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Research Article

FORMULATION AND EVALUATION OF COMPRESSION COATED TABLETS BASED ON MODIFIED OKRA MUCILAGE

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ABSTRACT

Recently there has been greater interest in modified release systems like extended release or delayed release systems to deliver required amount of drug at specific site for duration of therapy. These systems play an important role in the chronotherapy of asthma, angina and arthritis. Compression coated tablets are advantageous as they do not require solvents, and prevent the drug release in gastric region due to presence of coating layer. In the present study fast disintegrating core tablets of model drug diclofenac sodium were coated with coating material granules containing okra mucilage or cross linked okra mucilage in combination with HPMC K15M and evaluated for pre and post compression parameters. The in-vitro disintegration time for core tablets was 64.66±0.577sec; % friability was 0.76 % whereas the wetting time was found to be 41.66 ±0.57 sec. All other parameters were found to be satisfactory for core and coated formulations. Formulations CP1, CP2 and CP3 showed drug release of 96.789 ± 0.66994 %, 100.86 ± 0.42729 % and 95.15 ±0.7180 % in 24 hrs respectively. The prepared formulations showed greater drug release after 6 hrs indicating a burst release in intestinal environment, making the formulations suitable candidates for colonic drug release. All the prepared formulations followed first order kinetics with release exponent n>1.There was no significant difference in in-vitro dissolution in presence and absence of rat caecal content indicating drug release depends on pH, swelling and erosion. The formulations were found to be stable for duration of study.

Keywords: Okra mucilage, Compression coated, Diclofenac sodium, Cross linked okra mucilage.

INTRODUCTION

Recently there has been greater development in the field of modified release systems. An ideal drug delivery system should deliver the drug at a rate dictated by the needs of the body over the period of treatment and should provide spatial targeting to specific sites. These prerequisites lead to development of modified release technologies, which can improve the therapeutic efficacy and safety of a drug by targeting the drug to specific site in the body, thereby reducing both the size and number of doses required.[1] The various modified release dosage forms available, include: extended release dosage forms that are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time. Delayed release dosage form is designed to release the drug at a time other than promptly after administration.[2] The modified release systems with barrier coating are beneficial for the drugs having chrono-pharmacological behavior, first pass effect and having specific site of absorption in gastro intestinal tract (GIT). Diseases where the modified release systems are promising include asthma, cardiovascular diseases, arthritis, peptic ulcers and hypercholesterolemia.

Diclofenac sodium (DS) is a non-steroidal anti-inflammatory drugs widely used to control pain and inflammation.[3] The conventional therapy may result in local GI toxicity varying from minor gastric discomfort to ulceration and bleeding of the mucosa. In addition rapid systemic clearance of this drug, repeated daily dosing of 3 to 4 times is required in maintenance therapy that influence patient compliance. Colon targeted extended release formulations are thus warranted to promote patient compliance and to reduce upper GI toxicity to some extent. DS was selected as a model drug since it is well absorbed in the colon.[4] Colon-specific drug delivery system was developed to reduce side effects and achieve high local drug concentration at the absorption site in the colon, thereby enhancing therapeutic effectiveness and patient compliance.[5] The various approaches that have been studied for targeting orally administered drugs to the colon include use of pro-drugs, pH-sensitive polymers, time-dependent dosage forms and the use of carriers degraded by enzymes produced by colonic bacteria.[6]

Among the strategies, compression coated systems seem to be superior in preventing premature drug release in stomach and small intestine, and release the active agents at the proximal colon. The polysaccharides due to hydrophilic nature dissolve in the aqueous dissolution medium and show higher drug release. To overcome this problem, additional excipients like HPMC[7] or retardants like ethyl cellulose are required to be included.

The Okra (*Abelmuschus esculentus*) is a bulky annual plant cultivated throughout the tropical and subtropical areas of the world, particularly in India. The fresh green pods are rich in mucilage. The okra polysaccharide contains the major polysaccharide components differing widely in the molar ratios of galactose, galacturonic acid, and rhamnose[8].

In the present study it is proposed to use the okra mucilage and cross linked okra mucilage with chitosan in combination with HPMCK15M as coating polymer in compression coated formulations to achieve the colon specific release of diclofenac sodium for chronotherapy of arthritis

MATERIALS AND METHODS

Okra pods obtained from local market, diclofenac sodium as a gift sample from Emcure Pharmaceuticals Ltd, Pune, HPMC K15M and chitosan were obtained from SD Fine Chem, Mumbai and Sigma Aldrich, USA respectively. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) obtained from Spectrochem Ltd Mumbai. All other chemical are of analytical grade.

Extraction of okra mucilage[9]: Fresh unripe pods of okra (Ladies finger) were obtained from the local market. The pods were cut into very thin slices and the seeds were removed and then soaked in the distilled water (p^H 8) for 24 hrs, the swollen slices were then squeezed through muslin bags to obtain aqueous extract. To the aqueous extract twice the volume of alcohol (90%) was added to precipitate the mucilage. The mucilage was defatted and final precipitation was carried out with acetone.

Preparation of chemical cross linked okra mucilage.

Okra mucilage is a acidic polysaccharide containing repeating units of (1→4)-O-α-(D-galactopyranosyluronic acid)-(1→2)-O-α-L rhamnopyranose.[8]

Hydrolysis of okra mucilage revealed that the polysaccharide was composed of galacturonic acid, galactose, rhamnose and glucose (1.3: 1 .O: 0.1: 0.1).[8] The free –COOH group of Okra mucilage was

reacted with cationic polymer chitosan which is composed repeating units of N-acetylglucosamine.1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) was used as a zero length cross linking agent.

Optimized Conditions for cross linking

Ratio of okra mucilage: chitosan: 1:0.5, 1:2, 1:1, 2:1, 0.5:1

Concentration of EDC used: 10mM -40mM

Time of cross linking: 1 hr- 24 hrs

pH of reaction: ≤ 5 adjusted with 0.1 N HCl

Purification: soaked in deionised distilled water for 5hrs with occasional shaking and dialysis against deionised distilled water for 24 hrs to remove unreacted EDC.

Table 1: Reaction parameters for chemical cross linking of okra mucilage

Ratio	OM mg	PH	EDC m M	Time hr	Chitosan mg
1:2	100	≤5	10	1	200
	100		20	1	200
	100		30	1	200
	100		40	1	200
1:1	150	≤5	10	1	150
	150		20	1	150
	150		30	1	150
	150		40	1	150
2:1	200	≤5	10	1	100
	200		20	1	100
	200		30	1	100
	200		40	1	100

Method used for cross linking.

The okra mucilage was dispersed uniformly in deionised distilled water and shaken for 24 hrs using rotary shaker (Remi instruments Ltd, Mumbai, India). The pH of the reaction was adjusted to value of 5 using 0.1N hydrochloric acid. And then the EDC was added in required concentration as per table 1 and stirred on the rotary shaker for 1 hr to activate the carboxyl groups. Then the specified quantity of chitosan was added and stirred on the rotary shaker for 24 hrs to complete cross linking. Cross linked polymer was soaked in deionised distilled water for 5 hrs and then exhaustively dialysed against deionised distilled water for 24 hrs to remove unreacted water soluble EDC. The polymer was dried in hot air oven (Sunshine industries, Coimbatore, India) at 40 ^{0}C for 4 hrs and milled and stored in a desiccator till further use.

Evaluation parameters for cross linked polymer.

Percent yield

The yield of the dried modified polymers was determined. The ratio of polymers that gave highest yield was selected for further studies.

Swelling study

The modified polymers 100 mg were pressed in to discs using single station tablet machine with 7.0 mm flat punches (Cadmach machinery Co. Pvt, Ltd. Ahmedabad, India) and the swelling index in phosphate buffer pH 6.8 was determined. Discs were weighed individually (designated as W_1) and placed separately in a petri plate containing 15 ml of phosphate buffer pH 6.8 incubated at 37ºC ± 1ºC. At regular 1hr time intervals until 8 hr, the disc was removed from beaker, and the excess surface liquid was blotted carefully using the filter paper. The swollen disc was then re-weighed (W_2) and swelling index (SI) was calculated using the following formula, [9]

$$SI = \frac{(W2 - W1)}{W1} \times 100$$

Where W_1= Weight of dry disc, W_2= weight of swollen disc (n=3).

Preparation of core tablets of diclofenac sodium

The fast disintegrating core tablets of diclofenac sodium were prepared by direct compression (table 2). The drug, polymer and the super-disintegrant were sifted through sieve # 85. Then they were mixed in a plastic pouch for 10 min to get uniform mixture. The lubricants were added to the mixture and again mixed. The drug excipient blend was compressed on a single station rotary tablet machine (Karnavati Engg. Ltd, Gujarat, India) using 7mm convex punches.

Table 2: Optimized composition of core tablets of diclofenac sodium

S. No.	Ingredients	Composition /tablet(mg)
1	Diclofenac sodium	100 mg
2	Okra mucilage	05 mg
3	Sodium starch glycolate (6%)	9 mg
4	Lactose	33 mg
5	MgS+Talc	3 mg

MgS Magnesium stearate, Weight of core tablets=150mg.

Preparation of coating material and compression coated tablets

The formulations of compression coating, for coating of core tablets are shown in table 3. The coating granules were prepared by wet granulation technique using 2% w/v ethyl cellulose in isopropyl alcohol as a binder. The powders were blended in a plastic pouch to get uniform mixture and granulated with solution of ethyl cellulose. Then the granules were obtained by passing the wet mass through sieve #16. The granules were dried at 50^0 C for 1hr in a hot air oven (Sunshine industries, Coimbatore India). The dried granules were resized by passing through sieve # 22 and were lubricated with a mixture of talc and magnesium stearate. Then 45% weight of coating material granules were then kept in die cavity and then core tablet was placed carefully on it in centered position and then remaining 55% of coating material granules were added to cavity and compressed into tablets, by using convex punches of 10.05 mm diameter after optimizing the hardness and die cavity of rotary tablet machine, so that the tablets will be of uniform hardness and with minimal weight variation.

Table 3: Composition of coating material

Form Code	HPMC K15M mg	OM mg	CP mg	MCC mg	Talc mg	MgS mg
H	120	-	-	25	3	2
M1	96	24	-	25	3	2
M2	60	60	-	25	3	2
M3	24	96	-	25	3	2
CP1	96	-	24	25	3	2
CP2	60	-	60	25	3	2
CP3	24	-	96	25	3	2

2% w/v EC in isopropyl alcohol was added to each coating material as a binder, weight of coated tablets is 300 mg

(OM Okra mucilage, CP cross linked polymer, MCC Microcrystalline cellulose, MgS Magnesium stearate)

Evaluation of core and coated tablets

Compatibility study

Fourier Transform Infra Red (FTIR) of okra mucilage: The mixture of sample powders and KBr prepared in the form of potassium bromide pellets by applying a pressure of 7 tons for 5 min in a KBr press. The pellet was placed in the light path and the spectrum was obtained by scanning from 4000 cm-1 to 400 cm-1 using FT-IR spectrophotometer (FT-IR-8400S, Shimadzu, Japan).

Differential scanning Calorimeter study

Samples were subjected to Differential Scanning Calorimeter (DSC) for compatibility study (Mettler Toledo, USA). For DSC, aluminum pans are employed to place the samples which are then sealed with aluminum caps and kept under nitrogen purging (atmosphere). The

heating rate was kept at 10ºC rise per min up to 300 ºC to better integrate the information.

Physical evaluation of core and coated tablets

The core and coated tablets were evaluated for pre-compression[10]parameters like loose bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose using standard procedures. Mean of three readings was recorded

The thickness of the diclofenac sodium matrix tablets was determined by using dial micrometer (Mitutoya, Japan). Monsanto hardness tester was used to determine the tablet crushing strength. Percent friability was determined using Roche Friabilator.[11] Weight variation test was performed for 20 tablets and percent weight deviation was calculated.[12]

In- vitro Disintegration time

In-vitro disintegration time was determined for core tablets using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The phosphate buffer pH 6.8 was maintained at a temperature of 37±0.5^0 C and time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Wetting time

A piece of tissue paper folded twice was placed in a small petri dish containing 10 ml of phosphate buffer pH 6.8. A core tablet was put on the paper, and the time required for complete wetting was measured. Three trials were performed; average time for wetting with standard deviation was recorded.

Drug Content

Drug content uniformity test was performed to check dose uniformity in the formulation. Randomly ten tablets were weighed and powdered. A quantity equivalent to 100 mg of diclofenac sodium was placed a 100 ml volumetric flask and dissolved in 60 ml methanol, sonicated for 10 minutes and made up the volume up to the mark and filtered through 0.45µ membrane filter. After appropriate dilutions with phosphate buffer pH6.8, the drug content was determined by UV spectrophotometer at 276 nm against suitable blank using standard plot equation.

In-vitro release studies for core tablets

The core tablets were subjected to in-vitro dissolution studies in 900 ml phosphate buffer pH 6.8 for 1 hrs using an USP XXIII dissolution apparatus II at 50 rpm maintained at 37 ± 0.50^{0}C. The aliquot was withdrawn after every 10 min and filtered through 0.45µ membrane filter and diluted suitably and analyzed using UV-visible double-beam spectrophotometer (Shimadzu-UV 1601, Japan) at 276 nm. Equal amounts of fresh dissolution medium were replaced immediately after withdrawing an aliquot.

In-vitro release studies for coated tablets

The in-vitro drug release study was carried out using an USP XXIII dissolution apparatus II with 900 ml of dissolution medium maintained at 37 ± 0.50^{0}C for 24 hrs at 50 rpm. 0.1N hydrochloric acid of pH 1.2 was used as dissolution medium for first 2 hrs as average gastric emptying time is 2 hrs. The dissolution medium was replaced by phosphate buffer p^H 7.4 for further 3 hrs as small intestinal transit time is 3 hrs. Once again the dissolution medium was replaced by phosphate buffer p^H 6.8. A 5ml aliquot was withdrawn at predetermined time intervals, filtered through 0.45µ membrane filter and diluted suitably and analyzed using UV-visible double-beam spectrophotometer (Shimadzu-UV 1601, Japan) at 276 nm. Equal amounts of fresh dissolution medium were replaced immediately after withdrawing an aliquot. Samples were assayed in triplicate.

In-vitro drug release studies with and without 2% rat caecal contents

The rat caecal content (anaerobic in nature) was collected and immediately transferred into buffer saline solution pH 6.8 to obtain 2% w/v concentration. Solution was previously bubbled with carbon dioxide gas to maintain an anaerobic environment. The tablets of formulations CP2 were tested for drug release for 2 hours in pH 1.2 (100 ml) as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with phosphate buffer pH 7.4 (100 ml) and tested for 3 hours as the average small intestine transit time is about 3 hours, again the medium was replaced with 100 ml of pH 6.8 phosphate buffer with 2% w/v rat caecal contents and also with the same medium phosphate buffer pH 6.8 but without rat caecal content as control.

Release kinetics

The in- vitro dissolution data was fitted in to different kinetic models like zero and first order, Korsemeyer peppas and Weibull model to find out the drug release profile.[13]

$Q_t = K_o t$ ---- Zero order

$Q_t = Q_o(1-e^{-k_1 t})$ ----- -First order

$Q_t/Q_\infty = K_k t^n$ - ----- -Korsemeyer Peppas

In Peppas model Q_t/Q_∞ is the fraction of drug released at time *t, K_k* is constant and n is release exponent respectively.

Weibull model:

The data obtained were also fit to Weibull model to further elucidate mechanism of release. The Weibull equation expresses the accumulated fraction of the drug, *m*, in solution at time, *t*, by

$$m = 1 - e\left[\frac{-(t-T_i)^b}{a}\right]$$

In this equation, the scale parameter, *a*, defines the time scale of the process. The location parameter, T_i, represents the lag time before the onset of the dissolution or release process and in most cases will be zero and '*b*' is the shape parameter.[13]

Statistical analysis

The formulation CP2 was subjected to in- vitro drug release study with or without rat caecal content. The data obtained from the dissolution studies were statistically analyzed by one way ANOVA followed by post hoc Tukey method. The statistical analysis was performed using Graphpad Prism software Inc (USA Version 4.0). A probability value of P <0.05 was considered as statistically significant.

Stability studies

The stability studies were performed for the selected formulation CP2 which was maintained at 40°±2°C and 75 ± 5 % RH and also at room temperature in a desiccator at 25°±2°C and 60 ± 5 % RH for a period of six months. At the end of every month the formulations were observed for physical changes. After six months the formulations were tested for hardness, drug content and drug release profiles.

RESULTS AND DISCUSSION

Percent yield

The okra mucilage was modified by reaction with chitosan at different ratios (1:0.5, 1:1, 1:2 , 2:1 and 0.5:1) using 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride (EDC) as a cross linking agent at different concentration of 10, 20, 30 and 40 mM. The results of preliminary studies showed that at the ratio of 1:0.5 and 0.5:1 the % yield was negligible, hence only 1:1, 1:2 and 2:1 ratio were selected for further study.

The % yield of cross linked polymer was higher (72.57 to 83.1011 %) at polymer ratio of 2:1 between okra mucilage and chitosan. The concentration of cross linking agent 40mM gave the highest yield. Hence this polymer was used for further study. The modified polymer (polymer ratio of 2:1, cross linker concentration 40mM) was soaked in distilled water for 5 hr with occasional stirring and then exhaustively dialyzed against distilled water for 24 hrs to

remove the traces of unreacted chemicals. Carbodimides unlike gluteraldehyde or polyepoxide do not remain as a part of that linkage but simply change to water soluble urea derivative that have very low cytoxicity.[14] This urea can be removed by above treatment. It was reported that the supernatant solutions were not toxic when the polymers synthesized with 50mM EDC were sonicated for 30 sec in distilled water for five times to remove residual EDC.[15]From this it can be stated with exhaustive washing cycle the modified polymer was devoid of any residual EDC, hence not toxic.

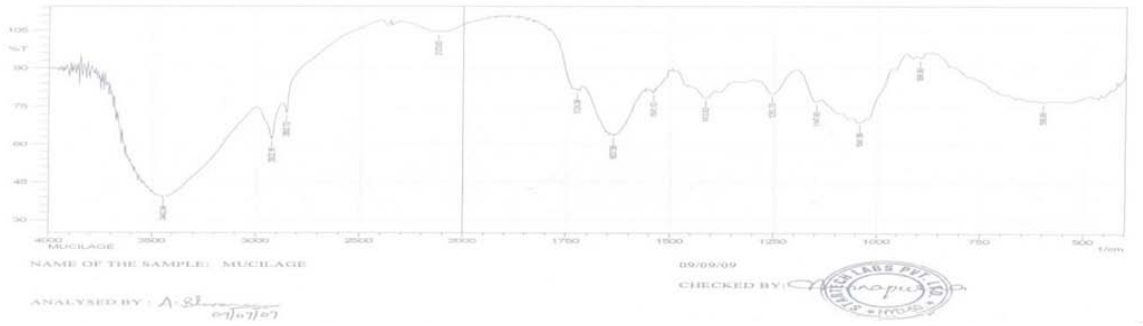
Swelling index

The swelling study was performed for cross linked polymers synthesized at different polymeric ratios and 40 mM concentration of cross linking agent in phosphate buffer pH 6.8. The swelling was highest and more sustained for modified polymers C3 (40mM, 2:1). The polymer C3 showed suitable properties to be used for modified release formulations.

FTIR studies

OM is characterized by several IR absorption bands. The absorption at 3442.94 cm^{-1} is characteristic of free OH- groups, 1637.56 cm^{-1} of symmetrical and asymmetrical oscillations is characteristic of ionized carboxyl groups, and 2922.16 cm^{-1} is attributed to the $-CH_2$ groups of OM. In addition, the minor absorption peak at 2123.63 cm^{-1} is attributed to CO_2 and H_2O. The occurrence of cross linking is ascertained by the slight increase in the amide bands at 1633.94 cm^{-1}, 1537.72 cm^{-1}, 1412.30 cm^{-1} and 1017.35 cm^{-1}(figure 1).

The FTIR spectra of formulations H, M1 and CP2 showed the presence of peaks associated with diclofenac sodium. The results indicated that no interaction has taken place between drug and the excipients.



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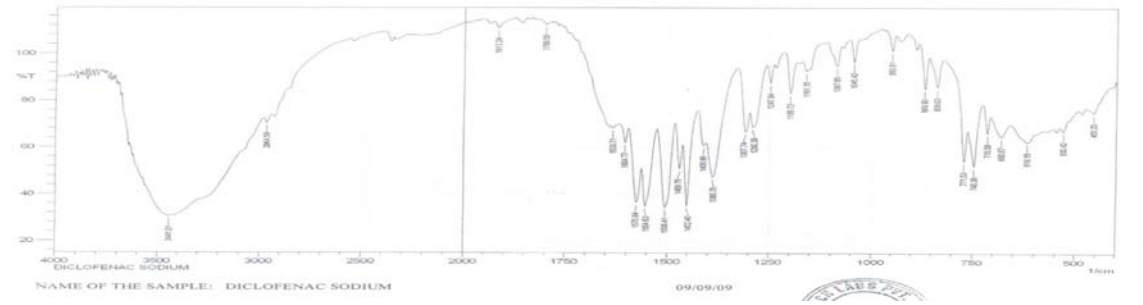

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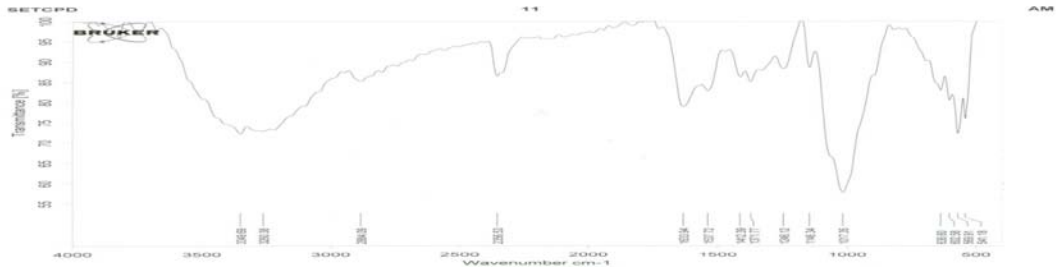

(C)

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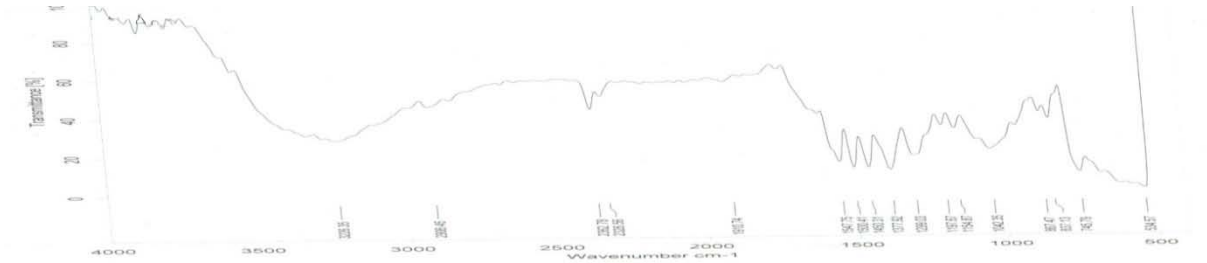
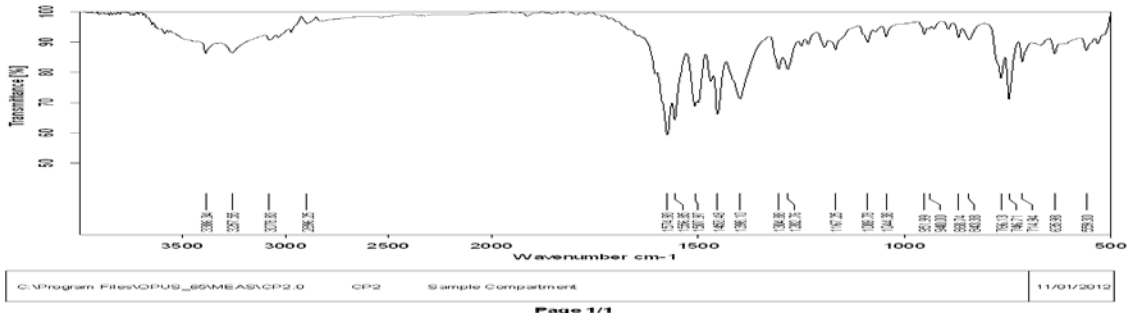


(E)

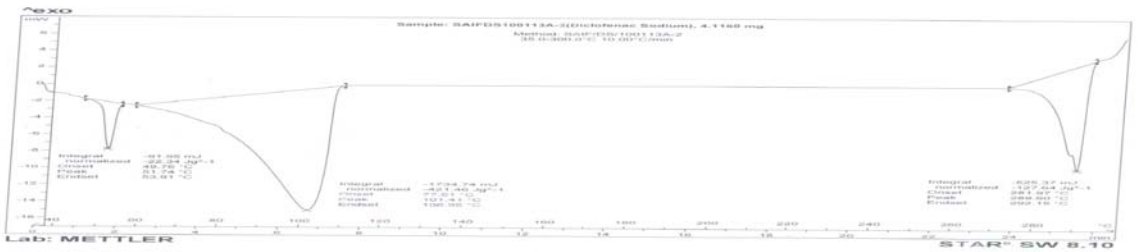


(F)

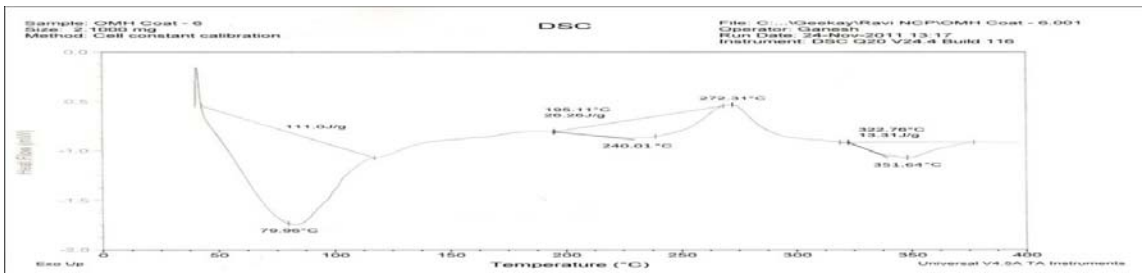
Fig. 1: FTIR spectra of okra mucilage (A), diclofenac sodium (B), cross linked okra mucilage at 2:1 ratio and 40 mM (C), formulation H (D), M1 (E) and CP2 (F)

Differential scanning calorimeter

The DSC thermograms of formulations M1 and CP2 showed endothermic peaks at 79.96^{0}Cand 272.31^{0}C and 84.05^{0}C and 277.01^{0}C (figure 2). The slight decrease in temperatures of the endothermic peaks and melting point of diclofenac sodium may be due to mixing of drug with excipients and change in thermal behavior of drug in presence of excipients. The results indicated that the drug and the excipients were compatible.



(A)



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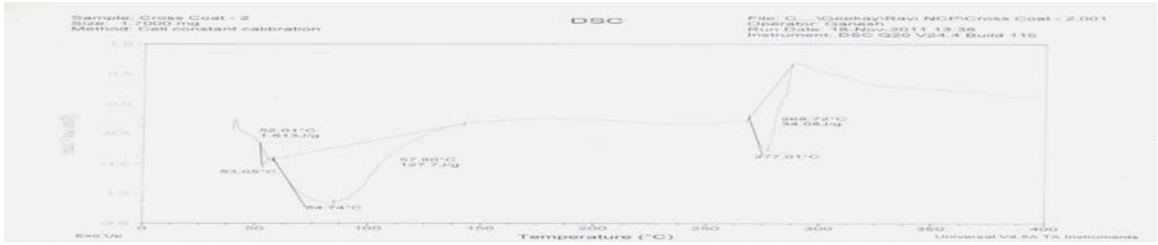

(C)

Fig. 2: DSC thermograms of diclofenac sodium (A), formulations M1 (B) and CP2(C).

Evaluation of core tablets

The fast disintegrating core tablets showed the in-vitro disintegration time of 64.66±0.577 sec, friability 0.76 % and the wetting of 41.66 ±0.57 sec. All other parameters were found to be satisfactory.

Physical evaluation of compression coated tablets

The results of pre-compression study showed good compressibility and flow property of prepared granules (table 4). The coating materials contained okra mucilage, cross linked okra mucilage with HPMC in the ratios of 4:1, 1:1 and 1:4. The compression coated formulations were prepared at core to coat ratio of 1:1. The post compression parameters of prepared formulations were evaluated and the results are shown in table 5. The results indicated good mechanical strength. The formulations showed drug content of 99.5505± 0.5945 % to 98.5018 ± 0.5655 %.The percent deviation in weights of the prepared formulations was found to be within the specified limits. The results indicated satisfactory physical properties of prepared formulations.

Table 4: Pre- compression parameters for coated tablets

Form Code	Bulk Density gm/mL	Tapped Density gm/mL	Carr's Index %	Hausner's Ratio	Angle of Repose θ
CORE	0.537±0.012	0.608±0.015	11.716±0.255	1.132±0.003	30.803±0.057
M1	0.389±0.008	0.482±0.007	19.993±0.823	1.238±0.042	31.119±0.1
M2	0.408±0.006	0.460±0.012	11.374±0.826	1.118±0.039	30.803±0.152
M3	0.391±0.011	0.452±0.025	13.450±0.732	1.154±0.031	30.493±0.2
CP1	0.422±0.010	0.520±0.009	17.184±0.615	1.232±0.035	30.040±0.288
CP2	0.383±0.006	0.464±0.006	17.393±0.198	1.210±0.0.002	30.803±0.057
CP3	0.382±0.007	0.451±0.009	15.309±0.692	1.180±0.009	30.040±0.115
H	0.322±0.010	0.368±0.014	12.306±0.263	1.155±0.032	30.646±0.1

Table 5: Post- compression parameters for coated tablets

Form Code	Thickness mm	Hardness Kg/cm²	Friability %	Drug Content	Weight ± % Deviation
Core	2.666±0.02	3.233±0.01	0.76	100.224±0.449	151±1.305
M1	4.27±0.01	5.6733±0.0461	0.3513	99.17±0.3432	304.55±1.268
M2	4.22±0003	5.9333±0.0577	0.2085	99.101±0.979	303.60±1.058
M3	4.09±0.03	6.3±0.1	0.2134	99.550±0.594	304±1.333
CP1	4.23±0.02	5.7666±0.1527	0.1982	98.8763±0.4494	304.8±0.9666
CP2	4.1633±0.01527	5.4666±0.1154	0.2154	98.8763±0.2247	301.95±0.9416
CP3	4.1566±0.0923	5.5333±0.1527	0.185	98.9512±0.7223	301.95±0.92
H	4.25±0.005	5.31±0.0953	0.3720	99.4756±0.686	303.25±1.1

In-vitro dissolution profiles

In case of formulations M1, M2 and M3 the drug release were 84.8 ±0.5042 %, 100.12 ± 0.5271 % and 99.98 ± 0.1435 % in 24 hrs respectively. The compression coated formulations containing cross linked polymer as coating material CP1, CP2 and CP3 showed drug release 100.05 ±0.1991% (24hrs), 100.5 ±0.7464 % (24 hrs) and 100.415 ±0.4937 % (8hr) respectively. These formulations extended the drug release for 24 hrs. The results of the study indicated that, as the proportion of HPMC increases in the coating material, the drug release decreases. The drug release from all these formulations was compared with a formulation prepared with only hydroxyl propyl methyl cellulose as coating material. The lower drug release was due to formation of stiff gel layer on the surface of the tablets. This indicated extended drug release from fromulation H. The prepared formulations showed greater drug release after 6 hrs indicating a burst release in intestinal environment, making the formulations suitable candidates for colonic drug release. When okra mucilage alone was used as a coating material, it swelled and formed gel from which the drug release was very slow. The results indicated the usefulness of the modified polymer and okra mucilage in combination with HPMC for extending the drug release.

Drug release kinetics

The release kinetics was estimated by fitting the in-vitro dissolution data into zero order and first order. The first order regression values were between 0.914 and 0.988 hence all the formulations followed first order kinetics (figure 3, table 6). The release exponent values were > 1 indicating a super case II mechanism of release. The beta values for Weibull model were >1 indicating sigmoid curve with initial slower drug release followed by faster release (figure 4).

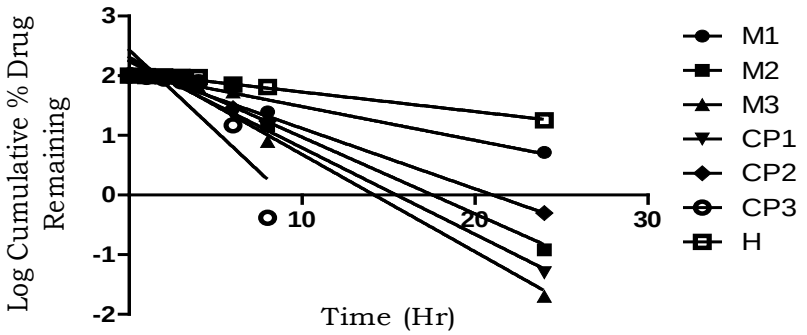

Fig. 3: First order plots for coated formulations of diclofenac sodium.

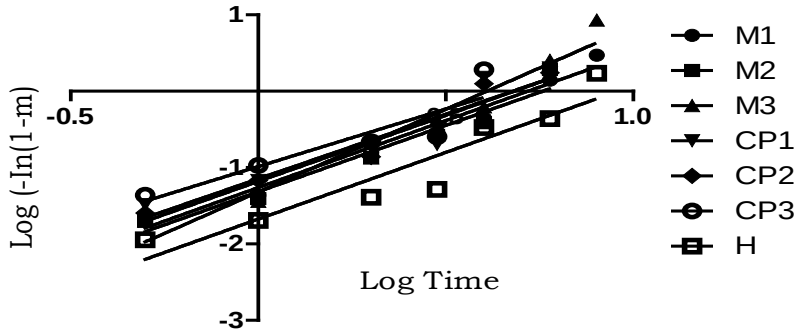

Fig. 4: Weibull plots for coated formulations of diclofenac sodium.

Table 6: Drug release kinetics of compression coated formulations

Form Code	First Order			Korsemeyer-Peppas			Weibull Model		
	K_1 (%h^{-1})	Intercept	R^2	n	Intercept	R^2	β	Logα	R^2
M1	-0.036	1.987	0.842	1.264	0.481	0.864	1.754	-0.261	0.975
M2	-0.128	2.255	0.966	1.364	0.390	0.897	1.734	-1.315	0.95
M3	-0.163	2.310	0.970	1.463	0.410	0.853	2.166	-1.320	0.952
CP1	-0.145	2.242	0.982	1.242	0.57	0.860	1.691	-1.147	0.875
CP2	-0.101	2.130	0.983	1.288	0.533	0.876	1.730	-1.181	0.934
CP3	-0.271	2.431	0.754	1.581	0.561	0.963	1.506	-0.986	0.824
H	-0.032	2.054	0.982	1.515	0.021	0.925	1.746	-1.675	0.881

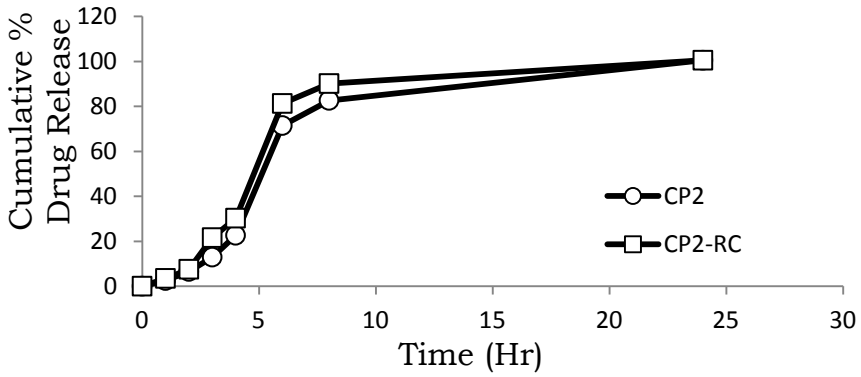

Fig. 5: In-vitro dissolution profile in presence or absence of rat caecal content for formulation CP2.

In-vitro drug release in presence and absence of rat caecal content

The effect of rat caecal enzymes on the drug release was investigated by performing in-vitro dissolution studies in presence of 2% w/v rat caecal content and in absence of the same (figure 5). The difference in the in-vitro drug release profile was found to be less significant ($p>0.05$).

Stability study

The stability study for the selected formulations CP2 and H was performed as per ICH guidelines. The results of the stability study indicated there was less significant decrease in the hardness of the formulations. The change in the % drug content and % drug release was also found to be less significant ($p>0.05$). This indicated satisfactory stability of the prepared formulations for the duration of study.

CONCLUSION

Okra mucilage and modified okra mucilage were successfully used as coating materials in combination with HPMC K15 M to deliver model drug diclofenac sodium to colon for chronotherapy of arthritis. The drug release was extended for 24 hrs in colon. The formulations followed first order kinetics with pH dependent swelling, polymer relaxation and erosion as release mechanisms.

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