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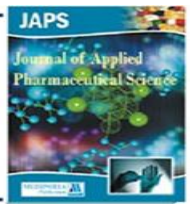

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Development of Oral Colon Specific pH Dependent Microcapsules of NSAID Drug Naproxen

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ABSTRACT

The objective of present study is to develop oral colon specific pH dependant microcapsule of NSAID Drug Naproxen, to release drug in the colon and minimize or avoid local side effect by avoiding drug release in the upper git. Naproxen is encapsulated with Eudragit S 100 using O/W emulsion-solvent evaporation technique. Compatibility study was performed by I.R., D.S.C., X.R.D study. Microcapsules were evaluated for angle of repose, bulk density, tapped density, Carr's index, particle size, drug loading, in-vitro drug release. The prepared microcapsules were white, free-flowing, and spherical in shape and particle size was in the range of 240.40-560.81µm. The drug-loaded microcapsules showed 69.88% to 98.73%. drug entrapment, angle of repose in the range of 28º.07" to 35 º.53", bulk and tapped densities in the range of 0.4000 gm/cm^3 to 0.4347 gm/cm^3 and 0.4347gm/cm^3 to 0.4787gm/cm^3 respectively, Carr's index ranges from 5.20 and 14.98. In vitro drug release studies were carried out up to 9th hr. in three different pH media, i.e., 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8 and 7.4). The drug-polymer concentration influences the particle size and drug release properties. All the formulations were following the Higuchi model of kinetic drug release.

Keywords: Naproxen, Eudragit S 100, Microcapsules, O/W Emulsion Solvent Evaporation, Release Kinetics.

INTRODUCTION

Colonic delivery refers to targeted delivery of drugs into the lower gastrointestinal tract, which occurs primarily in the large intestine (i.e. colon). The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as Ulcerative colitis, Crohn's disease, Amebiosis, Colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs (Philip and Philip, 2010; Reid *et al*., 2011). Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. Inflammatory bowel disease (IBD) idiopathically majorly encompasses of Crohn's disease and ulcerative colitis. Crohn's disease and Ulcerative Colitis gets differentiated by the location and nature of the inflammatory changes. Crohn's disease can affect any part of the G.I.T., from mouth to anus, majorly affecting the terminal ileum. Ulcerative colitis, in contrast affects the colon and the rectum majorly (Kumar *et al*., 2007).

Naproxen is used as the drug in the treatment of inflammatory bowel disease. Naproxen inhibits the activity of an enzyme called cyclooxygenase 2 (COX-2). COX-2 facilitates the production of a class of compounds in the body known as prostaglandins. Naproxen blocks the active site on a COX-2 molecule that catalyzes the formation of COX-2 molecules with the result: no COX-2; no prostaglandins; no pain and inflammation. Since naproxen inhibits COX-2, but not COX-1, it is known as a selective inhibitor NSAID (Kuhbacher *et al*., 2007).

Microencapsulation is relatively easy method of coating in which coating at micron sized particle is done. The method of microencapsulation is efficient in terms of production yield, percentage entrapment and uniformity of coat.

By considering all above established data present study is designed to fabricate the colon specific microcapsules of Naproxen.

MATERIALS AND METHODS

Naproxen of pharmaceutical grade was supplied as gift samples by Crenstien Therapeutics Hyderabad, India. Eudragit S 100 Pharma Grade as gift sample from Evonik Industries, Mumbai. Chloroform and Sodium CMC obtained from L.R. Grade Loba Chemie Pvt. Ltd., Mumbai, India.

λ max determination:

It was determined for naproxen in three different dissolution medias.

Calibration Curve of Naproxen in 0.1N HCL pH 1.2, phosphate buffer solution pH 6.8 and 7.4

50 mg of pure Naproxen was accurately weighed and dissolved in small amount of 0.1N HCL pH 1.2 and volume was made up to 100ml using 0.1N HCL pH 1.2. From this stock solution serial dilutions were made to obtain solutions in the concentration ranging from 50 to 250µg/ml. The absorbances of the solutions were measured at 331 nm using UV-Visible spectrophotometer. A graph of Concentration vs. Absorbance was plotted. The standard Beer's range follows from 50µg/ml to 250µg/ml. The above procedure was repeated for Phosphate buffer pH 6.8 and 7.4 instead of 0.1N HCL pH 1.2 (Maheshwari *et al*., 2010).

Experimental design

A 3^2 Full factorial design with two independent variables at three levels is employed in this study. This 3^2 factorial designs were employed for Eudragit S 100 and drug-polymer mixtures of microcapsules. Table no.1 indicates the factor combination used along with the translation of their coded levels in the studies (Shivkumar *et al*., 2008; Patel *et al*., 2007). Table no. 2, 3 show independent and dependent variables.

Preparation of microcapsules

The Naproxen microcapsules were prepared by O/W emulsion solvent evaporation method. The formulations were prepared on the basis of factorial design. The drug: polymer ratio were been modified for each batch to study the dependent variables (Patrik *et al*., 1997, Chowdary *et al*., 2011, Chowdary *et al*., 2012; Reddy *et al*., 2011).

Table. 1: The 3^2 Full Factorial Design Layouts of Microcapsules Containing Naproxen.

BATCH CODE	X_1	X_2
MC 1	-1	-1
MC 2	-1	0
MC 3	-1	1
MC 4	0	-1
MC 5	0	0
MC 6	0	1
MC 7	1	-1
MC 8	1	0
MC 9	1	1

Table. 2: Independent Variables With Code Levels.

Sr. No.	Independent Variables		Code Levels Low Level (-1)	Medium Level (0)	High Level (1)
1.	X_1	Naproxen	100	200	500
2.	X_2	Eudragit S100 Concentration (Mg)	250	500	1000

Table. 3: Dependent Variables.

Sr. No.	Dependent Variables	
1.	E.E.	Encapsulation Efficiency
2.	Rel_{4h}	Drug Release At 4th Hour
3.	Rel_{9h}	Drug Release At 9th Hour

Procedure

Naproxen was added accordingly to the polymeric solution containing Eudragit S 100 and chloroform. The above solution containing drug and polymer was added drop wise to a beaker containing 200ml mucilage of sodium carboxy methyl cellulose (Na-CMC). Then it was stirred at 2000 rpm to emulsify the added dispersion to fine droplets. The solvent was removed by continuous stirring at room temperature (37^oc) for 4 hrs. to produce spherical microcapsules. The microcapsules were collected by vacuum filtration and washed repeatedly with water and then air dried to get the microcapsules. The different formulation parameters are given in the table below (Patrik *et al*., 1997; Chowdary *et al*., 2011; Chowdary *et al*., 2012; Reddy *et al*., 2011).

Percent yield

The percentage yields of microcapsules formulated were determined from the ratio of the practical yield to the theoretical yield (theoretical yield including the drug and polymer quantity) (Patrik *et al*., 1997; Chowdary *et al*., 2011; Chowdary *et al*., 2012; Reddy *et al*., 2011).

$$\text{Percentage Yield (\%)} = \frac{\text{Practical Yeild}}{\text{Theorotical Yeild}} \times 100$$

Optical Microscopy

The size distribution analysis of microcapsules was carried out using optical microscopy using calibrated eyepiece micrometre. The samples was placed on greaseless slide and observed under microscope. The projected diameter of total of 200

microcapsules was observed for all the formulations. From the data mean particle size was calculated using the following equation (Patrik *et al*., 1997, Chowdary *et al*., 2011, Chowdary *et al*., 2012, Reddy *et al*., 2011).

Mean Particle Size (μm) = Σnd / Σn

Where 'n' and 'd' are number of particles and mean size range in μm respectively.

Drug content

Drug content in microcapsules was estimated by using UV-Visible double beam Spectro-photometer at 331nm. A quantity of microcapsules equivalent to 50mg were powdered and transferred into a 100ml volumetric flask, sufficient amount of chloroform was added to produce 100ml, shaken for 20min. and filtered. Then 2ml of filtrate was diluted to 100ml with phosphate buffer pH 7.4 (Chowdary *et al*., 2012, Reddy *et al*., 2011).

$$\text{Drug content} = \frac{\text{Amount of drug encapsulated in particles x100}}{\text{Amount of particles}}$$

ENCAPSULATION EFFICIENCY

About 25 mg of accurately weighed microcapsules were added to 10 ml of chloroform, used as common solvent of drug and polymer. The drug was extracted three times from chloroform using phosphate buffer pH 7.4. Each time extraction was carried out using separating funnel with shaking time of 15mins. After complete extraction of drug, the amount of drug was quantified spectrophotometrically at 331 nm using UV-Visible double beam Spectro-photometer. The encapsulation efficiency of microcapsules was calculated by using the eq^{n} (Chowdary *et al*., 2012; Reddy *et al*., 2011).

$$\text{Encapsulation Efficiency (\%)} = \frac{\text{Calculated drug content x100}}{\text{Theoretical drug content}}$$

Scanning electron microscopy (SEM)

Morphology and surface topography of the microcapsules were examined by scanning electron microscopy (SEM-Joel, JSM-6360).

Infrared Spectroscopy (FTIR)

Drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for empty and drug-loaded microcapsules using FTIR JASCO (Model No. 410). Samples were prepared in KBr disks (2 mg sample in 200 mg KBr). The scanning range was 400-4000 cm $^{-1}$ and the resolution was 2 cm $^{-1}$.

Differential Scanning Calorimetry (DSC)

The DSC analyses of empty and drug-loaded microcapsules were carried out using a DSC, SDT 2960, TA. Inc.USA. to evaluate any possible drug-polymer interaction. The analysis was performed at a rate 10.00^{0} C min $^{-1}$ from 25^{0} C to 250^{0} C temperature range under nitrogen flow of 25 ml min $^{-1}$.

X-ray powder Diffractometry (X-RD)

X-ray powder diffractometry was carried out to investigate the effect of microencapsulation process on crystallinility of drug. Powder X-RD patterns were recorded on PW 3710 based diffractometer using a voltage of 40kV and a current of 30mA.The scanning rate employed was 5^{0} min $^{-1}$, over the 5^{0} to 40^{0} diffraction angle (2θ) range. The X-RD patterns of empty and drug-loaded microcapsules were recorded.

In vitro drug release studies and release kinetic study

The in vitro release studies of drug-loaded microcapsules were carried out at 37^{0} C and 75 rpm using prepared 0.1N HCL pH 1.2 for two hrs.; phosphate buffer pH 6.8 for two hrs.; and phosphate buffer pH 7.4 solutions (900 ml) in a USP dissolution apparatus type II (basket type) under sink conditions. Accurately weighed samples of microcapsules (50mg) were placed in muslin cloth which was closely tied and kept in baskets. At specific time intervals 5ml aliquots were withdrawn and replaced by an equal volume of fresh dissolution medium. After suitable dilution, the samples were analysed spectophotometrically at 331 nm. The concentration of Naproxen in samples was calculated using a regression equation of the calibration curve (Thakral *et al*., 2010).

Data analysis

To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix, Krosmeyer`s Peppas model and Hixon Crowell model. In this by comparing the R-values obtained, the best-fit model was selected (Nayak *et al*., 2009; Dash *et al*., 2010).

RESULT AND DISCUSSION

λmax

λmax was found to be 331 nm for naproxen in all the three dissolution medias.

Standard calibration curve of Naproxen

The standard calibration curve of Naproxen showed slope values and regression values as stated in the table no.4

Table. 4: Slope values and regression values of standard calibration curve at different pH.

Sr. no.	pH	Slope value	Regression value
1	1.2	0.0064	0.9999
2	6.8	0.0055	0.9998
3	7.4	0.0056	0.9995

Percent yield

The percentage yield for the formulated Naproxen-Eudragit S 100 microcapsules showed the following results as shown in the table below, which describes that there is proper encapsulation and increased yield as the polymer and drug concentration increases. The percent yield obtained was in the range from 57.42% to 96.46%.

Optical Microscopy

The particle size analysis was performed by optical microscopy. The mean particle size ranged from 240.40-560.81µm in different formulations. The particle size was influenced by the content of Eudragit polymer used and its ratio in the formulation. The particle size increased with an increase of polymer concentration.

DRUG CONTENT AND ENCAPSULATION EFFICIENCY

The actual drug content of all the formulations were calculated and found to be in the range from 34.94 % w/w to 49.36 % w/w. The drug content of all formulations are been mentioned in the table below. The encapsulation efficiency of prepared microcapsules was found to be from 69.88% to 98.73%. Hence the encapsulation efficiency of Naproxen-Eudragit S100 microcapsules increases with an increase in the polymer concentration. The formulations MC 3, MC 6 and MC 9 show high encapsulation efficiency due to the presence of higher polymer concentration.

SCANNING ELECTRON MICROSCOPY (S.E.M)

Morphology and surface topography of all the microcapsule formulations were examined by Scanning Electron Microscopy (S.E.M.). It is found that all Naproxen microcapsule formulations are spherical in shape with rough surface prepared by o/w emulsion solvent evaporation method using Eudragit S 100 as polymer. Figure no. 1 shows S. E. M. of prepared microcapsules.

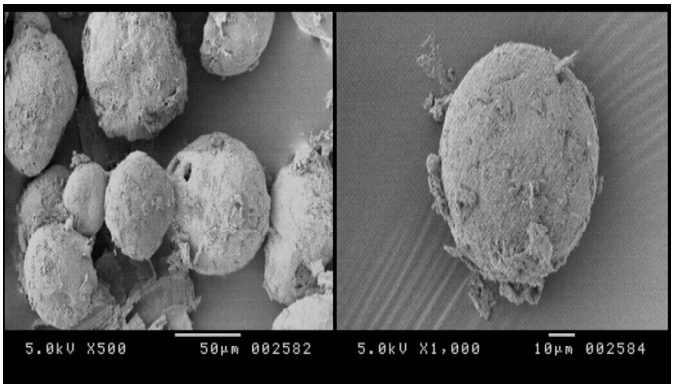

Fig. 1: S.E.M. of microcapsules.

IR SPECTROSCOPY OF NAPROXEN (FTIR)

Based on I.R. Studies there appears to be no possibility of interaction between Naproxen and Eudragit S 100 in various proportions. All the peaks present in I.R. spectra of Naproxen are present in the I.R. spectra of microcapsules. Figure no. 2, 3, 4 shows I.R. spectras.

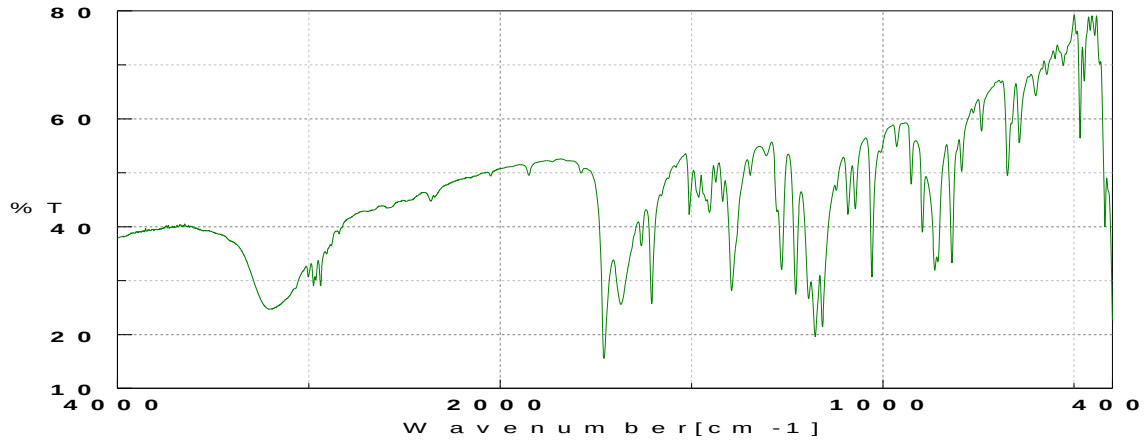

Fig. 2: I. R. Spectra of Naproxen.

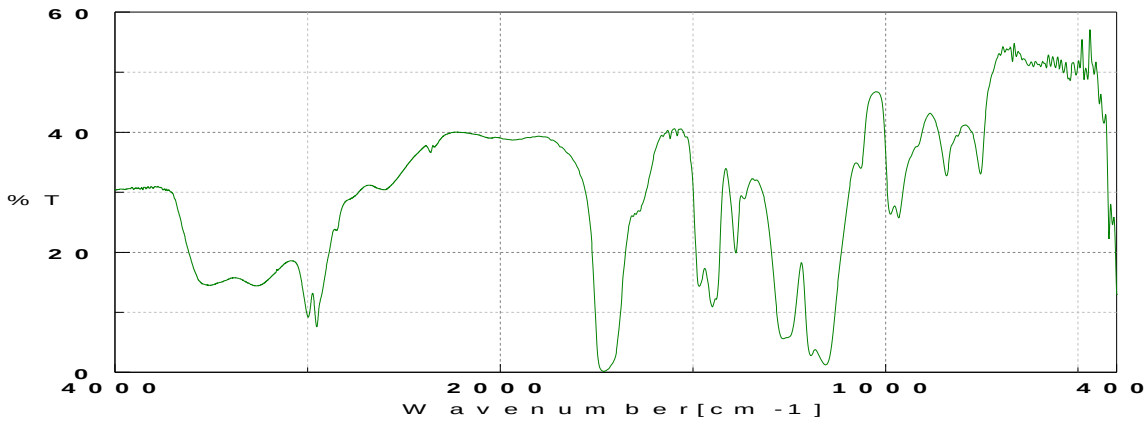

Fig.3: I.R. spectra of Eudragit S 100.

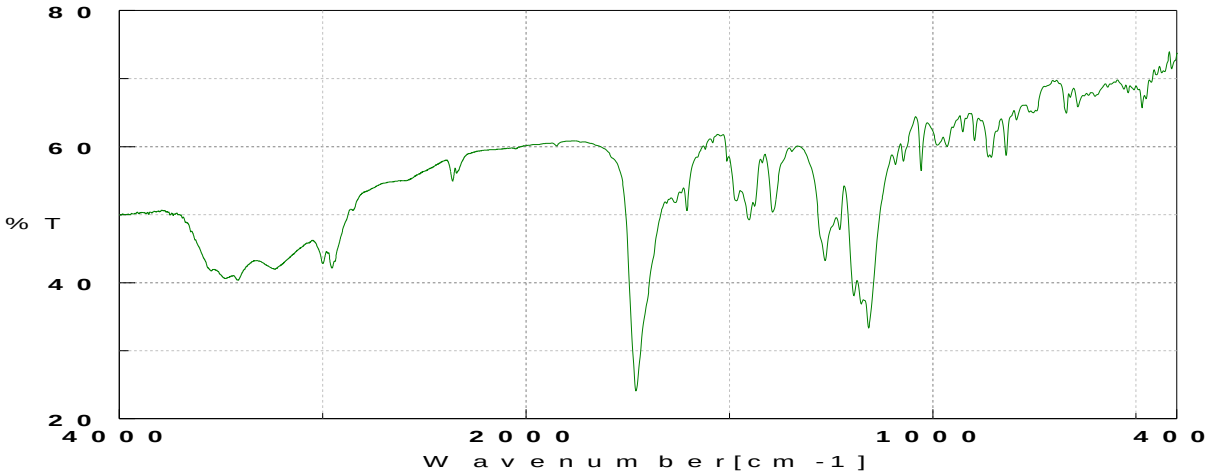

Fig. 4: I.R. spectra of Naproxen-Eudragit S 100 microcapsules.

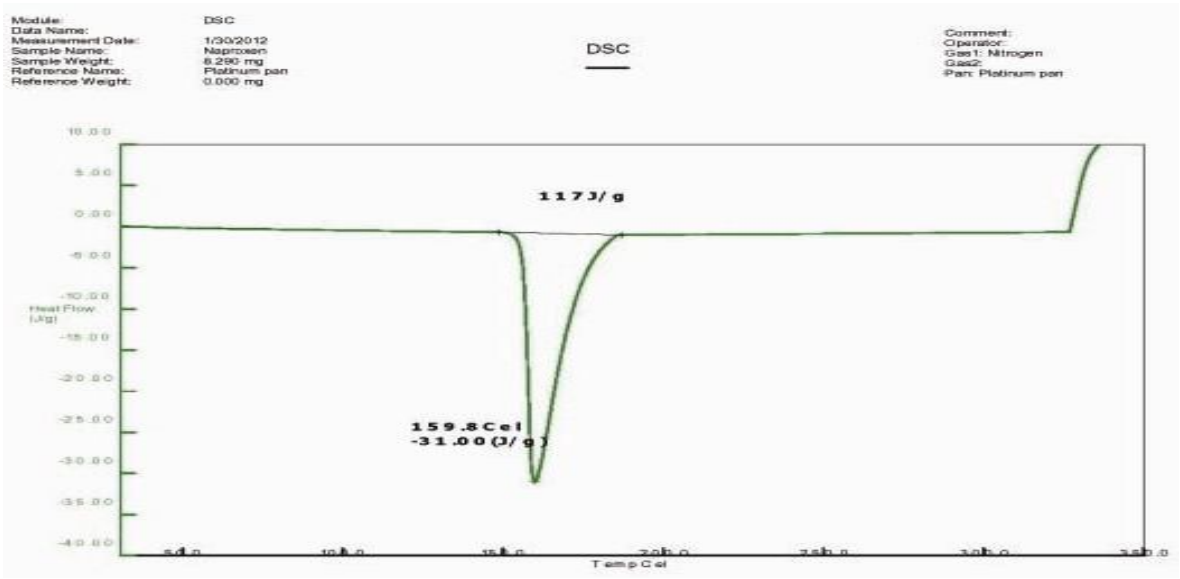

Fig. 5: DSC graph of Naproxen.

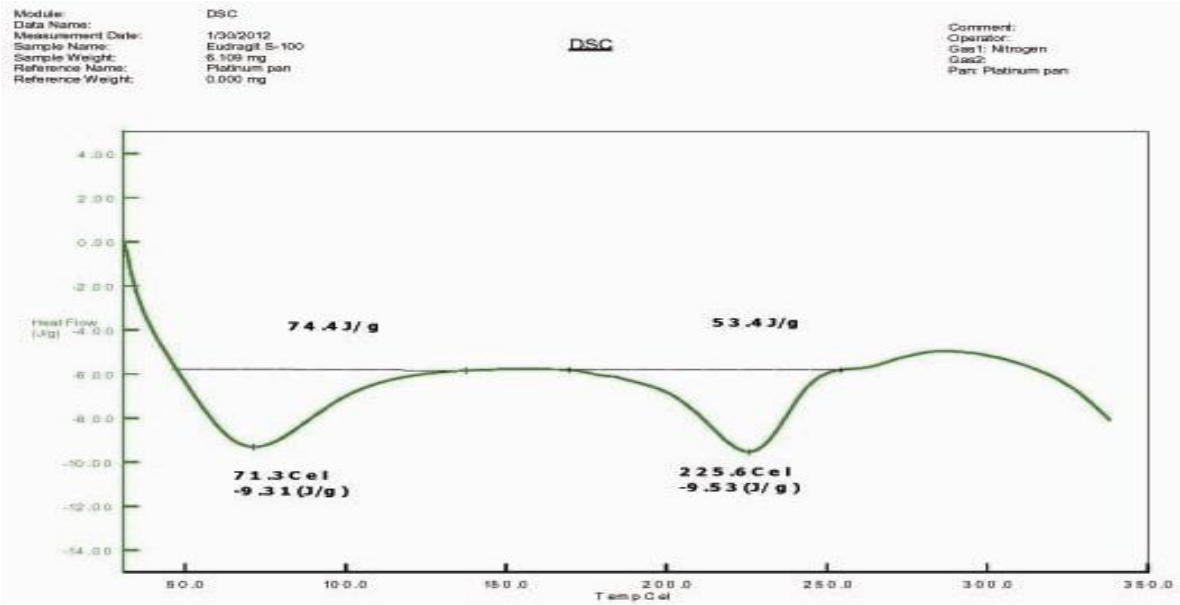

Fig. 6: DSC graph of Eudragit S 100.

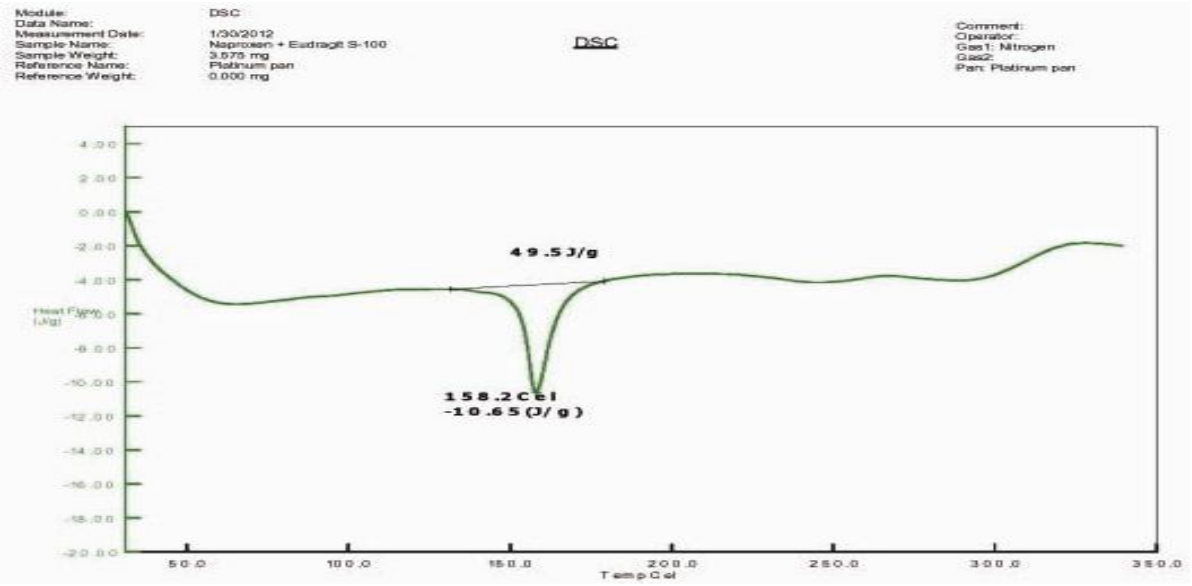

Fig. 7: DSC graph of Microcapsule.

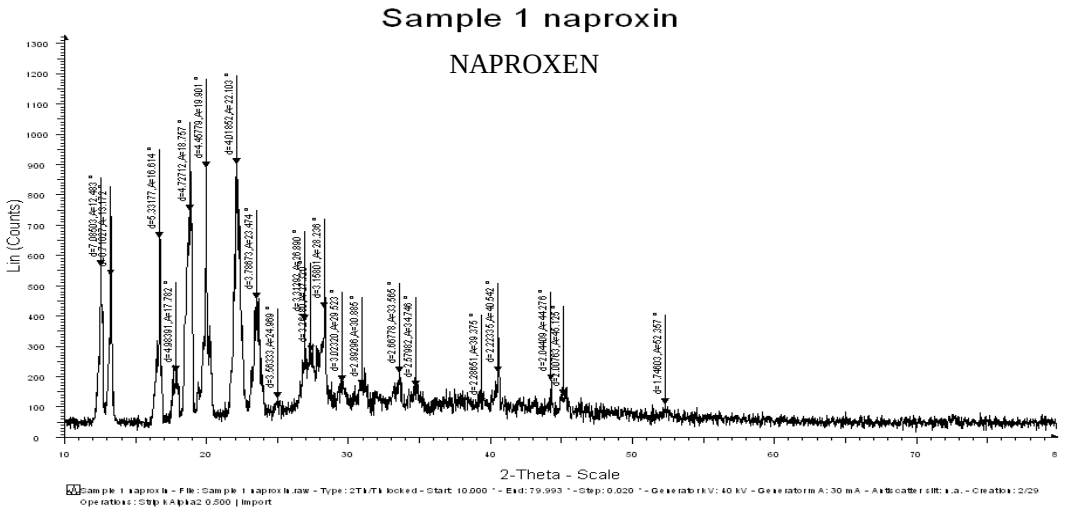

Fig. 8: X-Ray Powder Diffraction Studies For Naproxen.

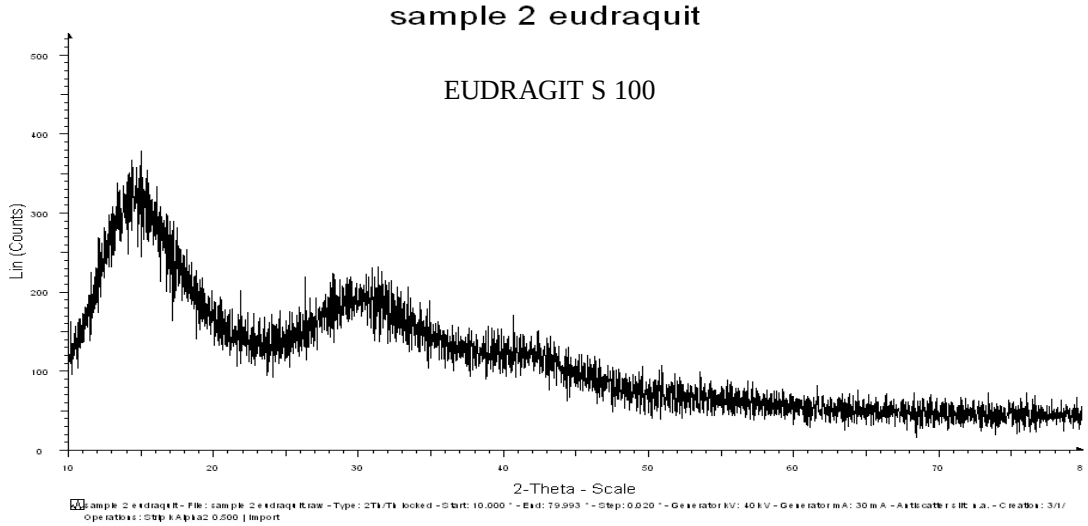

Fig. 9: X-Ray Powder Diffraction Studies For Eudragit S 100.

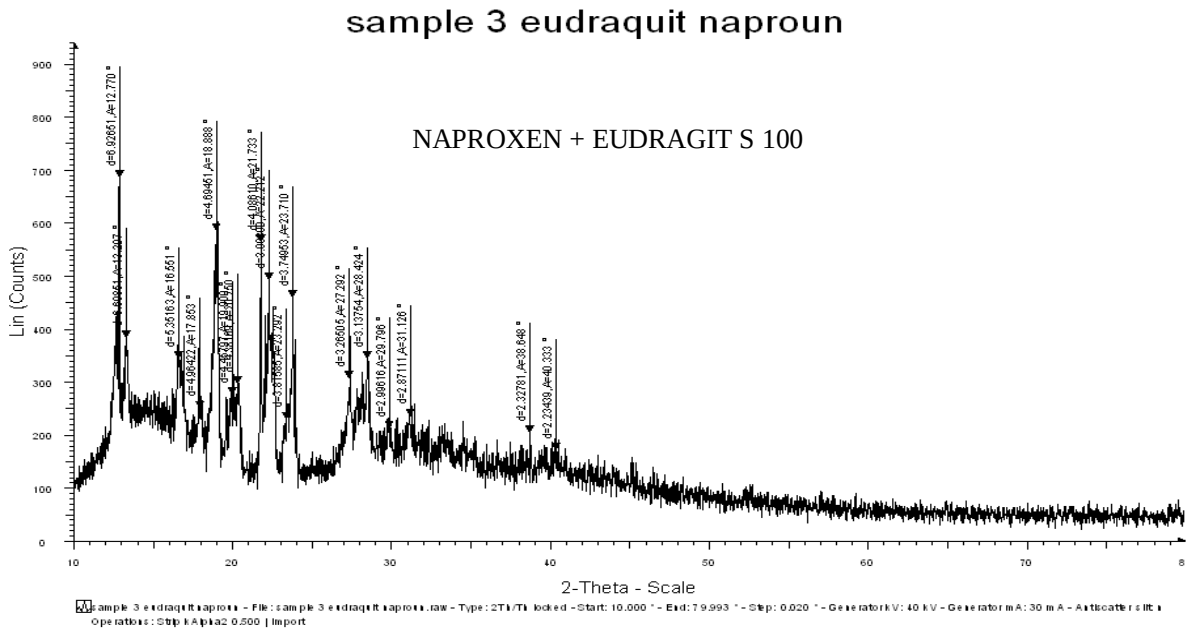

Fig. 10: X-Ray Powder Diffractometry (X-Rd) For Formulation.

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

The DSC thermogram indicates melting point peak of naproxen was present in the microcapsules indicating drug dispersed in the microcapsules as a crystalline form. Table no. 5 shows DSC peak values and Figure no. 5, 6, 7 show DSC graphs.

Table 5: Dsc Peak Value of Naproxen, Eudragit S 100 and Microcapsules.

Sr. no.	Sample	DSC Peak
1	Naproxen	159ºC
2	Eudragit S 100	71.3 ºC and 225.6 ºC
3	Microcapsules	158 ºC

X-RAY POWDER DIFFRACTOMETRY (X.R.D.) OF NAPROXEN

Pure Naproxen, Eudragit S 100 and microcapsule with optimum release were characterised by prominent peak in the range of 0-80º 2θ during XRD study. The drug peak also appeared in formulation which revealed that the drug is in crystalline state in formulation which is revealed previously in DSC study. Figure no. 8, 9, 10 shows XRD graphs.

IN VITRO DRUG RELEASE

Almost all the formulations released the drug in acidic pH condition. This is attributed to drug adhered on the surface of microcapsules. Formulation MC 9 has shown the minimum drug release upto 2nd hr. i.e. 13.16%, from 2nd to 4th hrs. there is significant built up in the concentration was seen, which resulted in release of drug upto 24.15 to 67.67% for all formulation. Drug release study from 4th to 9th hr. were done in phosphate buffer pH 7.4 resulted in maximum percentage of drug release as compared to first two dissolution mediums, where MC 1, MC 2, MC 3, MC 4, MC 5, MC 6, MC 7, MC 8, MC 9 released 90.22%, 86.59% 70.07%, 99.03%, 80.86%, 70.08%, 99.35%, 97.94%, 96.79% respectively.

The release retardation was maximum for the formulation MC 3 and MC 6 which represent the highest proportion of coating material used.

Table no. 6 shows cumulative drug release at 2nd, 4th, and 9th hr.

Table. 6: Cumulative Drug Release Profile At 2nd, 4th And 9th Hr.

FORMULATIONS	CUMMULATIVE PERCENT DRUG RELEASE		
	0-2 HRS.	2-4 HRS.	9TH HR.
MC 1	46.25	63.74	90.22
MC 2	24.22	67.67	86.59
MC 3	16.06	57.47	70.07
MC 4	29.62	63.16	99.03
MC 5	24.10	47.55	80.86
MC 6	24.18	57.55	70.08
MC 7	27.63	52.17	99.35
MC 8	13.21	51.82	97.94
MC 9	13.16	50.46	96.79

The result of all formulations were plotted in five modes of data treatment as follows.

1. Zero Order Kinetics: - Time V/S. % Cumulative Drug Release.
2. First Order Kinetics : - Time V/S. Log % Cumulative Drug Remaining.
3. Higuchi Plot : - Square Root Of Time V/S. Cumulative % DRUG RELEASED.
4. Peppas Plot : - Log Time V/S. Log Of % Cumulative Drug Released.
5. Hixon Crowell Plot : - Time V/S. (Percent Drug Retained)1/3.

The graphs of all kinetic models are shown in figure no. 11, 12, 13, 14, 15. All the data of the plots were subjected to linear regression analysis and the results are shown in the table no. 7 and 8.

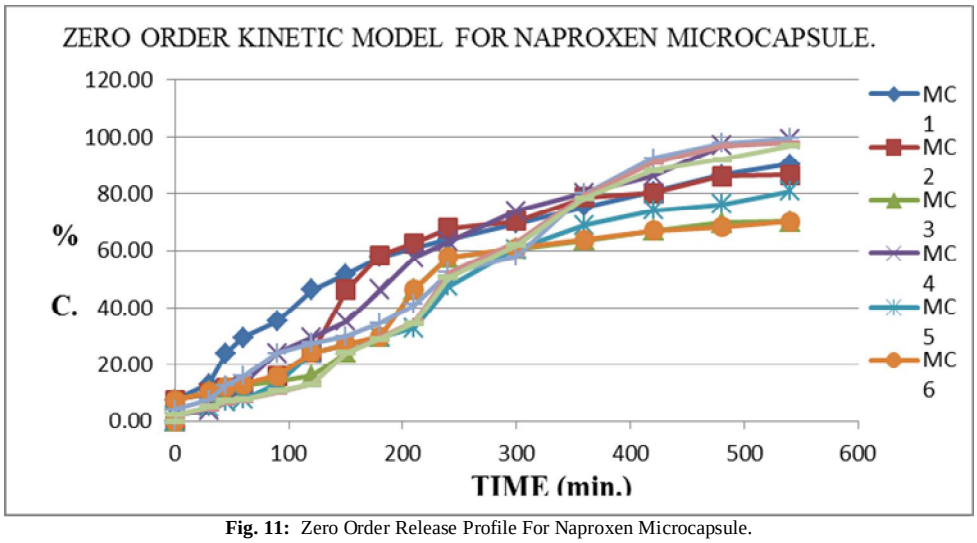

Fig. 11: Zero Order Release Profile For Naproxen Microcapsule.

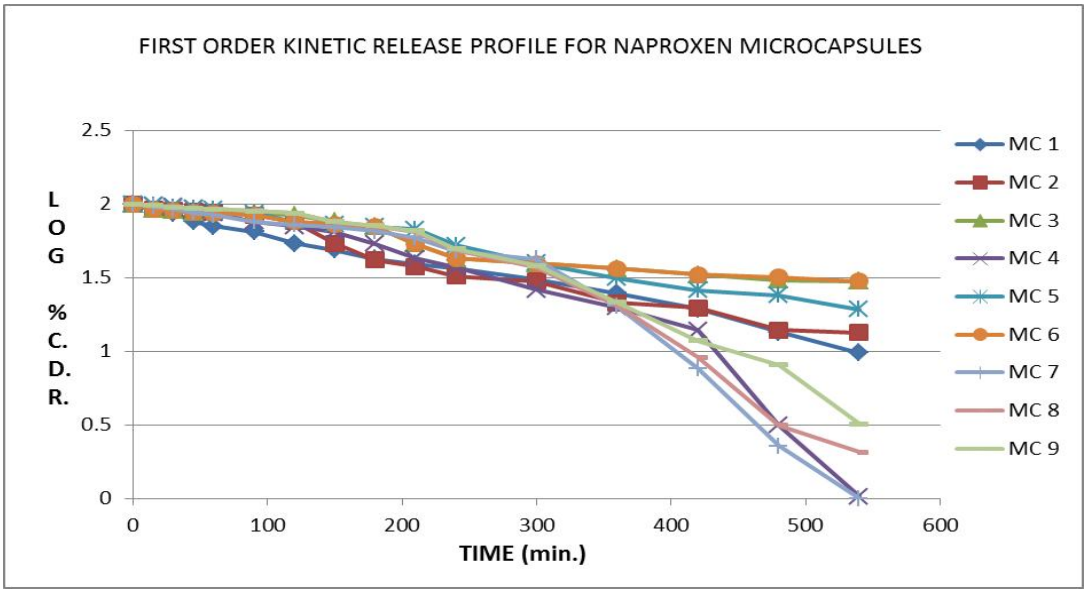

Fig. 12: First Order Release Profile For Naproxen Microcapsule.

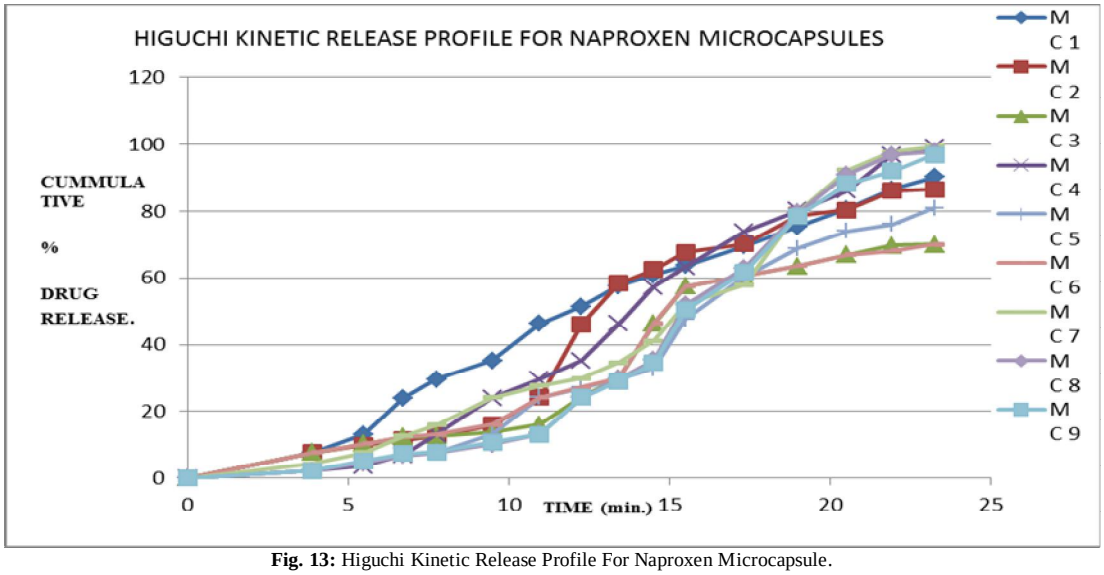

Fig. 13: Higuchi Kinetic Release Profile For Naproxen Microcapsule.

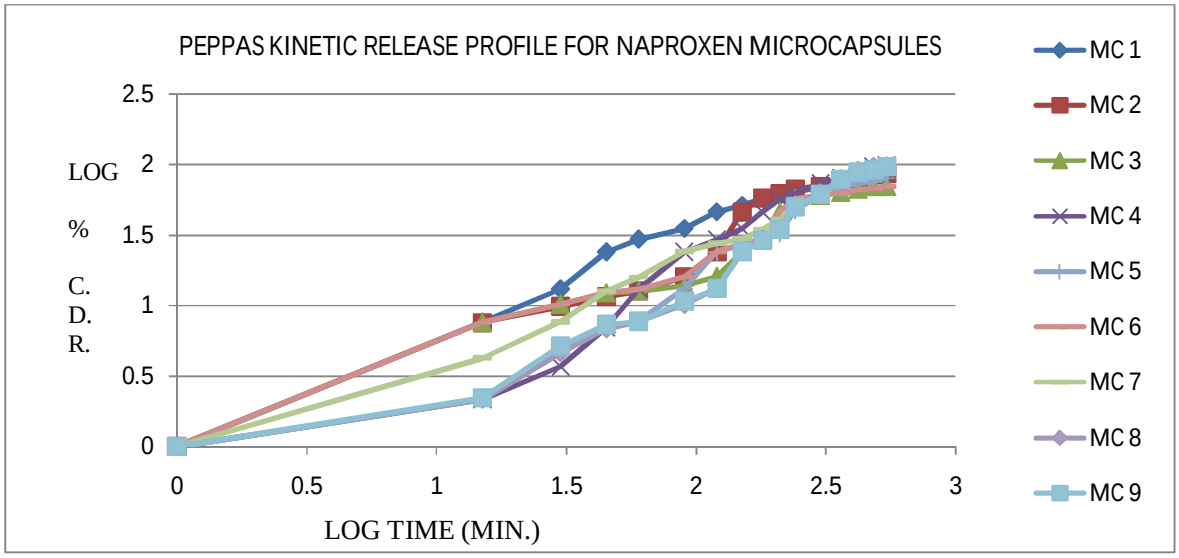

Fig. 14: Peppas Kinetic Release Profile For Naproxen Microcapsule.

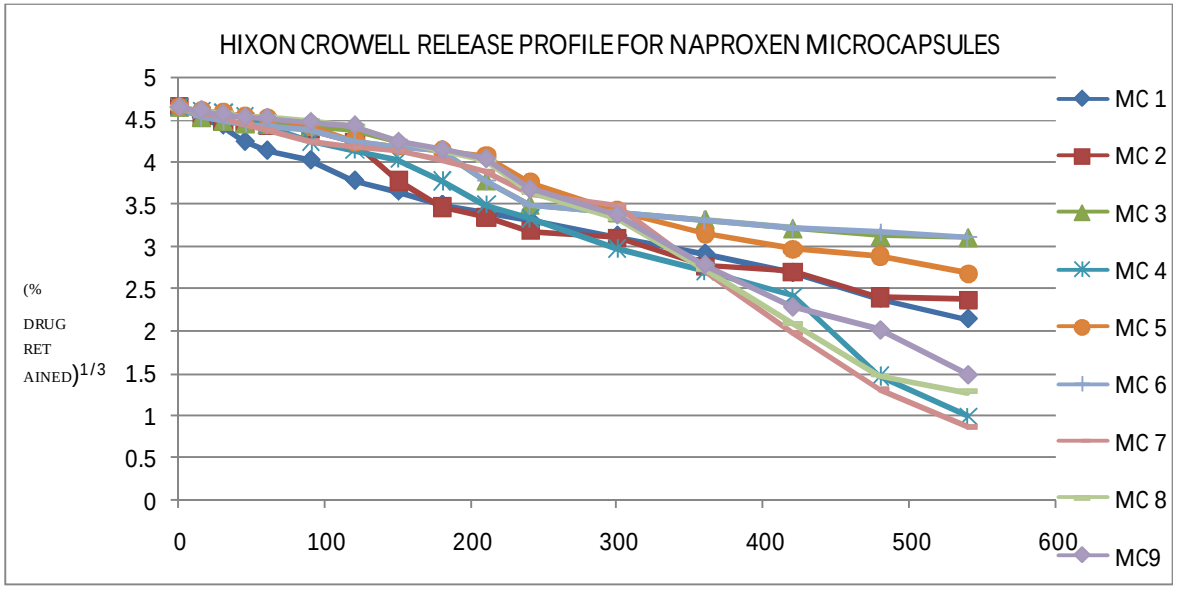

Fig. 15: Hixon Crowell Kinetic Release Profile For Naproxen Microcapsule.

Table. 7: 'R' Value And 'K' Value For Zero Order, First Order And Higuchi Model.

	Zero order		First order		Higuchi model	
	R	k	R	K	R	K
MC 1	0.8218	0.2087	0.9006	0.0042	0.9916	3.9759
MC 2	0.8223	0.2030	0.9666	0.0040	0.9966	3.7750
MC 3	0.8419	0.1612	0.9699	0.0026	0.9848	2.9677
MC 4	0.8772	0.2128	0.9176	0.0060	0.9549	3.8828
MC 5	0.8848	0.1693	0.8826	0.0029	0.9538	3.0516
MC 6	0.8353	0.1621	0.8715	0.0026	0.9802	3.0054
MC 7	0.8912	0.2035	0.8847	0.0063	0.9293	3.6709
MC 8	0.8012	0.1970	0.8083	0.0055	0.8954	3.4742
MC 9	0.8272	0.1921	0.8249	0.0047	0.8987	3.3925

Table. 8: 'R' Value and 'K' Value for Peppas Kinetic Model and Hixon Crowell Model.

Formulation code	PEPPAS KINETIC			HIXON CROWELL	
	R	n	k	R	K
MC 1	0.9801	0.42	1.6610	0.8940	0.0011
MC 2	0.8659	0.43	0.6143	0.8747	0.0010
MC 3	0.8579	0.39	0.7693	0.9240	0.0007
MC 4	0.9164	0.21	0.1121	0.8125	0.0013
MC 5	0.8943	0.47	0.1256	0.8586	0.0008
MC 6	0.9166	0.41	0.8533	0.9337	0.0007
MC 7	0.8161	0.36	0.3967	0.8558	0.0013
MC 8	0.8999	0.34	0.0831	0.8144	0.0012
MC 9	0.8892	0.35	0.0978	0.8428	0.0011

The interpretation of data showed that maximum linearity was found for all the formulation to Higuchi classical model of diffusion with highest 'R' values for all the formulations as compared with other kinetic models. Thus it specifying that drug release mechanism may be via diffusion process.

To ascertain this diffusion process to be Fickian or non-Fickian log plots were plotted. The plot of Peppas showed that 'n' values are less than 0.5 which suggest that diffusion process is obeying Fick's law of diffusion.

CONCLUSION

Naproxen microcapsules were prepared using Eudragit S 100 as polymer as pH dependent colon specifically. The compatibility studies showed to interaction between naproxen and eudragit s 100. The microcapsules showed rough surface and were spherical in shape. The maximum linearity was found for all the formulation by Higuchi classical model of diffusion with highest 'R' values for all the formulations as compared with other kinetic models. Thus it specifying that drug release mechanism may be via diffusion process.

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