International Journal of PharmTech Research
CODEN (USA): IJPRIF, ISSN: 0974-4304
Vol.7, No.1, pp 185-195, 2014-2015

In Vitro Evaluation and Mechanism of Drug Release from Natural Mucilage-Based Colon-Site Specific Drug Delivery System

Ilango K B*[1, 2], Kavaimani S[3]

[1]Karpagam College of Pharmacy, Othakkalmandapam, Coimbatore-641032, India
[2] Mewar University, Chittorgarh, Rajesthan, India
[3]Mother Theresa Post Graduate and Research Inst. of Health Sciences, Puducherry, India

Abstract: In this investigation, okra polysaccharide with ethylcellulose in the form of compression coated tablets formulated had been evaluated for its ability to remain intact in the physiological environment of stomach and small intestine but deliver drug in colon and also to predict mechanism of drug release using mathematical models. Okra polysaccharide was isolated from *Abelmuschus esculentus* L. (Moench.) and used for tablet formulations (F1, F2, F3, F4 & F5) with ibuprofen as a core tablet. The compression coated tablets were subjected to *in vitro* drug release studies. The release studies were carried out for 2 hours in pH 0.1 N HCl, 3 hours in pH 7.4 phosphate buffer and continued in pH 6.8 PBS. *In vitro* drug release studies were performed for the F1 formulation in absence and in presence of rat cecal contents in pH 6.8 PBS. The drug release profiles were compared using model dependent and independent methods using DDSolver software. Result showed the drug release dependent upon the amount of okra polysaccharide used in formulations and also showed enhanced release in presence of rat cecal content, because of microbial degradation of polysaccharide. In this study, drug release was dependent on combination of diffusion, erosion and relaxation of polymer chains. These observations drive us to conclude that the okra polysaccharide under investigation has the potential to carry the drug almost intact to the intended site i.e. Colon. Thereby both the aims contemplated are achieved.
Keywords : Okra ▪ Compression coated▪ DDSolver ▪ Bootstrap f2 method ▪ Release mechanism

Introduction

Colon specific drug delivery systems have gained increased importance for systemic delivery of drugs [1-2], as well as for local delivery for the diseases of the colon, like ulcerative colitis, Crohn's disease and colon cancer. Colon targeting not only reduces the dose to be administered, and also eliminates the incidence of possible adverse effects associated with these drugs to the other organs enroute [3]. Colon-specific delivery systems can be used to improve the bioavailability of protein and peptide drugs [4,5]. Well documented approaches to achieve colon-specific delivery include pro-drugs [6], pH-dependent systems [7], time-dependent systems [8], and biodegradable systems [9]. Efficient colon drug delivery system is vital since it responds only to the physiological conditions particular to the colon. Hence, attempts are made to bring out ideal colon-specific delivery systems with improved site specificity and adequate drug release at the appropriate site and developed to accommodate different therapeutic needs. The use of bacterially degradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches. These polymers shield the drug from the environments of the stomach and the small intestine and are able to deliver the drug to the colon intact. On reaching the colon, they undergo assimilation by micro-organism [10] or degradation by enzyme [11] or breakdown of the polymer backbone [12] leading to a subsequent reduction in their molecular weight and loss of mechanical strength. They are then unable to hold the drug entity any longer

[13]. Considering the aspect of the anaerobic bacteria of the colon able to react to the constantly changing mixture of complex carbohydrates entering the colon by recognizing a variety of substrates and producing the appropriate digestive enzyme, various systems have been developed for drug delivery to colon [14-15]. Recent trends towards the use of natural polysaccharides such as vegetables, animal and of microbial origin have increased. There are several reports about the successful use of hydrophilic polymers derived from plants, like guar, carrageenan, karaya, locust bean etc. in pharmaceutical preparations [16]. Guar gum has been investigated for its application in colon specific dosage forms [16]. Abelmuschus esculentus gum had been used as mini matrix for furosemide and diclofenac sodium tablets [17], okra mucilage in colon specific drug delivery as matrix tablets [18] and investigated as well in release of indomethacin from bioadhesive tablets with carbopol [19]. Besides, this mucilage had been evaluated as a controlled-release agent in modified release matrices,in comparison with sodium carboxymethylcellulose (NaCMC) and hydroxypropylmethyl cellulose(HPMC),using Paracetamol as a model drug[20]. The Okra (Abelmuschus esculentus) is a bulky annual plant cultivated throughout the tropical and subtropical areas of the world, particularly in India, gives fruits which are green pods of various shapes. The okra mucilage contains the major polysaccharide component differing widely in the molar ratios of galactose, galacturonic acid, and rhamnose [21] and with some fractions of glucose, mannose, arabinose and xylose [22]. In recent years researchers pay much attention to okra mucilage in pharmaceutical formulation. The present investigation is an attempt made to utilize the presence of polysaccharide in okra mucilage, as a carrier for microbially triggered colon-site-specific delivery system using ibuprofen as model drug. In this investigation, okra polysaccharide with ethylcellulose in the form of compression coated tablets formulated had been evaluated for its ability to remain intact in the physiological environment of stomach and small intestine. The susceptibility of okra to undergo biodegradation only in colon site is assessed by conducting *in vitro* drug release studies in the presence of rat cecal contents in pH 6.8 phosphate buffered saline (PBS) using ibuprofen as model drug. Mathematical models can be applied to express the dissolution data as a function of parameters related to pharmaceutical dosage to characterize *in vitro* drug release behavior. Dissolution data analyses were performed by comparing dissolution profiles statistically or using mathematical models to quantify or characterize the drug release from compression coated tablet. Similarity factor and rescigno index were used to predict the equivalence between dissolution profiles, in presence and in absence of rat cecal content.

Materials and Methods

Sodium metabisulfite was purchased from Merck specialties Pvt. Ltd., India, Acetone from Nicechemicals Pvt. Ltd., India, Ibuprofen gifted by Yarrowchem products, Mumbai, Ethylcellulose were from GlaxoSmithKline Pharmaceutical Ltd Lactose monohydrate, talc, sodium hydroxide and potassium dihydrogen phosphate were purchased from S D-Fine chemicals, Mumbai. Magnesium stearate from Loba chemie Pvt.,Ltd., Mumbai, ethanol from Changshu YangYuan Chemicals, China. All other chemicals were also of higest grade.

Extraction of the polysaccharide from okra fruits

The reported method [18] was used for the extraction of Okra polysaccharide.

Preparation of compression coated tablets

Preparation of ibuprofen core tablets

Each core tablet (average weight 80 mg) for *in vitro* drug release studies consisted of ibuprofen (50 mg), okra polysaccharide (27 mg), talc (2 mg) and magnesium stearate (1 mg). Okra polysaccharide was added to give better binding and to undergo biodegradation in colon site. The materials were weighed, mixed and passed through a 60 mesh to ensure complete mixing. The thoroughly mixed materials were then directly compressed into tablets using 6 mm round, flat and plain punches on12-station rotary tablet mini press -II MT (Remek, Ahmedabad, India). Tablet quality control tests such as weight variation, hardness, friability, thickness, and dissolution in different media were performed on the core tablets.

Compression coating of core tablets

The core tablets were compression coated with different quantities (Table 1) of coating material containing of okra polysaccharide/ethylcellulose with different coat weights. Ethylcellulose was included in the coat formulations to impart enough hardness. Since okra polysaccharide alone did not give enough strength to

the coats. Half the quantity of the coating material was placed in the die cavity; the core tablet was carefully placed in the centre of the die cavity and was filled with the other half of the coating material. The coating material was compressed using 9 mm round, flat and plain punches. In this study, we have used a high molecular weight ethylcellulose in combination with okra polysaccharide to enforce the mechanical resistance of the tablet during its transit in the GI tract. Tablet quality control tests such as weight variation, hardness, friability, thickness, and dissolution rates in different media were performed on the compression coated tablets. Hardness of randomly selected tablets was tested using Monsanto hardness tester. Friability of core tablets and compression coated tablets were carried out on a Roche friabilator (Electrolab, Mumbai, India) using 20 accurately weighed tablets.

Table 1. Quantity (mg) present in the coat formulation

Ingredients	Formulation codes				
	F1	F2	F3	F4	F5
Okra polysaccharide	100	125	150	200	250
Ethylcellulose	20	20	20	20	20
Microcrystalline cellulose	25	25	25	25	25
Talc	3	3	3	3	3
Magnesium stearate	2	2	2	2	2
Total	150	175	200	250	300

***In vitro* Drug Release Studies** [23, 24].

The formulated ibuprofen compression coated tablets using okra polysaccharide with ethylcellulose were evaluated for their integrity in the physiological pH of stomach, the small intestine and colon. These studies were carried out using a USP XXIII dissolution rate test apparatus (Apparatus 1,100 rpm, 37 °C).The tablets were tested for drug release for 2 hours in pH 1.2 (900 ml) as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with pH 7.4 phosphate buffer (900ml) and tested for 3 hours as the average small intestine transit time is about 3 hours, the medium was once again replaced with pH 6.8 PBS (900ml) and the study continued for 10 more hours.

***In vitro* drug release studies with and without 4% rat cecal contents [23, 24].**

The tablets 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 pH 7.4 phosphate buffer (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 4% w/v rat cecal contents and also with the same medium (pH 6.8 PBS) but without rat cecal content as control. The release study with rat cecal content was used to assess the susceptibility of the okra polysaccharide to the enzymatic action of colonic bacteria. At the end of each time period, 1ml sample was withdrawn, suitably diluted and analyzed for ibuprofen content at 265 nm using Double beam UV-visible spectrophotometer-2220 (SYSTRONICS, India). The cecal contents were obtained from male albino rats after pretreatment of the animal for 7 days with 1ml of 2% okra polysaccharide dispersion in order to induce enzymes specifically acting on okra polysaccharide in the cecum this provides the best condition for the in vitro evaluation of okra polysaccharide. Thirty minutes before the commencement of drug release studies, rats were killed by spinal traction, their abdomen opened, the cecal bags isolated and ligated at both ends. The cecal bags were opened, their contents individually weighed, pooled and transferred to pH 6.8 (previously bubbled with CO2) to give a final dilution of 4% w/v. All the operations were carried out under continuous CO_2 supply. The studies of drug release under the simulated environment in colon were carried out in USP XXIII dissolution rate test apparatus with slight modification. A beaker (capacity 150 ml internal diameter 55mm) containing 100 ml of dissolution medium was immersed in water-filled 1000 ml vessel, which in turn placed in the water bath of dissolution apparatus. The matrix tablets were placed in the beaker containing pH 6.8 phosphate buffers containing the rat cecal matter. The experiments were carried out with the continuous CO_2 supply into the beaker to simulate anaerobic environments of cecum. The above study was carried out on optimized okra matrix tablet without rat cecal content also in pH 6.8 phosphate buffer (control).

Data analysis

The calibration curve and the raw dissolution data were analyzed.

Interface

DD Solver is a menu-driven add-in program for Microsoft Excel written in Visual Basic for applications. Calculation using Excel offers a number of advantages over other software packages, the most attractive of which is ease of use. All data were entered into Excel according to the example format for each built-in module of the DD Solver. The relevant parameters were calculated following the equations step-by-step utilizing an Excel spreadsheet. The equivalence can be predicted by dissolution profile comparison through Similarity factor, Rescigno index using DDSolver software. The best model choice was based on model performance on the available data and several measures of goodness of fit were implemented.

Model dependent and independent Approach

Mathematical modeling of drug release can be used in optimizing the design of dosage forms, elucidate the underlying drug release mechanisms, and adequately estimate the required parameters and preparation procedures for different dosage forms [25].

Ethical committee approval

Committee for the Purpose of Control and Supervision of Experiments of Animals (CPCSEA).
The Institutional Animal Ethical Committee (IAEC).

Result and discussion

The present work is to find out the ability of the okra polysaccharide to deliver the model drug ibuprofen intact to colon and to undergo microbial degradation there. The intention was the formulated compression coated tablet protected from degradation in stomach and intestine until it reached the colon. The polysaccharide obtained from okra is composed of glactose, rhamnose and glacturonic acid. It was contemplated to exploit the presence of above saccharides for the microbially triggered drug delivery system of okra polysaccharide compression coated tablet to the colon.

Evaluation of compression coated tablet

The hardness of the tablet ranged between 5.97 and 6.5 kg/cm^2.The percentage friability of the prepared tablets was well within the acceptable limit. There was no significant weight variation observed between average weight and individual weight of tablets. The percentage drug content in all the batches were within the range of 98.29 - 99.19%, ensuring uniformity of drug content in the formulations.

***In vitro* studies**

The results of drug release profile of compression coated tablet formulations F1, F2, F3, F4 and F5 in 0.1 N HCl (2 h), pH 7.4 phosphate buffers (3 h) and pH 6.8 PBS are shown in Fig 1. The result show that the dissolution of drug decreased as the amount of okra polysaccharide increased, this is evident from Fig 1. Thus, okra polysaccharide in the form of compression coated tablet was capable of releasing minimal quantity of the drug in the physiological environment of stomach and small intestine. This may be due to the contact of polymer with the dissolution medium, followed by absorption of the fluid, swelling and formation of protective layer of hydrated gel that slowed down further seeping-in.

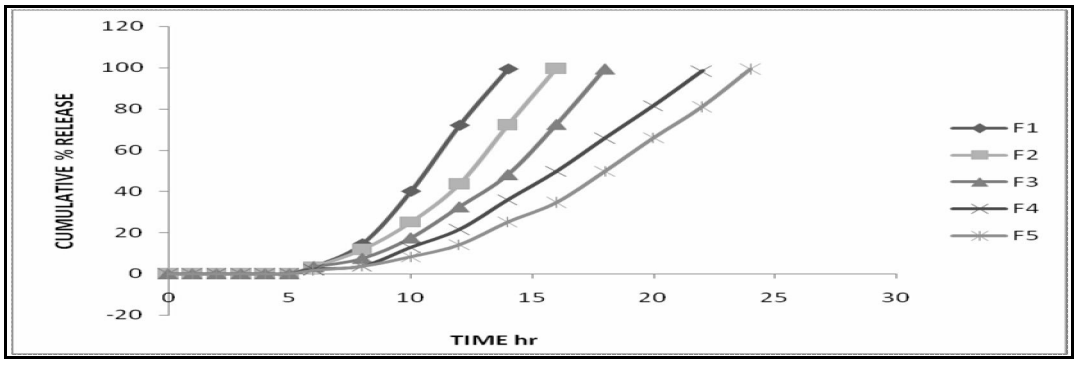

Figure 1 in vitro release profile of okra gum based compression coated tablets (Mean ± S.D., n =3)

***In vitro* dissolution studies in presence and absence of rat cecal matter**

In vitro dissolution studies of okra polysaccharide compression coated tablet were carried out using 0.1N, pH 7.4 and pH 6.8 in presence and absence of rat cecal matter in order to mimic conditions from mouth to colon environment. The results of % drug release at pH 1.2, pH 7.4, pH 6.8 PBS without rat cecal matter were shown in Fig 1. The study was repeated with one more set of optimized tablets (F1), and the results of % drug release at pH 1.2, pH 7.4 and in pH 6.8 PBS in presence and in absence of rat cecal content were shown in Fig 2.

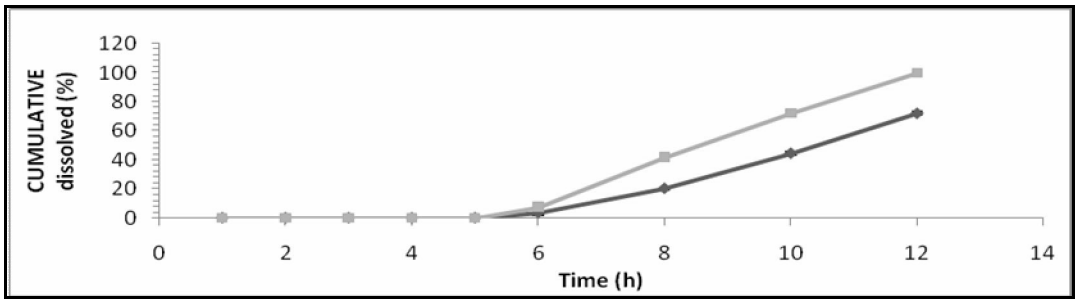

Figure 2 *In vitro* release in presence and in absence of rat cecal matter (Mean ± S.D., *n* = 3)

Release kinetics

Table 2 Goodness of Fit

Model	Zero Order					Higuchi				
Parameter	F1	F2	F3	F4	F5	F1	F2	F3	F4	F5
Rsqr	0.697113	0.674837	0.752879	0.812975	0.782632	0.420573	0.4066745	0.4765775	0.5371823	0.511365
Rsqr_adj	0.697113	0.674837	0.752879	0.812975	0.782632	0.420573	0.4066745	0.4765775	0.5371823	0.511365
MSE	372.2542	372.793	260.9808	208.8952	233.5685	712.2999	680.37072	552.98133	517.16597	525.265
MSE-root	19.29386	19.3073	16.15456	14.45227	15.28173	26.6886	26.083837	23.515458	22.741266	22.91865
SS	3722.542	4100.724	3131.769	2924.533	3503.528	7122.999	7484.0779	6635.7759	7240.3236	7878.975
WSS	3722.542	4100.724	3131.769	2924.533	3503.528	7122.999	7484.0779	6635.7759	7240.3236	7878.975
AIC	92.44373	101.8256	106.6405	121.7095	132.5793	99.58135	109.04625	116.40279	135.31127	145.5512
MSC	0.762774	0.74285	0.981993	1.261501	1.158658	0.1139	0.1411333	0.2310485	0.3547141	0.347914

Several kinetic models had been used in this study to describe the release characteristics of a drug from compression coated tablet. The dissolution data were fitted to the different models. Identification of a suitable model for dissolution data was essential, not only for quantitative evaluation of drug release characteristics but also for comparison of dissolution profiles using model-dependent approaches. In this study the best model fits were identified using R^2adjusted, AIC, and MSC. The R^2 adjusted value was used as the model selection criterion with the best model exhibiting the R^2 adjusted value closest to 1. When comparing different models, using the MSC, the most appropriate model will be that with the largest MSC. The more negative the value of the AIC, the better the model describes the data. AIC is based on both the fit to the data and the number of estimated parameters, if two models each fit the data well, the AIC will be lower for the model. As observed in Table 2, for formulations F1, F2, F3, F4 & F5 for zero-order and Higuchi model, AIC values were of 92.44373,101.8256,106.6405,121.7095,132.5793 and 99.58135,109.04625,116.40279,135.31127,145.5512

respectively, MSC values were of 0.762774,0.74285,0.981993, 1.261501& 1.158658 and0.1139,0.1411333, 0.2310485,0.3547141,0.347914 respectively, Rsqr_adj values 0.697113, 0.674837, 0.752879, 0.812975 & 0.782632 and 0.420573, 0.4066745, 0.4765775, 0.5371823, 0.511365 respectively.

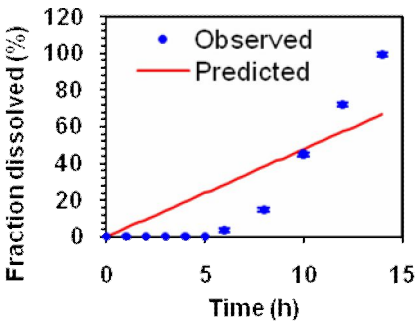

Fig 3 Zero order

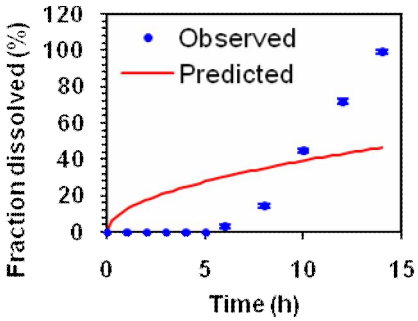

Fig 4 Higuchi model

All formulations follow neither zero order kinetics nor Higuchi model. This can be confirmed through Fig 3 & Fig 4. From the Table 3 k_0 value decreases from 4.774289 to 2.883478, this shows that as coat thickness increases the drug release decrease. Further confirmed through secondary parameter such as T90 values increase from formulation F1 to F5 as 18.85614 to 31.22311(Table 4).

Table 3 Best-fit Values

Model	Zero-order		Higuchi	
Parameter	k_0		k_H	
Formulation	Mean	SD	Mean	SD
F1	4.774289	0.096698	12.50579	0.277112
F2	3.96588	0.077188	11.10422	0.243272
F3	3.677343	0.082085	11.18806	0.27708
F4	3.294127	0.070499	11.32075	0.270355
F5	2.883478	0.065586	10.29982	0.264659

Table 4 Secondary Parameter

Model		Zero Order		Higuchi	
Formulation	Parameter	Mean	SD	Mean	SD
F1	T25	5.237818	0.106322	4.000239	0.177977
	T50	10.47564	0.212644	16.00096	0.711908
	T75	15.71345	0.318966	36.00215	1.601794
	T80	16.76102	0.34023	40.96245	1.822485
	T90	18.85614	0.382759	51.8431	2.306583
F2	T25	6.305366	0.122976	5.073663	0.222835
	T50	12.61073	0.245952	20.29465	0.891341
	T75	18.9161	0.368929	45.66297	2.005518
	T80	20.17717	0.393524	51.95431	2.281834
	T90	22.69932	0.442714	65.75467	2.887946
F3	T25	6.800648	0.152003	4.999243	0.248181
	T50	13.6013	0.304006	19.99697	0.992722
	T75	20.40194	0.45601	44.99319	2.233626
	T80	21.76207	0.48641	51.19225	2.541369
	T90	24.48233	0.547211	64.79019	3.216421
F4	T25	7.591589	0.162878	4.882331	0.234227

	T50	**15.18318**	**0.325755**	**19.52932**	**0.936907**
	T75	**22.77477**	**0.488633**	**43.94097**	**2.108041**
	T80	**24.29308**	**0.521209**	**49.99506**	**2.398482**
	T90	**27.32972**	**0.58636**	**63.275**	**3.035579**
F5	**T25**	**8.673085**	**0.197758**	**5.899244**	**0.304429**
	T50	**17.34617**	**0.395516**	**23.59698**	**1.217715**
	T75	**26.01925**	**0.593274**	**53.0932**	**2.739859**
	T80	**27.75387**	**0.632826**	**60.40826**	**3.11735**
	T90	**31.22311**	**0.711929**	**76.4542**	**3.945396**

Table 5 Goodness of Fit

Model	**Korsmeyer-Peppas**					**Makoid-Banakar**					**Peppas-Sahlin**				
Parameter	**F1**	**F2**	**F3**	**F4**	**F5**	**F1**	**F2**	**F3**	**F4**	**F5**	**F1**	**F2**	**F3**	**F4**	**F5**
R_obs-pre	**0.999439**	**0.996998**	**0.997557**	**0.998676**	**0.999088**	**0.999343**	**0.999701**	**0.999439**	**0.999624**	**0.999697**	**0.995538**	**0.997016**	**0.999525**	**0.999288**	**0.999467**
Rsqr	**0.998727**	**0.993858**	**0.99426**	**0.996858**	**0.997897**	**0.998651**	**0.999399**	**0.998806**	**0.999237**	**0.999391**	**0.990989**	**0.993948**	**0.999049**	**0.998559**	**0.998919**
Rsqr_adj	**0.998545**	**0.99309**	**0.993622**	**0.996616**	**0.997746**	**0.998314**	**0.999266**	**0.998567**	**0.999109**	**0.999297**	**0.988736**	**0.992603**	**0.998859**	**0.998319**	**0.998752**
MSE	**0.3321**	**1.409796**	**1.723199**	**3.775228**	**2.415157**	**2.069673**	**0.840687**	**1.518912**	**0.998478**	**0.756977**	**13.83172**	**8.47686**	**1.210153**	**1.877285**	**1.339554**
MSE_root	**0.571808**	**1.182569**	**1.310446**	**1.941328**	**1.547319**	**1.436759**	**0.91439**	**1.228024**	**0.993515**	**0.869091**	**3.717796**	**2.910787**	**1.092809**	**1.369754**	**1.156415**
SS	**2.3247**	**11.27837**	**15.50879**	**49.07797**	**33.8122**	**16.55738**	**7.56618**	**15.18912**	**11.98174**	**9.840705**	**110.6538**	**76.29174**	**12.10153**	**22.52743**	**17.41421**
WSS	**2.3247**	**11.27837**	**15.50879**	**49.07797**	**33.8122**	**16.55738**	**7.56618**	**15.18912**	**11.98174**	**9.840705**	**110.6538**	**76.29174**	**12.10153**	**22.52743**	**17.41421**
AIC	**11.31647**	**28.06782**	**34.07957**	**62.34984**	**60.05185**	**36.81748**	**30.1516**	**41.17843**	**42.89468**	**42.51488**	**57.75491**	**58.00292**	**38.06099**	**52.70397**	**51.66223**
MSC	**6.066735**	**4.54331**	**4.518142**	**5.21881**	**5.691625**	**5.819705**	**6.715687**	**6.017537**	**6.51582**	**6.787685**	**3.916303**	**4.394744**	**6.25734**	**5.861868**	**6.215976**

The release kinetics was further subjected to different models such as Korsmeyer-Peppas, Makoid-Banakar, Peppas-Sahlin, Hopfenberg, Hixson–Crowell, Baker–Lonsdale, Quadratic, Weibull, Quadratic and Logistic to predict the exact release mechanism. Among those models Korsemeyer-Peppas, Makoid-Banakar and Pepps-Sahlin showed goodness of fit based on the Rsqr_adj, AIC and MSC values from Table 5.

From Table 6, for Korsmeyer-Peppas, n values greater than 0.89 had been observed, which had been regarded as Super Case II kinetics. The values of release parameters *n* and *k* were inversely related. Lower values of kKP suggest that it did not undergo burst release from the tablet. On further analysis of the release data, the parameter k of the Makoid-Banakar model did not equal to zero for all the formulations and in this situation this model did not approach Korsmeryer-Peppas power law. Thus the mechanism of drug release from tablet was not only due to diffusion. From the Table 6 the diffusion parameter showed K1 as -2.14401, -0.84157, -0.33106, -1.17142 & -0.54529, the relaxation value K2 as 0.419925, 0.095735, 0.073393, 0.290505 & 0.093827 and m as 1.103973, 1.307507, 1.269004, 0.980624 & 1.125671 for F1, F2, F3, F4 & F5 respectively which can be reported as an insignificant effect of Fickian diffusion on drug release compared to the relaxation process. The rate of drug release from a surface eroding device was determined by the relative contribution of the drug diffusion and the degradation. Further from Table 7, T80 & T90 values increase from formulation F1 to F5, which showed the release retardation of drug increased from formulation F1 to F5. The dissolution profiles were further subjected to model analysis. The fit of dissolution data to the Weibull distribution and logistics model emphasized the S-shaped or sigmoidal dissolution profiles. These models cannot describe drug release kinetics, but those can describe the curve in terms of applicable parameters. From the Table 8 as the value for shape parameter β was higher than 1, showed “S” shaped with an upward curvature which reduced the release phase and abrupt termination.

Table 6 Best-fit Values

Model	Korsmeyer-Peppas			Makoid-Banakar			Peppas-Sahlin		
Formulation	Parameter	Mean	SD	Parameter	Mean	SD	Parameter	Mean	SD
F1	kKP	0.000356	0.000241	kMB	5.60564	4.57463	k1	-2.14401	0.110183
	n	5.171627	0.29372	n	9.554709	0.556611	k2	0.419925	0.045236
				k	0.591548	0.042078	m	1.103973	0.019218
F2	Parameter	Mean	SD	Parameter	Mean	SD	Parameter	Mean	SD
	kKP	0.000313	0.000229	kMB	0	0	k1	-0.84157	0.035362
	n	4.841263	0.277902	n	10.11237	0.800727	k2	0.095735	0.013597
				k	0.519369	0.05187	m	1.307507	0.025854
F3	Parameter	Mean	SD	Parameter	Mean	SD	Parameter	Mean	SD
	kKP	0.031288	0.009879	kMB	0.016893	0.008188	k1	-0.33106	0.026841
	n	2.799554	0.118511	n	3.211661	0.270218	k2	0.073393	0.008244
				k	0.028484	0.013819	m	1.269004	0.019388
F4	Parameter	Mean	SD	Parameter	Mean	SD	Parameter	Mean	SD
	kKP	0.070549	0.013168	kMB	0.005206	0.003145	k1	-1.17142	0.021732
	n	2.355327	0.058614	n	3.899304	0.345219	k2	0.290505	0.026633
				k	0.093294	0.016584	m	0.980624	0.014944
F5	Parameter	Mean	SD	Parameter	Mean	SD	Parameter	Mean	SD
	kKP	0.025949	0.005963	kMB	0.002071	0.001838	k1	-0.54529	0.071833
	n	2.608299	0.071912	n	4.091837	0.462704	k2	0.093827	0.002977
				k	0.080122	0.020622	m	1.125671	0.00682

Table 7 Secondary Parameter

Formulation	Models	Korsmeyer-Peppas		Makoid-Banakar		Peppas-Sahlin	
F1	Parameter	Mean	SD	Mean	SD	Mean	SD
	T25	8.918965	0.101696	8.772057	0.105766	8.561932	0.111408
	T50	10.20075	0.039823	10.49366	0.079274	10.76974	0.094838
	T75	11.03452	0.018598	12.0753	0.067858	12.45748	0.077087
	T80	11.1734	0.023969	12.41759	0.069419	12.75788	0.073528
	T90	11.43138	0.036975	13.17701	0.083591	13.33058	0.066442
F2	T25	10.66736	0.127679	10.54699	0.134178	10.34682	0.139165
	T50	12.31283	0.047347	12.4676	0.08365	12.70854	0.099018
	T75	13.39094	0.029527	14.14815	0.053468	14.44996	0.065784
	T80	13.57107	0.037772	14.49393	0.051186	14.75522	0.059712
	T90	13.90609	0.055935	15.22465	0.054148	15.33365	0.048121
F3	T25	11.02051	0.199089	11.00866	0.183483	10.97251	0.17827
	T50	14.11947	0.111149	14.03486	0.121958	14.01797	0.134302
	T75	16.32242	0.044315	16.23889	0.08958	16.24206	0.098184
	T80	16.70352	0.039045	16.62557	0.085485	16.63099	0.091521
	T90	17.42214	0.045348	17.35945	0.079291	17.36744	0.078633
F4	T25	12.14895	0.228391	12.2535	0.235323	12.10032	0.225905
	T50	16.30675	0.187398	16.02239	0.1548	16.16283	0.183053
	T75	19.37089	0.139933	19.17056	0.122877	19.31593	0.140799
	T80	19.90918	0.130311	19.77428	0.123343	19.8817	0.132453
	T90	20.93042	0.111093	20.97528	0.133111	20.96409	0.115877

F5	**T25**	**14.02593**	**0.254098**	**14.10967**	**0.263301**	**13.99156**	**0.247631**
	T50	**18.29665**	**0.197906**	**18.066**	**0.153256**	**18.18287**	**0.182485**
	T75	**21.37504**	**0.140152**	**21.22092**	**0.11398**	**21.33121**	**0.136115**
	T80	**21.91074**	**0.128842**	**21.80759**	**0.114278**	**21.88827**	**0.128006**
	T90	**22.92327**	**0.106545**	**22.95484**	**0.12393**	**22.94801**	**0.112646**

Table 8 Comparison of Weibull & Logistic

Formulation	Model	Parameter	Mean	SD
F1	**Weibull**	**α**	**294628.3126**	**56088.20465**
		β	**5.200854234**	**0.060034618**
	Logistic	**α**	**-17.7674626**	**0.178752425**
		β	**17.5652651**	**0.110403304**
F2	**Weibull**	**α**	**3248023.924**	**1065661.667**
		β	**5.792333769**	**0.124031426**
	Logistic	**α**	**-20.9561034**	**0.447046628**
		β	**19.28856664**	**0.355723968**
F3	**Weibull**	**α**	**157798.8371**	**52680.13689**
		β	**4.422523953**	**0.110269546**
	Logistic	**α**	**-15.8914053**	**0.439413142**
		β	**14.08813431**	**0.329369785**
F4	**Weibull**	**α**	**53834.04062**	**14094.74083**
		β	**3.811485759**	**0.076815295**
	Logistic	**α**	**-14.6985569**	**0.316574046**
		β	**12.37114216**	**0.21098355**
F5	**Weibull**	**α**	**261611.6832**	**84121.82222**
		β	**4.199648758**	**0.094220291**
	Logistic	**α**	**-16.8360318**	**0.388352009**
		β	**13.57050383**	**0.259495459**

Bootstrap Similarity Factor f_2 & Rescigno index

The dissolution profiles of optimized formulation F1 was studied for equivalence in presence and in absence of rat cecal matter in the dissolution medium (pH 6.8 PBS) using model independent approach such as Bootstrap similarity factor and rescigno index and the values were shown in the Table 9 and 10. The kurtosis of *f*2 values distribution was −0.251 indicating a relatively small flat distribution compared with the normal distribution. The skewness of *f*2 values distribution was 0.112 indicating a distribution with an asymmetric tail extending towards more positive values. *f*2 values obtained was lower (41.222) than the limit value of 50, indicating a dissimilarity between the two dissolution profiles in presence and absence of rat cecal matter. It was further confirmed through rescigno index values from the Table 10, ξ1 as 0.2414 and ξ2 as 0.2238. So the presence of rat cecal matter in the dissolution medium increased the drug release much higher than the dissolution medium without rat cecal matter.

Table 9 Bootstrap f2 of F1 formulation

Statistics	Value
Observed f2	**41.222**
Number of bootstrap	**5000**
Bootstrap mean	**41.234**
Bootstrap median	**41.222**
5% percentile	**40.392**
95% percentile	**42.105**
Skewness	**0.112**
Kurtosis	**-0.251**
Is 5% percentile ¡Ý 50	**No**
Similarity of R and T	**Reject**

Table 10 Overall Statistics of Rescigno index of F1 formulation

Rescigno index	Mean_R vs Individual_T		Mean_R vs Mean_T
	Mean	SE	
ξ 1	0.2414	0.0051	0.2415
ξ 2	0.2238	0.0046	0.2239

Table 11 Peppas-Sahlin 2 with Tlag of F1 formulation

Best-fit Values	Parameter	In absence		In presence	
		Mean	SD	Mean	SD
	k1	**-12.2639**	**4.543913**	**10.6422**	**2.4926**
	k2	**15.50473**	**0.57486**	**11.82239**	**0.874293**
	Tlag	**5.333372**	**0.577406**	**5.783346**	**0.022915**
Secondary Parameter	**T25**	**8.327781**	**0.123244**	**6.934385**	**0.078169**
	T50	**10.33666**	**0.093209**	**8.522269**	**0.092992**
	T75	**12.25861**	**0.090817**	**10.22802**	**0.073522**
	T80	**12.63671**	**0.091563**	**10.57769**	**0.067122**
	T90	**13.38811**	**0.093429**	**11.28352**	**0.052523**
Goodness of Fit	**Parameter**	**In absence**		**In presence**	
	R_obs-pre	**0.999501**		**0.999985**	
	Rsqr	**0.998935**		**0.99997**	
	Rsqr_adj	**0.99863**		**0.99996**	
	AIC	**30.21741**		**-7.11609**	
	MSC	**6.054577**		**9.839926**	

From Table 11, K1, K2 & Tlag values -12.2639, 15.50473 & 5.333372 and 10.6422, 11.82239 & 5.783346 in the absence and in the presence of rat cecal matter respectively. K1 value was negative which showed that the release in absence of rat cecal matter was dominated by polymer erosion. But in presence of rat cecal matter K1 & K2 values showed diffusion and erosion. Tlag value in presence of rat cecal matter was higher, which showed the release stared early. Further T90 values 13.38811 and 11.28352 in the absence and the presence of rat cecal matter respectively. T80 & T90 values were much less in presence of rat cecal matter than in absence. It is very clear that the drug release was dominated by polymer degradation, polymer relaxation and polymer erosion by enzymes produced by microbes which are present in the rat cecal matter.

Conclusion:

In vitro release studies of the formulations prepared from okra polysaccharide in presence and in absence of rat cecal contents indicated that rate of drug delivery enhanced in the presence of rat cecal contents, which enhance the rate of biodegradation of the polysaccharide used. This is due to the presence of enzymes secreted by the bacteria present in the cecal contents. Comparison of the release profiles of the formulation indicated that, drug release depends on amount of polysaccharides. F1 tablet showed optimized composition for effective drug delivery. With the present experimental work, it can be concluded that, okra polysaccharide proved to be the most suitable polysaccharide. Kinetic release revealed combination of release mechanisms. Thereby both the aims contemplated are achieved. The study revealed that natural polysaccharide can be used for selective delivery to colon for the treatment of local as well as systemic disorders.

However, further investigations have to be realized in order to improve the system, and to study other variables.

References

1. Janovska L. Vetchy D. and Rabiskova M., New systems for colonic drug targeting, Ceska Slov Farm., 2006, 55, 203–209.
2. Van den Mooter G., Colon drug delivery, Expert. Opin. Drug. Deliv., 2006, 3, 111–125.
3. Sujja-Areevath J. Munday D. L. Cox P. J.and Khan K.L., Release characteristics of diclofenac sodium from encapsulated natural gum matrix formulations, Int. J. Pharm., 1996, 139, 53-62.

4. Sinha V. Singh A. Kumar R.V. Singh S. Kumria R. and Bhinge J., Oral colonspecific drug delivery of protein and peptide drugs, Crit. Rev. Ther. Drug. Carrier. Syst., 2007, 24, 63–92.
5. Malik D. K. Baboota S. Ahuja A. Hasan S. and Ali J., Recent advances in protein and peptide drug delivery systems, Curr. Drug. Deliv., 2007,4,141–151.
6. Jain A. Gupta Y. and Jain S.K., Azo chemistry and its potential for colonic delivery, Crit. Rev. Ther. Drug. Carrier. Syst., 2006, 23, 349–400.
7. Mahkam M., New pH-sensitive glycopolymers for colon-specific drug, Delivery. Drug Deliv., 2007, 14, 147–153.
8. Gazzaniga A. Maroni A. Sangalli M.E. and Zema L., Time-controlled oral delivery systems for colon targeting, Expert. Opin. Drug. Deliv., 2006, 3, 583–597.
9. Musial W. and Kubis A., Biodegradable polymers for colon-specific drug delivery, Polim. Med. 2005, 35, 51–61.
10. Potts J.E. Clendinnings R. A. Ackard W. B. and Wiegisch W. D., The biodegradability of synthetic polymers. In: Guillet, Polymer Science and Technology. vol.3, Plenum Press, New York, 1973, 61–79.
11. Swift G., Biodegradable polymers in the environment: are they really biodegradable, Proc. ACS. Div., Polym. Mat. Sci. Eng., 1992, 66, 403–404.
12. Hergenrother R.W. Wabers H. D. and Cooper S. L., The effect of chain extenders andstabilizers on the in vivo stability of Polyurethanes, J. Appl. Biomat., 1992, 3,17– 22.
13. Park K. Shalaby S. W. W. and Park H., Biodegradation.In: Biodegradable Hydrogels for Drug Delivery, Technomic, USA, 1993 , 13–34.
14. Sinha V. R. and Kumria R., Review Polysaccharides in colon-specific drug delivery, Int. J. Pharm., 2001 , 224 , 19–38.
15. Vandamme Th. F. Charrueau C. and Chaumeil J. C., The use of Polysaccharides to target drugs to the colon, Carbohydr. Polym., 2002,48, 219-231.
16. Panda D. S. Choudhury N.S.K. Yedukondalu M. and Gupta R., Evaluation of Gum of Moringa oleifera as a Binder and Release , Retardant in Tablet Formulation, In. j. pharm. sci., 2008, 70, 614-618.
17. Ofoefule S.I. and Chukwu A., Application of Abelmoschus esculentus gum has been used as mini matrix for furosemide and diclofenac sodium tablets, Indian J Pharm Sci., 2001, 68, 532-535.
18. Ilango K. B. Manisha M. Sridurga Devi. Rajsekaran A. Senthil kumar M. and Subburaju T., *In vitro* and *in vivo* evaluation of okra polysaccharide-based colon-targeted drug delivery systems, In. J. of Pharma. Sci. Rev. and Res., 2010, 5(1), 138-45.
19. Attama A.A. Adikwu M.U. and Amorha C.J., Release of indomethacin from bioadhesive tablets containing carbopol 941 modified with Abelmuschus esculentus(okra) gum, Boll.Chim. Farm., 2003, 142, 298-302.
20. Kalu V.D. Odeniyi M.A. and Jaiyeoba K.T., Matrix Properties of a New Plant Gum in Controlled Drug Delivery, Arch. Pharm. Res., 2007, 30, 884-889.
21. Mishra A. and Clark J.H. and Pal S., Modification of Okra mucilage with acrylamide: Synthesis, characterization and swelling behavior, Carbohydr. Polym., 2008,72, 608-615.
22. Ndjouenkeu R. Goycoolea F.M. Morris E.R. and Akingbala., Rheology of okra and dika nut poysaccharides, Carbohydr. Polym., 1996, 29,263-269.
23. Krishnaiah Y.S.R. Bhaskar Reddy P.R. Satyanarayana V. and Karthikeyan R.S., Studies on the development of oral colon targeted drug delivery systems for metronidazole in the treatment of amoebiasis, Int. J. Pharm., 2002, 236, 43–55.
24. Raghavan C.V. Muthulingam C. Amaladoss J. Jenita J.L. and Ravi T.K. An in Vitro and in Vivo Investigation into the Suitability of Bacterially Triggered delivery System for Colon Targeting, Chem.Pharm. Bull., 2002, 50,892—895.
25. Costa P. and Lobo J. M. S., Review Modeling and comparison of dissolution profiles, Eur. J. Pharm. Sci., 13, 123 – 133 (2001).

*****

International Journal of ChemTech Research

(Oldest & Original)

CODEN (USA): IJCRGG, ISSN: 0974-4290 [www.sphinxsai.com]

Subject areas: Chemistry, Chemical Technology.

http://www.scimagojr.com/journalrank.php?area=1500&category=1501&country=IN&year=2011&order=tc&min=0&min_type=cd

Please log on to - www.sphinxsai.com
http://www.scimagojr.com/journalsearch.php?q=19700175055&tip=sid&clean=0

SCOPUS[Elsevier]

- **Source Normalized Impact per Paper (SNIP) 2013= 0.635**
- **Impact per Publication (IPP) 2013= 0.57**

Check at= http://www.journalmetrics.com/display2.php

[Add Start Year of IMPACT =2011,Origin Year of Journal= 2009]

Indexing and Abstracting.

International Journal of ChemTech Research is selected by -

CABI, CAS(USA), SCOPUS, MAPA (India), ISA(India),DOAJ(USA),Index Copernicus, Embase database, EVISA, DATA BASE(Europe), Birmingham Public Library, Birmingham, Alabama, RGATE Databases/organizations for Indexing and Abstracting. It is also in process for inclusion in various other databases/libraries.

Please log on to - www.sphinxsai.com

*****