5.36.

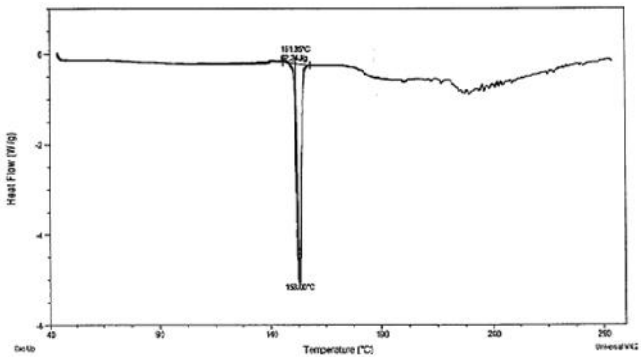

Figure 1: DSC of Aceclofenac pure API

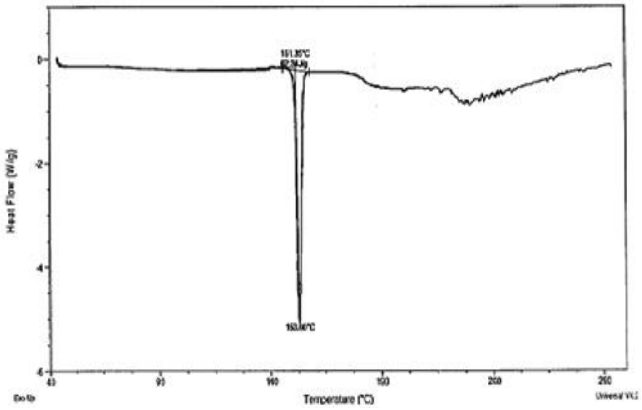

Figure 2: DSC of Aceclofenac + polymer physical mixer

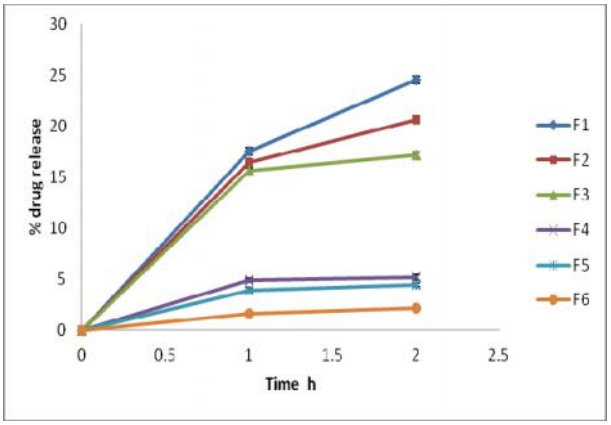

Figure 3: In-vitro drug release in 0.1 N HCl

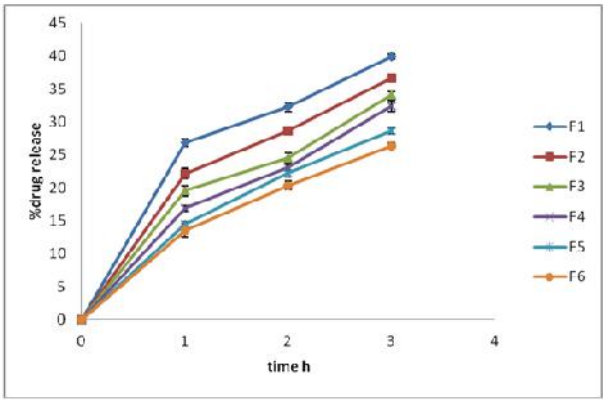

Figure 4: *In-vitro* drug release in pH 7.4 Phosphate buffer

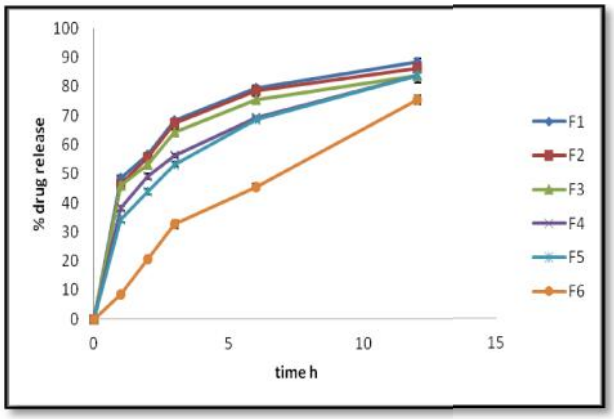

Figure 5: In-vitro drug release in pH 6.8 Phosphate buffer

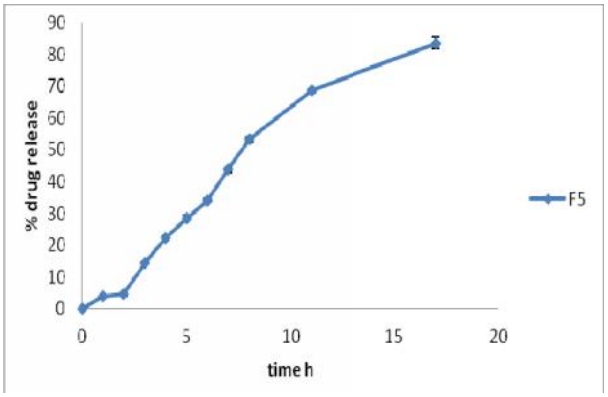

Figure 6: In-vitro drug release of batch F5 in Continuous media

4. Conclusions

The conclusion is summarized for the research work carried out on design of colontargeted drug delivery systems for Aceclofenac. Multi-unit dosage from selected to target drug for site specific action because of its advantage to bypass the dose dumping over single unit. Two different type of design approach exploited in this thesis, one with time dependent outer coating and swelling layer formation coating on inner layer which can impart sustained release of drug at colon; Aceclofenac a nun-steroidal non-inflammatory drug indicated for rheumatic arthritics was selected. The formulation design can impart sustained drug release with a lag time which is convenient for the patient suffering from rheumatoid arthritis. Whereas the second approach, Aceclofenac exhibit low solubility, hence it's a right candidate to formulate delayed release colon targeted multiple release units. In the present investigation, polymer combination that is Hydroxy Propyl cellulose (HPC) as inner coating and Ethyl cellulose as outer coating for Aceclofenac Manufacturing method selected for making colonic delivery using multiple coating on drug layered pellets was well known in industry. So that it can produce on commercial level in a realistic dispensation time using convectional powder layering and/ fluidized-bed coating technique.

These processes were scalable, simple, reproducible and a well-known technique in pharmaceutical industry. The core drug pellets of optimum formulation trials were subjected to percentage drug dissolved analysis and results were found 98% in 30 min for Aceclofenac The compatibility of polymer to active drug at end of four weeks at 40^0c 75% RH conditions reveals that there no physical and chemical interaction was evident from DSC and FTIR studies, this indicate the right selection polymer's for formulation design. The morphology study by scanning electron microscopy exhibits the pellets were spherical shape and cross sectional diagram of pellet shows coating thickness of Aceclofenac pellets were 7.9 mm The dissolution study results showed that coating of time dependent polymer ethyl cellulose at level of 20% and the sustained release polymer hydroxypropyl cellulose at a level of 7% able to retard the formulation. The swelling sub-coating layer transforms drug release after delay in various medium.

Coating build up 12% was also reason to achieve lag time for delivery of Aceclofenac pellets. The delivery systems manufactured for this study ought not to be gravely exaggerated by amplify or a decline in the habitation time because the outer coat is pH-dependent and/ independent. Nevertheless, further studies are required to assess the usefulness of these designs in patients for Rheumatic arthritis by Aceclofenac.

Table 1: Physical mix of Aceclofenac for compatibility studies

S.NO	Name of the Binary Mixture	Composition Ratio
1	Aceclofenac	Not Applicable
2	Aceclofenac + Sugar Sphere	1 : 5
3	Aceclofenac + Hydroxypropyl Cellulose (Klucel LF)	1 : 1
4	Aceclofenac + Ethyl cellulose 7 cps	1 : 1
5	Aceclofenac + Polyethylglycol 6000	1 : 0.5
6	Aceclofenac + Hypromellose (Methocel E5)	1 : 0.5
7	Aceclofenac + Hypromellose + Ethyl cellulose + Hydroxypropyl Cellulose	1:0.5:1:1

Table 2: Physical description results of Aceclofenac and physical mixtures

S.No.	Name of the Binary Mixture	Composition Ratio	Physical Observations
1	Aceclofenac	NA	No colour change
2	Aceclofenac + Sugar Sphere	1 : 5	No colour change
3	Aceclofenac + Hydroxypropyl Cellulose	1 : 1	No colour change
4	Aceclofenac + Ethyl cellulose 7cps	1 : 1	No colour change
5	Aceclofenac + Poly Ethylglycol 6000	1 : 0.5	No colour change
6	Aceclofenac + Hypromellose	1 : 0.5	No colour change
7	Aceclofenac + Hypromellose + Ethyl cellulose + Hydroxypropyl Cellulose	1:0.5:1:1	No colour change

Table 3: Physical characteristics of Aceclofenac CDDS DR pellets

Characteristics	F1	F2	F3	F4	F5	F6
Bulk density (g/ml)	0.548	0.556	0.545	0.521	0.550	0.534
Tapped density (g/ml)	0.616	0.626	0.607	0.637	0.609	0.634
Angle of repose (°)	33	32	33	33.4	32.6	33.2
Hausner's ratio	1.12	1.12	1.11	1.11	1.10	1.18
Carr's index (%)	11.0	11.18	10.21	10.54	9.69	11.0

Table 4: Result of drug pellets contents

Formulation	Drug content (mg/100 mg pellets)	% drug content
Fa	18.34 ± 0.15	91.7
Fb	20.12 ± 0.14	100.6
F1	20.36 ± 0.15	101.8
F2	20.42 ± 0.12	102.1
F3	20.39 ± 0.14	102.0
F4	20.38 ± 0.12	101.9
F5	20.40 ± 0.11	102.0
F6	20.32 ± 0.15	101.5

Table 5: Cumulative % Drug release in 0.1 N HCl media

Time (h)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	17.52±0.43	16.4±0.46	15.6±0.61	4.9±0.76	3.9±0.36	1.6±0.07
2	24.52± 0.46	20.64±0.45	17.13±0.44	5.14±0.77	4.45±0.35	2.17±0.17

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