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Formulation and Evaluation of Aceclofenac Compression Coated Tablets for Colon Drug Delivery

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ABSTRACT

The purpose of this study was to formulate and evaluate compression coated tablets of Aceclofenac using different polymers such as guar gum and HPMC as coating materials. The tablets were prepared by using guar gum and HPMC in various proportion. The core tablet was prepared by wet granulation technique. The core tablet was then coated using different proportions of guar gum and HPMC by direct compression. The coated tablets and the core tablets were evaluated for drug content, drug loading efficiency, disintegration time and in vitro drug release. The 9 batches of compression coated tablets were prepared. It was found that the compression coated formulation release 0 to 6.09% of Aceclofenac in the physiological environment of the stomach and small intestine. The compression coated formulation containing only guar gum released a maximum of 29.79% at the end of 6 hours without rat cecal contents. The invitro studies were then carried out in the presence of rat cecal contents for 6 hours and the drug release was found to be 91.85%. It was concluded that the batch CF6 was the optimized formulation as it released 91.85% of the drug in 6hours. The results revealed that the tablets compression coated with guar gum:HPMC in the ratio 4:1 provided targeting of Aceclofenac to colon as it released minimal drug in the physiological environment of the stomach, small intestine and more than 90% in the colon.

Keywords: Aceclofenac, guar gum, HPMC, compression coating, colon targeted drug delivery

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INTRODUCTION

Colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e.colon). These delayed mechanisms are designed to improve the efficacy of the drug by concentrating the drug molecules where they are needed most, and also minimize the potential side effects and drug instability issues associated with premature release of drug in the upper parts of the GIT, namely stomach and small intestine.

The criteria for the selection of drugs for CDDS are the best Candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery. Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems.

Compression coating has gained increased interest in the recent years for creating modified released products. It involves the compaction of granular materials around a preformed tablet core using specially designed tableting equipment. Compression coating is a dry process. This type of tablet (compression coated tablet) has two parts, internal core and surrounding coat. The core is a small porous tablet and prepared on one turret. For preparing the final tablet, a bigger die cavity in another turret is used in which first the coat material is filled to half and then core tablet is mechanically transferred, again the remaining space is filled with coat material and finally compression force is applied.

MATERIALS AND METHODS

Aceclofenac was obtained as a gift sample from Sun Glow Pharmaceuticals Ltd, microcrystalline cellulose was obtained from Indian Research Products, cross linked PVP and starch were obtained from SISCO Research Laboratory Pvt. Ltd., magnesium stearate , talc and guar gum were obtained from Loba Chemie Pvt. Ltd and HPMC was obtained as a gift sample from Orchid Pharmaceuticals Pvt. Ltd.

Preparation of fast disintegrating Aceclofenac core tablets

Rapidly disintegrating aceclofenac core tablets (average weight 125mg) were prepared by direct compression technique. A weighed quantity of the drug, Cross linked PVP, lactose, talc and magnesium stearate required for 50 tablets of each batch was thoroughly mixed with

mortar, and pestle and passed through the mesh (250µm) to ensure complete mixing. The uniformity of mixing was assessed by conducting content uniformity test on the sample of powder mixture. Quantity weighing 125mg was taken and compressed into tablets using 8mm round; flat and plain punches on a single station tablet punching machine (Cadmach, India).The quality control tests such as thickness, weight variation, hardness, disintegration, friability and dissolution were performed on the core tablets.

Preparation of Aceclofenac compression-coated tablets

After confirming compliance with the above mentioned tests, the formulated core tablets were compression-coated with the different granular coat formulation of GG-LBG mixture and HPMC in different ratios with a coat weight of 350mg. For compression coating about 45% (180mg) of coat weight granular 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 remainder 55% (220mg) of the coat granular material. The coating material was then compressed around the core tablet by using 11 mm round flat and plain punches.

Table 3 Composition of fast disintegrating Aceclofenac core tablets

Ingredients	Quantity (mg) Present In Core Formulation
Aceclofenac	**100**
Micro Crystalline Cellulose	**15**
Cross Linked PVP	**6.25**
Magnesium Stearate	**2.50**
Talc	**1.25**
Total Weight	**125**

Table 4 Composition of granular coat formulation for Aceclofenac core tablets

Ingredients	QUANTITY PRESENT IN THE COAT FORMULATION (mg)								
	CF1	**CF2**	**CF3**	**CF4**	**CF5**	**CF6**	**CF7**	**CF8**	**CF9**
Guar Gum	280	245	210	175	157.5	140	148.75	157.5	166.25
HPMC K4 M	-	-	-	-	-	35	26.25	17.5	8.75
Micro Crystalline Cellulose	61.25	96.25	131.25	166.25	80	70	70	70	70
Talc	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25	5.25
Magnesium Stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total	350	350	350	350	350	350	350	350	350

EVALUATION OF TABLETS

The compressed tablets are evaluated for physicochemical parameters such as thickness, weight variation, hardness, friability, drug content, disintegration and in vitro dissolution studies. The thickness and diameter of tablet carried out using micrometer screw gauge. For estimating weight variation, twenty tablets of each formulation were selected

at random, individually weighed in a single pan electronic balance and the average weight was calculated. The hardness of the tablets was measured using Monsanto hardness tester. Five tablets from each batch were used for hardness studies and results were expressed in Kg/cm^2. The friability of five tablets was measured using Roche friability test apparatus for 4 mins at 25 rpm. The disintegration of the core tablets was carried out using the disintegration apparatus. The time for disintegration of ODTs is generally <1min and actual disintegration time that the patient can experience ranges from 5 to 30s. The drug content studies were done to assess the uniformity of drug content in the core tablets.

Drug content uniformity:

The core and the compression coated tablets of Aceclofenac were tested for their drug content. The 10 tablets were finely powdered and quantity of powder equivalent to 100mg of aceclofenac was weighed accurately and transferred to 100ml volumetric flasks containing 50ml of phosphate buffer pH 6.8 and allowed to stand for 8 hours with intermittent shaking to ensure complete solubility of the drug. The solution was then made up to 100ml with phosphate buffer pH6.8 and mixed thoroughly. The solution was filtered, diluted and drug content was estimated by UV- spectrophotometer at 276nm.

Dissolution studies

In vitro drug release studies in artificial gastric and intestinal fluid

The ability of the prepared compression-coated tablet formulation to prevent or remain intact with respect to time in the physiological environment of stomach and small intestine in pH conditions prevailing in stomach and small intestine was assessed by in vitro drug release in the USP dissolution test apparatus type I, 100rpm, 37°C ± 0.5^oC temperature for 2 h in pH 1.2 (900ml) as the average gastric emptying time is 2h. Then the dissolution media is replaced with pH7.4 phosphate buffer (900ml) and dissolution was carried on for another 3h as the usual small intestine transit time is 3-5h. Dissolution was then continued in pH 6.8 phosphate buffer till the completion of 24h as the usual colon transit time is 20-30h. At the end of time periods 5ml sample was withdrawn and analyzed for percentage drug release by UV spectrophotometer at 276nm.

In vitro drug release studies in artificial rat cecal content fluid

The in vitro drug release studies were carried out using USP dissolution test apparatus type I, 100rpm, 37 °C with slight modifications. A beaker (capacity 200ml) containing 150ml of 4% rat cecal content medium was immersed in phosphate buffer pH 6.8 maintained in 1000ml vessel which in turn was placed in the water bath of the apparatus. The swollen formulation after completing the dissolution studies in 0.1M HCl (2h) and phosphate buffer pH 7.4 (3h) were placed in the basket of the apparatus immersed in the rat cecal content medium maintained in the 200ml beaker. As the cecum is naturally anaerobic, the experiment was carried with

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continuous supply of carbon dioxide into the beaker. At the end of the time period, 3ml sample was withdrawn, centrifuged, diluted and analyzed for percentage drug release by UV spectrophotometer at 276nm.

The drug release mechanism can be studied by using mathematical model equations such as zero order, first order, Higuchi`s model and Korsmeyer-Peppas model.

Table 1: Mechanism of drug release

Mechanism of drug release	Equation
Zero order	$\%R = K_0t$
First order	$\text{Log \% UR} = \log R_\infty - k_1t/2.303$
Higuchi`s equation	$\% R = K_2(t)^{0.5}$
Korsmeyer-Peppas equation	$\% R = K_3t^n$

Where, R is the percentage of drug released or dissolved
UR is the percentage of drug unreleased
K_0, K_1, K_2, K_3 are the rate constants for zero order, first order, Higuchi`s and
Korsmeyer – Peppas equations respectively
t is the time
n is the release exponent
The n value is used to characterize different release mechanisms as given in table 1 for cylindrical shaped matrices.

Table 2 Limits for transport system

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case II transport
n>0.89	Super Case II transport

There are several simultaneous process considered in this model:

- Diffusion of water into the tablet
- Swelling of the tablet as water enters
- Formation of gel
- Diffusion of drug and filler out of the tablet
- Dissolution of the polymer matrix

Key attributes of the model include:

- Tablet geometry is cylindrical
- Water and drug diffusion coefficients vary as functions of water concentration
- Polymer dissolution is incorporated
- Change in tablet volume is considered

By incorporating the first 60% of release data, mechanism of release can be indicated according to Korsmeyer where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxational release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport

mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. describes the limits of this analysis for cylindrical shape, e.g. a tablet. The value of the release exponent in ibuprofen sustained release obtained as 0.2465 which as per table 1 is beyond the limits of Korsmeyer model so-called power law. The power law can only give limited insight into the exact release mechanism of the drug. Even if values of the exponent n are found that would indicate a diffusion controlled drug release mechanism.

RESULTS AND DISCUSSION

The rapidly disintegrating Aceclofenac core tablets were prepared by wet granulation method. The hardness of the core tablet was found to be 3.0 kg/cm^2 hardness. The average weight of the core tablet was fixed as 125mg in order to accommodate maximum amount of the coating material. The physical parameters of the core tablet formulation was found to be within the limits. The disintegration time of the core tablet was found to be 50 sec. The friability of the core tablets was found to be 0.4% and the thickness was found to be 2.08mm. The core tablets showed 99.26% of the labeled amount of drug indicating uniformed drug content. All the tablet formulations complied with the in-house specification for weight variation, drug content, hardness and friability.

The core tablets were coated with guar gum and HPMC polymers blend by compression coating technique. The coating blend was prepared using various ratios of guar gum and HPMC. The ability of the compression coated tablet to remain intact in the physiological condition of the stomach was tested in0.1N HCl, pH 1.2 for 2 hours and phosphate buffer, pH 7.4 for 3 hours. At the end of 5 hours, the buffer was replaced with phosphate buffer, pH 6.8 without rat cecal contents for 6 hours as mentioned in the above table.

The invitro study was then carried out with rat cecal contents in phosphate buffer pH 6.8 for 6 hours and the drug release was found as mentioned in the above table. In formulation batches CF1 to CF5, guar gum was the single polymer used and the drug release increased as the concentration of guar gum decreased, 68.56%, 70.45%, 77.89%, 79.26% and 81.14%.

In formulation batches, CF6 to CF9, guar gum and HPMC blend were used in various ratios ranging from 19:1 to 4:1. When the polymer ratio was decreased, the drug release was more, as the polymer coat was completely hydrated and subsequently degraded by the cecal enzymes. Hence, as the ratio of polymers was increased, the drug release was decreased.

When guar gum was formulated as single polymer, sudden bursting of tablets was seen. This might be due to the rapid swelling of the gum polymer. When it was mixed in high concentration, the drug release was reduced due to the decrease in porosity. As the concentration of guar gum was increased, on swelling, tortuocity increased as a result of which the channels get zigzagged and the drug was unable to come out of the system. In order to

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improve the mechanical strength and to control the initial bursting of the tablet, HPMC was added as a polymer.

The drug release from the core tablet was explained by the use of mathematical model equations such as zero order, first order, Higuchi`s and Korsmeyer-Peppas equations.

From table 7, it was concluded that the optimized formulation, CF6, followed zero order release where the drug was released by diffusion and followed super case II transport.

Table 5: Physical properties of Aceclofenac core and compression coated tablets

FORMULATION	DRUG CONTENT (%)	FRIABILITY (%)	HARDNESS (kg/cm$^{2)*}$	Deviation in weight variation (%)*	THICKNESS (mm)*
Core tablet	101.32	0.40	3.0±0.14	±1.870	2.2±0.06
CF1	99.65	0.17	5.1±0.11	±1.074	4.2±0.03
CF2	100.25	0.26	5.4±0.13	±1.053	4.7±0.02
CF3	99.56	0.54	5.2±0.12	±1.061	4.7±0.04
CF4	98.54	0.45	5.0±0.15	±1.055	4.6±0.03
CF5	99.25	0.38	5.2±0.14	±1.047	4.5±0.04
CF6	101.45	0.52	5.3±0.11	±1.075	4.3±0.02
CF7	101.25	0.68	5.5±0.15	±1.072	4.4±0.05
CF8	100.56	0.46	5.2±0.13	±1.032	4.3±0.03
CF9	99.45	0.34	5.6±0.12	±1.065	4.6±0.05

***All values are average of five determinations ± S.D.values**

Table 6: In vitro dissolution in Phosphate buffer 6.8 at the end of 6th hour

	Absence of rat cecal contents	Presence of rat cecal contents
Formulation		
CF1	21.93	68.56
CF2	16.09	70.45
CF3	20.47	77.89
CF4	16.89	79.26
CF5	21.43	81.14
CF6	25.77	91.85
CF7	17.51	65.10
CF8	12.08	83.34
CF9	21.69	60.25

Table 7: Mechanism of drug release

Formulation	Zero order	First order	Higuchi`s Plot	Korsmeyer-Peppas Plot		
	R^2	R^2	R^2	n	k	R^2
CF1	0.991	0.962	0.934	0.695	1.234	0.968
CF2	0.968	0.947	0.921	0.659	1.248	0.954
CF3	0.972	0.900	0.893	0.666	1.280	0.936

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CF4	0.985	0.943	0.917	0.686	1.305	0.936
CF5	0.984	0.937	0.914	0.791	1.210	0.477
CF6	0.971	0.846	0.957	0.473	1.640	0.865
CF7	0.990	0.973	0.942	0.646	1.256	0.955
CF8	0.974	0.969	0.973	0.501	1.483	0.947
CF9	0.995	0.972	0.931	0.838	1.086	0.985

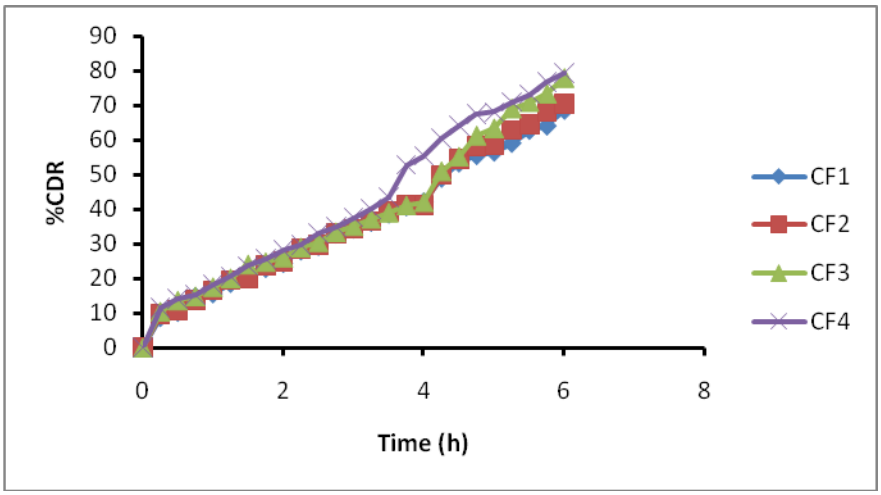

Figure 1 % CDR of Aceclofenac in the presence of rat cecal content

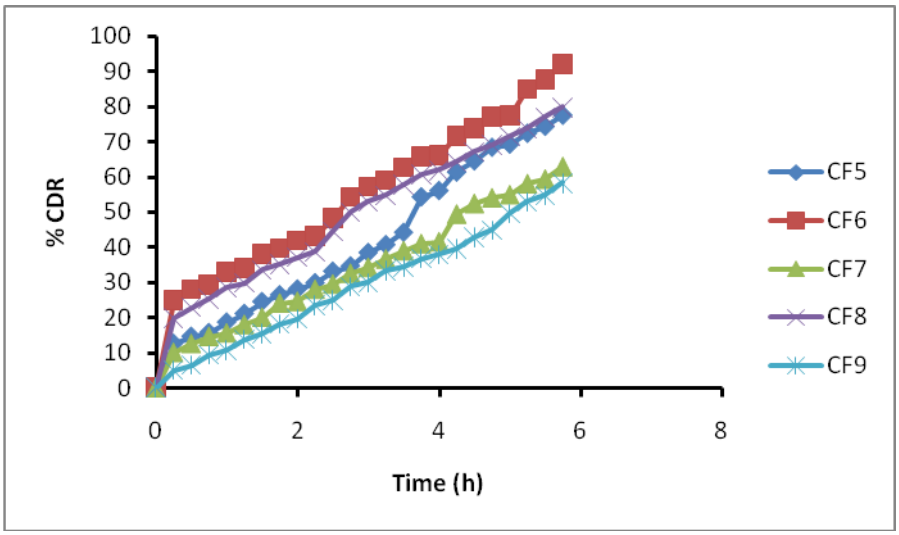

Figure 2 % CDR of Aceclofenac in the presence of rat cecal contents

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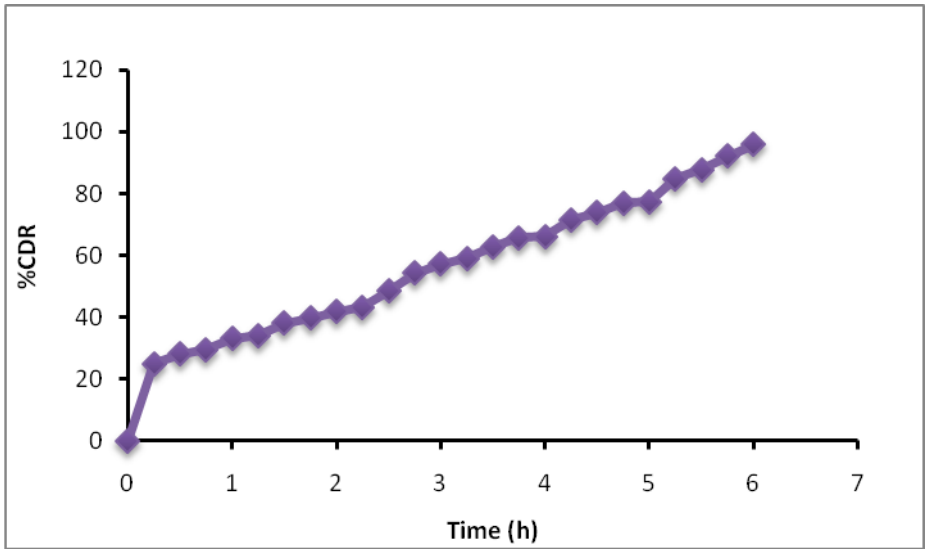

Figure 3 % CDR of optimized formulation CF6 in the presence of rat cecal contents

CONCLUSION

The objective of this study was to design compression coated tablets of Aceclofenac for an effective and safe therapy of ulcerative colitis and inflammatory bowel disease using guar gum and HPMC as carriers. The core tablets of Aceclofenac coated with guar gum : HPMC in the ratio 4:1 released only 1.9% of the drug in the physiological environment of the stomach and small intestine, but released 95.81% of drug in the target area; colon. The Guar gum and HPMC blend in the form of compression coated tablets protected the core tablet from being released in the upper GIT. Thus, based on these results it was concluded that the tablets containing guar gum : HPMC in the ratio 4:1 showed significant drug release in the colon without much drug release in the stomach and small intestine. The release pattern of the above formulation was best fitted to zero order. The mechanism of drug release was Non-Fickian (super case II) transport.

REFERENCES

[1] Anil KP, Betty P. Oman Med J 2010; 25:1-9.
[2] Akhgari A, Afrasiabi GH, Sadeghi F, Azimaiev M. Int J Pharm 2005; 305: 22-30.
[3] Alaa EBY, Ibrahim AA, Fars KA, Abdullah MA, Abdulrahaman AA and Omar AA. JDT 2010; 18:59-66.
[4] Arulraj P, Saraswathy R, Nair CR, Gopal V, Venkatnarayanan R. Int J A Pharm 2010; 1(2):408-413.
[5] Chickpetty SM, Raga B. Int J Pharm Tech Research 2010; 2(3): 1714-1722.
[6] Chickpetty SM, Raga B, Nanjwade BK. As J Pharm Clin Res 2010; 3(2):110-113.
[7] Chan ES, Zhang Z. Process Biochem 2005; 40:3346-3351.
[8] Ghule PJ, Karle GD, Saumaya D. J Pharm Res 2010; 3(5): 1082-1086.

[9] Josephine LJJ, Vijaya K, Suma R, Bincy R, Ayesha S. Int J Pharm Tech Res 2010; 2(1):535-541.
[10] Krishnaiah YSR, Bhaskar RPR, Satyanarayana V, Karthikeyan RS. Int J Pharm 2002; 236:43-55.
[11] Krishnaiah YSR, Satyanarayana S, Rama Prasad YV, Narasimha RS. Int J Pharm 1998; 171: 137-146.
[12] Nasara MA, EL-Massik MA, Naggar VF. As J Pharm Sci 2007; 2(1):18-28.
[13] Murat T, Timucin U. Eur J Pharm Biopharm 2002; 53:65-73.
[14] Prabhakar RV, Rajendra PM. Acta Pharmaceutica Scientia 2010; 52: 281-294.
[15] Pratik S, Pragna S. Int J Pharm Res 2010; 2(1): 52-61.
[16] Soad AY, Ahmed HE, Ibrahim S and Ahmed HS. AAPS Pharm Sci Tech 2009; 10(1):147-157.
[17] Soravoot R, Roland B. Eur J Pharm Biopharm 2010; 76:486-492.
[18] Timucin U, Murat T, Umran SG, Bureak GA. Eur J Pharm Biopharm 2007; 67:202-210.