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Formulation and Evaluation of Colon Targeted Aceclofenac Sodium sustained release Tablets

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Abstract : The aim of the study was to develop and evaluate SR matrix tablet of Aceclofenac for colonic delivery by exploiting prolonged release characteristics of HPMC K4M with pH dependent solubility property of a Eudragit S100. Extended release matrix tablet were prepared by using combination of hydrophilic polymer HPMC and Synthetic Eudragit S100. The pH dependent release was achieved by coating matrix tablet with Eudragit S100, soluble at pH7. The formulation HS3 was most likely to provide targeting of aceclofenac in the colon owing to its minimal release of the drug in the first 4 hr and give release up to 12 hr with 67.78%. The presence of hydrophilic HPMCK100M sustains the drug release in colon due to formation of gel layer around the core tablet and EudragitS100 releases drug slowly over prolong period of time by forming pores.
Key words : Aceclofenac sodium, colon target, sustained release, Eudragits.

Introduction:

Oral drug delivery is a widely accepted route of administration of therapeutically active moieties; the gastrointestinal tract presents several types of barriers to oral drug delivery. Colon targeted drug delivery is useful in colonic diseases treatment like IBS, IBD, Crohn's disease and ulcerative colitis, oral delivery of proteins and peptides.[1] Introduction of compression coated tablets as sustained release has given a new breakout for novel drug delivery system (NDDS).[2] A medical rationale for the development of colonic drug delivery platforms includes: reduction of adverse effect in treatment of colonic inflammation and colon motility disorders, elucidation of mode of action of some non-steroidal anti-inflammatory drugs, absorption of drug efficiently in colon, enhancement of drug absorption works better in colon than small intestine, better anticipated absorption of protein/ peptide drugs from large bowel owing to reduced proteolytic activity, the unique metabolic activity of colon.[3]

Aceclofenac is one of the emerging NSAID molecules for arthritis treatment. A newer derivative of Diclofenac and has less gastrointestinal complications.The short biological half-life (4 h) and frequent dosing make Aceclofenac an ideal candidate for sustained release dosage forms.[4]Aceclofenac is a 2-[2-[2-[(2,6-dichlorophenyl) amino] phenyl]acetyl]oxy]-acetic acid, a highly potent member of a new class of compounds of non steroidal anti-inflammatory drug available in oral formulations for the management of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac directly blocks PGE2 secretion at the site of inflammation by inhibiting IL-beta and TNF in the inflammatory cells.[5]Aceclofenac shows pH dependant solubility.

NSAID'S also exerts preventive effect against cancer.[6] Hydrophilic polymers are widely used for formulation of SR dosage form.[2]Hydroxypropyl methyl cellulose (HPMC) widely used to prolong the drug

release due to rapid hydration and gelling characteristic along with low toxicity. Due to non-toxicity, easy handling and no requirement of specified technology for production of sustained release tablets, HPMC is often used as release retarding materials. [7,8]The EudragitS100 is the pH dependant polymer. The presence of Eudragit in coat helps to retard initial swelling in acidic environment, but in alkaline pH it helps in drug release by formation of pores. An important issue in the SR dosage form development is to design an optimized formulation of appropriate dissolution rate with minimum number of trials.[9]

Materials and Method

Materials:

Aceclofenac and was received from VamaPharma, Nagpur India as a gift sample. HPMCK100M was received from Alkem laboratories from Mumbai and EudragitS100 from Degussa (Evonik) Mumbai as a gift sample.

Methods:

Drug polymer compatibility studies

FT-IR studies

Drug polymer compatibility studies were carried out using FT-IR (Shimadzu 8400 S, CE). Infrared spectrum of pure drug was seen in between 400-4000 cm^{-1}.

DSC studies

Thermal analysis of drug and polymer was carried out using Differential Scanning Calorimetry (Mettlor Toledo DSC 822).

Spectrophotometric method for estimation of Aceclofenac

Spectrophotometric estimation of Aceclofenac was done in three different medium as 1.2 pH buffer, 6.8 pH phosphate buffer, 7.4 pH phosphate buffer at 273 nm in 1.2 pH buffer and 275 nm in 6.8 and 7.4 pH phosphate buffer and calibration curves were plotted.

Preparation of core tablets

For the preparation of core tablet granules of Aceclofenac and excipient was prepared utilizing wet granulation technique with 5% starch paste as binder. The prepared granules was then passed through sieve no. 22 and evaluated for granule property. The prepared granules then compressed as core tablet using 6 mm round punch optimizing the hardness.

Table 1: Formulation of core tablet

Sr. no.	Ingredients	Amount (mg)
1	Aceclofenac	100
2	Magnesium stearate	2
3	Talc	2
4	Microcrystalline cellulose	46
5	Starch paste 5%	q. s.

Preparation of Aceclofenac plain polymer compression coated tablet

The core tablets were coated with plain polymers alone (core tablet +HPMCK100M) and (core tablet + EudragitS100) in ratios as depicted in table 2anmd in combination as shown in table 3.. The prepared tablets were evaluated for tablet properties same as for core and compression coated tablets. In-vitro drug release studies were carried out maintaining all the conditions same as the previous one.

Table No 2:Formula for plain polymer coated tablet

Sr.No	**Polymers**	**Quantity (mg)**		
		H1	H2	H3
1	HPMCK100M	50	100	150
Sr.No	**Polymers**	**Quantity (mg)**		
		S1	S2	S3
2	EudragitS100	50	100	150

Table No 3:formulation contianing Combination of plomers

Tablet ingredients (mg)	**Formulation code**		
	SH1	**SH2**	**SH3**
Aceclofenac	100	100	100
HPMCK100M	100	75	50
EudragitS100	50	75	100
Magnesium stearate	1.5	1.5	1.5
Talc	1.5	1.5	1.5
Microcrystalline cellulose	47	47	47
Total (mg)	225	330	375

Physical characterization of core and compression coated tablets

The designed core and compression coated tablet formulations were studied for their physical properties like weight variation, hardness, friability, diameter, thickness and drug content uniformity. For estimating weight variation 20 tablets from each formulation were weighed using a single pan electronic balance (Elico, Mumbai, India). The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability of six tablets from each formulation was determined in a Roche's friabilator respectively. The diameter and thickness of five core and compression coated tablets was determined by using Vernier caliper's and average weight were calculated. For the estimation of dug content, six tablets were crushed, and the aliquots of powder equivalent to 100 mg of drug was dissolved in phosphate buffer 7.4 pH and analyzed spectrophotometrically at 275 nm.

In-vitro drug release studies of compression coated tablets

Integration of compression coated Aceclofenac tablets in the physiological environment of stomach and small intestine were evaluated under the conditions mimicking mouth to colon transit was assessed by in-vitro drug release studies. The In-vitro drug release was determined by USP apparatus- type II, paddle dissolution test apparatus (Tab machine dissolution tester Model No. DRS-14).The release of Aceclofenac from coated tablets was performed at 37±0.1^{0}C. The rotation speed was 50 rpmand the volume of the dissolution medium was 900 ml in three different medium. The tablets were tested for drug release for 2 hr in 1.2 pH/0.1N HCL (900 ml) as the average gastric emptying time is about 2 hr. Then the dissolution medium was replaced with 6.8 pH phosphate buffer (900 ml) for next 3 hr as average intestinal transit time is about 3 hr. Then again the dissolution medium was replaced with 7.4 pH phosphate buffer (900 ml) for next 7 hr as the average colonic transit time is about 23 hr, to complete total 12 hr dissolution study. At the end of time periods, the 5 ml sample were taken separately, from which 1 ml was pipette out and replaced with fresh media after each hr. solution samples were analyzed by UV spectrophotometer at their respected wavelength.The % drug release and % cumulative drug release at different time intervals was calculated using PCP DISSO–V3 software.(Poona College of Pharmacy, Pune, India).

Release kinetic study of compression coated tablets

The release models employed for study of kinetics include zero-order; first-order, Higuchi Eq.and Hixson-Crowell Eq. The exponential relation was utilized by these scientists to describe the Fickian and Non-Fickian release behavior of controlled release systems.[10-13]

Dissolution parameters

Mean Dissolution Time (t_{25}, t_{50}, t_{75})

The MDT is the arithmetic mean value of any dissolution profile[14]. The technique that is used to calculate MDT can be divided into model-independent and model-dependent methods. In order to compare the release profile of different formulas with possible difference in release mechanisms, a mean dissolution time (MDT) was calculated using the following equation.

MDT = (n/n+1). K-1/n

Where n = release exponent and k = release rate constant

Percent swelling and erosion study

The swelling studies were carried out by measuring initial diameter, height and weight of the tablet. The tablets placed in a dissolution medium as 1.2 pH buffer, 6.8 pH phosphate buffer and 7.4 pH phosphate buffer at $37^0 \pm 0.1^0$ c for 12 hr. Swollen tablets were withdrawn from medium at an interval of 1 hour.[15,16] Extra buffer present on surface was gently wiped out with soft tissue paper and the swelling index was measured at predetermined time interval. The swelling ratio was calculated by formula

SR = Wg – Wo/ Wo

Where SR = swelling ratio, Wo= initial weight of tablet, Wg = final weight of tablet. Take weight of tablet after every hour for 12 hr.Erosion study was done by formula,

E = 100 (Wi – Wf) / Wf

Where, Wf = final mass of same dried sample, Wi = initial mass of sample.

Statistical Analysis:

The data was subjected to two ways ANOVA followed by Bonferronipost test for analyzing the statistical difference using the software Graph pad prism (San Diego, CA) and in all the cases $p < 0.001$ was considered as significant.

Result and Discussion

The present study was aimed at developing oral colon targeted formulation of Aceclofenac. The release of small percentage of drug from the tablet in the physiological environment of stomach and small intestine is the serious consideration for drugs showing deleterious effects on stomach and small intestine. The drug delivery targeted to colon should remain intact in the stomach and small intestine, but should release the drug in colon.

Study of physical interaction between drug and polymer:

The FT-IR specra of pure Aceclofenac and its physical mixture revealed no considerable changes in IR peaks of Aceclofenac, indicating absence of interaction between drug and polymer used. Fro the results of DSC studies it was concluded that no appreciable change in the melting endotherm was found which further supports the IR spectroscopy results.

Tablet characteristics:

The tablet hardness, thickness, weight variations, and friability for each formulation are presented in Tabel 4 and 5. In determinations of tablet weights, all formulations weights were found to be within pharmacopoeia limits. A plain punch with the same radius each time was used for all formulations in tablet pressing, and the differences in tablet radius was not significant ($P < 0.05$).Friability value of all formulations and commercial tablets less than 1% indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed. The average percentage deviation of all tablet formulations was found to be within the above limit, as per official pharmacopeia requirements. The manufactured tablets showed low weight variations and a high degree of drug content uniformity.

Table No 4: Physical characterization of plain tablets

F.Cod	Hardness† (Kg/cm^2)	Friability* (%)	Weight Variation(gm)#	Diameter (mm)	Thickness† (mm)	Drug Content#
H1	4.9±0.049	0.203±0.01	0.457±0.04	10.01±0.053	3.12±0.03	98.18±0.5
H2	5.3±0.11	0.242±0.030	0.508±0.08	9.97±0.07	4.88±0.02	98.01±1.3
H3	4.97±0.04	0.305±0.03	0.423±0.11	10.02±0.03	4.60±0.02	98.24±1.3
S1	50.2±0.07218	0.212±0.01	0.577±0.19	9.83±0.10	3.05±0.01	97.97±1.4
S2	5.2±0.0781	0.247±0.045	0.424±0.06	10.03±0.07	4.47±0.01	99.08±0.2
S3	.1±0.1723	0.302±0.03	0.512±0.20	10.03±0.09	4.59±0.35	99.51±0.9

Table No 5: Physical characterization of core and combination tablets

FCo	Hardness† (Kg/cm^2)	Friability* (%)	WeightVariation (gm)#	Diameter (mm)	Thickness† (mm)	Drug Content#
core	3.08±0.02	0.298±0.08	0.157±0.02	5.97±0.03	2.97±0.048	99.18±0.5
SH1	5.12±0.09	0.342±0.05	0.220±0.018	10.03±0.04	5.08±0.02	98.76±1.1
SH2	5.18±0.07	0.482±0.03	0.327±0.07	10.07±0.37	5.23±0.019	98.22±1.2
SH3	5.14±0.04	0.327±0.04	0.379±0.01	10.01±0.10	5.04±0.040	99.96±1.1

Drug release studies:

The cumulative amount of Aceclofenac released from physical mixture coated tablets of batches H1- S3 was shown in figure 1 .The HPMCK100M and EudragitS100 as a compression coat has the potential to protect the drug from being released in the physiological environment of stomach and small intestine. The plain polymer batches confirms as concentration of polymer increases drug release decreases.(statistically found significant as $p<0.001$). In-vitro drug release study of combination tablet formulations as (HS1HS2 , HS3 and Marketed tablet) was as shown in table 2.

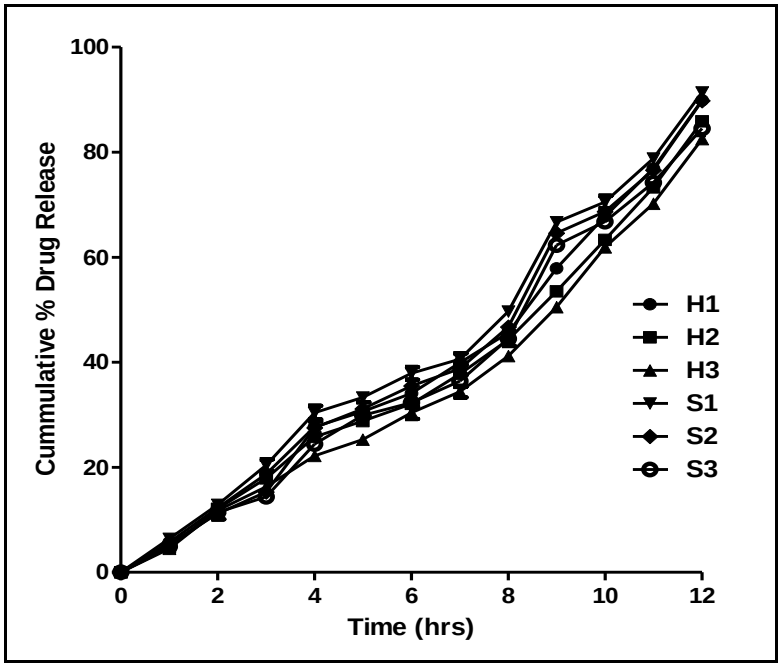

Figure 1:Cummultive Percent release of Batch H1-S3

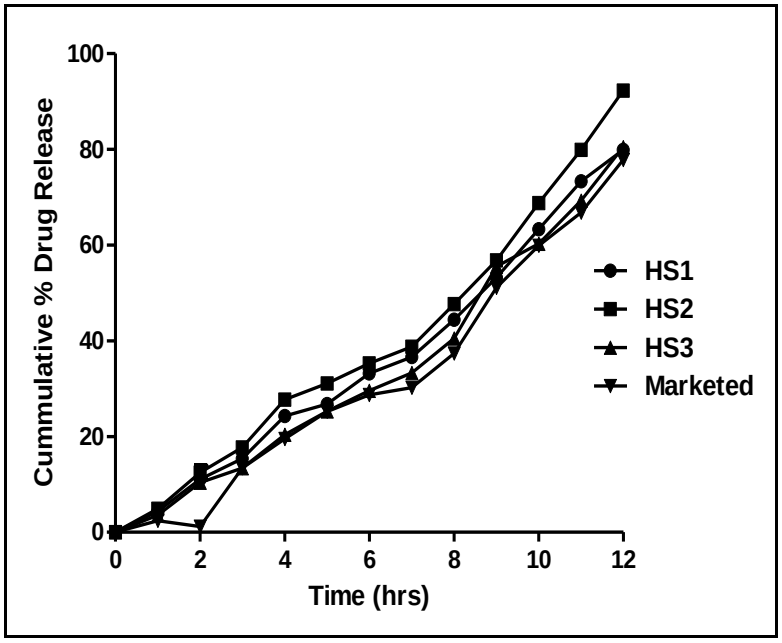

Figure 2:Cummultive Percent release of Batch H1-S3

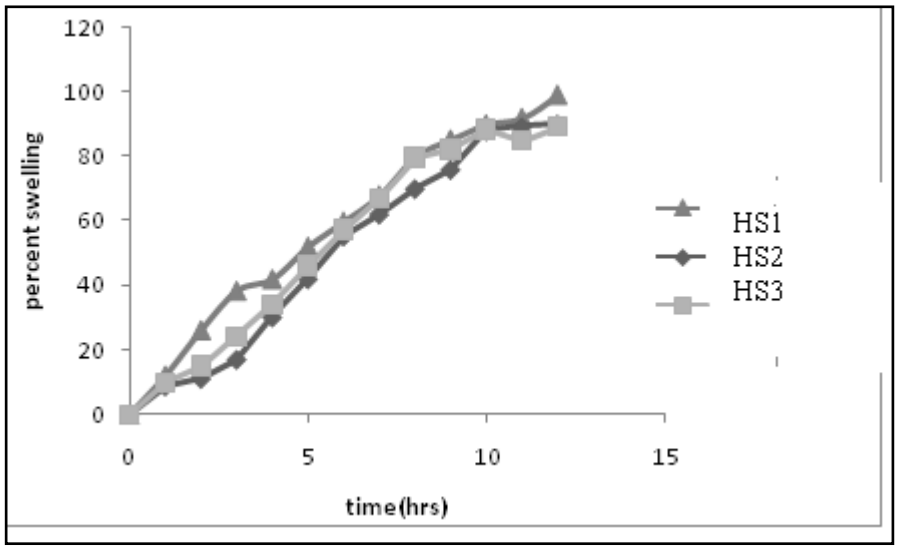

Figure 3: Degree of Percentage Swelling

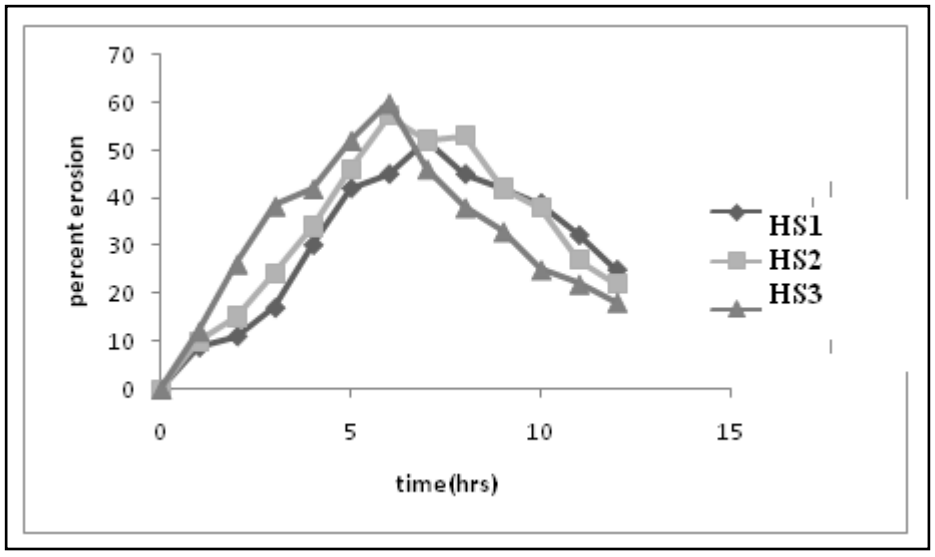

Figure4: Degree of Percentage Erosion

Release kinetic study of compression coated tablets

The release models employed for studyof kinetics include zero-order; first-order, Higuchi Eq.and Hixson-Crowell Eq. The exponential relation was utilized by these scientists to describe the Fickian and Non-Fickian release behavior of controlled release systems. The tablets coated with EudragitS100 (S1, S2 and S3) alone showed Higuchi release. batch H1 H2 and H3 showed Higuchi release kinetics. Batch SH1, SH2and SH3 showed Hixon-crowell release.

Dissolution study:

The dissolution parameters as t25%, t50%, t75% and MDT for all the tablet batches were studied. The MDT were found to be significantly higher when the combination of HPMCK100M with EudragotS100 were carried out than the plain polymers alone, which clearly indicated sustained release nature of the combination. The dissolution parameters was as shown in table 6.

Table 6: Dissolution parameters for Plain and combination batches

F Code	t_{25}(%)	t_{50}(%)	t_{75}(%)	Mean Dissolution Time (hr)
H1	2.5	5.0	7.5	3.40
H2	2.8	5.6	8.5	3.54
H3	5.7	12.8	22.9	3.73
S1	2.7	4.8	6.7	3.31
S2	1.3	5.1	11.4	3.61
S3	2.7	10.8	2.42	4.12
SH1	3.2	10.3	13.1	4.20
SH2	3.3	10..5	13.5	4.35
SH3	2.2	11.3	19.0	5.24

Swelling study of optimized compression coated tablet

All the combiantion batches HS1 HS2 and HS3shows increase in weight. There was significant increase in percent swelling of tablet with increased concentration of polymer. Among all three batches HS3 batch shows more swelling index as compaired to HS1 and HS2 respectively aqs shown in Table 3 and 4 which indicated that percent erosion decreased with increase in polymer concentration.

Conclusion:

Thus from the above study it was concluded that, the presence of Eudragit S 100 in the coat reduces initial swelling of HPMCK100M which retard the drug release in physiological environment of GIT and ensures maximum drug release in colon due to its pH dependant solubility in dissolution fluid.The presence of hydrophilic HPMCK100M sustains the drug release in colon due to formation of gel layer around the core tablet and EudragitS100 releases drug slowly over prolong period of time by forming pores.

This investigation clearly indicates that HPMCK100M and EudragitS100 in the form of compression coat could be used as potential carrier for drug targeting in colon.

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