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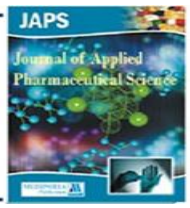

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Design and Evaluation of Compression Coated Formulations for an Antiinflammatory Drug Based on Modified okra Mucilage

Ashwini Rajendra, Bushetti SS and Archana Giri

Ashwini Rajendra
JNT University,
Kukatpalli, Hyderabad, India.

Bushetti SS
HKE's College of Pharmacy,
Gulbarga, India.

Archana Giri
Centre for Biotechnology,
IST, JNT University,
Hyderabad, India.

For Correspondence
Ashwini Rajendra
Department of Pharmaceutical sciences, JNT University, Hyderabad, India.
Phone: 9844487640

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. In the present study fast disintegrating core tablets of model drug diclofenac sodium were coated with coating material granules containing okra mucilage or modified 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±0.577 sec and the wetting time was 41.66 ±0.57 sec. All other parameters were satisfactory for core and coated formulations. Formulations P1, P2 and P3 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.

Keywords: okra mucilage, compression coated, diclofenac sodium, modified 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 during the period of treatment. 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 (Vyas *et al.,* 2002). 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 (USP 2004).

The extended release dosage forms have the advantages of the less fluctuation in drug blood levels, reduced frequency in dosing, improved patient's convenience and compliance, reduction in adverse side effects and reduction in costs (Allen *et al.,* 2006). These modified release systems with barrier coating are beneficial for the drugs having chrono-pharmacological behavior (where night time dosing is required), 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 (Martindale 1999). 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 formulation 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 (Lee 2002). Colon-specific drug delivery system was developed to reduce side effects and achieve high local drug concentration at the afflicted site in the colon, thereby enhancing therapeutic effectiveness and patient compliance (Krishnaih *et al.,* 2002). 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 (Krishnaih *et al.,* 1998).

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 (Chikpetty *et al.,* 2010) or retardants like ethylcellulose 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 component differing widely in the molar ratios of galactose, galacturonic acid, and rhamnose (Tomada *et al.,* 1980).

In the present study it is proposed to use the okra mucilage and polyelectrolyte complex (PEC) of 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. All other chemical are of analytical grade.

Extraction of okra mucilage (Wahi et al., 1985)

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 polyelectrolyte complex of okra mucilage and chitosan

The polyelectrolyte complex was prepared and evaluated by a method developed by us (Ashwini *et al.,* 2012). Briefly 0.2 % w/v solutions of okra mucilage and chitosan were prepared separately in sodium acetate –acetic acid buffer pH 5 and mixed to get different ratios of 9:1, 8:2, 7:3, 1:1, 3:7, 2:8, 1:9. The flasks were shaken on a rotary shaker for 4 hrs and kept aside for 24 h. The complex of the OM-CH was precipitated. The complexes were centrifuged at 2000 rpm for 10 min (Remi Research Centrifuge). The supernatant was decanted and the precipitate was washed with distilled water and dried at 50° C to constant weight and the yield of the dried polyelectrolyte complex was calculated. The ratio of 9:1 between okra mucilage and chitosan was found to be the most suitable as it gave higher yield of complex, higher % transmittance and lower relative viscosity for supernatant solutions indicating complete reaction between the two polymers hence it was selected for further study.

Preparation of core tablets of diclofenac sodium

The fast disintegrating core tablets of diclofenac sodium were prepared by direct compression (table1). The drug, polymer and the super-disintegrants were sifted through sieve # 85. Then they were mixed in a plastic pouch for 10min 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. 1: Optimized composition of core tablets of diclofenac sodium

Sr 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 tablet are shown in table 2. 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. 2: Composition of coating material

Form Code	HPMC K15M mg	OM mg	PEC $_{9:1}$ mg	PM 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
P1	96	--	24	-	25	3	2
P2	60	-	60	-	25	3	2
P3	24	-	96	-	25	3	2
PM1	96	-	-	24	25	3	2
PM2	60	-	-	60	25	3	2
PM3	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, $PEC_{9:1}$ Polyelectrolyte complex at 9:1 ratio between okra mucilage and chitosan, PM Physical mixture of the polymers, 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).

Physical evaluation of core and coated tablets

The core and coated tablets were evaluated for pre-compression (Martin *et al.*, 1995) 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 (Lachmann *et al.*, 1991). Weight variation test was performed for 20 tablets and percent weight deviation was calculated (Indian Pharmacopoeia 1996).

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 added in to 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 ± 0.50^0C. 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 ± 0.500C 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 P2 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 (Costa *et al.*, 2001).

$Q_t = K_0 t$ ---- 1

$Q_t = Q_o(1-e^{-k_1 t})$ ----2

$Q_t/Q_\infty = K_k t^n$ ----3

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 (Costa *et al.*, 2001).

Statistical analysis

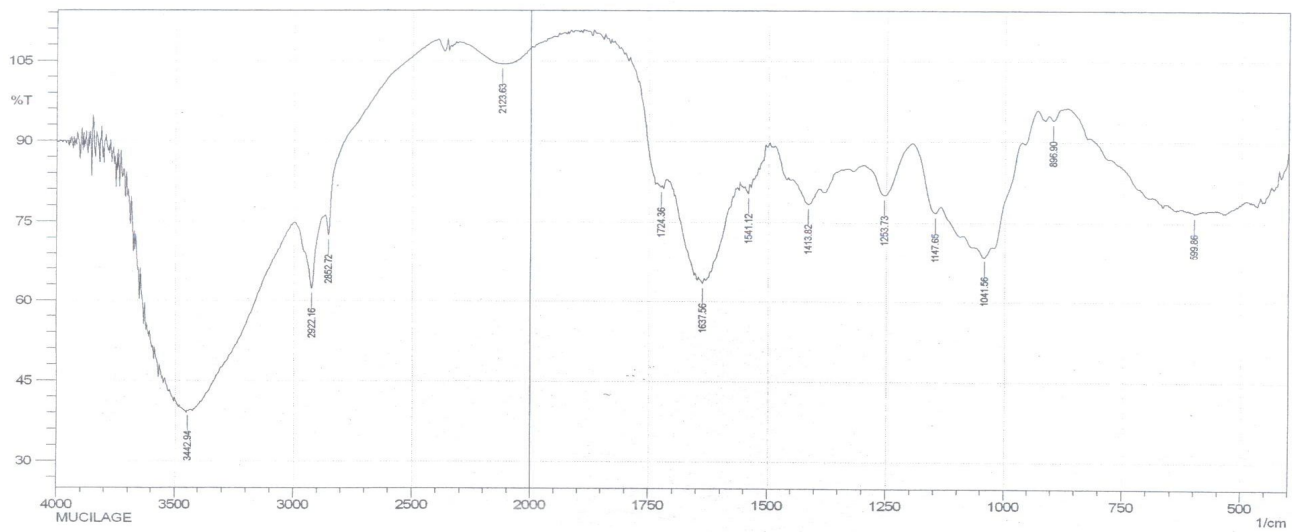
The Formulations P2 studied for in- vitro drug release with or without 2% rat caecal content. The data obtained from the dissolution studies were statistically analyzed by one way ANOVA followed by post hoc Tukey method. The statistical analysis was performed using Graphpad Prism software Inc (USA Version 4.0). A probability value of $P < 0.05$ was considered as statistically significant.

Stability studies

The stability studies were performed for the selected formulations P2 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.

RESULTS AND DISCUSSION

The stoichiometric ratio for the formation of PEC was selected to be 9:1 for okra mucilage to chitosan based on the % yield obtained, % transmittance and viscosity values of the supernatant solutions. In the FTIR spectra of chitosan, the amino group of 2-aminoglucose unit and the carbonyl group of the 2-acetaminoglucose unit of chitosan showed absorption band at 1580.01 cm^{-1} and 1641.42 cm^{-1}. The peak at 1724.36 cm^{-1} in the IR spectrum of okra mucilage was assigned to the carbonyl group of carboxylic acid. The IR spectrum of chitosan showed characteristic C=O band of amide at 1641.42 cm-1 and N-H (s) band of amine at 1580 cm−1. This band assigned to the amine group of chitosan was shifted to 1560.41 cm−1, indicating that the amine group was protonated to a NH3 + group in PEC. These results suggested that the polyelectrolyte complex between okra mucilage and chitosan was formed by an electrostatic interaction between the COO− group of okra mucilage and NH3 + group of chitosan. The FTIR spectra of formulations (figure1) showed no change in peaks associated with drug indicating compatibility between drug and polymers. 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.



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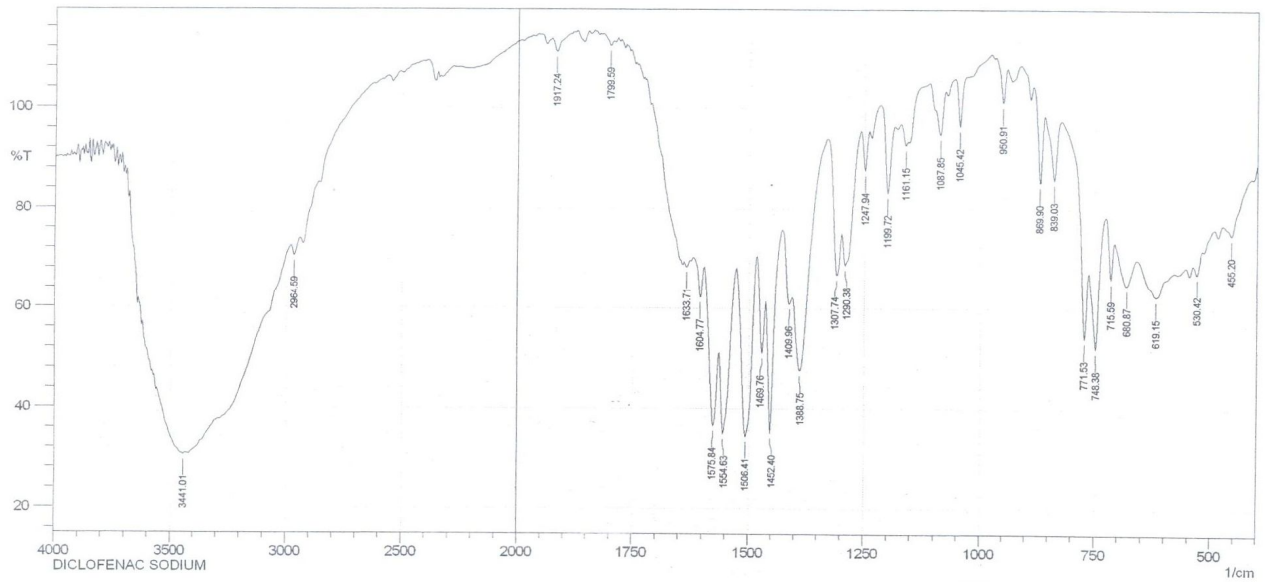
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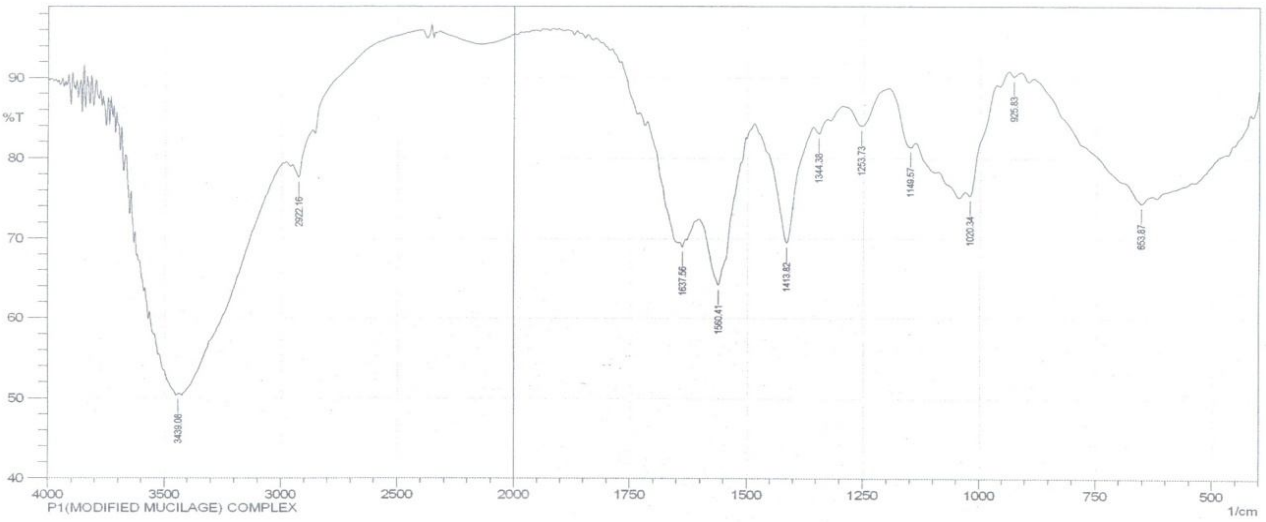
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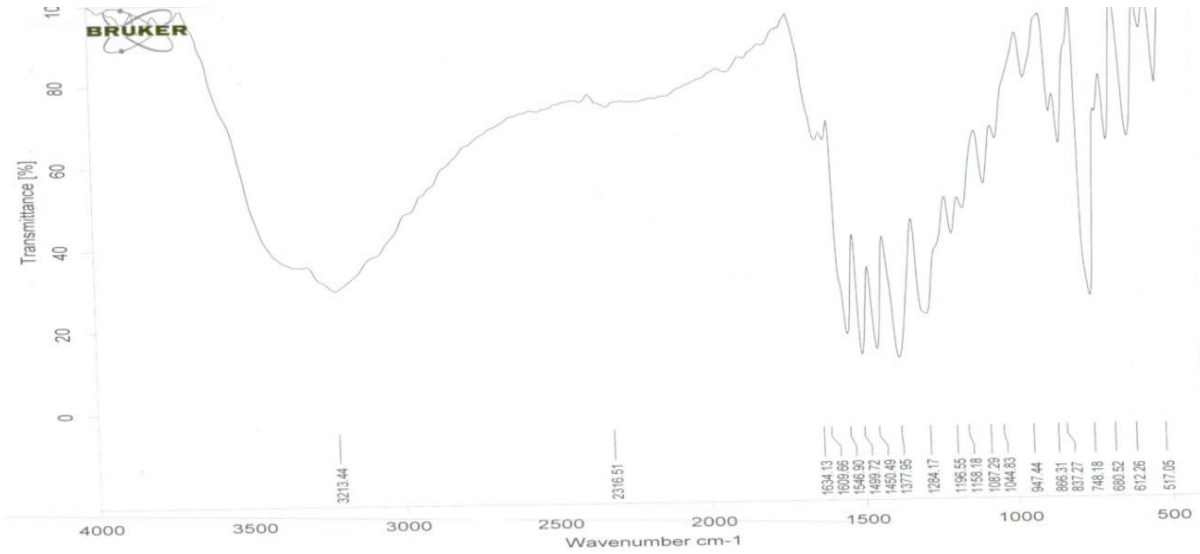
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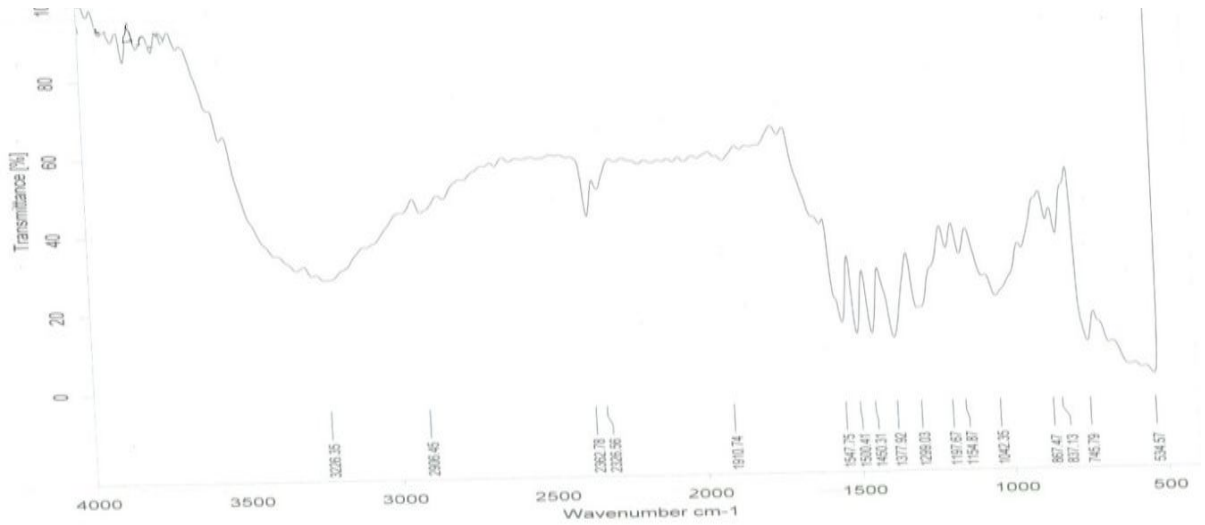

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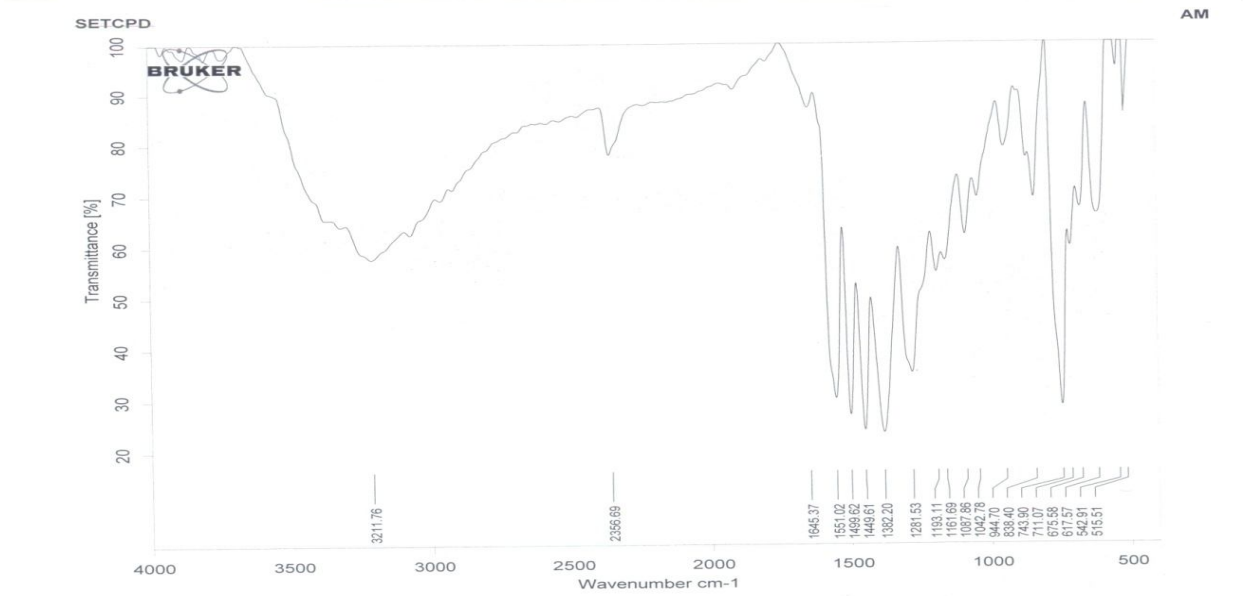

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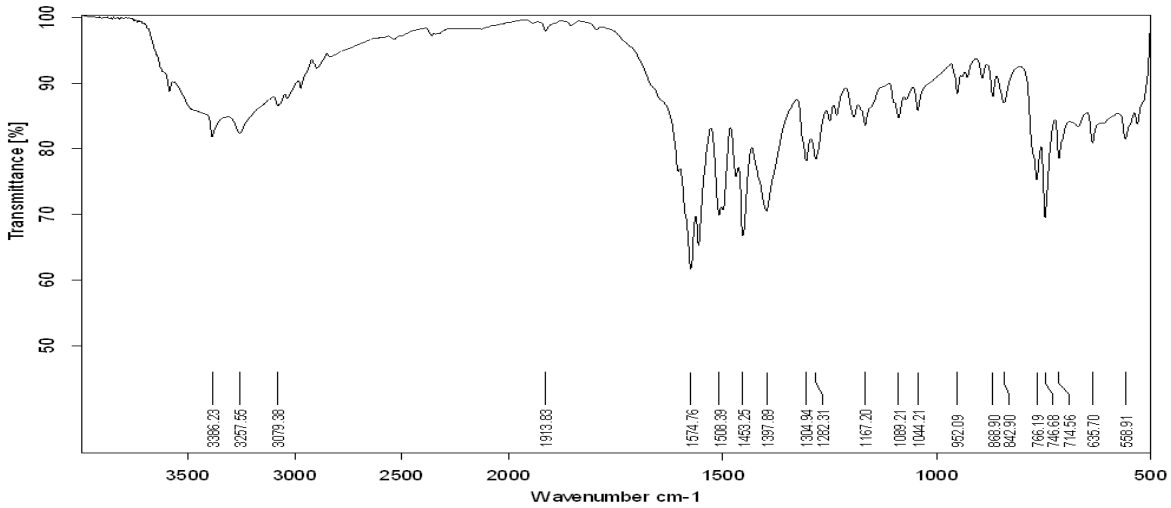

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Fig.1: FTIR spectra of mucilage (A), Diclofenac sodium (B), Polyelectrolyte complex(C), Formulations H (D), M1 (E), PM1 (F) and P2 (G).

Physical evaluation of compression coated tablets

The pre-compression parameters of the prepared coating materials were evaluated and the results are shown in the table 3. The results of pre-compression study showed good compressibility and flow property of prepared granules.

The coating materials contained okra mucilage, polyelectrolyte complex and the physical mixture of okra mucilage with chitosan with HPMC in the ratios of 4:1, 1:1 and 1:1. 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 4. 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.

In-vitro dissolution profiles

In case of formulations M1, M2 and M3 the drug release was 84.8 ±0.5042 %, 100.12 ± 0.5271 % and 99.98 ± 0.1435 % in 24 hrs respectively. These formulations extended the drug release for 24 hrs. Formulations P1, P2 and P3 showed drug release of 96.789 ± 0.6699 %, 100.86 ± 0.4272 % and 95.15 ±0.7180 % in 24 hrs respectively. These formulations also extended the drug release for 24 hrs. For the formulations PM1, PM2 and PM3, the drug release was 100.12 ± 0.6141(8hr), 100.21 ±0.0572 (6 hr) and 100.2 ± 0.3844 % in 4 hrs respectively. The reason for this may be higher swelling followed by faster erosion of the formulations. 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 polyelectrolyte complex and the modified polymer and okra mucilage in combination with HPMC for extending the drug release.

Table. 3: 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
P1	0.311±0.004	0.364±0.004	14.538±0.897	1.170±0.014	31.441±0.0577
P2	0.442±0.017	0.523±0.027	15.399±0.822	1.181±0.011	30.803±0.0577
P3	0.345±0.003	0.413±0.006	16.228±0.775	1.199±0.016	31.119±0.173
PM1	0.361±0.001	0.433±0.013	16.611±0.832	1.194±0.014	30.493±0.152
PM2	0.330±0.013	0.394±0.010	16.268±0.922	1.091±0.022	31.441±0.152
PM3	0.337±0.008	0.368±0.008	9.314±0.484	1.232±0.035	31.119±0.1
H	0.322±0.010	0.368±0.014	12.306±0.263	1.155±0.032	30.646±0.1

Table. 4: Post- compression parameters for coated tablets

Form Code	Thickness mm	Hardness Kg/cm^2	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
P1	4.173±0.02	5.5666±0.0577	0.197	99.101±0.810	305.8±1.1633
P2	4.22±0.026	5.7±0.107	0.156	98.501±0.565	306.55±1.283
P3	4.2±0.0173	5.7333±0.0577	0.2895	99.400±0.343	304.7±0.7533
PM1	4.086±0.04	5.4333±0.0577	0.254	99.250±0.343	302.75±1.091
PM2	4.12±0.04	6.2±0.0707	0.375	98.651±0.898	303.4±1
PM3	4.16±0.045	6.2666±0.1154	0.425	99.3258±0.224	303.35±1.15
H	4.25±0.005	5.31±0.0953	0.3720	99.4756±0.686	303.25±1.1

Table. 5: Drug release kinetics of compression coated formulations.

Form Code	First Order			Korsemeyer-Peppas			Weibull Model		
	K_1 (% h^{-1})	Inte rcept	R^2	n	Inter cept	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
P1	-0.066	2.029	0.942	1.480	0.353	0.866	1.825	-1.204	0.962
P2	-0.057	2.028	0.971	1.346	0.466	0.851	1.853	-1.257	0.991
P3	-0.090	2.090	0.988	1.362	0.495	0.817	1.916	-1.224	0.975
PM1	-0.403	2.469	0.914	1.333	0.444	0.930	1.936	-0.615	0.960
PM2	-0.444	2.461	0.845	1.270	1.094	0.957	1.598	-0.462	0.962
PM3	-0.468	2.473	0.864	1.527	0.926	0.917	1.987	-0.560	0.948
H	-0.032	2.054	0.982	1.515	0.021	0.925	1.746	-1.675	0.881

Drug release kinetics

The release kinetics was estimated by fitting the in-vitro dissolution data into zero order and first order equations. The first order regression values were between 0.914 and 0.988 hence all the formulations followed first order kinetics (table 5, figure 2). 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 3).

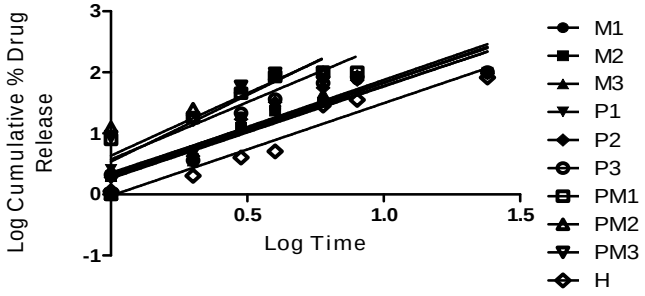

Fig. 2: First order plots for formulations M1 (●), M2 (■), M3 (▲), P1 (▼), P2 (♦), P3 (○), PM1 (□), PM2 (Δ), PM3 (▽) and H (◊).

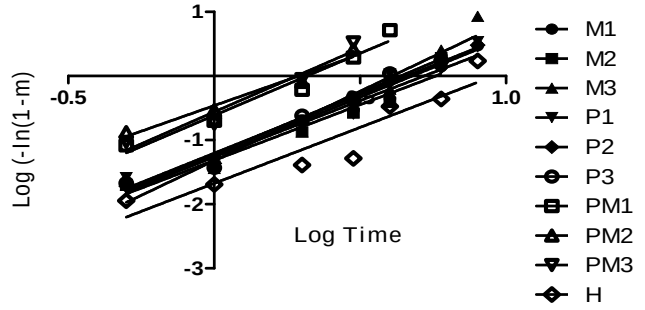

Fig. 3: Weibull plots for formulations M1 (●), M2 (■), M3 (▲), P1 (▼), P2 (♦), P3 (○), PM1 (□), PM2 (Δ), PM3 (▽) and H (◊).

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 4). The difference in the in-vitro drug release profile was found to be less significant (p>0.05).

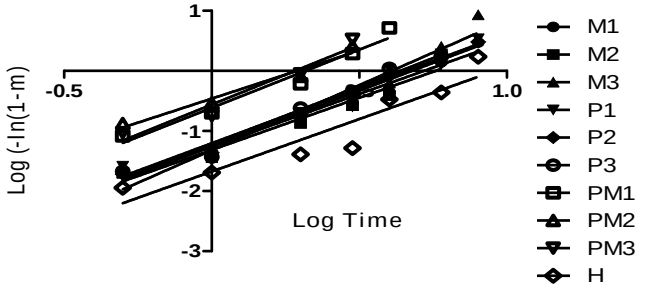

Fig. 4: In-vitro dissolution profile in absence of rat caecal content for formulation P2 (Δ) and in presence of rat caecal content P2-RC (□).

Stability study

The stability study for the selected formulations P2 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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