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# Colon targeting xanthan gum microspheres of mesalamine for the treatment of ulcerative colitis and its kinetics

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Present work deals with the synthesis of small size microspheres by ionic gelation method using mesalamine as model drug for the treatment of Crohn's disease. Mesalamine loaded xanthan gum microsphere was effectively used for the colon-targeted as well as management of ulcerative colitis. Particle size study revealed that mesalamine loaded xanthan gum microspheres were of micron size. The optimized formulation F3 showed 80% maximum entrapment efficiency and the maximum drug release was found to be 90% within 24 h. It was revealed from the experimental results that ionic gelation based formulation for microspheres formation with controlled shape or size and sphere are effective in ulcerative colitis drug delivery. Kinetic release data of the prepared xanthan gum microspheres were studied with different kinetic models like first order, zero order, Korsmeyer and Higuchi, where Higuchi model was observed as best fit model. Which indicated that the drug release from mesalamine loaded xanthan gum microspheres was followed Fick's law of diffusion.

Keywords: Mesalamine, xanthan gum, *in vitro* drug release, kinetic model.

## Introduction

Oral medication characterizes one of the frontier areas of drug delivery systems. Such as dosage regimen treats normal concern which exists in region of patient obedience, cost-efficient management, good bioavailability and ideal drug delivery[1–3]. Colon specifically delivery systems have increased expanding consideration for the management of disease, for example Chrohn's disease, ulcerative colitis and irritable bowel syndrome. Ulcerative colitis is a kind of inflammatory bowel disease which affects the covering of more intestine or colon as well as rectum. Revised inflammation prompts congealing of the intestinal divider. Thoughtful contamination or death of colon tissue might be happen by extreme ailment[4–7]. In colonic delivery, a drug should be protected from absorption from the environment of the upper gastrointestinal tract (GIT) and after that it suddenly discharged into the proximal colon, which is viewed as the ideal site for colon-targeted delivery of drugs. Colon targeting is significant for the topical treatment of colon diseases e.g. colorectal cancer and amebiasis[8]. Mesalamine otherwise called mesalamine [5-aminosalicylic acid (ASA)] is the amino derivative of salicylic acid, this molecule has an amphoteric character due to the presence of the carboxyl and amino groups[9,10]. The oral administration of mesalamine altogether protects the intestinal mucosa and enhances mucosal permeation against injury in ulcerative colitis disease[11,12]. Mesalamine 5-ASA is a typical anti-inflammatory agents used for the management of ulcerative colitis and crohn's disease[13,14]. Mesalamine is preconized for the treatment of gentle to direct dynamic ulcerative colitis; it is a strong inhibitor of cyclooxygenase, which prompts the lessening of the production of prostaglandin E2 delivered amid intestinal aggravation. It obstruct the way of lipoxygenase, which will prompt hindrance of the generation of hydro-peroxy-

eicosatetrienoïc acid and leukotriene B4. Its effectiveness as an anti-inflammatory agent is possibly because of its impact on the metabolism of leukotrienes[15,17]. Different drug formulations have been created with a specific end goal to upgrade the drug effectiveness and to accomplish the drug controlling and targeting, these details particularly utilize a pH- dependent release mechanism[18–20]. In the current study effort has been made to develop mesalamine drug microspheres through ionic gelation technique by xanthan gum as natural polymer and cross-linking agent such as glutaraldehyde (GLA). The natural gelling property of xanthan gum the arrival of the release from the dosage regimen susceptible to degradation in the colonic condition[21,22]. Xanthan gum is used as an excipients in different pharmaceutical industries[23,24].

Present work deals with the synthesis of small size microspheres by ionic gelation method using mesalamine as model drug for the treatment of Crohn's disease. The dispersion medium was stirred using electrical magnetic stirrer. The stirring of dispersion were constantly for 3 h and prepared xanthan gum microspheres were centrifuged by centrifuge machine and washed twice with solvent such as hexane, which are used to remove oily phase from the containing solution and customized mesalamine drug loaded xanthan gum and evaluated by several variables process to optimize the best formulation from the prepared microspheres in the expressions of entrapment efficiency, particle size. Initially drug release profile was determined in various physiological salt solution to demonstrate the prospective of mesalamine xanthan gum microspheres act as colon specific controlled delivery system[25,26].

## Materials and methods

*Materials:*

The materials used were mesalamine (5-aminosalicylic acid) was purchased from Balaji Drugs, Gujarat, India. Xanthan gum was purchased from HI Media Laboratories Pvt. Ltd. Mumbai, India. Tween-60 were procured from QualiKems, glutaraldehyde (25% aqueous solution) and hexane was procured from Nice. All reagents used were of analytical grade.

*Method for preparation of mesalamine xanthan gum microspheres:*

Mesalamine loaded xanthan gum microspheres were prepared through ionic gelation technique. An aqueous dispersion containing xanthan gum was dispersed in a specified volume of deionized water. Accurately weighed 10 mg of mesalamine was dissolved in 1 mL (10% v/v HCl) and 10 mL of deionized water, both solutions were sonicated separately for 25 min. This solution was added drop wise in 10 mL quantity of castor oil and 3 ml of Tween-60 by using an electrical mechanical stirrer and pH was adjusted by 1 *M* NaOH solution. After mixing GLA was added to the dispersion and the final solution was homogenized at 8000 rpm for 4 h at 51± 1°C. The mesalamine loaded polymeric gum microspheres were collectively formed by sedimentation through decantation of oil. Oil containing microsphere were washed several times with hexane to remove traces of oil[14,27,28].

*Drug saturation solubility:*

Drug saturation solubility study was carried out by taking a large amount of mesalamine drug in the vial containing 20 mL of deionized water. The vial was kept for 24 h at room temperature, whereas the amount of the drug was dissolved and analyzed after 24 h using UV spectrophotometer at range 303 nanometer (nm)[29–31].

*pH Determination:*

The pH of xanthan gum was performed by digital pH meter. It was found to be 7.5. Xanthan gum is well known for maximum viscosity at a neutral pH. This helps in there trad-

**Table 1.** Microsphere formulation composition

| Formulation code | Mesalamine (mg) | Xanthan gum (mg) | Castor oil (mL) | Tween-60 (mL) | GLA (mL) | Water (mL)(qst) |
|---|---|---|---|---|---|---|
| F1 | 10 | 20 | 8 | 2 | 5 | 20 |
| F2 | 10 | 10 | 8.5 | 1.5 | 5 | 20 |
| F3 | 10 | 30 | 9 | 1 | 5 | 20 |
| F4 | 10 | 30 | 8 | 2 | 5 | 20 |
| F5 | 10 | 20 | 8.5 | 1.5 | 5 | 20 |

ing impact for the improvement of sustained release formulation. Neutral pH causes lowest irritation to gastrointestinal tract[32].

**Characterization and evaluation of microsphere**

*Particle size determination by master sizer:*

The prepared particle size was determined by master sizer (Master sizer 2000; Malvern instruments corp, UK). The analysis was determined at scattered angle at 90 or temperature at 25°C by sample suitably diluted by with filtered distilled water.

*Zeta potential determination:*

Zeta potential was also measured by using (Delsa Nano™ Common, Beckman Coulter) under the same conditions. Previously the samples were kept in low conductivity zeta cell in order to meet the instrumental conditions and then the reading was taken[33].

*Drug entrapment efficiency:*

The entrapment efficiency of prepared microsphere was determined by using an indirect entrapment technique. The xanthan gum microspheres suspension was centrifuged for 20 min at 6000 revolution per minutes. 10.0 mg of microspheres was suspended in 10 mL of the solution (0.5 mL 0.1 *N* HCl + 9.5 mL PBS) and centrifuged for 15 min at 6000 rpm. The suspension was then filtered and the absorbance was determined using UV-Vis double beam spectrophotometer at 303 nm. The calculation was determined the amount of drug present in the supernatant[34]. The following formula was use for determination of entrapment efficiency (EE%) of drug.

$$EE\% = \frac{\text{(Total amount of drug – Drug left in supernatant)}}{\text{Total amount of drug}} \times 100$$

***In vitro* drug release study performed by dialysis membrane**

*Preparation of dialysis membrane:*

The dialysis bag membrane (mol. wt. 12000 KD) was soaked 24 h in a buffer solution so as to open the pores of the membrane. After the period of 24 h dialysis membrane bag was taken out. It was used in the *in vitro* drug release study.

*Determination of in vitro drug release of mesalamine:*

A prepared dialysis membrane bag was used for drug release from the xanthan gum microspheres. Mesalamine loaded microspheres were then introduced in dialysis bag. Dialysis membrane bag retain prepared microspheres, which allow the free drug in dissolution media. The equivalent amount of 50 mg of mesalamine containing microsphere were occupied in the dialysis bag. The other end of dialysis bag was fixed through thread. The bag was kept in the beaker containing 250 to 500 mL of getting phase as a media. The system was retained under electrical magnetic stirring condition at 50 rpm. Samples of formulations were withdrawn from each medium at predetermined at the time intervals replacing with same volume of respective medium. The sample was analyzed by UV-Vis spectrophotometer at 303 nm. All the drug release studied was carried out in triplicate.

*Kinetic release model:*

The mathematical models were used to determine the kinetics of drug release from drug delivery systems, which was describe the dissolution profile[35–37]. When a suitable model has been chosen then the dissolution profiles are estimated depending upon the determined model of different parameters.

*Zero order kinetics:*

This model signifies to a perfect release profile so as to attain the pharmacological prolonged activity. Drug dissolution profile from dosage forms regimen that do not disaggregate. The drug was discharge slowly that can be expressed as follow[37–39]:

$$Q_t = Q_o + K_{ot}$$

where $Q_t$ is the amount of drug dissolved in time $t$, $Q_o$ is the initial amount of drug in the solution and $K_o$ is the zero order release constant, for practical purpose the equation is rearranged:

$$\text{Percent drug released} = K_t$$

*Higuchi model:*

This model is based on the drug release as a diffusion process based in Fick's law, square root dependent. The following equation is used to express the model:

$$Q_t = K_{ht}^{1/2}$$

where $Q_t$ is the amount of drug dissolved in time $t$, $K_h$ is the first order release constant.

The equation is rearranged for practical purpose:

Percent drug released = $K_t^{1/2}$

*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 following equation is used to express the model:

$\log Q_t = \log Q_0 + K_t/2.303$

where $Q_t$ is the amount of drug dissolved in time $t$, $Q_0$ is the initial amount of drug in the solution and $K$ is the first order release constant. The equation is rearranged for practical purpose and is represented as:

log % of drug unreleased = $K_t/2.303$

*Korsmeyer-Peppas model:*

This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

The following equation is used to express the model:

$Q_t/Q_\infty = K_{tn}$

where $Q_t$ is the amount of drug dissolved in time $t$ and $Q_\infty$ is the amount of drug dissolved in infinite time, $n$ is the release exponent indicative of drug release mechanism and $K$ is the kinetic constant.

The equation is rearranged

log percent drug released = log $K$ + $n$ log $t$

Peppas used $n$ value in order to characterize different release mechanism. The values $n$ = 0.5 implies Fickian diffusion and if the value of $n$ lies in between 0.5 to 1.0, then it correspond for anomalous transport (corresponds to diffusion, erosion and swelling mechanism or mixed order kinetics) and if the value is higher than 1, then it implies case-II diffusion mechanism[40].

## Results and discussion

*Determination of $\lambda_{max}$ by UV spectroscopy:*

The standard solution of mesalamine drug in 0.1 *N* HCl, pH 6.8 and 7.4 Phosphate buffer saline was prepared. In which drug (10 μg/ml) was scanned 200–400 nm through double beam UV-Visible spectrophotometer (UV-1800). The $\lambda_{max}$ of drug was found to be 303 nm.

*Melting point:*

The melting point of mesalamine drug was found to be in the average range of 282–283°C, which is in accordance with standard value.

*Fourier transformed infrared spectroscopy (FTIR):*

The FTIR absorption spectrum of the pure mesalamine drug was taken in the range of 4000–400 $cm^{-1}$ using KBr pellet method. A broad peak at 2976.52 $cm^{-1}$ was found in the spectrum, indicating the C-H stretching of the aromatic group and the peak observed at the 1194.90 $cm^{-1}$ indicate the presence of C-O group. The major peaks of drugs were described for evaluation of purity.

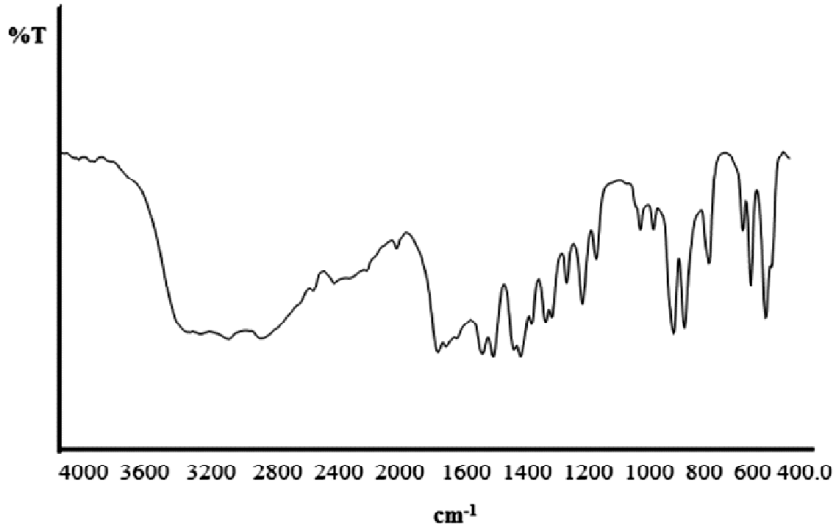



**Fig. 1.** FTIR spectrum of mesalamine.

**Table 2.** Interpretation of FTIR spectra of mesalamine

| Sr. No. | Functional group | Peaks observed ($cm^{-1}$) |
|---|---|---|
| 1. | C=C stretch of the aromatic group; N-H bond scissoring | 1621.24 |
| 2. | C-H stretch of the aromatic group | 2976.52 |
| 3. | C-C stretching mode | 1487.79 |
| 4. | O-H deformation of the hydroxyl groups | 1582, 1487, 1450 |
| 5. | C-O stretching mode | 1194.90 |
| 6. | In-plane bending mode | 1192.24–1265.96 |
| 7. | C-H bond out-of-plane bending mode; Ring deformation of the aromatic group | 685.01 |

*X-Ray diffraction study (XRD):*

XRD was employed with an intention to confirm the characteristics of pure drug. The sharp and intense peaks were observed in the XRD pattern of mesalamine at 15° and 18° asshown in Fig. 2, this confirmed the presence of crystalline nature of pure drug when it is compared with standard.

*Determination of zeta potential measurement:*

Analysis of zeta potential of the formulation was performed by Beckman coulter. The best fit prepared formulation was identified through the Delsanano was analyzed for zeta potential. A higher value of zeta potential results in greater electrostatic repulsion between the particles thus minimizing aggregation/flocculation. The observe value of particle surface charge revealed the stability of micro suspension at microscopic stage of zeta potential of mesalamineis –21.11 (mV).

*Determination of particle size by master sizer:*

The best optimized F3 formulation was analyzed under master sizer for different particle size parameter distribution width (nm) (D10 – 164, $D_{50}$ – 2608, $D_{90}$ – 7.699), mean particle size (MPS) is 926.3, specific surface area (SA) ($m^2g$) is 15 and span is 2.506. The results were presented in the Fig. 4.

*Determinationof entrapment efficiency of formulation:*

The entrapment efficiency of formulations were determined by triplicate method and demonstrated through appropriate procedures. The percentage entrapment efficiency of formulation was found to be lowest in F1 which is 64±0.98 and the highest was found to be within F3 i.e. 80±1.06.

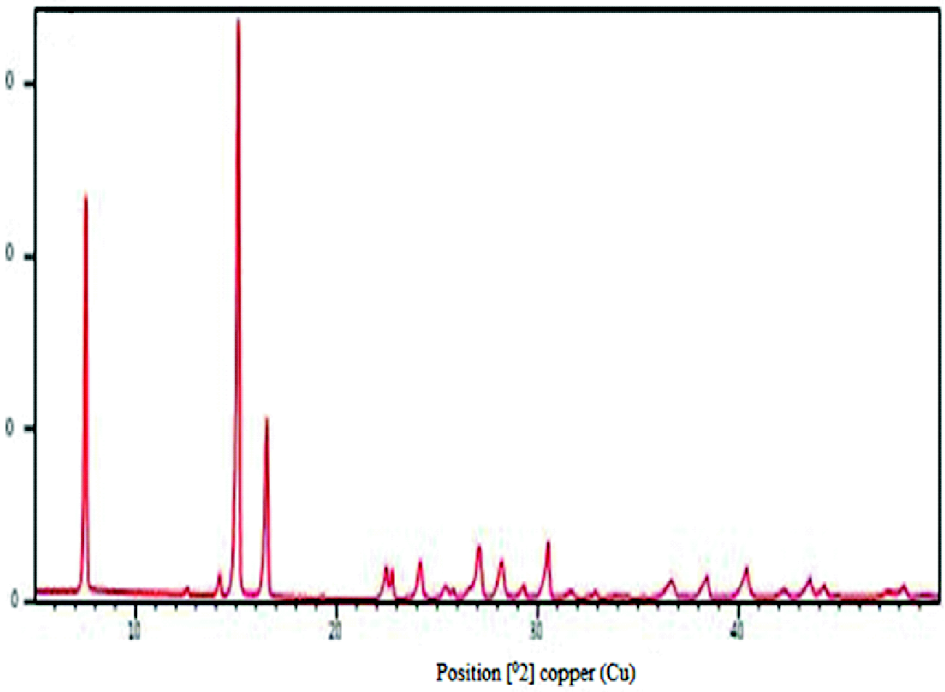



**Fig. 2.** XRD of mesalamine.

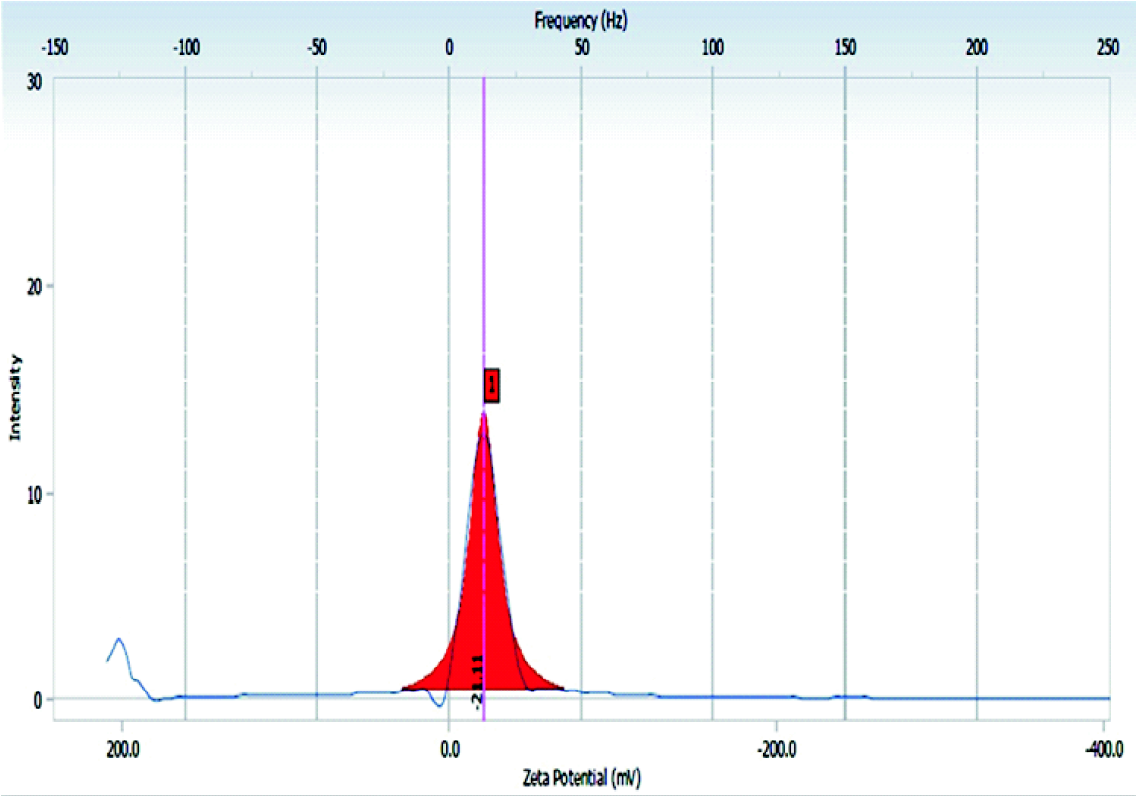



**Fig. 3.** Zeta potential of mesalamine.

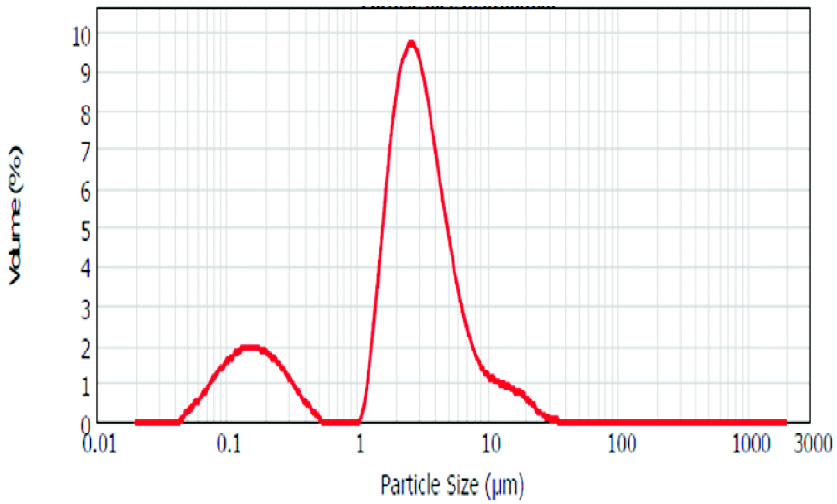



**Fig. 4.** Particle size of mesalamine.

*In vitro drug release from mesalamine loaded microspheres at different pH:*

Release studies were performed by various buffers saline like 0.1 *N* HCl (1.2 pH), 6.8 phosphate buffer saline and 7.4 phosphate buffer to midiron the GI conditions of colon, stomach or intestine respectively. The release results were

**Table 3.** Drug entrapment efficiency of mesalamine microspheres

| Sr. no. | Formulation code | Entrapment efficiency percentage |
|---|---|---|
| 1. | F1 | 64±0.98 |
| 2. | F2 | 71±1.47 |
| 3. | F3 | 80±1.06 |
| 4. | F4 | 68±0.85 |
| 5. | F5 | 75±1.04 |

obtained between percentages of cumulative drug release vs time (hours) which is shown in Fig. 6a. It was clear from the results that drug release was increased with increase in time and the maximum drug release occurred in F3 formulation. Drug release was studied at different pH and it was found from the results that (Fig. 6b) drug release was in-

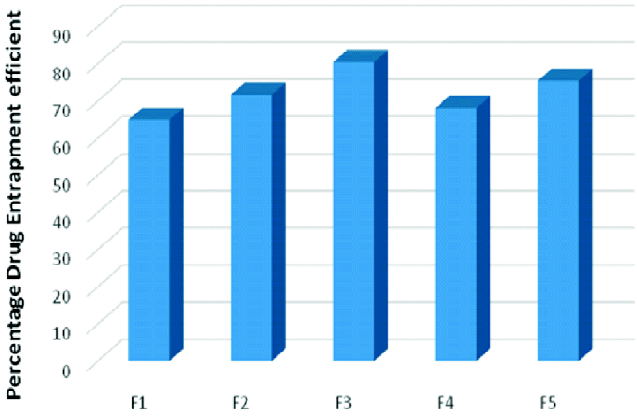
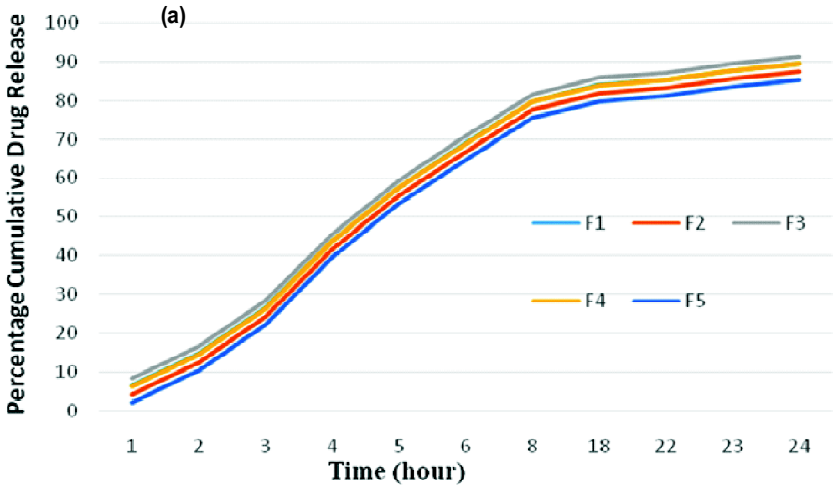



**Fig. 5.** Entrapment efficiency (EE) of mesalamine.



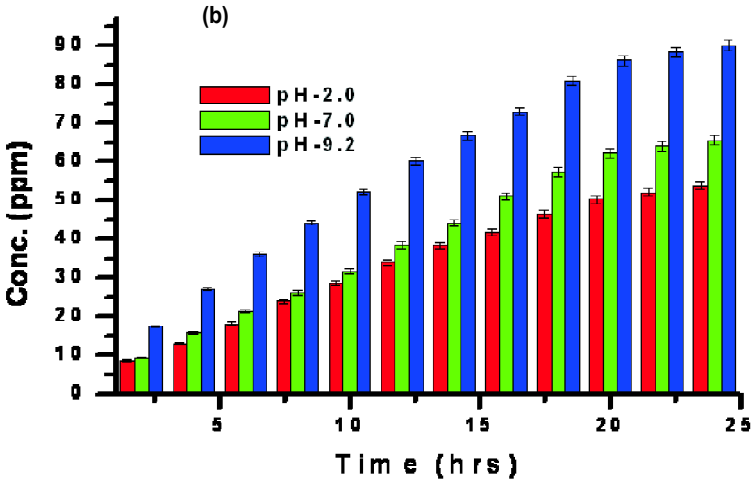




**Fig. 6.** *In vitro* drug release profile of mesalamine loaded microspheres at different (**a**) time and (**b**) pH.

creased with increase in pH and maximum drug release occurred at alkaline medium. This can be explained on the basis that at acidic pH are contracted due to absence of electrostatic repulsive forces, but as the pH increased to alkaline condition the carboxylate groups are ionized, which increases the repulsive forces, this leads to increase in the swelling capacity, thus increased the drug release rate from synthesized xanthan gum microspheres. This specifies that synthesized device is effective for colon targeting of the drug release for the treatment of ulcerative colitis.

*Kinetic release model:*

The formulations were studied by fitting the drug release time profile with the various equations such as zero order, first order, Higuchi and Korsmeyer-Peppas model.

*Zero order kinetics:*

The release kinetics data indicates that the prepared microsphere showed dissolution based release profile, that is, drug from optimized batch follows zero order ($r^2$ = 0.92) (Fig. 7) and show the osmotic systems.

*Higuchi model:*

The release kinetics data indicates that the prepared microsphere showed diffusion based release profile, that is, Higuchi kinetics ($r^2$ = 0.99) (Fig. 8). The overall release of drug from optimized batch follows Higuchi model, having correlation coefficient 0.96.

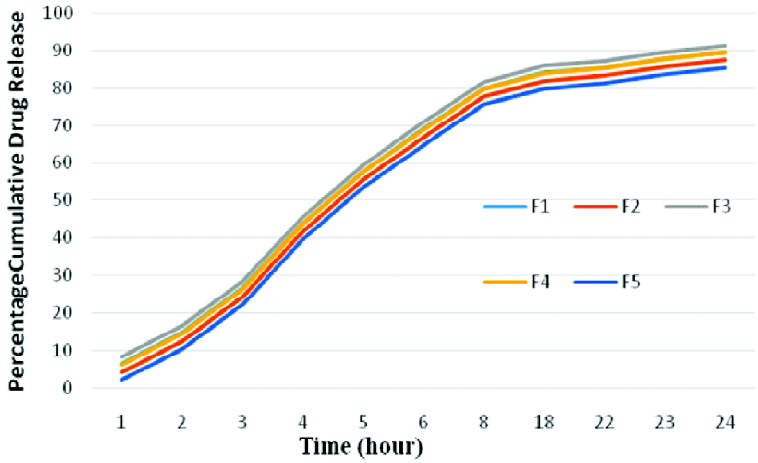



**Fig. 7.** Zero order release profile of mesalamine loaded microspheres.

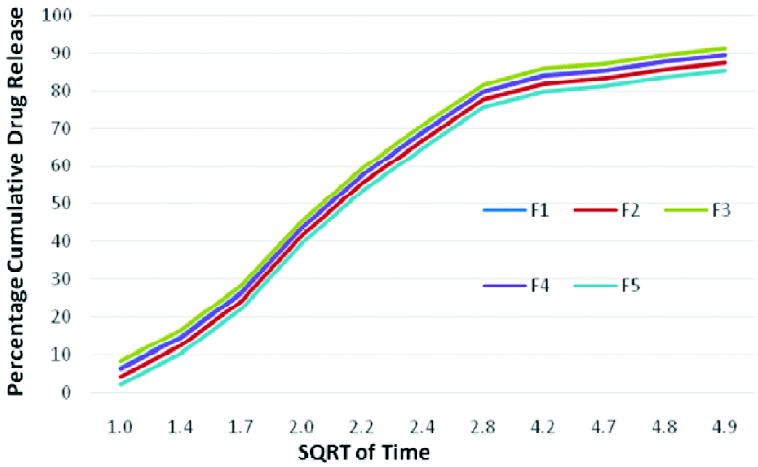



**Fig. 8.** Higuchi release profile of mesalamine loaded microsphere.

*First order kinetics:*

From the first order release data indicate that the prepared microsphere showed dissolution based release profile is first order (($r^2$ = 0.99) (Fig. 9) and shows drugs is in porous matrices[41].

*Korsmeyer-Peppas model:*

In this release data showed that the prepared microsphere showed dissolution based release profile, that is, drug from optimized batch follows Korsmeyer-Peppas ($r^2$ = 0.78) model (Fig. 10).

## Discussion

Mesalamine loaded xanthan gum microsphere were developed by ionic gelation technique. All formulated batches were preliminarily evaluated by different method. Results enclosed the preparation of microspheres with controllable shape or size and sphere and effective in delivery of colon targeted for ulcerative colitis. The optimized formulation of microspheres F3 showed maximum 80% entrapment efficiency, whereas maximum drug release was found to be 90% within 24 h. The drug release mechanism of the mesalamine from prepared microspheres remained showed Fick's diffusion.

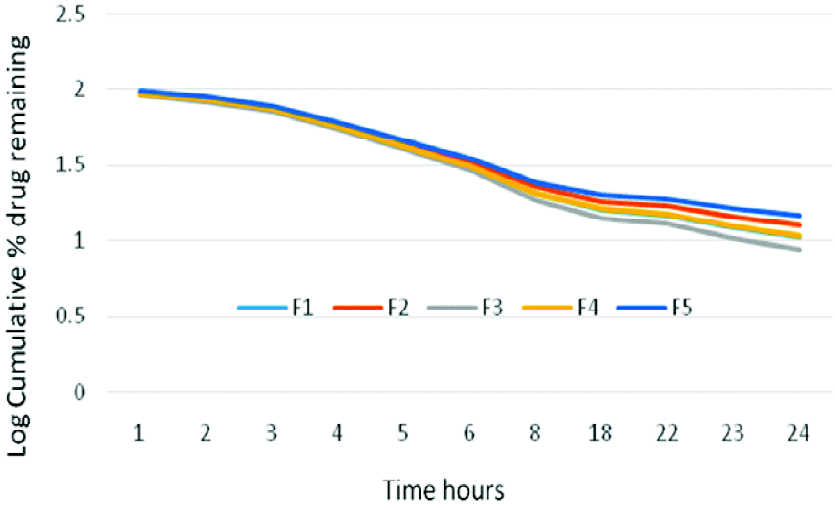



**Fig. 9.** First order release profile of mesalamine loaded microsphere.

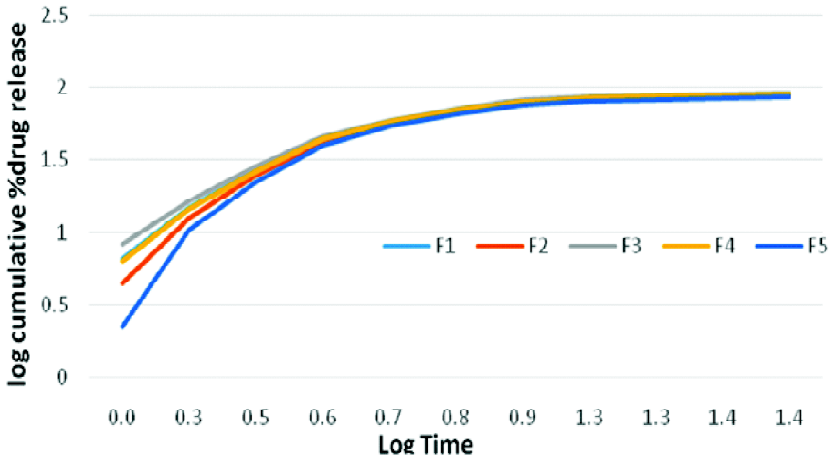



**Fig. 10.** Kors-Peppas release profile of mesalamine loaded microsphere.

**Table 4.** Kinetic release mechanisms from mesalamine loaded microspheres

| Formula code | Zero order plot Regression coefficients ($r^2$) | First order plot Regression coefficients ($r^2$) | Higuchi's plot Regression coefficients ($r^2$) | Koresmeyer-Peppa's plot Regression coefficients ($r^2$) |
|---|---|---|---|---|
| F1 | 0.90 | 0.97 | 0.99 | 0.77 |
| F2 | 0.89 | 0.96 | 0.92 | 0.75 |
| F3 | 0.92 | 0.95 | 0.96 | 078 |
| F4 | 0.91 | 0.93 | 0.91 | 0.75 |
| F5 | 0.90 | 0.95 | 0.92 | 0.70 |

## Conclusion

The present experimental studied was an effort to improvement of reconstituted microsphere of upper gastrointestinal tract and drug release at target site. The prepared microspheres were of particle size distribution, having micron size, glossy surface, controlled drug release and good entrapment efficiency. The formulated microspheres might be used as a good carrier for controlled release of drug, appropriate for colonic release of mesalamine resisting release in gastrointestinal medium. They showed maximum release in colonic region and may offer a new avenue of research.

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