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Formulation and Evaluation of Anti-Inflammatory Drug Microspheres for Colon Targeted Drug Delivery

Pramod R*[1], Felix Joe.V[1] , Vishwanath B.A[1]
1. Department of pharmaceutics, Aditya Bangalore Institute for Pharmacy Education & Research, Bangalore- 560064.

ABSTRACT

The purpose of this investigation is to prepare and evaluate colon specific microspheres of indomethacin for the treatment of colorectal cancer. sodium alginate microspheres are prepared by ionotropic gelation method using different ratios of indomethacin and sodium alginate (1:1, 1:2, 1:3, 1:4, 2:1, 2:3 & 4:1). Eudragit S-100 coating of indomethacin and sodium alginate microspheres are performed by coacervation phase separation technique. The microspheres were characterized by shape, particle size, size distribution. Entrapment efficiency, invitro drug release and stability studies. The outer surface of core and coated microspheres , which was spherical in shape, were rough and smooth respectively. The size of the core microspheres ranged from 20 -50 µm and the size of the coated microspheres ranged from 107 – 124 µm. The core microspheres sustained the release for 10 hrs in a pH progression medium mimicking the condition of GIT. The release studies of coated microspheres were performed in a similar dissolution medium as mentioned above. In acidic medium the release rate was much slower, however the drug was released quickly at pH 7.4 and their release was sustained upto 24 hrs. It is concluded from the present investigation that Eudragit coated sodium alginate microspheres are promising controlled release carriers for colon targeted delivery of indomethacin.

Keywords: Indomethacin, colon-specific, microspheres, sodium alginate, Eudragit S-100 & multiparticulate system.

*Corresponding Author Email pramodrpharma@gmail.com
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INTRODUCTION

Microspheres are well accepted technique for developing a new dosage form,to sustain the drug release from the dosage form to improve bioavailability, reduce the adverse action and prolong the action of drug, high sensitivity and specificity, stability to the encapsulated drug, reduce absorption difference in patients, reduce the dosing frequency and adverse effects during prolong treatment. It is needed to formulate in long acting dosage form reaching to effective biological site rapidly.[1] A microsphere is a structure made of a continuous phase of one or more polymers in which particulate drug is dispersed, as either the macroscopic(particulate) or molecular (dissolution) level, whereas a microcapsule is a system that contains a well defined core and a well defined envelope. The difference between the two systems is the nature of the microsphere matrix, in which no well defined wall or envelope exists.[2] Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Mono or multinuclear active ingredient embedded in spherical coating of polymer matrix is called as microspheres. These can be manufactured from various natural and synthetic materials.[3] The colon has recently been accepted as an increasingly important site for drug delivery. Among all the routes of drug administration that have been explored for the development of controlled release systems the oral route has by far achieved the most attention and success. It is to the ease of administration as well as to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes.[4]

Indomethacin is anonsteroidal anti-inflammatory drug (NSAID) that reduces fever, pain and inflammation. Indomethacin works by reducing the production of prostaglandins. Prostaglandins are chemicals that the body produces and which cause the fever and pain that are associated with inflammation. Indomethacin blocks the enzymes that make prostaglandins (cyclooxygenase 1 and 2) and thereby reduces the levels of prostaglandins. As a result, fever, pain and inflammation are reduced. Indomethacin is available in an extended release form. Indomethacin is used for the treatment of inflammation caused by rheumatoid arthritis, ankylosing spondylitis, gouty arthritis, osteoarthritis, and soft tissue injuries such as tendinitis and bursitis.[5]

The main objective of the study is to develop a colon-specific microsphere delivery system of Anti-inflammatory drug using natural and enteric coating polymer as a carrier and to develop the colon-specific delivery that has potential for use as an adjuvant therapy for colorectal cancer.

MATERIALS AND METHODS

Indomethacin was procured from Dr. Reddy's Labs., Hyderabad, India, Chitosan was procured

from Yarrow chem products, Mumbai,Cellulose acetate phthalate was procured from Medrich, Bangalore, HPMC K4M,Eudragit-RS100 was procured from S D Fine Chem Limited, Mumbai.All other reagents used were of analytical grade.

Pre-formulation studies

Pre-formulation testing is the first step in the rational development of dosage forms of a drug. It can be defined as an investigation of Physical and chemicalproperties of drug substance, alone and when combined with excipients.

FTIR Spectroscopy

The FTIR spectrum of the obtained sample of drug was compared with the standard FTIR spectra of the pure drug.FTIRspectrum of drug and physical mixture of drug with polymers were obtained on FTIR instrument. The samples were mixed with KBr. The spectrum was scanned over the wave number range of 4000-400 cm^{-1}.IR helps to confirm the identity of the drug and to detect the interaction of the drug with the carriers.

Preparation of chitosan based microspheres of Indomethacin

Different concentration of chitosan ismixed well with the drug with different proportion of polymer as shown in Table.1, to form polymeric- drug dispersion. In briefly, 100 ml of paraffin oil containing 1 ml of span 80 was allowed to stir for 30 minutes. Then the polymeric-drug dispersion was incorporated drop wise with constant stirring at 750 rpm. Add 1 ml of glutaraldehyde after 5minutes of dispersion incorporation and stirring was continued for 1hour at 750-1500 rpm. Allow to stand for 30 minutes. Microspheres were settled down slowly in the dispersion. The obtained microspheres were collected by filtration and was twice with diethyl ether, dried at room temperature and stored in desiccators for further evaluation.

Table 1: Formulation of Indomethacin Microspheres

Formulation Code	Core:Coat	Drug (Indomethacin) (mg)	Chitosan (mg)	HPMC K4m (mg)	Eudragit RS100 (mg)	Polycarbophil (mg)
F1	1:1	500	300	200	-	-
F2	1:2	500	800	200	-	-
F3	1:3	500	1300	200	-	-
F4	1:1	500	300	-	200	-
F5	1:2	500	800	-	200	-
F6	1:3	500	1300	-	200	-
F7	1:1	500	300	-	-	200
F8	1:2	500	800	-	-	200
F9	1:3	500	1300	-	-	200

Evaluation of microspheres

Percentage Yield

The prepared microspheres of all batches were accurately weighed. The measured weight of prepared microspheres was divided by the total amount of all the excipients and drug used in the preparation of the microspheres, which give the total percentage yield of floating microspheres. It was calculated by using following equation.

% Yield = actual weight of product/total weight of excipients and drug × 100

MicromeriticStudies[6,7]

The prepared microspheres are characterized by their micromeritic properties such as microsphere size, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose.

Bulk Density

The bulk density is defined as the mass of powder divided by bulk volume.The bulk density was calculated by dividing the weight of the samples in grams by the final volume in cm

Bulk density = Mass of microspheres/ Volume of microspheres before tapping

Tapped Density

Tapped density is the volume of powder determined by tapping by using a measuring cylinder containing weighed amount of sample. The cylinder containingknown amount of microspheres was tapped for about 1 minute on a tapped density apparatus until it gives constant volume.

$$\text{Tapped density} = \frac{\text{Mass of microspheres}}{\text{Volume of microspheres after tapping}}$$

Carr's Compressibility Index

This is an important property in maintaining uniform weight. It is calculated using following equation

$$\%\ \text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

A similar index like percentage compressibility index has been defined by Hausner. Values less than 1.25 indicate good flow, where as greater than 1.25 indicates poor flow. Added glidant normally improves flow of the material under study. Hausner's ratio can be calculated byformula,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of Repose (θ)

Angle of repose is defined as the maximum angle possible between the surface and thehorizontal plane.The diameter of the powder cone so formed wasmeasured and the angle of repose was calculated using the following equation,

$\tan\theta = h/r$

$\theta = \tan^{-1}(h/r)$

Where: θ= angle of repose

h = height of the pile and,

r = radius of the powder cone respectively.

For good flowing materials, the angle of repose should be less than 30°.

Particle Size Determination[8]

The particle size of the microspheres was determined by using optical microscopy method.Approximately 100 microspheres were counted for particle size using a calibrated optical microscope.

Morphological Study using SEM

The morphological study was carried out by Scanning Electron Microscope (SEM). Microspheres were scanned and examined under Electron MicroscopeHITACHI SU 1500, Japan connected with Fine coat, JEOL JFC-1100E Ion sputter. The sample was loaded on copper sample holder and sputter coated with carbonfollowed by Gold.

Drug Loading and Drug Entrapment[9]

Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extractingwith aliquots of phosphate buffer solution at p^H 6.8 repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up usingphosphate buffer solution at p^H 6.8. The solutionwas filtered and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, Japan) at 320 nm against appropriate blank. The amount of drug loaded and entrapped in the microspheres was calculated by the following formulas:

$$\% \text{ Drug loading} = \frac{\text{Weight of the drug loaded in the microspheres (DC)}}{\text{Total weight of the microspheres}} X \ 100$$

$$\% \text{ Drug entrapment} = \frac{\text{Amount of drug actually present (DC)}}{\text{Theoretical drug load expected}} X \ 100$$

Where:-(DC- Actual Drug Content)

***In-vitro* release study[10]**

The drug release study was performed for microsphere containing quantity equivalent to 15 mg of Indomethacin by using USP dissolution apparatus Type II in 900 mlof phosphate buffer p^H 6.8 at 50 rpm and 37±0.5°C temperature. 5 ml of sample was withdrawn at predetermined time interval

for 12 hrs and same volumeof fresh medium was replaced to maintained sink condition. Withdrawn samples were filtered through a 0.45 µm membrane filter, diluted suitably and assayed spectrophotometrically at 320 nm. The cumulative % drug release was calculated using standard calibration curve.

Release kinetics[11]

The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for therelease and release rate kinetics of the dosage form, the data obtained was fitted in to, Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. In this bycomparing the r-values obtained, the best-fit model was selected.

Zero Order Kinetics

Drug dissolution from Pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and noequilibrium conditions are obtained can be represented by the following equation:

$Q_t = Q_o + K_o t$

Where,

Q_t= Amount of drug dissolved in time t

Q_o = Initial amount of drug in the solution and

K_o = Zero order release constant.

First order kinetics

To study the first order release kinetics the release rate data were fitted to the following equation.

$$\text{Log } Q_t = \log Q_o + K_1 t / 2.303$$

Where,

Q_t= Amount of drug released in time t

Q_o = Initial amount of drug in the solution and

K_1 = First order release constant.

Higuchi model

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semi-solid and/or solid matrixes. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. The Higuchi equation is

$$Q_t = K_H \times t_{1/2}$$

Where,

Q_t= amount of drug released in time t and

K_H= Higuchi dissolution constant

Korsmeyer-Peppas model

To study this model, the release rate data is fitted to the following equation.

$$M_t / M_\infty = K. t^n$$

Where,

M_t / M_∞ = Fraction of drug release,

K = Release constant

t = Drug release time and

n = Diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.

The values of 'n' are,

n = 0.45 Fickian (case I) release.

0.45< n < 0.89 Non-Fickian (Anomalous) release.

n = 0.89 Case II (Zero order) release.

> 0.89 Super case II type release.

Hixson–Crowell model

To study the Hixson–Crowell model,the release rate data are fitted to the following equation.

$$W_o^{1/3} – W_t^{1/3} / K_s t$$

Where,

W_o= Amount of drug in the pharmaceutical dosage form,

W_t = Remaining amount of drug in the pharmaceutical dosage form,

K_s = Constant incorporating the surface-volume relation.

Stability Studies[12,13]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety ofenvironmental factors such as temperature, humidity, light, and enables recommended storage conditions.ICH guidelines the length of study and storage conditions:Accelerated testing - 40°C/75% RH for 6 months.The accelerated stability study of the best formulations was carried out as per the ICH guidelines.In the present study, stability study was carried out for a period up to the 60 days for selected formulations.The selected formulations were analyzed for the physical appearance, drug entrapment, and *in-vitro* release study.

RESULTS AND DISCUSSION

Pre-Formulation Studies

FTIR Spectroscopy

The FT-IR spectrum of the Indomethacin pure drug was found to be similar to the standard spectrum of Indomethacin as in IP.

Compatibility studies

From the FT-IR spectra of the pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristic peaks of Indomethacin werepresent in the combination spectra as well thus indicating the compatibility of the drug with the polymers used.The individual FT-IR spectra of the pure drug Indomethacin, polymers: chitosan, HPMC.K4M, Eudragit RS-100 and polycarbophil as well as the combination spectra of the drug and polymers are shown in the Figure:1.

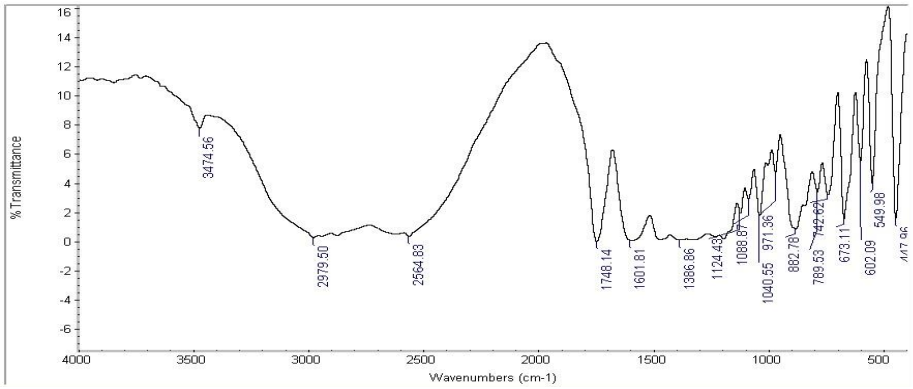

Figure 1: FTIR Spectra of Indomethacin

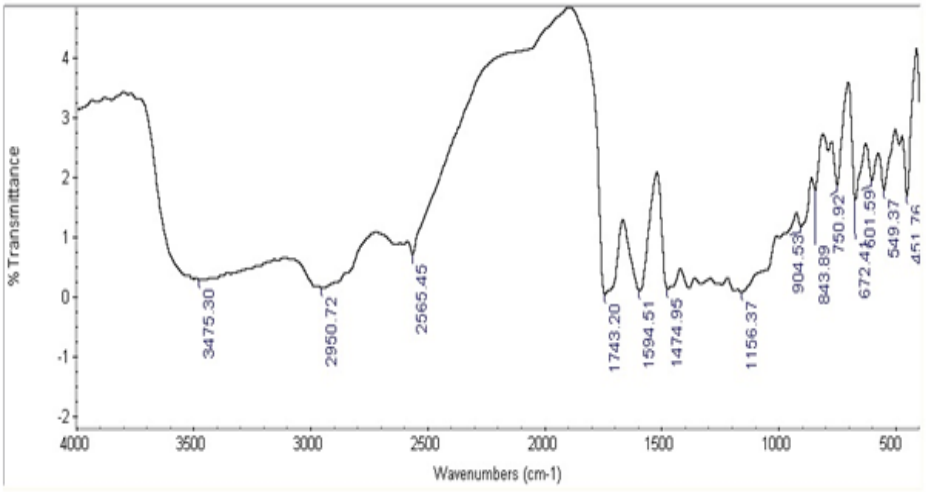

Figure 2: FTIR Spectra of Indomethacin with Chitosan, HPMC K4M, Eudragit RS-100 and Polycarbophil

Percentage yield

Percentage yield of different formulation F1 to F9 were calculated and the yield was found to be 75.20%, 73%, 64.80%, 76.40%, 73.13%, 64.4%, 74.70%, 72.60% and 65.50% respectively. The percentage practical yield slightly decreased as the polymer ratio increased. The results of all formulations F1 to F9 of microsphere are shown in Table 2 and Figure 3.

Table 2: Practical Yield of Indomethacin Microspheres

Formulation Code	Theoretical Wt(mg)	Practical Yield (mg)	%Yield
F1	1000	752	75.2
F2	1500	1095	73
F3	2000	1296	64.8
F4	1000	764	76.4
F5	1500	1097	73.13
F6	2000	1288	64.4
F7	1000	747	74.7
F8	1500	1089	72.6
F9	2000	1310	65.5

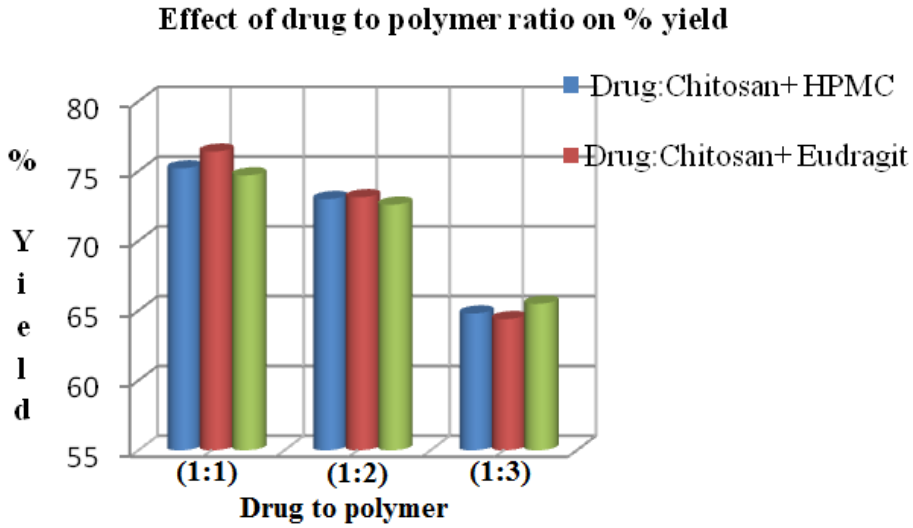

Figure 3: Comparison of % Yield of the Prepared Microspheres

Micromeritic Properties

The results of all formulations F1 to F9 of microsphere are shown in Table 3, which were evaluated for variable parameters such as bulk density, tapped density, % Compressibility index, Hausner's ratio and angle of repose. The % Compressibility index was in the range of 11-18 for all the formulations F1 to F9indicating good flow property. The values of angle of repose for formulations F3, F6 and F9 was found to be in the range of 25-30 which indicated the good flow potential and the formulations F1, F2, F4, F5, F7 and F8 showed below 25 which indicated excellent flow.

Table 3: Micromeritic properties of Indomethacin microspheres

Formulation Code	Bulk Density ($g/cm^{3)}$	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.4426±0.005	0.5126±0.009	13.65±1.21	1.158±0.02	21.93±0.23
F2	0.4986±0.008	0.5814±0.004	14.24±1.32	1.166±0.05	24.74±0.24
F3	0.5234±0.015	0.6243±0.008	16.16±1.27	1.193±0.011	27.94±0.17
F4	0.4813±0.009	0.5446±0.005	11.94±1.34	1.131±0.019	23.81±0.14
F5	0.5418±0.013	0.6183±0.001	12.36±1.04	1.141±0.02	24.67±0.36
F6	0.6168±0.011	0.7136±0.012	13.56±1.02	1.156±0.08	27.08±0.16
F7	0.4576±0.014	0.5228±0.008	12.47±1.21	1.142±0.03	23.61±0.64
F8	0.4754±0.013	0.5845±0.011	15.24±1.03	1.229±0.023	24.54±1.07
F9	0.5438±0.016	0.6432±0.014	15.45±0.84	1.183±0.026	25.12±1.51

Particle Size Analysis

Average particle size of microspheres as determined by optical microscopy by using stage micrometer and ocular micrometer are shown in Table 4.The mean particle size for the formulation F1 to F3 containing chitosan-HPMC K4M was found to be in range from 283±6.35 µm to 456±12.42 µm. For formulation F4 to F6containing chitosan-Eudragit RS-100, the mean particle size was found to be in range from 278±7.14 µm to 443±12.24 µm and for formulation F7 to F9 was found to be in range from 270±8.69 µm to 440±12.51 µm respectively. With increase in polymers concentration in the microspheres from F1 to F9, the particle size of microspheres increasesrespectively. This is because the viscosity of the polymer solution increases with increasing polymer concentration, which in turn decreases the stirring efficiency.

Table 4: Average Particle Size of Indomethacin Microspheres

Formulation code	Average particle size (µm)±SD
F1	283±6.35
F2	342±11.28
F3	456±12.42
F4	278±7.14
F5	350±10.73
F6	443±12.24
F7	270±8.69
F8	385±11.46
F9	440±12.51

Scanning Electron Microscopy

The determination of shape and surface morphology was done by scanning electron microscope HITACHI SU 1500, Japan. SEM analysis of the samplesrevealed that all microspheres prepared were spherical in shape.The microspheres of Indomethacin with chitosan-Eudragit RS-100,chitosan-polycarbophil were smooth, spherical and slightly aggregated particles when compared with the microspheres of Indomethacin with chitosan-HPMC K4M which were porous,

rough, grossly, discrete spherical. Scanning electron photomicrographs of the formulations F6 and F9 are shown in Figure 4.

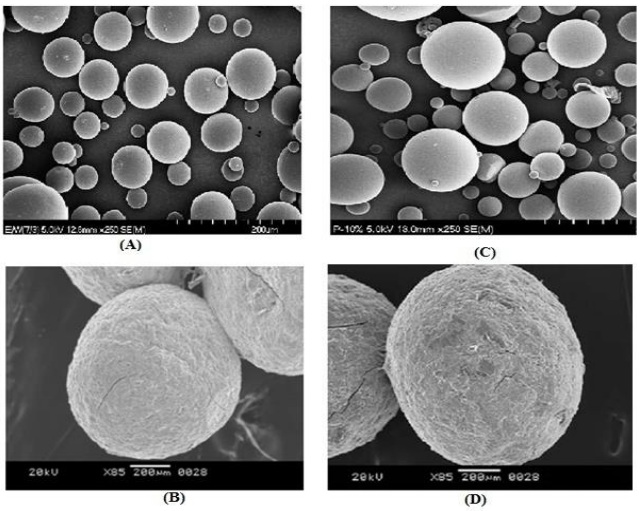

Figure 4: SEM images of F6 and F9 formulation

* (**A**) and (**B**) are images of F6 formulation, (**C**) and (**D**) are images of F9 formulation

Drug Loading and Drug Entrapment

The values of % drug loading and % entrapment efficiency are shown in Table 5. As the polymer concentration was increased the % drug loading decreased and% entrapment efficiency was increased due to increase in the viscosity of the solution. This can be attributed to the permeation characteristics of each polymer used, that could facilitate the diffusion of part of entrapped drug to the surrounding medium during preparation of mucoadhesive microspheres. Comparison of % drug loading and % entrapment efficiency are shown in Figure 5 and 6. Microspheres with chitosan-polycarbophil showed higher incorporation efficiency than those with chitosan-HPMC K4M and chitosan-eudragit RS-100

Table 5: Drug Loading and Drug Entrapment of Indomethacin Microspheres

Formulation Code	Actual Drug Content (mg)	Theoretical Drug Content (mg)	Total Weight of Microspheres (mg)	% Drug Loading	%Drug Entrapment
F1	19.28	25	50	38.56	78.12
F2	13.75	16.67	50	27.5	82.48
F3	11.30	12.5	50	22.60	90.40
F4	19.53	25	50	39.06	78.12
F5	13.94	16.67	50	27.88	83.62
F6	11.43	12.5	50	22.86	91.44
F7	19.72	25	50	39.44	78.88
F8	14.16	16.67	50	28.32	84.94
F9	11.56	12.5	50	23.12	92.48

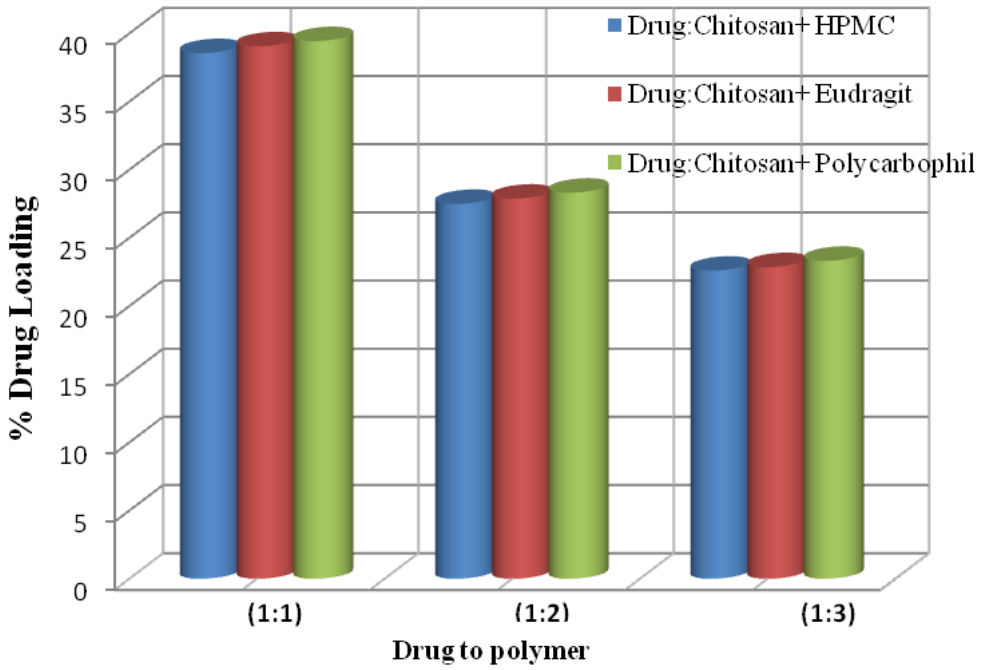

Figure 5: Comparison of % Drug Loading of the Prepared Microspheres

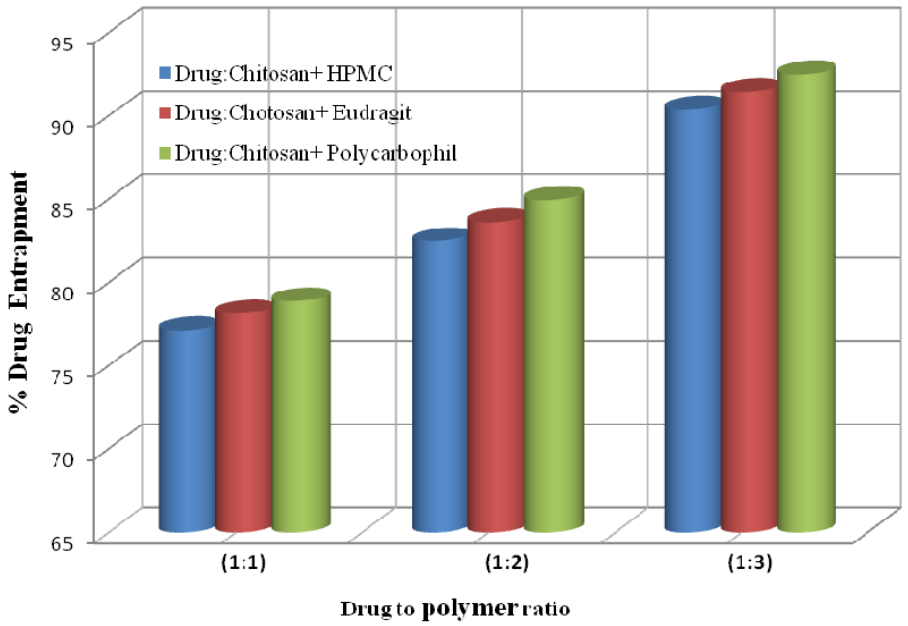

Figure 6: Comparison of % Drug Entrapment of the Prepared Microspheres

***In-vitro* drug release studies**

Dissolution studies on all the nine formulations of Indomethacin microspheres were carried out using a USP dissolution apparatus Type II.6.8 pH phosphate buffer was used as the dissolution medium. The *in-vitro* drug release data of different formulations are shown in Table 6.

Furthermore, smaller microspheres are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release.

Table 6: *In–vitro* drug release for Indomethacin Microspheres in 6.8 pH phosphate buffer

Time (hrs)	Cumulative % drug release of formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	16.47	14.38	13.46	14.98	14.10	13.18	13.76	13.11	12.54
2	30.18	28.25	24.70	27.55	24.83	24.15	22.94	20.56	18.37
3	42.46	40.38	38.74	40.62	38.35	36.87	36.29	31.90	27.50
4	54.84	51.46	50.12	50.82	47.65	46.18	42.74	40.58	38.34
5	64.30	59.43	57.58	58.01	56.21	54.06	53.49	51.41	47.85
6	71.29	66.85	64.34	65.64	62.73	61.74	57.50	55.28	51.47
7	75.94	71.81	68.53	71.26	68.47	65.93	62.78	60.49	53.52
8	79.84	76.52	72.25	73.72	71.58	68.71	70.18	68.52	57.41
9	83.23	80.14	74.31	77.16	74.69	71.18	75.26	72.76	62.50
10	85.01	81.89	75.53	80.59	77.93	73.68	77.39	74.84	65.57
11	86.89	83.11	77.04	82.43	79.85	74.81	80.61	77.60	68.83
12	88.38	84.42	78.29	84.30	81.12	75.90	82.32	79.72	72.69

Release Kinetics

The curve fitting results of the release rate profile of the designed formulation are shown in the Figure 8 which gave an idea on the release rate and the mechanism of release. The values were compared with each other for model and drug equation as shown in Table 7 based on the highest regression values (r^2), fitting of the release rate data to various models revealed that all the formulations (F1 to F9) follow first order release kinetics with regression values ranging from 0.9552 to 0.9960. All the formulations were subjected to Korsmeyer-Peppas plots, 'n' value ranges from 0.4196 to 0.4992 indicating that the drug release was by non-fickian (anomalous) diffusion mechanism.

Table 7: Model Fitting Release Profile of Indomethacin Microspheres

Formulation code	Mathematical Models (Kinetics)						Best Fit Model
	Korsmeyer–Peppas		Higuchi	Hixson–Crowell	First order	Zero order	
	R^2	n	R^2	R^2	R^2	R^2	
F1	0.9405	0.4196	0.9633	0.9668	0.9893	0.8892	First order
F2	0.9352	0.4480	0.9687	0.9636	0.9834	0.8979	First order
F3	0.9239	0.4608	0.9499	0.9308	0.9552	0.8678	First order
F4	0.943	0.4374	0.9748	0.9731	0.9914	0.9084	First order
F5	0.9466	0.4574	0.9748	0.9686	0.9868	0.9103	First order
F6	0.9349	0.4631	0.9618	0.9422	0.963	0.8874	First order
F7	0.967	0.476	0.9908	0.9899	0.996	0.950	First order
F8	0.972	0.4992	0.9885	0.9868	0.9942	0.9504	First order
F9	0.9676	0.4958	0.9855	0.9809	0.9896	0.9471	First order

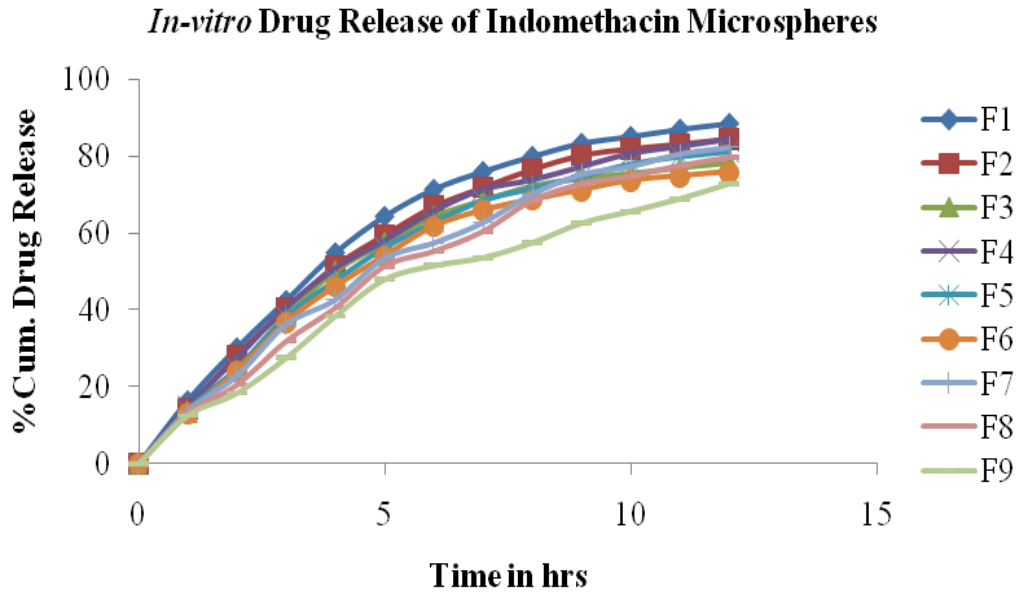

Figure 7: Comparative *In-vitro* Dissolution Profile of Indomethacin Microspheres

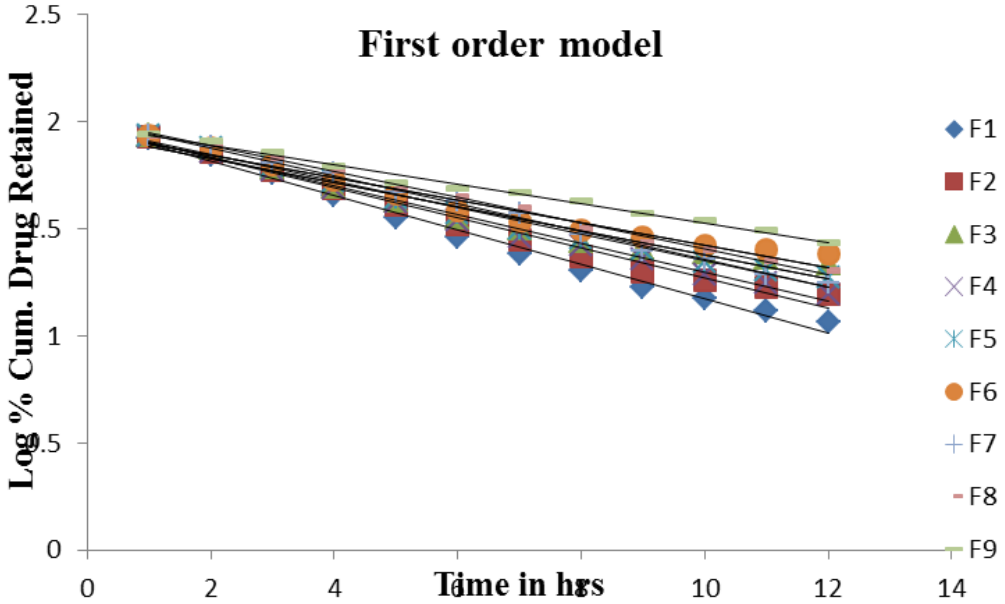

Figure 8: Plot of log % Cumulative Drug Retained Vs Time

Stability study

Stability study was conducted for the prepared microspheres of formulation F6 and F9 at 40°C/75% RH respectively for a period of 60 days. Then, the sample was analyzed for physical appearance, entrapment efficiency and drug release studies of the microsphere at the end of 15, 30, 45 and 60 days.The results of stability studies are given in the Table 8.There was no significant change in the physical appearance, drug entrapment and in-vitro release study of the microspheres.

Table 8: Stability Studies for Formulations Stored at 40ºC/75% RH

Tested after days	% Drug Entrapment		% CDR	
	F6	F9	F6	F9
15	91.40	92.46	75.85	72.88
45	91.30	92.37	75.73	72.64
60	91.26	92.32	75.69	72.60

CONCLUSION

The main objective of the study is to develop a colon-specific microsphere delivery system of Anti-inflammatory drug using natural and enteric coating polymer as a carrier and to develop the colon-specific delivery that has potential for use as an adjuvant therapy for colorectal cancer. From the experimental results it can be concluded that,FTIR study shows no significant shifting of the peaks therefore it confirms the short term stability of the drug in the microspheres.Biocompatible polymers like chitosan, HPMC K4M, Eudragit RS-100 and polycarbophil can be used to formulate a microparticulatesystem.Good percentage drug entrapment and practical yields were obtained with all the polymers.The flow properties of all formulations were within the acceptable range and therefore they could be easily filled into capsules.The particle size analysis revealed that the formulations with chitosan-HPMC K4M (F1, F2 and F3) gave particles in the range of 283±6.35 to 456±12.42µm, the formulations with chitosan-Eudragit RS-100 (F4, F5 and F6) gave particles of the size range 278±7.14 to 443±12.24 µm,while the formulations with chitosan-polycarbophil (F7, F8 and F9) gave particles of the size range 270±8.69 to 440±12.51.Cumulative percentage drug release significantly decreased with increase in polymer concentration. The overall curve fitting into various mathematical models was found to be on an average. The formulations F1 to F9 were best fitted into first order kinetic model and the drug release from the formulation was by non-fickcian (anomalous) diffusion mechanism.Selected F6 and F9 formulated microspheres were stable and compatible at the selected temperature and humidity in storage for 60 days.From the stability studies it was found that there was no significant change in the drug entrapment, release characteristics and *in-vitro* adhesive behavior of the microspheres.

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