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# DESIGN AND CHARACTERIZATION OF ETHYL CELLULOSE-BASED COLON SPECIFIC MICROSPHERE CONTAINING NAPROXEN USING $3^2$ FACTORIAL DESIGNS

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**ARTICLE INFO**

**Key Words**

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## ABSTRACT

The objective of the present study was to formulate and optimize colon targeted Naproxenmicrospheres. To achieve these objective nine formulations of microspheres werepreprepared by emulsion solvent evaporation method using Eudragit and Ethyl cellulose polymer. A $3^2$ factorialdesign was employed in formulating the microspheres with concentration of Ethyl Cellulose ($X_1$) and PEG 600 ($X_2$) as independent variables. Percent drug release was considered asdependent variable. The effect of drug-polymer concentration, surfactant concentration,cross-linking agent and stirring speed were evaluated with respect to entrapment efficiency,particle size, surface characteristics, micromeritic properties, DSC study and in vitro drug release studies. The particle size and entrapment efficiency were found to bevaried by changing various formulation parameters like surfactant concentration andstirring speed etc. IR study confirmed the drug-polymer compatibility and scanning electronmicroscopy indicates that the microspheres have the rough and porous surface due toarising as a trace of solvent evaporation during the process.

## INTRODUCTION:

Oral drug delivery still is the preferred route of administration for drug products. The evolution of oral drug delivery technology may be described by a three-stage course to reach its current level. With every step forward in drug delivery technology, scientists strive to gain more control over the pharmacokinetics of the drug substance with the goal to increase the therapeutic benefit-risk ratio or to improve bioavailability.[1,2] Delivery of drug substances to the ileocolonic region may be an essential element of successful drug treatment (improved efficacy or reduced systemic toxicity) in topical treatment of the colon. Release of mesalazine and corticosteroids in the ileocolonic region has proved to be a successful approach for the treatment of ulcerative colitis. Extension of this approach to other anti-inflammatory and immunosuppressive drug substances (e.g.

6-thioguanine, tacrolimus, ciclosporin A) is envisaged as a promise. Moreover, topical treatment of other colon pathologies also appears to be rational from a clinical pharmacological point of view, such as Crohn's disease (budesonide , infliximab), colon cancer (sulindac) [3,4] luminal amoebiasis (antibiotics) , diarrhea (prebiotics) an inflammatory bowel disease (probiotics) . The common denominator of these therapies is that a high intraluminal concentration of drug substance in the ascending colon is related to a beneficial outcome of drug treatment. Another reason for investigating oral ileocolonic drug delivery may be found in food science to support weight management and the treatment of obesitas. Consumer research has highlighted the need to better control hunger when on a diet to enhance and sustain compliance in maximizing weight loss success. According to recent market research in the United States, the majority (53%) of respondent's claim to cheat on a diet because they are hungry**.** Microspheres have played a major role in the development of controlled and or sustained release drug delivery systems. Microspheres have been of particular interest from the pharmaceutical point of view providing the possibility to achieve sustained and controlled drug release.5 There are several publications based on drug-containing microspheres using the Eudragit series of polymers as the encapsulating materials. The Eudragits are a family of polymers based on acrylic and methacrylic acids suitable for use in orally administered drug delivery systems. These polymers are available in various grades possessing a range of physicochemical properties[8,9].

The objective of the investigation is to design and develop colon targeted drug delivery system of tinidazole microspheres by using Eudragit L 100 and Ethyl cellulose as a pH sensitive polymer. by directly targeting the drug to colon.

**Materials and methods**

**Materials:** Naproxen was a gift sample from Dr.Reddy Lab Hyderabad,Eudragit L100 and Ethyl cellulose was procured from MSN Lab Hyderabad.,all the solvents are purchased from Evonik India Pvt. Ltd .

Method:

**Preliminary studies for surfactant level selection:** Span 60 was used as surfactant in the microsphere formulation, at various concentration Span 60 was added and evaluated for EE% and DR%,from data obtained below it was confirmed that when the surfactant concentration is 1.8 ml EE% is high at various rpm the formulation of microsphere trial formulation was prepared

**Table: 1 Level of selection of span60**

| Batch code | Span 60(ml) | Drug(g.m) | Polymer Ratio Eudragit:EC | EE% | DR% |
|---|---|---|---|---|---|
| A1 | 1.8 | 0.9 | 1:2 | 56.01±0.03 | 87.11±0.43 |
| A2 | 1.8 | 0.9 | 1:2 | 61.33±0.11 | 89.02 ±0.72 |
| andA3 | 1.1 | 0.9 | 1:2 | 42.01±0.33 | 72.66±0.17 |
| A4 | 0.4 | 0.9 | 1:2 | 40.31±0.22 | 69.23±0.66 |

**Preliminary studies for RPM level selection**
**and evaluated for EE% and DR%,The trial results are given below in table noXXXX**

| Batch code | RPM | Drug(g.m) | Polymer Ratio Eudragit:EC | EE% | DR% |
|---|---|---|---|---|---|
| A5 | 2000 | 0.9 | 1:2 | 64.31±0.83 | 77.11±0.43 |
| A6 | 2000 | 0.9 | 1:2 | 63.23±0.01 | 80.02 ±0.12 |
| A7 | 1500 | 0.9 | 1:2 | 52.01±0.23 | 77.66±0.27 |
| A8 | 1000 | 0.9 | 1:2 | 50.31±0.12 | 70.23±0.26 |

**Table no: 2Level of selection of RPM**

**Preparation of Naproxen microspheres**

Naproxen microspheres were prepared by emulsification solvent evaporation method. Accurately weighed EL 100 and EC in 1:2 ratios were dissolved in ethanol and acetone to form a homogenous polymer solution. Tinidazole was added into the polymer solution and mixed thoroughly. Plasticizer (dibutyl phthalate 50% w/v) was added to above solution. The above organic phase was slowly poured at 30 $^0$ C into liquid paraffin (15 mL) containing span 60 of different concentrations with stirring speed at different rpm to form a smooth emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone and ethanol evaporated and smooth walled, rigid and discrete microspheres were formed. The microspheres were collected by decantation and the product was washed with petroleum ether ($40^0$ -$60^0$C ), three times and dried at room temperature for 3 h. The microspheres were then stored in a desiccators over fused calcium chloride for further use. Nine batches were performed with optimization[10,11]

**Table no: 3 Experimental Variables in $3^2$ Factorial Design**

| Independent Variables | Dependent Variables |
|---|---|
| $X_1$=surfactant concentration | $Y_1$= % of drug release |
| $X_2$=RPM | $Y_2$= Entrapment efficiency |

**Table no: 4 -$3^2$ Factorial Design for Tinidazole microsphere**

| Formulation code | $X_1$ | $X_2$ |
|---|---|---|
| F1 | +1 | -1 |
| F2 | +1 | 0 |
| F3 | +1 | +1 |
| F4 | 0 | -1 |

| Coded value | Actualvalue X1(%) | $X_2$(rpm) |
|---|---|---|
| -1 | 0.4 | 1000 |
| 0 | 1.1 | 1500 |
| +1 | 1.8 | 2000 |

| | | |
|---|---|---|
| F5 | 0 | 0 |
| F6 | 0 | +1 |
| F7 | -1 | -1 |
| F8 | -1 | 0 |
| F9 | -1 | +1 |

**Table no: 5-Fomulation chart of Tinidazole Microsphere**

| **Formulation code** | **Drug(gm)** | **Polymer** | **Surfactant** | **RPM** |
|---|---|---|---|---|
| **EL:EC** | **concentration** | | | |
| **F1** | **0.9** | **1:2** | **1.8** | **2000** |
| **F2** | **0.9** | **1:2** | **1.8** | **1500** |
| **F3** | **0.9** | **1:2** | **1.8** | **1000** |
| **F4** | **0.9** | **1:2** | **1.1** | **2000** |
| **F5** | **0.9** | **1:2** | **1.1** | **1500** |
| **F6** | **0.9** | **1:2** | **1.1** | **1000** |
| **F7** | **0.9** | **1:2** | **0.4** | **1000** |
| **F8** | **0.9** | **1:2** | **0.4** | **1500** |
| **F9** | **0.9** | **1:2** | **0.4** | **2000** |

**Characterization of Tinidazole microspheres**

**Drug-polymer interaction (FTIR) study**

FTIR spectroscopy was performed on Fourier transform infrared spectrophotometer (IR Affinity-1, Shimadzu, Japan).

**Particle size:** The particle size of the microbeads was evaluated using an optical microscope fitted with a calibrated eyepiece micrometer under a magnification of 40X. The particle diameters of about 50 microbeads were measured randomly and the average particle size was determined using the Edmondson's equation:

$$D_{mean} = \Sigma\, nd / \Sigma n$$

Where, n - stands for the number of counted microbeads, and d - mean size range.

**% Drug content:** Accurately weighed 100 mg microbeads were taken in a mortar pestle, finely crushed and then small quantity of water is added. It was then kept overnight for complete solubilization of pectin and drug release from it. After suitable dilutions in methanol, absorbance was measured in uv-vis spectrophotometer and accordingly drug content is calculated. The study was repeated threetimes.[12,13]

**Entrapment efficiency:** Microspheres containing equivalent to 10 mg of drug was allowed to equilibrate in 100 mL of phosphate buffer pH 7.4 for 24 h. The solution was filtered using Whatman filter paper (44). The resulting solution was analyzed using a UV spectrophotometric method at 318nmin the presence of a blank prepared from microspheres containing all materials except the drug.

$$\%\text{Drugentrapment} = \frac{\text{calculated drug concentration}}{\text{theoretical drug concentration}} \times 100$$

**Differential scanning colorimetry (DSC)**

DSC studies were performed using a DSC METTLERSwitzerland with thermal analyzer. Accurately weighed samples (about 5 mg) were placed in a sealed aluminium pan, before heating under nitrogen flow (20 mL/min) at a scanning rate of 20 _C per min from 40 to 300 _C. An empty aluminium pan was used as reference. DSC thermograms of pure substances, their physical mixtures and drug-loaded micro particles were recorded.

**Surface morphology (SEM)**

Scanning electron microscopy has been used to determine the surface morphology and texture. SEM studies were carried out by using JEOL Model JSM-6390LV scanning microscope.

**Micromeritic properties of microspheres:** The flow properties of microspheres were investigated by determining the angle of repose, bulk density, tapped density, Carr's and Hausner's ratio. The angle of repose was determined by the fixed-based funnel method. Bulk and tapped densities were measured in 10 mL of a graduated cylinder. The cylinder was tapped from a height of 2 inches until a constant volume was obtained. The volume occupied by the sample after tapping was recorded and bulk density, tapped density, Carr's index and Hausner's ratio was calculated.

**In vitro drug release studies:** In vitro release study of microspheres was performed in pH progression medium at $37^0$ C $\pm 0.5^0$ C. The drug dissolution test of microspheres was performed by the paddle method (USP dissolution apparatus Type II, Electro lab Limited, India). Microspheres equivalent to 100 mg were weighed accurately and put in muslin cloth and tied this to paddle over the surface of 900 mL of dissolution medium. The content was rotated at 100 rpm. The pH of the dissolution medium was kept 1.2 for 2 h using 0.1 N HCl. After 2 h, the pH of the dissolution medium was adjusted to 7.4 with 0.1 N NaOH and maintainedup to 8 h. The samples were withdrawn from the

dissolution medium at various time intervals using a pipette. The rate of drug release was analyzed using UV spectrophotometer (JASCO, Ahmadabad, India).[14]

***Kinetic treatment of dissolution data***

There are number of kinetic models, which described the overall release of drug from the dosage forms. One of the approach to investigate the kinetics of drug release from controlled release formulation is by using model dependent methods. Model dependent methods are based on different mathematical functions, which describe the dissolution profile. Once a suitable function has been selected, the dissolution profiles are evaluated depending on the derived model parameters. Following models are evaluated.[15]

***Zero order Kinetics***

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$Q_0 — Q_t = K_0 t$

Rearrangement of equation (9) yields

Where, $Q_t$ is the amount of drug dissolved in time *t,* $Q_0$ is the initial amount of drug in the solution (most times, $Q_0 = 0$) and $K_0$ is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug released *versus* time

***First order Kinetics***

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis. The release of the drug which followed first order kinetics can be expressed by the equation:

$$\log C = \log C_0 - K_E t/2.303$$

where $C_0$ is the initial concentration of drug, K is the first order rate constant, and t is the time. The data obtained are plotted as log cumulative percentage of drug remaining *vs.* time which would yield a straight line with a slope of -K/2.303.

*Higuchimodel*

This model is based on the hypotheses that (i) initial drug concentration in the matrix is much higher than drug solubility; (ii) drug diffusion takes place only in one dimension (edge effect must be negligible); (iii) drug particles are much smaller than system thickness; (iv) matrix swelling and dissolution are negligible; (v) drug diffusivity is constant; and (vi) perfect sink conditions are always attained in the release environment.In a general way it is possible to simplify the Higuchi model as,

$f_t = Q = K_K \times t_{1/2}$

where, $K_H$ is the Higuchi dissolution constant. The data obtained were plotted as cumulative percentage drug release versus square root of time

*Hixson-Crowell model*

Hixson and Crowell (1931) recognized that the particles regular area is proportional to the cube root of its volume. They derived the equation:

$W_O — W_t = nt$. Where, $W_0$ is the initial amount of drug in the pharmaceutical dosage form, $W_t$ is the remaining amount of drug in the pharmaceutical dosage form at time t and n (kappa) is a constant incorporating the surface volume relation. The equation describes the release from systems where there is a change in surface area and diameter of particles or tablets. Tostudy the release kinetics, data obtained from *in vitro* drug release studies were plotted as cube root of drug percentage remaining in matrix *versus* time.

**Statistical design**

Design-Expert software (Design Expert trial version 8.0.7.1;State-Ease Inc., Minneapolis, MN, USA) was used. A two-

factor three-level full factorial design was used for systemic study of combination of polymers. Polynomial models including interaction and quadratic terms were generated for the entire response variables using multiple linear regression analysis (MLRA) approach. The general form of the MLRA model is represented in the equation. Where Y is the dependent variable; b0 is the arithmetic average of all the quantitative outcomes of nine runs. b1, b2, b12 are the estimated coefficients computed from the observed experimental response values of Y and X1 and X2 are the coded levels of the independent variables. The interaction term (X1X2) shows how the response values change when two factors are simultaneously changed. Table 1 summarizes the translation of the coded levels to the experimental units used in the study and Table X summarizes the experiment runs used. In this study factorialdesign based on the response surface method was adoptedto optimize effective factors for the release of the drugfrom the microspheres.Analysis of variance (ANOVA) and all statistical analysiswere also performed using the software. Calculation of theeffects was performed. The significant effects would constitutethe model. The F-value was then calculated by comparingthe treatment variance with the error variance. The multiplecorrelation co-efficient was calculated which is a measure ofthe amount of variation about the mean, which is explainedby the model. The main effects and interactions are plottedand results interpreted. All assumptions underlying theANOVA are checked. For statistical purposes, the assumptions made that residuals are normally distributed and independent with constant variance.[16] Spectrometric estimation of Naproxen. The Lamda max of drug was obtained by scanning 20µg/ml solution concentration in the range of 200-400nm using UV-Visible spectrometer and it was found that 317.9nm for phosphate buffer pH 6.8 and pH 7.4

Table-1 Solubility of Naproxen in various solvents

| SOLVENT | SOLUBILITY |
|---|---|
| Water | Not soluble |
| Methanol | Soluble |
| PH -6.8 buffer | Partially Soluble |
| PH- 7.4 buffer | Soluble |
| PH- 5.8 buffer | Not soluble |

## RESULTS & DISCUSSION

Preparation of standard calibration curve of Naproxen: Tinidazole (10 mg) was dissolved in 0.1 N HCl and volume was made up to 100 mL in 100 mL volumetric flask. This solution (100 mcg/mL) was further dilutedwith 0.1 N HCl to obtain solution of 5 to 40 mcg/mL. Absorbance of each solutionwas measured at 228 nm using Shimadzu UV-1601 UV/Vis double beamspectrophotometer and 0.1 N HCl as reference standard. The standard curvewas generated for the entire range from 5 to 40 mcg /mL. The results of standardcurve preparation are shown in the Table 6,7 and Figure 1&2

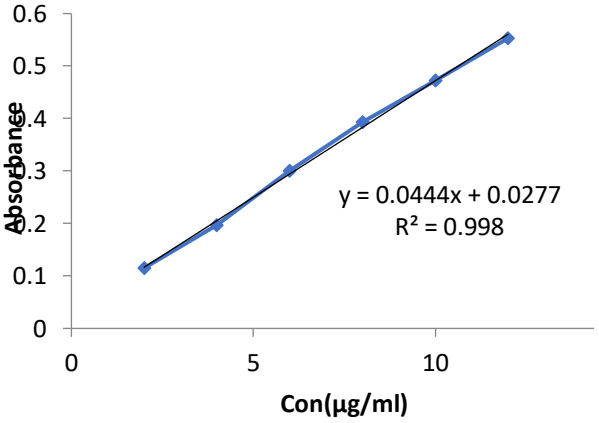
**Drug –polymer compatiblity results:** The FTIR spectra of pure drug, Eudragit and tinidazolemicrospheres were shown in (Fig: 3). It shows that no incompatibility reactions took place between drug and excipients.

**DSC Study:** DSC thermograph of tinidazole, Eudragit and tinidazoleloaded Eudragit microspheres are shown in Fig 5 The pure drug tinidazole Fig. 5(a) gives rise to a sharp peakthat corresponds to melting point at 126 $^0$C, indicates itscrystalline nature. The pure polymer Eudragit L 100 and Eu ragit S 100 exhibits a peak at 223 $^0$C and 222 $^0$C respectively,referring to the relaxation that follows the glass transition .peak of drug did not appear inthe thermogram of prepared microspheres, it may indicatethe drug was uniformly dispersed at the molecular level in themicrospheres in Fig. 5

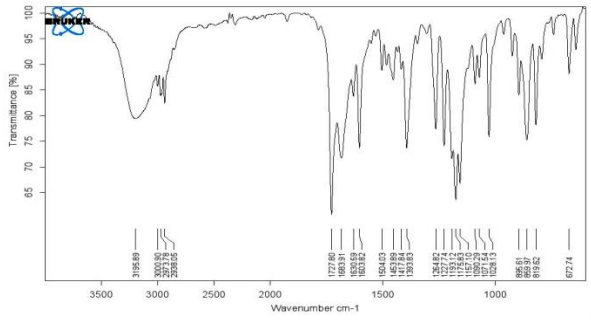
Table-2 Calibration data of Naproxen in pH 6.8 phosphate buffer at 235nm

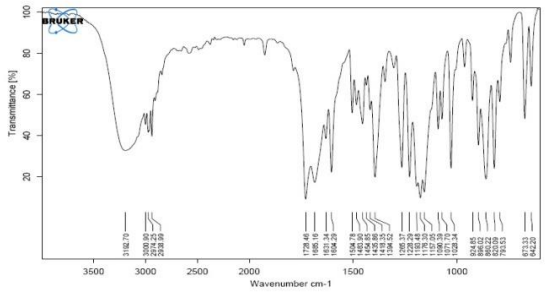
| | Absorbance II | | III | Mean absorbance |
|---|---|---|---|---|
| 2 | 0.115 | 0.113 | 0.115 | 0.114 |
| 4 | 0.197 | 0.198 | 0.195 | 0.196 |
| 6 | 0.301 | 0.300 | 0.303 | 0.301 |
| 8 | 0.393 | 0.393 | 0.391 | 0.392 |
| 10 | 0.473 | 0.472 | 0.474 | 0.473 |
| 12 | 0.553 | 0.552 | 0.553 | 0.552 |

**Standard curve of Naproxen in pH 6.8 phosphate buffer at 235nm**



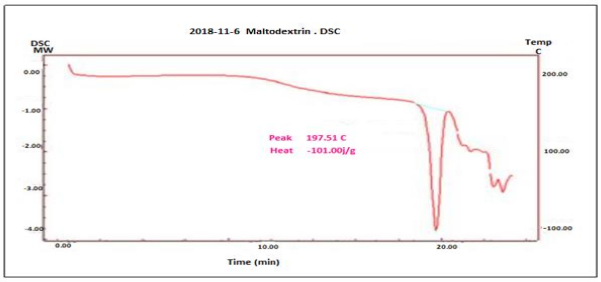

**FTIR RESULTS for Naproxen**

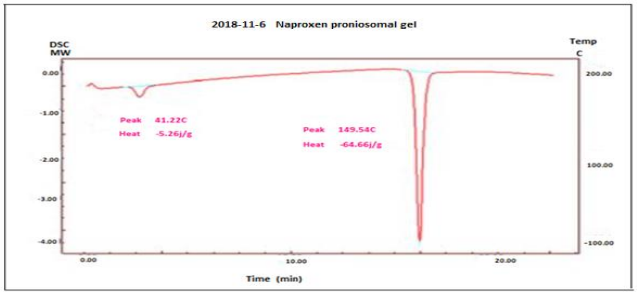


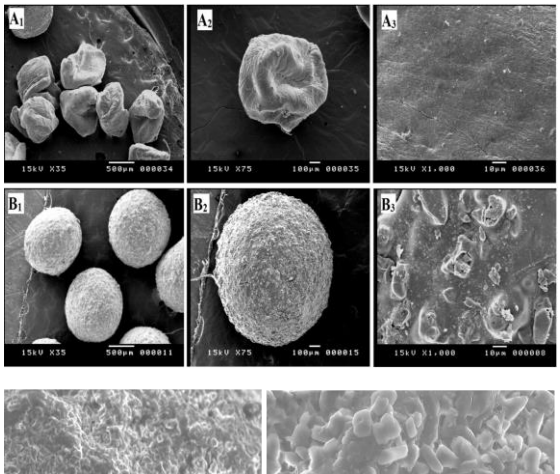



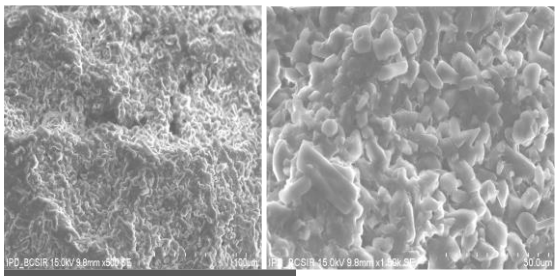

**Spectra analysis of Naproxen**

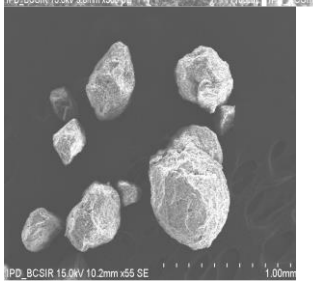
**DSC RESULTS**





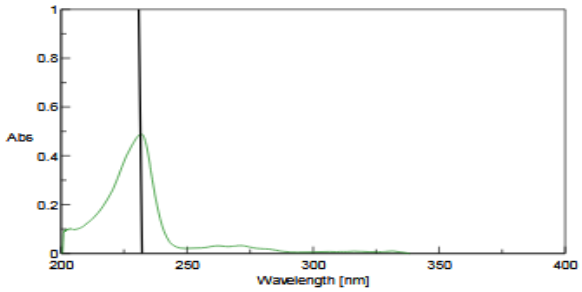



**Table 5.5: FTIR Spectra of Standard and Procured Naproxen**

| Functional group present | Wave Number (cm-1) | | |
|---|---|---|---|
| | Standard Peak Region | Standard drug | Procured drug (from figure 13) |
| Carboxyl group (-COOH) O-H stretch C=O stretch C-O stretch | 3500-2400 1730-1700 1320-1210 | 3175 1728 1229 | 3170.4 1727.91 1229.4 |
| Aromatic ring C=C-C stretch | 1615-1580 | 1604 | 1604.48 |
| Ethyl Aryl-O stretch Alkyl C-O stretch | 1270-1230 1150-1050 | 1260 1092 | 1264.11 1090.55 |

| Run | Factor 1 A:Ethyl Cellulose mg | Factor 2 B:PEG 600 mg | Response 1 EE % | Response 2 Particle Size um | Response 3 DR% % |
|---|---|---|---|---|---|
| 1 | 1.8 | 0.2 | 85.36 | 656.14 | 79 |
| 2 | 2 | 0.2 | 88.44 | 659.74 | 82 |
| 3 | 1.8 | 0.6 | 89.34 | 649.12 | 67 |
| 4 | 2 | 0.4 | 90.16 | 652.31 | 89 |
| 5 | 1.8 | 0.4 | 86.79 | 651.11 | 90 |
| 6 | 2.2 | 0.2 | 91.48 | 653.32 | 98 |
| 7 | 2.2 | 0.4 | 90.23 | 652.31 | 89 |
| 8 | 2 | 0.6 | 86.01 | 648.61 | 70 |
| 9 | 2.2 | 0.6 | 79.22 | 649.65 | 71 |

## Micromeritic results

The value of angle of repose of formulation within therange of 17.43±0.13 to 29.13±0.22 indicating good flow properties for the microspheres. The bulk density Values ranged between.0.197±0.53 to0.127±0.43 The tapped density values ranged between0.219±0.03 and0.299±0.33 (gm/cm$^3$). The Carr's index values ranged between28.63±0.03and28.63±0.03 which can describe by Table 8

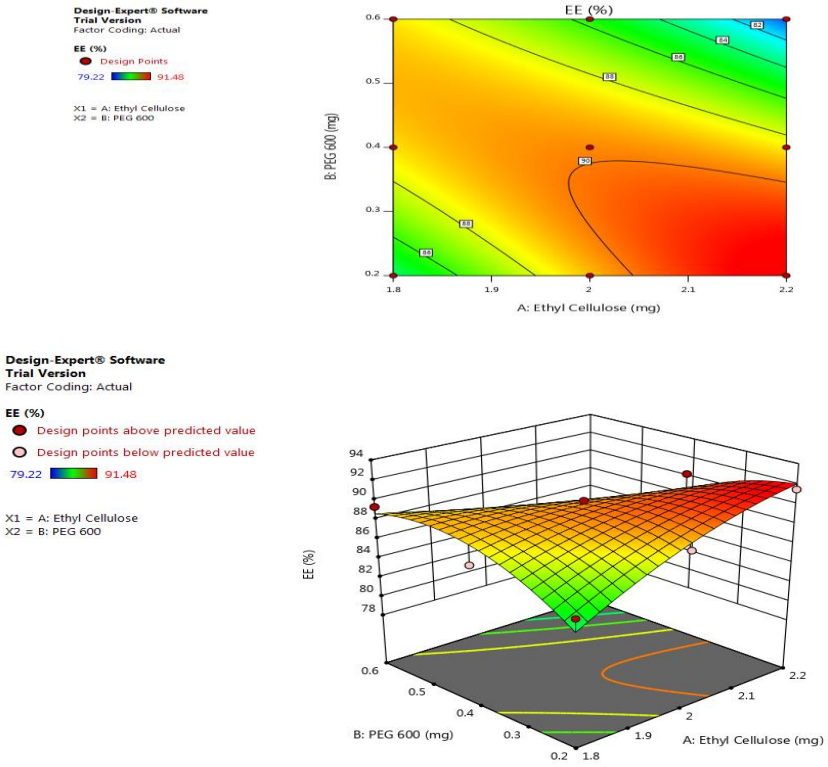
## *In vitro* drug release profile

The in vitro release study was carried out by buffer change method to mimic the GIT environment. Drug release for the initial 2 h i.e. in 0.1 N HCL, The drug release is found 91.84% at the end of 8 min pH 7.4 phosphate buffer, shown in Fig.6

## Charaterisation of Microsphere of different batches

| Formulation code | Entrapment efficiency (%) | Avarage particle Mean Dameter (µm) | Specific Surface area(m2/g ×10-2) |
|---|---|---|---|
| F1 | 85.36±0.03 | 656.14±0.04 | 1.34 |
| F2 | 88.44±0.13 | 659.74±0.02 | 1.36 |
| F3 | 89.34±0.13 | 649.12±0.01 | 1.34 |
| F4 | 79.16±0.0 | 652.31±0 | 1.36 |
| | 1 | .32 | |
| F5 | 86.79±0.03 | 651.11±0.31 | 1.38 |
| F6 | 88.13±0.13 | 640.11±0.33 | 1.38 |
| F7 | 42.65±0.07 | 652.31±0.28 | 1.32 |
| F8 | 52.65±0.07 | 648.61±0.18 | 1.31 |
| F9 | 49.65±0.08 | 649.65±0.07 | 1.32 |

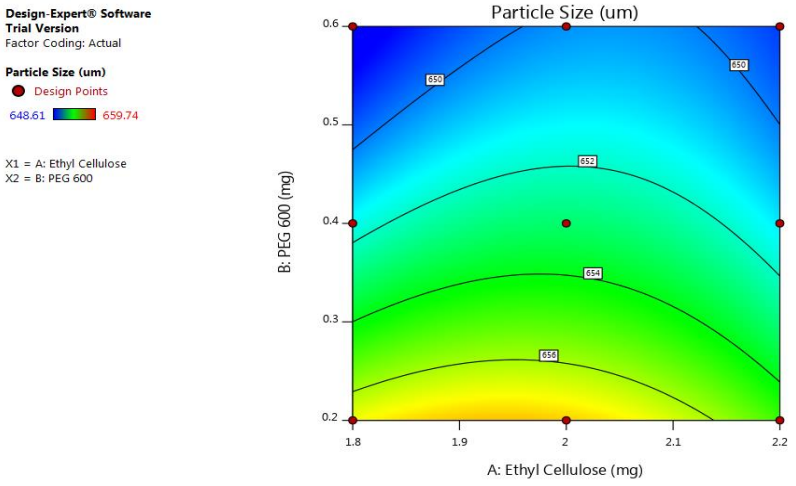
**OPTIMIZATION RESULTS FOR NAPROXEN MICROSPHERE**

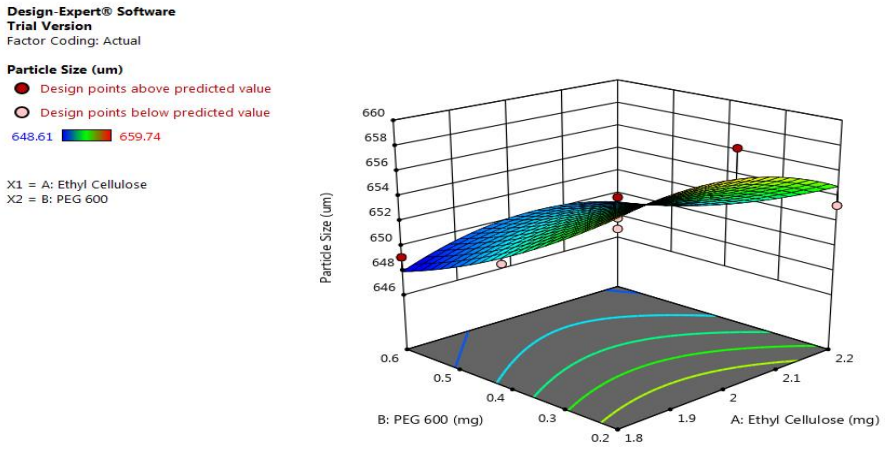



ANOVA for Quadratic model

**Response 1: EE**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| Model | 99.37 | 5 | 19.87 | 5.37 | 0.0986 | significant |
| A-Ethyl Cellulose | 0.0523 | 1 | 0.0523 | 0.0141 | 0.9129 | |
| B-PEG 600 | 19.12 | 1 | 19.12 | 5.16 | 0.1077 | |
| AB | 65.93 | 1 | 65.93 | 17.81 | 0.0243 | |
| $A^2$ | 2.57 | 1 | 2.57 | 0.6939 | 0.4660 | |
| $B^2$ | 11.70 | 1 | 11.70 | 3.16 | 0.1736 | |

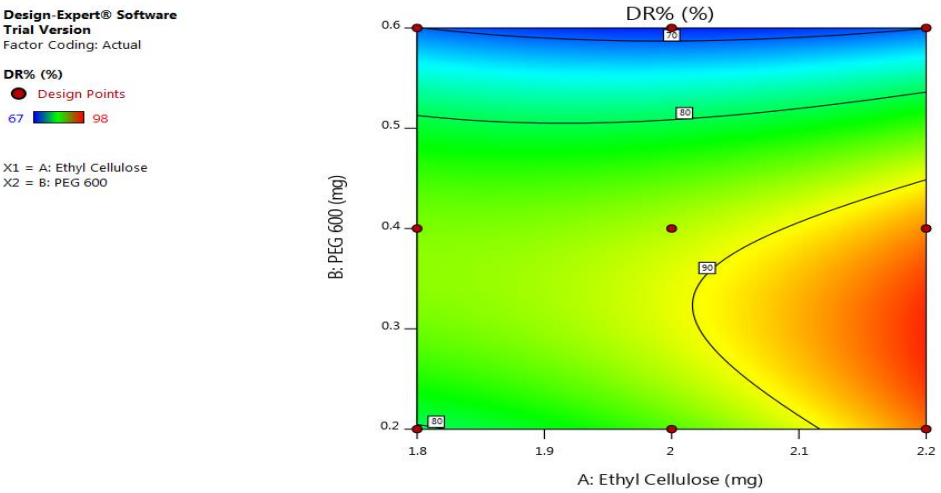


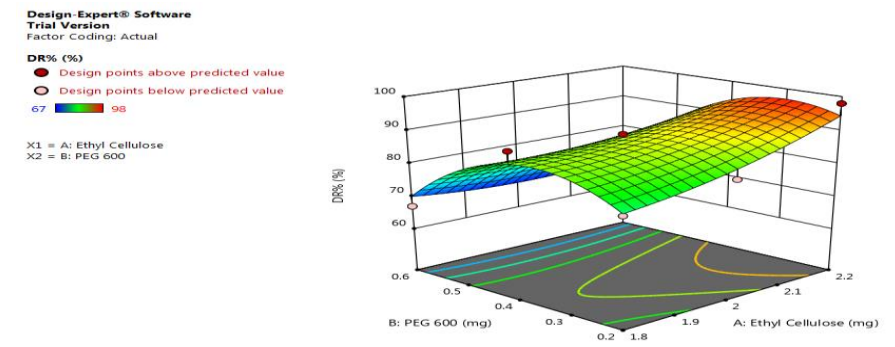



## ANOVA for Quadratic model

## Response 2: Particle Size

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| Model | 89.01 | 5 | 17.80 | 3.81 | 0.1500 | significant |
| A-Ethyl Cellulose | 0.1980 | 1 | 0.1980 | 0.0424 | 0.8500 | |
| B-PEG 600 | 79.35 | 1 | 79.35 | 16.99 | 0.0259 | |
| AB | 2.81 | 1 | 2.81 | 0.6007 | 0.4948 | |
| $A^2$ | 5.19 | 1 | 5.19 | 1.11 | 0.3690 | |
| $B^2$ | 1.46 | 1 | 1.46 | 0.3118 | 0.6155 | |



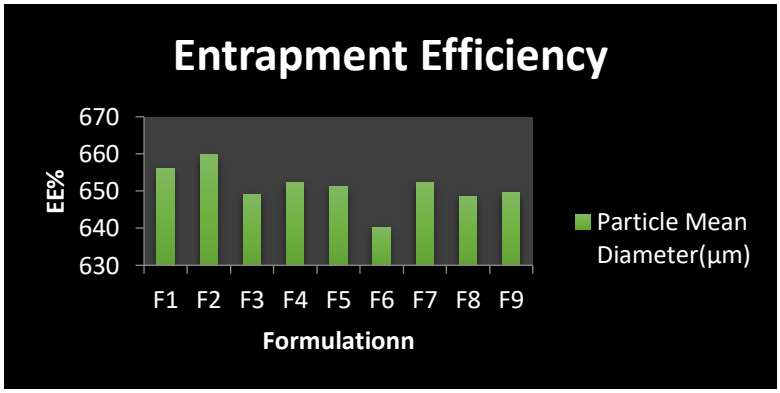
**ANOVA for Quadratic model**

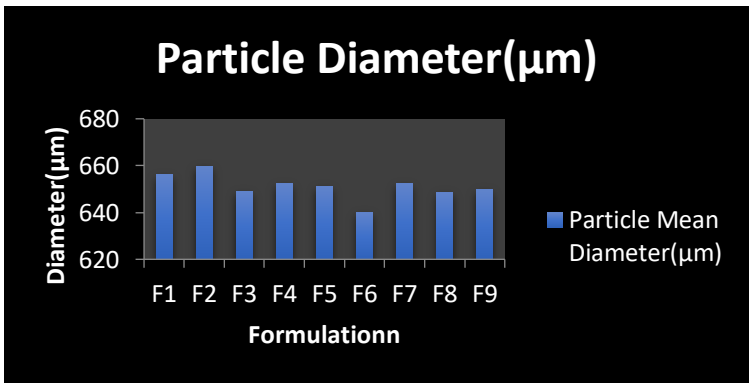
**Response 3: DR%**

| Source | Sum of Squares | df | Mean Square | F-value | p-value | |
|---|---|---|---|---|---|---|
| Model | 842.92 | 5 | 168.58 | 6.92 | 0.0711 | significant |
| A-Ethyl Cellulose | 80.67 | 1 | 80.67 | 3.31 | 0.1664 | |
| B-PEG 600 | 433.50 | 1 | 433.50 | 17.79 | 0.0243 | |
| AB | 56.25 | 1 | 56.25 | 2.31 | 0.2259 | |
| $A^2$ | 8.00 | 1 | 8.00 | 0.3284 | 0.6067 | |
| $B^2$ | 264.50 | 1 | 264.50 | 10.86 | 0.0459 | |

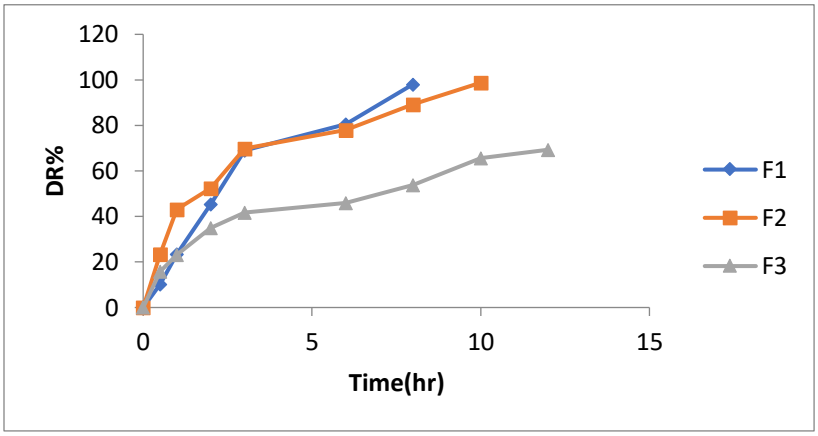
| Batch | Angle of Repose | Bulk density(gm/cm$^3$) | Tapped density(gm/cm$^3$) | Carr;s Index | Hausner ratio |
|---|---|---|---|---|---|
| F1 | 30.13±0.03 | 0.177±0.13 | 0.289±0.13 | 33.63±0.33 | 1.21 |
| F2 | 31.23±0.13 | 0.189±0.03 | 0.299±0.33 | 41.63±0.33 | 1.03 |
| F3 | 29.17±0.33 | 0.187±0.03 | 0.219±0.03 | 46.63±0.33 | 1.33 |
| F4 | 29.44±0.03 | 0.147±0.13 | 0.289±0.03 | 33.63±0.33 | 1.25 |
| F5 | 38.33±0.03 | 0.177±0.03 | 0.289±0.03 | 33.63±0.23 | 1.26 |
| F6 | 24.33±0.13 | 0.185±0.02 | 0.289±0.03 | 33.63±0.13 | 1.22 |
| F7 | 27.33±0.11 | 0.167±0.03 | 0.269±0.03 | 32.63±0.08 | 1.13 |
| F8 | 21.33±0.13 | 0.188±0.23 | 0.279±0.03 | 33.63±0.06 | 2.03 |
| F9 | 29.66±0.03 | 0.186±0.03 | 0.286±0.03 | 28.63±0.04 | 1.06 |

**Micromeritic Properties of different batches of Naproxen Microsphere**



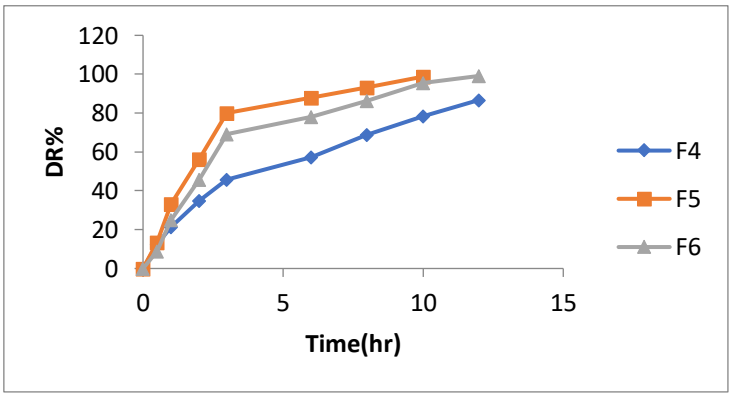



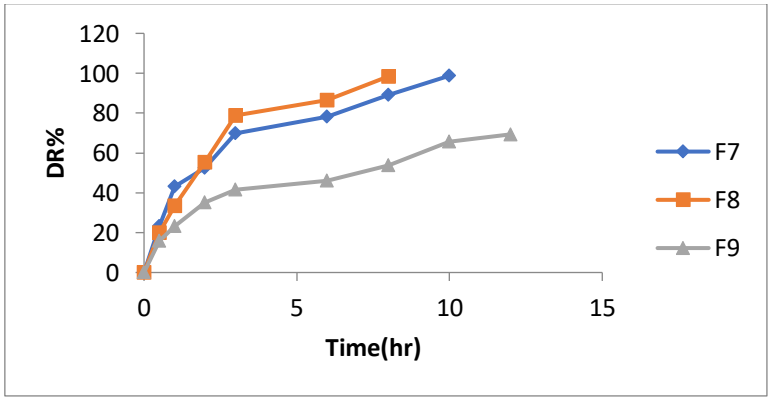
**_In-Vitro Release_ Profile of Naproxen Microsphere (F1-F3)**




| Time(h) | *In-Vitro* Release Profile(%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 0.5 | 10.12 | 23.33 | 15.77 | 12.33 | 13.33 | 8.98 | 23.33 | 20.12 | 15.77 |
| 1 | 23.43 | 43.12 | 23.11 | 21.33 | 33.12 | 25.12 | 43.12 | 33.43 | 23.11 |
| 2 | 45.31 | 52.33 | 34.99 | 34.77 | 56.33 | 45.77 | 52.33 | 55.31 | 34.99 |
| 3 | 68.90 | 69.95 | 41.66 | 45.87 | 79.95 | 69.13 | 69.95 | 78.90 | 41.66 |
| 6 | 80.66 | 78.10 | 45.99 | 57.32 | 88.10 | 78.13 | 78.10 | 86.66 | 45.99 |
| 8 | 98.11 | 89.13 | 53.86 | 68.98 | 93.13 | 86.13 | 89.13 | 98.41 | 53.86 |
| 10 | - | 98.77 | 65.66 | 78.42 | 98.77 | 95.44 | 98.77 | - | 65.66 |
| 12 | - | - | 69.33 | 86.77 | | 99.13 | | - | 69.33 |

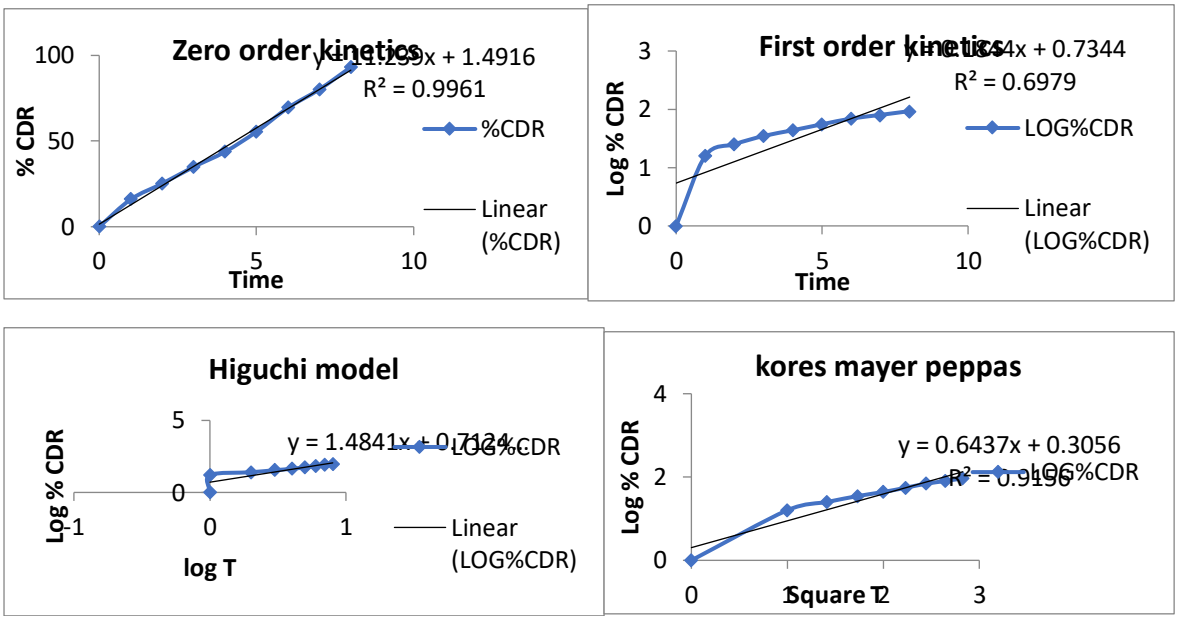
**_In-Vitro_ Release Profile of Naproxen Microsphere (F4-F6)**




**_In-Vitro_ Release Profile of Naproxen Microsphere (F7-F9)**

**RELEASE KINETICS OF NAPROXEN MICROSPHERE**




| TIME | %CDR | SQARE T | LOG T | LOG%CDR | ARA | LOG%ARA |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 15.96 | 1 | 0 | 1.203033 | 84.04 | 1.924486 |
| 2 | 25.17 | 1.414214 | 0.30103 | 1.400883 | 74.84 | 1.874134 |
| 3 | 34.91 | 1.732051 | 0.477121 | 1.54295 | 65.09 | 1.813514 |
| 4 | 43.75 | 2 | 0.60206 | 1.640978 | 56.25 | 1.750123 |
| 5 | 55.48 | 2.236068 | 0.69897 | 1.744136 | 44.52 | 1.648555 |
| 6 | 69.41 | 2.44949 | 0.778151 | 1.841422 | 30.59 | 1.485579 |
| 7 | 80.18 | 2.645751 | 0.845098 | 1.904066 | 19.82 | 1.297104 |
| 8 | 93.15 | 2.828427 | 0.90309 | 1.969183 | 6.85 | 0.835691 |

**Release kinetics Results**

Release kinetics was performed for the optimized batch. In vitro drug release of check point batch was best explained by zero order as the plot showed highest linearity. The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.Further, the mechanism of drug release fitted well with Hixon-crowell model, indicating sustain release mechanism. The plots and results of this study are shown in Figure

## CONCLUSION

Eudragit microspheres of tinidazole were successfullyprepared by emulsion solvent evaporation technique. Theresults shown in Table indicates that optimum concentrationof surfactant (1. 8 ml) and stirring speed (2000 rpm)showed higher percent of entrapment efficiency while changein stirring speed up to optimum range and change thesurfactant concentration up to optimum range change thepercent entrapment efficiency (Table 4).

## RFERENCES

1. Philip AK, Philip B. Colon targeted drug delivery system: a review on primary and novel approaches. Oman Med J.2010; 25(2):79-87.

2. ChourasiaMKandJainSK,"Pharmaceuticalapproachestocolontargeteddrugdelivery systems." *J. Pharm. Sci*. **2003**, 33-66.
3. Chourasia MK and Jain SK, "Potential of guar gum microspheres for target specific drug release to colon." *J. Drug Targeting*. **2004**, 12,435-442.
4. Vinay kumar KV, Siva kumar T and Tamizh mani T, "Colon targeting drug delivery system: A review on recent approaches" *Int. J. Pharm. Biomed. Sci.* **2011**, 2(1),11-19.
5. Choudhury P K, Panigrahi T K, Murthy P N, Tripathy N K, Behera S and Panigrahi R, "Novel Approaches and Developments in Colon Specific Drug Delivery Systems- A Review." *Webmed central com.* **2012**,1-20.
6. Shendge RS and Sayyad FJ, "Multiparticulate colon targeted drug delivery systems: Prospects and perspectives."*Inventi impact NDDS*, **2012**, Issue 1,12-16.
7. Asghar LFA and Chandran S, "Multiparticulate Formulation Approach to Colon Specific Drug Delivery: Current Perspectives." *J. Pharm. Pharmaceut. Sci.* **2006**, 9 (3),327-338.
8. Cook W, Quinn ME, Sheskey PJ, Pectin. In: Raymond RC, Sheskey PJ and Quinn ME, Handbook of pharmaceutical excipients, 6th Edn, Pharmaceutical press and American pharmaceutical association, London, 2009, pp478-479
9. Chang RK, Peng Y, Trivedi N, Polymethacrylates. In: Raymond RC, Sheskey PJ and Quinn ME, Handbook of pharmaceutical excipients, 6th Edn, Pharmaceutical press and American pharmaceutical association, London, 2009, pp525-533.
10. Pellett MA, Calcium chloride. In: Raymond RC, Sheskey PJ and Quinn ME, Handbook of pharmaceutical excipients, 6th Edn, Pharmaceutical press and American pharmaceutical association, London, 2009, pp89-90.
11. Yin Hsu F, Ding-Syuan Yu and Huang CC, "Development of pH-sensitive pectinate/alginate microspheres for colon drug delivery." *J. Mater. Sci: Mater. Med.***2012**.
12. Mennini N, Furlanetto S, Cirri M and Mura P, "Quality by design approach for developing chitosan-Ca-alginate microspheres for colon delivery of celecoxib-hydroxypropyl-þ-cyclodextrin-PVP complex." *Eur. J. Pharm. Biopharm*. 2012, 80,67–75.
13. Das S, Chaudhury A and Ka-Yun N, "Preparation and evaluation of zinc–pectin– chitosan composite particles for drug delivery to the colon: Role of chitosan in modifying in vitro and in vivo drug release." *Int. J. Pharm*. **2011**, 406,11–20.
14. Simi SP, Saraswathi R, Sankar C, Krisnan PN, Dilip C and Ameena K, "Formulation and evaluation of albendazole microcapsules for colon delivery using chitosan." *Asian Pacific J. Tropical Medicine*. **2010**,374-378.
15. Lucinda-Silva RM, Nunes Salgado HR and Evangelista RC, "Alginate–chitosan systems: *In-vitro* controlled release of triamcinolone and *in-vivo* gastrointestinal transit." *Carbo. Poly*. **2010**, 81,260–268.
16. Oliveira GF, Carvalhob LQ and Evangelista RC, "Chitosan–pectin multiparticulate systems associated with enteric polymers for colonic drug delivery." *Carbo. Poly*. **2010**, 82, 1004–1009.