ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Development and evaluation of colon targeted delivery of budesonide polymeric nanoparticles for colitis therapy

Shrikrishna D Gite*[1], Kishor S Salunkhe[2], Ravindra B Chintamani[1], Shubhangi S G[3]

[1]Research Scholar, Amrutvahini College of Pharmacy, Sangamner, Maharashtra, India
[2]Department of Pharmaceutics, Sanjivani College of Pharmaceutical Education and Research, Kopargaon, Maharashtra, India
[3]Department of Pharmaceutics, Vidyabharati College of Pharmacy, Amravati, Maharashtra, India

Article History:

Received on: 06 Dec 2019
Revised on: 30 Jan 2020
Accepted on: 08 Feb 2020

Keywords:

Budesonide,
Capsule,
Eudragit S100,
Colitis,
Nanoparticles

ABSTRACT

Targeted delivery of the drug at site of action in case of Inflammatory Bowel Disease like colitis is the big challenge for formulators. The case where conventional drug delivery fails in severe stages of Inflammatory Bowel Disease, Nanoparticles is a good dosage form to targeted inflammatory site. The idea of this research was to prepare Nanoparticles with polymer Eudragit S100 and Surfactant Poloxamer containing Budesonide which finally filled in capsules providing immediate release at the ileocecal site, the most affected area in IBD i.e. pH dependent release. Nanoparticles are prepared by nano precipatation technique. Budesonide was used as a drug because of its therapeutic potential for in IBD. This study compares the different ratios of drug to olymer and drug to surfactant with optimized solvent and anti-solvent concentration in preparation of Nanoparticles. Optimized formulation ratio of drug to polymer was 1:2 and drug to surfactant was 1:1. The optimized batch of nanoparticles was filled in capsule and was evaluated for in-vitro studies.

*Corresponding Author

Name: Shrikrishna D Gite
Phone: +91-8830691436
Email: gitesd.pharma@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i2.2187

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

Major population worldwide is getting affected by Inflammatory Bowel Disease (IBD) and the prevalence of the disease is increasing day by day (Xavier and Podolsky, 2007). This colitis (inflammation of colon) etiology and pathogenesis are not completely understood. Symptoms of IBD like ulceration, bloody diarrhoea, weight loss and which further lead to complete obstruction of the gastrointestinal (GI) tract, affect very badly on day today life of people (Frank *et al.*, 2007). Most accepted move towards treating IBD and to reduce the need for surgeries and hospitalizations is by facilitating mucosal healing; induce remission of outbreaks (Xiao *et al.*, 2014). Systemic corticosteroids and mesalazine are used to treat Symptoms of mild-to-moderate IBD (Colombel *et al.*, 2010). These drugs mentioned above are preferred in many cases of pharmacotherapy for colon inflammation consisting of permanent administration of either of drug. It is necessary to take in consideration the quality and severity of adverse effects of these therapeutic regimens. For successful IBD treatment, it is necessary to involve innovative strategies for exact and adequate drug delivery to the inflammed colon for a long-lasting period in a sustained manner to minimize the risk of systemic adverse effects (Lautenschläger *et al.*, 2014). For efficient treatment of colonic disorder, colon precise drug delivery is necessary. Nowadays, it is more complicated to tar-

get drug delivery to colon, so new techniques like nanotechnology are emerging out. Nanotechnology is used to aim description, manufacture and application of structure, having nanometer size scale. According to the direction of International System of Units (SI) nanotechnology is typically measured in nanometers scale of 1 billionth of a meter referred as the "tiny science". Minute size molecules and particle act in a different way, as an intact unit in requisites to provide a variety of advantages. Nanoparticles (NPs) are distinct particles of size 1 and 100 nanometres drug transporter.

The drug is attached to a Nanoparticles matrix. Nanospheres and nanocapsules collectively called as nanoparticles. In nanocapsules drug is restricted to a cavity which is enclosed by a distinct polymer membrane, and in nanospheres consist of matrix systems in which the drug is physically and uniformly dispersed. Where conventional techniques reach their limits, nanotechnology provides opportunities for the medical applications (Hua *et al.*, 2015). For colon specific drug delivery, now a days we can make use of Eudragit polymers (RS100, L100 and S100) or cellulose acetate phthalate, which are soluble at or above pH 7, or dissolving at pH 6 respectively. In the current study, we used Eudragit S100 to manufacture micro carriers for a definite colon release of Budesonide. Eudragit, RS100 and RL100 are copolymers based on acrylic and methacrylic acid esters, which has a low level of quaternary ammonium group. As compared to Eudragit -RL (8.8-12% Ammonium groups) Eudragit -RS has a lesser content of charged groups (4.5-6.8%), due to which it is less permeable to water. Due to insolubility at physiological pH the co-polymers will swell form permeable film which will facilitate to manufacture sustained release formulation (Kadian and Harikumar, 2009; Paharia *et al.*, 2007) drag it is used in various studies for colon targeting since low content in ammonium group permitting a low solubility in gastric fluid.

MATERIALS AND METHODS

Materials

Budesonide was obtained from Wockhardt Ltd. Aurangabad. Eudragit S100 was obtained from Evonik Pvt. Ltd. Poloxamer from Mody Chemi-Pharma. Ethanol and Methanol were obtained from Fisher Scientific Pvt. Ltd. Acetone from Fisher Scientific Pvt. Ltd. Hydrochloric Acid from Benzer multitech Pvt. Ltd. Tribasic Sodium Phosphate and Sodium Hydroxide from Merck Specialities Pvt. Ltd. All other raw materials used were of pharmaceutical grade.

Method

Pre-formulation

Preformulation parameters like Oraganoleptic properties, Solubility, Melting point for drug and excipients was determined. Compatibility between drug and excipient was determined using FT-IR spectroscopy. DSC was performed to check thermal properties of the drug.

Infra-Red spectra

Infra-Red spectrum of Budesonide

IR spectra of Budesonide were taken on IR spectrophotometer by simply placing small amount of drug in powder form on selenium bromide crystal. In a spectrum, peaks were found at 3497.81 for O-H stretching, 2942.03 for C-H stretching.cm^{-1}. IR spectrum of Budesonide was found as given in Figure 1.

The Budesonide pure drug shows functional peaks at 1719.22 cm^{-1} hence the (-C=O group) confirmed and at 1618.20, 1242.31, 1237.91, 1068.48cm^{-1}) shows functional group Ethylene (C=C), carbon-carbon (C-C) Bending, Ether (C-O-C) Bending, Argon (Ar-O-R) Stretching. On the basis of above frequency conclude that Budesonide as a pure drug.

FT-IR spectra of Eudragit S100

FT-IR spectra are used for functional group identification in compound. A small amount of Eudragit S100 in the form of powder was placed on selenium bromide crystal and spectrum was run. The Infra-Red spectra of Eudragit S100 are as depicted in Figure 2.

The IR peaks of Eudragit S100 were compared with standard graph of Eudragit S100 and found to be similar.

FT-IR spectra of Poloxamer

A small amount of Poloxamer in the form of powder was placed on selenium bromide crystal and spectrum was run. The Infra-Red spectra of Poloxamer are depicted in Figure 3.

Infra-Red peaks for Poloxamer were compared with standard graph of Poloxamer and found to be similar.

DSC analysis

The DSC thermogram of Budesonide was obtained to evaluate the thermal behaviour of pure drug in as given in Figure 4. Differential Scanning Colorimetric is a thermo-analytical techniques. A calorimeter gives endothermic and exothermic peaks which indicate heat into or out of test sample of DSC thermograms of Budesonide. Changes in the shape of the

Table 1: Drug excipient ratio for compatibility study

Drug + Excipient	Ratio	Total Weight (mg)
Budesonide + Eudragit S100	1:1	20
Budesonide + Poloxamer	1:1	20

Table 2: Compatibility study of drug-Excipient mixture

Days	Compatibility results after 14 day study
Drug + Eudragit S100	Drug is compatible with Eudragit S100
Drug + Poloxamer	Drug is compatible with Poloxamer

Table 3: Design of Trial Batches

Batcl	Drug (mg) Budesonide	Polymer (mg) ES100	Surfactant (mg) Poloxamer	Solvent (ml) Ethanol	Anti-solvent (ml) Water	Result
F1	50	100	50	15	30	Particles formed
F2	50	75	50	15	30	Particles not formed
F3	50	50	50	15	30	Particles not formed
F4	50	100	30	15	30	Particles formed
F5	50	75	30	15	30	Particles not formed
F6	50	50	30	15	30	Particles not formed
F7	50	100	50	15	15	Particles formed
F8	50	75	50	15	15	Particles not formed
F9	50	50	50	15	15	Particles not formed
F10	50	100	30	15	15	Particles not formed
F11	50	75	30	15	15	Particles not formed
F12	50	50	30	15	15	Particles not formed

peak, shift of peak, absence of endothermic and/or exothermic peaks, generation of new peak shows there is interaction.

Differential Scanning Colorimetric (DSC) was carried out on pure Budesonide. DSC is performed and scan was recorded by keeping parameters like heating rate of 10ºC/min and window kept for temperature was 30 º-300ºC. In this scan reference used was empty standard aluminium pan.

The DSC peak of Budesonide shows sharp endothermic peak onsets from 259.14 and ends at 262.corresponds to standard DSC thermogram of Budesonide.

Compatibility by FT-IR Study

It is necessary to study the compatibility of the excipient with drug. Here drug and excipient is compatible or not was determined with the help of IR spectroscopy. The relative amount of drug and excipient is as given in Table 1.

The compatibility study was performed at the temperature of 55°C ±2°C and duration for study was

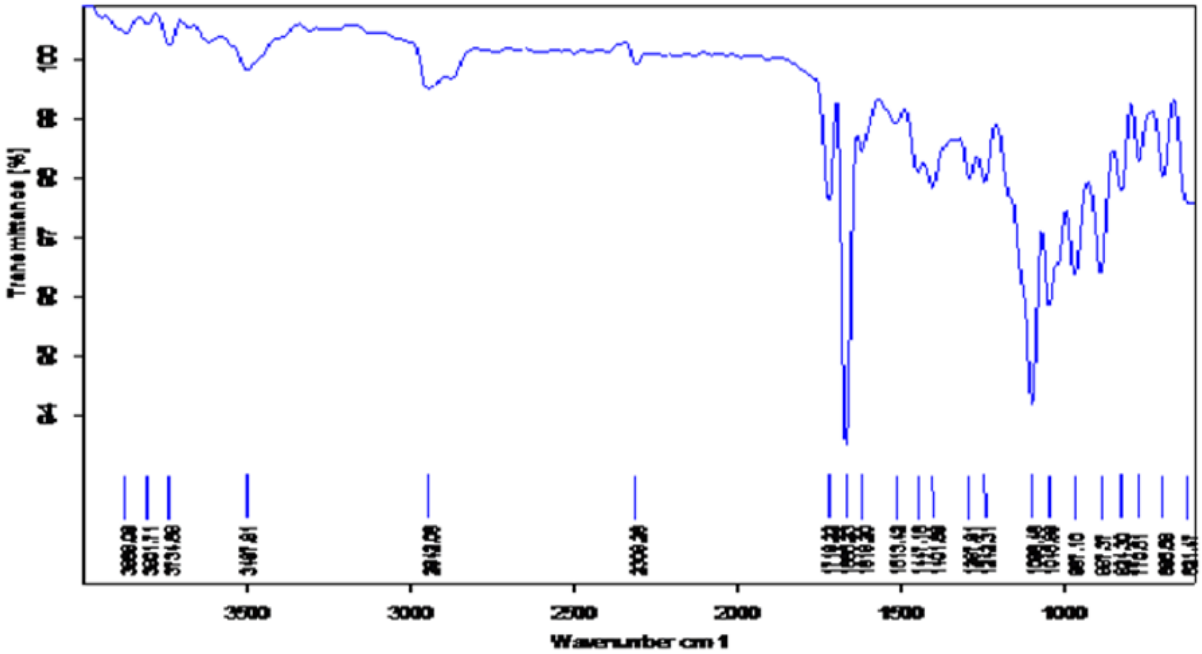

Figure 1: Infra-Redspectrum of Budesonide

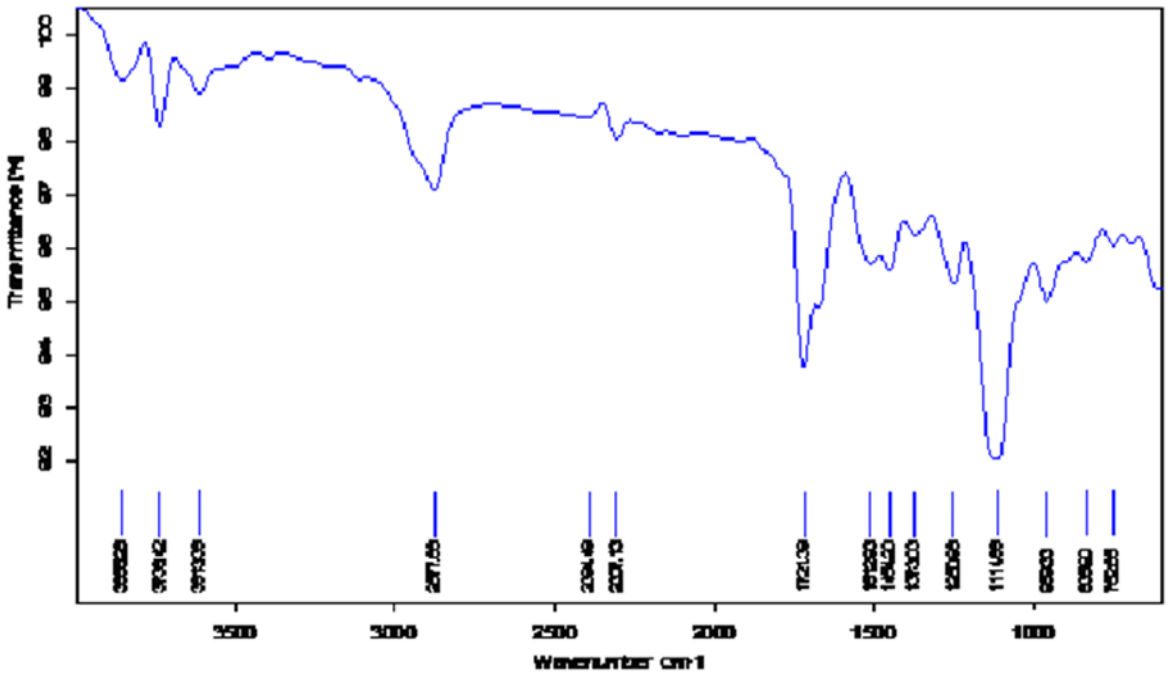

Figure 2: FT-IR of E S100

14 days. Individual drug and Drug: Excipient (as ratio 1:1) was kept in vial which was sealed properly. IR scan were taken for drug, polymer and surfactant prior to initiation of study and these raw materials were kept in vials for the ratio and duration as mentioned above. These glass containers were checked for tests like liquefaction, gas formation, caking and colour change if any. IR scan was taken at last after 14 days of study, spectra given in below Figures 5 and 6.

Both physical and chemical Compatibility study was carried out in the absence of moisture at 40º C in hot air oven for 14 days and found it compatible.

Infra-Red spectrum of mixture

Infra-Red spectrum of Drug+ Eudragit and Drug+ Poloxamer are as given in Figures 5 and 6 respectively.

Drug + Eudragit S100

Drug+Poloxamer

The drug-excipient mixtures were observed for

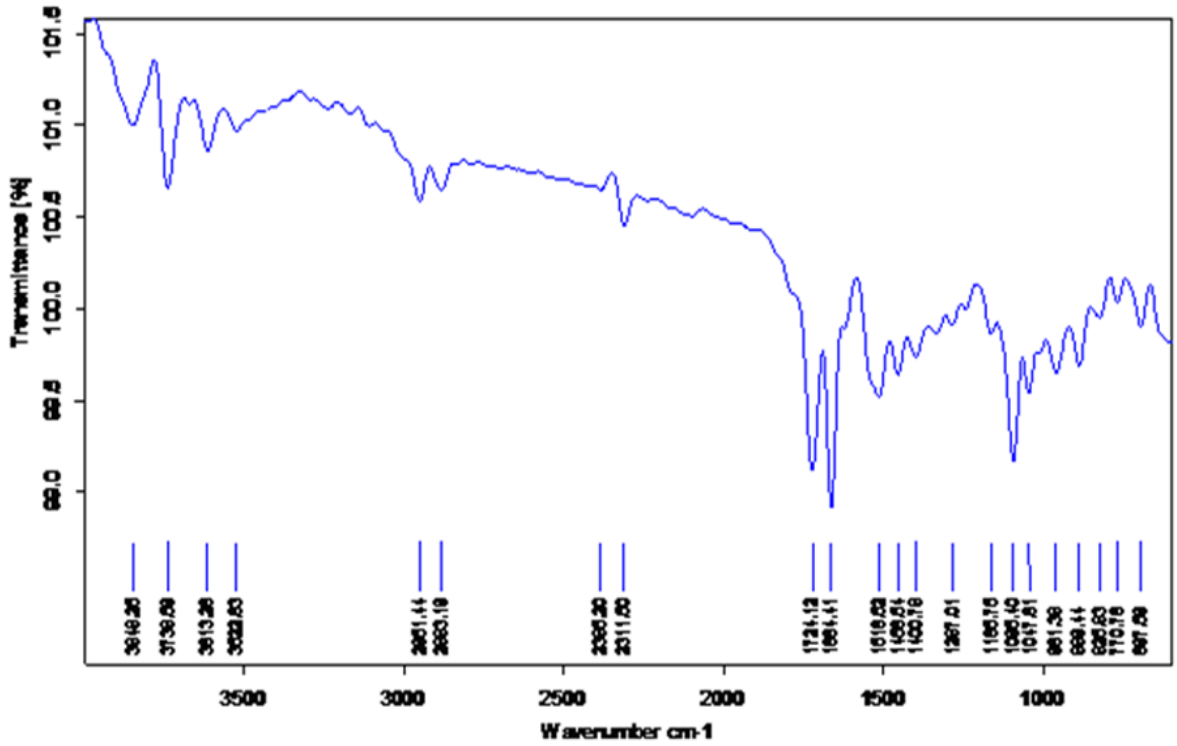

Figure 3: Infra-Red of Poloxamer

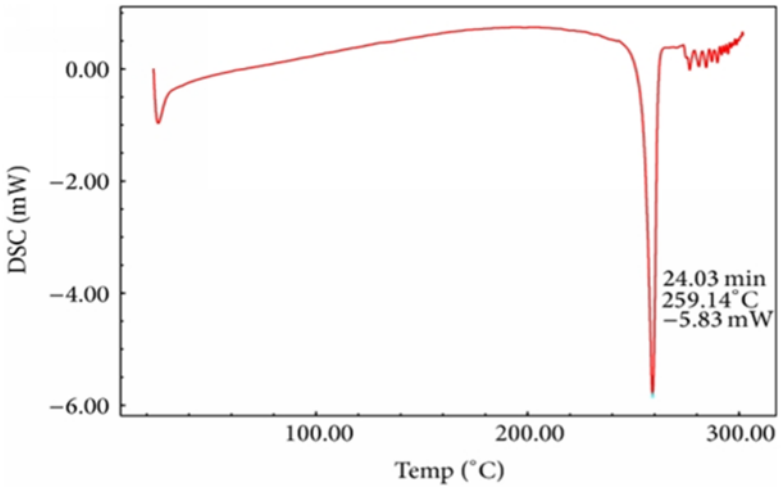

Figure 4: DSC analysis of Budesonide

physical incompatibilities such as colour change, liquefaction, caking, and Gas formation and chemical incompatibilities with the help of FT-IR study. The results obtained are as given in Table 2.

Formulation

To prepare polymeric Nanoparticles with a required particle size and to attain a constant formulation, the effect of various process variables was investigated. Variety of organic solvents which could dissolve Eudragit S100 and Drug, i.e. ethanol, methanol, acetone and dimethyl sulfoxide (DMSO) were screened for preparation of Nanoparticles (Radhika *et al.*, 2011; Yoo *et al.*, 2015). Ethanol was finalized as organic phase based on initial screening and was used to dissolve Eudragit S 100 and Drug (Sanjay *et al.*, 2016; Leonard, 2012).

Nanoparticles were prepared by using modified Nano precipitation method using probe sonication. Required amount of Budesonide and Eudragit S100 were weighed properly and dissolved in Ethanol as organic phase. Then this solution was added drop wise into the water containing Poloxamer as aqueous phase under probe sonication for 10 - 15 min. The nano suspension was then subjected to rotavapour for removal of free ethanol. The above mixture placed in to oven for drying the Nanoparticles.

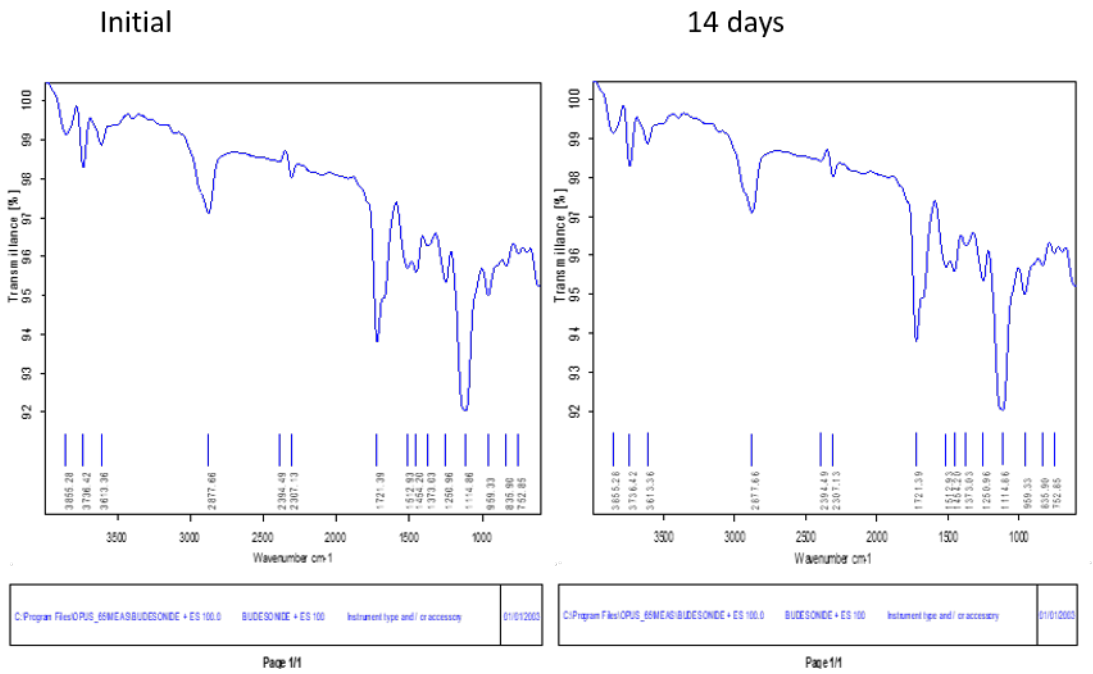

Figure 5: FT-IR Drug+ES100

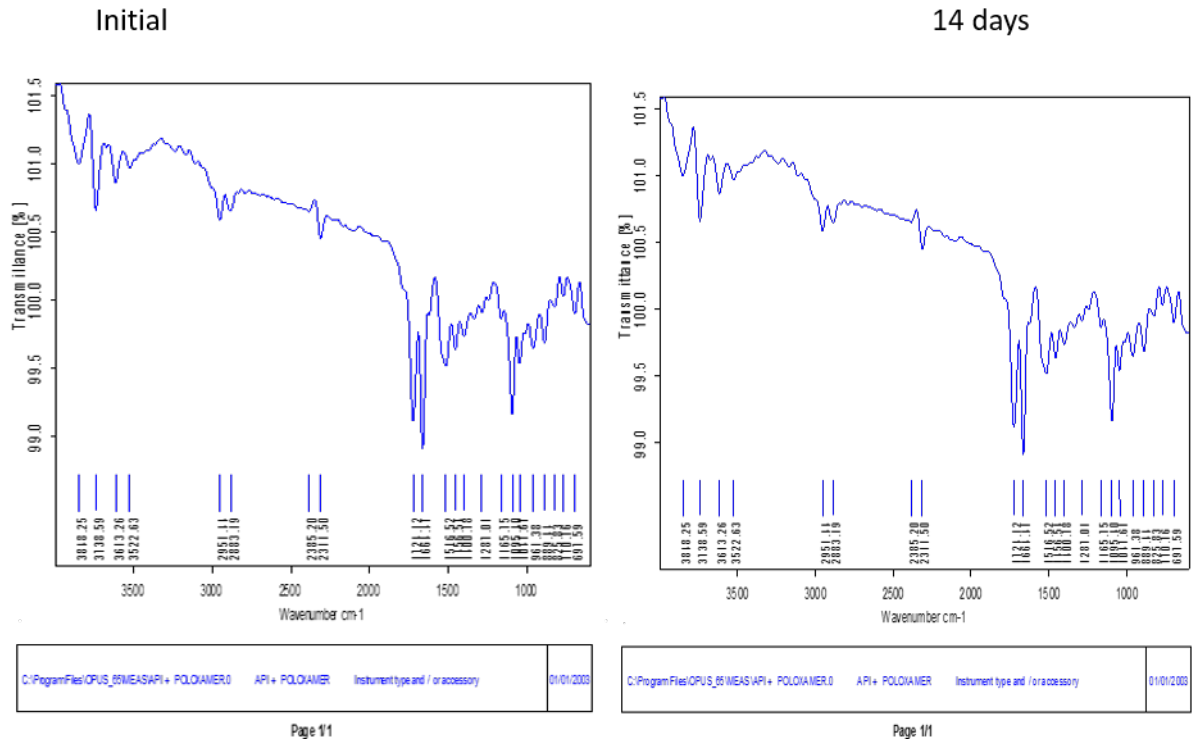

Figure 6: FT-IR of Drug + Poloxamer

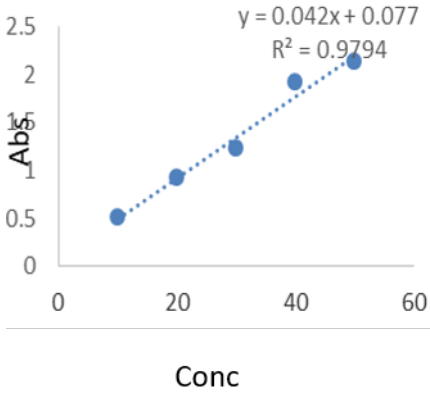

Figure 7: Calibration of Budesonide in Ethanol

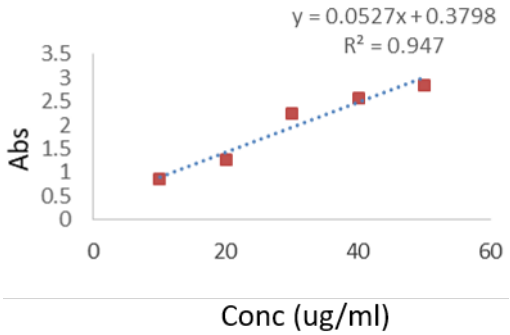

Figure 8: Calibration ofBudesonide in 0.1N HCL

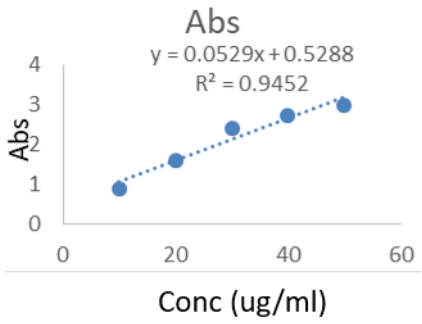

Figure 9: Calibration of Budesonide in 6.8 buffer

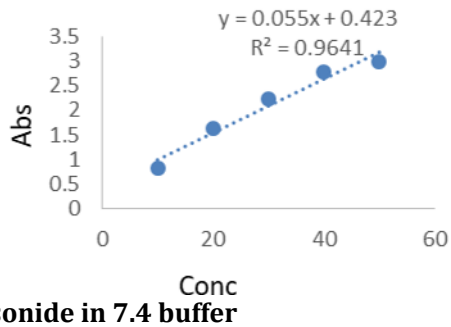

Figure 10: Calibration of Budesonide in 7.4 buffer

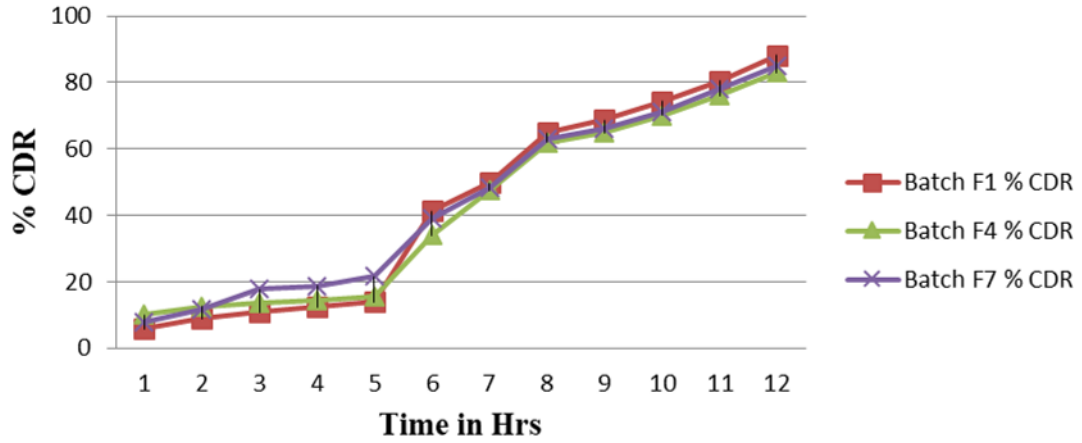

Figure 11: In-vitro release profile of Nanoparticles

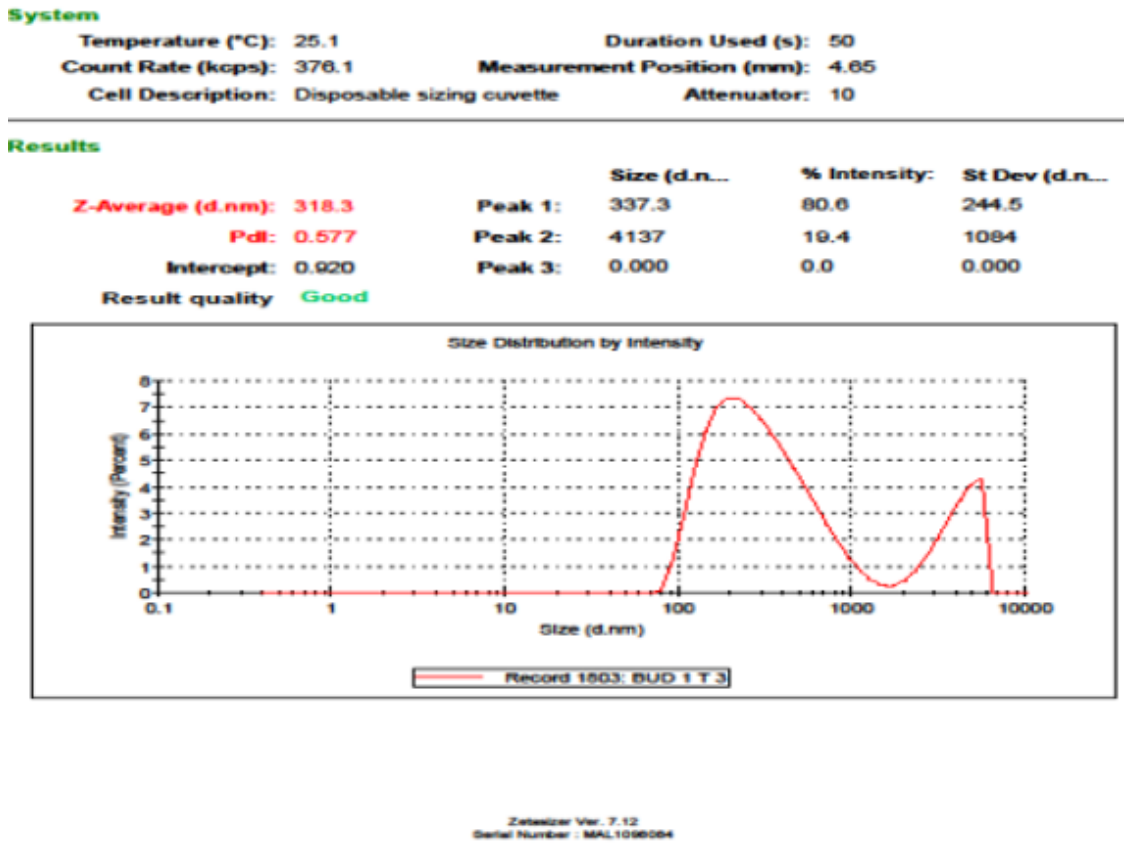

Figure 12: Particle size Result of Batch F1

On the basis of literature survey and laboratory work the Nano precipitation method was selected for the preparation of Nanoparticles. Preliminary batches were prepared to whether Nanoparticles formed for this combination or not and if formed at what will be concentration and ration of drug, polymer and surfactant.

With the preliminary knowledge we understand that for preparation of nanoparticles it is necessary to select the proper ratio of the Budesonide and Eudragit S100, it was determined by taking ratio such as 1:1 and 1:2 and 1:3 likewise respectively by taking further given in Table 3 and which selected on the basis of extensive literature survey for preparation of colon specific nanoparticles having high entrapment efficiency (EE) and optimized particle size. This method is based on trial and error with the base of preliminary batches results.

The amount of Budesonide was kept constant and the ratio of drug to polymer and drug to surfactant was varied as mentioned in Table 3 table. All the batches were manufactured according to experimental design described previously. In the batch F1, F4 and F7 the particles were formed so the batch

Results

			Size (d.n...	% Intensity:	St Dev (d.n...
Z-Average (d.nm):	523.4	Peak 1:	764.6	51.4	216.6
PdI:	0.770	Peak 2:	154.1	45.3	35.43
Intercept:	0.941	Peak 3:	5560	3.3	0.000
Result quality	Refer to quality report				

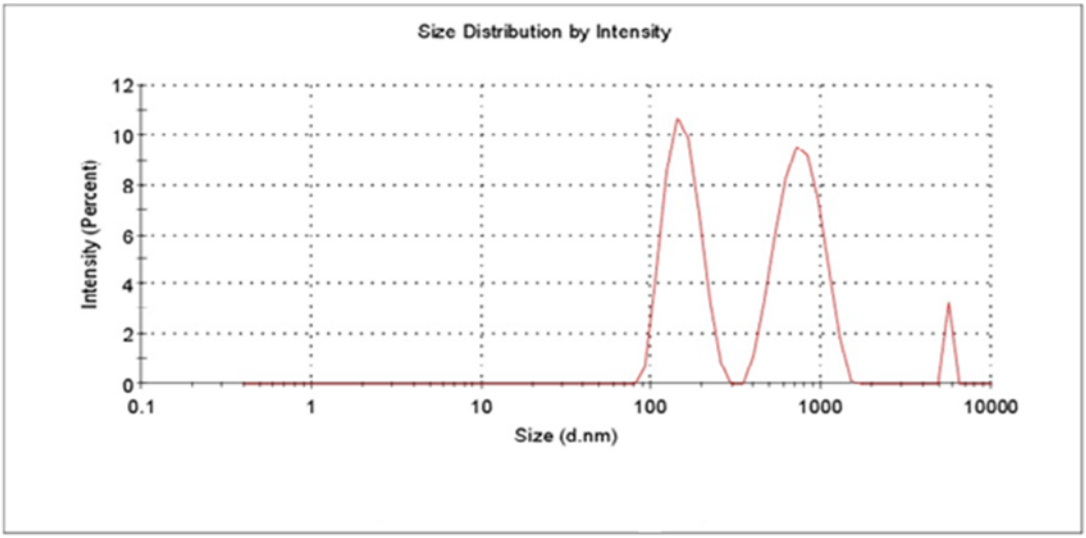

Figure 13: Particle Size results of Batch F7

System

Temperature (°C):	25.0	Zeta Runs:	11
Count Rate (kcps):	159.1	Measurement Position (mm):	4.50
Cell Description:	Zeta dip cell	Attenuator:	6

Results

			Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV):	3.88	Peak 1:	3.88	100.0	5.08
Zeta Deviation (mV):	5.08	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm):	1.31	Peak 3:	0.00	0.0	0.00
Result quality	Good				

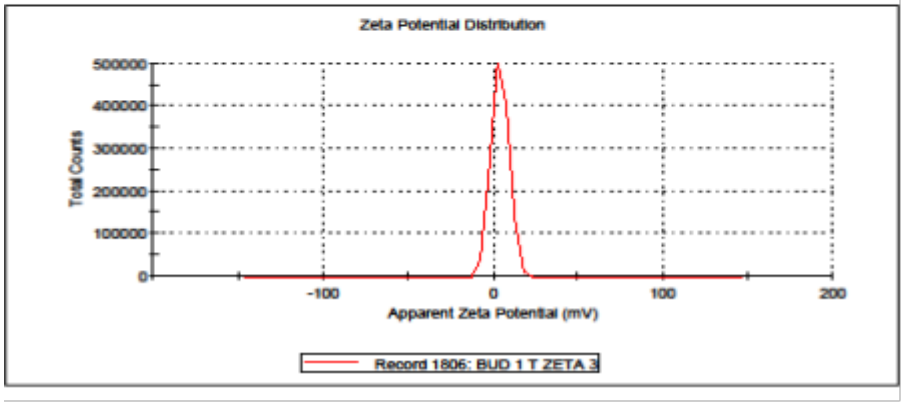

Figure 14: Result of zeta potential (Batch F1)

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -0.496	Peak 1:	-0.496	100.0	5.99
Zeta Deviation (mV): 5.99	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm): 0.333	Peak 3:	0.00	0.0	0.00

Result quality See result quality report

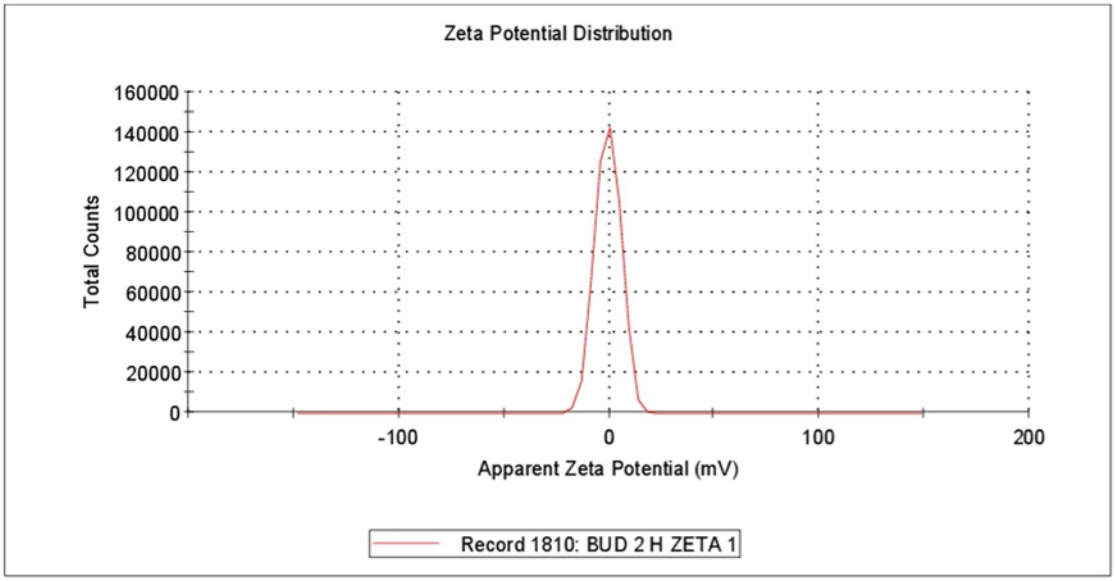

Figure 15: Result of zeta potential (Batch F7)

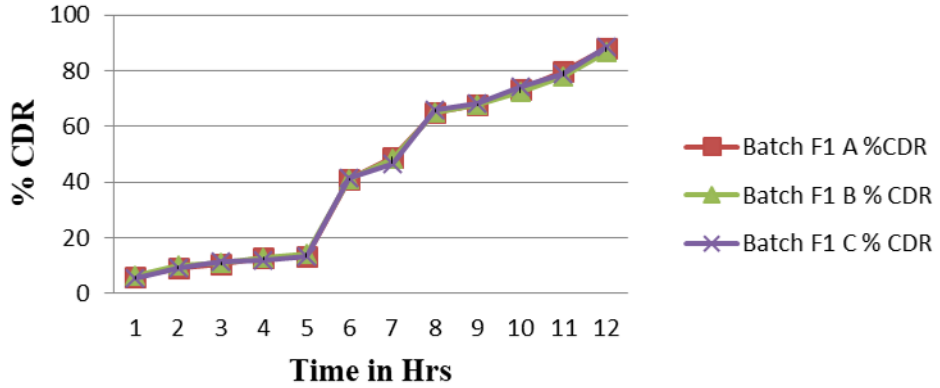

Figure 16: Drug release of capsule containing Nanoparticles of batch F1 in triplicates

F1, F4 and F7 was selected for entrapment efficiency and drug release study.

Evaluation of Nanoparticles

Drug entrapment efficiency

Encapsulation efficiency of Nanoparticle was determined by separating free budesonide from budesonide suspension by centrifuging at 5000 rpm for 15 min (Nikam *et al.*, 2014; Tiruwa, 2016). The clear liquid (supernatant) was taken and diluted with ethanol to calculate un-entrapped drug absorbance measured at 254 nm to calculate encapsulation efficiency. The percentage of drug entrapment efficiency was calculated using subsequent Equation (Yoo *et al.*, 2015; Lathaeswari *et al.*, 2013)

Encapsulation efficiency %

$$= \frac{Total\ drug\ - free\ drug \times 100}{Total\ drug}$$

Drug release study

The drug release study of budesonide nanoparticles was carried out in dissolution test apparatus II (TDT 08 L Electrolab) at a speed of 50 rpm which contains 900 ml medium at 37^0C. The capsules are transferred in the medium and samples were taken at certain time interval and analysed by UV at 254nm. The constant dissolution was used by simulating gastric

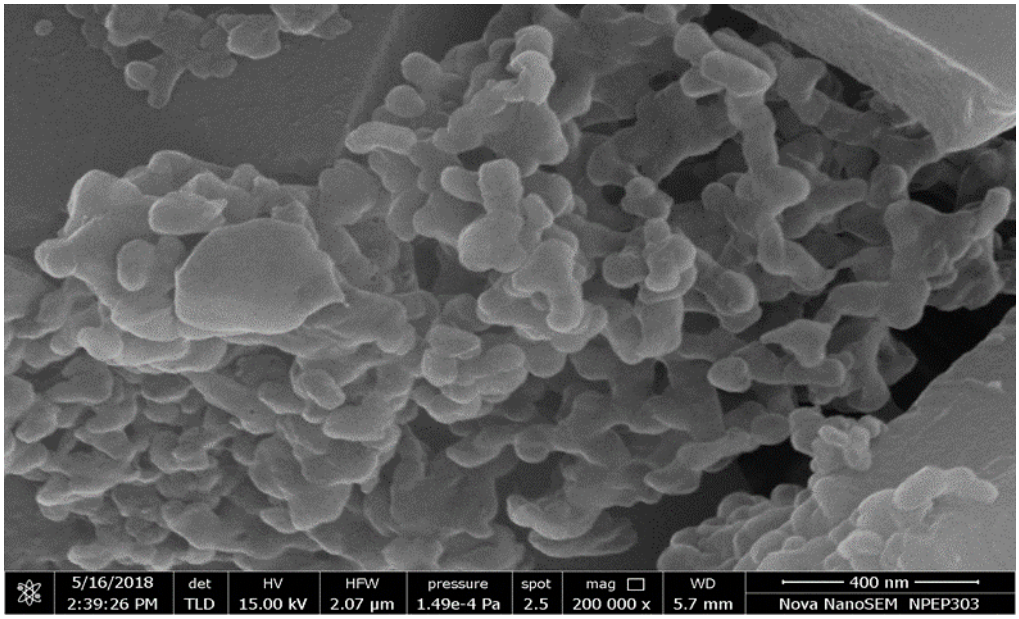

Figure 17: Scanning Electron Microscopy of Batch F1

conditions of the gastrointestinal area. For dissolution capsule placed in 700 ml of 0.1 N HCL (pH1.2) for 2 hours. At the end of 2 hours 200 ml of tribasic sodium phosphate was added to dissolution vessel pH adjusted to 6.8 for 3 hrs and finally 7.4 by using 2M NAOH (Sanjay *et al.*, 2016).

Particle size determination

Nanoparticle formulation (1ml) was diluted with 10 ml deionized water in a beaker with constant stirring using a glass rod. The resultant solution was then subjected to particle size analysis. With the help of Dynamic light scattering (DLS) technique, using a zetasizer (Nano ZS, Malvern Instruments, UK) the droplet size was calculated (Nikam *et al.*, 2014; Tiruwa, 2016).

Zeta potential

Zeta potential of the formulation was determined with laser diffraction analysis.

Resultant solution was then subjected to particle size analysis. Zeta potential measured by Dynamic light scattering (DLS) technique with a zetasizer (Nano ZS, Malvern Instruments, UK) (Nikam *et al.*, 2014; Tiruwa, 2016).

Scanning Electron Microscopy

Scanning electron microscopy analysis of the nanoparticle formulation was performed to understand surface morphology of Budesonide loaded nanoparticles.

RESULTS AND DISCUSSION

Determination of absorption maxima (λ_{max}) and preparation of calibration curves

The calibration curve for Budesonide using double beam UV spectrometer

The calibration curve for Budesonide in Ethanol, 0.1 N HCl, pH 6.8 and pH 7.4 buffers was prepared by plotting absorbance versus concentration at practically obtained λ_{max} 254 nm. Calibration curve was plotted in replicate manner. Ranges selected for concentration were of 10, 20, 30, 40, 50 μg/ml. The calibration curve of Budesonide in 0.1 N HCl of pH 1.2 and phosphate buffer of pH 6.8, pH 7.4 were found as shown in Figures 7, 8, 9 and 10 respectively.

From the calibration curve of the Budesonide the regression was found to be 0.947 in 1.2 pH HCl buffer and 0.945 in 6.8 pH phosphate buffer and 0.964 in pH 7.4 buffer. The regression shows that the drug was pure.

Percent Entrapment Efficiency (EE)

The range of percent EE was established from 80% to 90 %. EE of optimized formulation was found to be 89.52%. Trial batches result prove that, polymer concentration shows positive influence of the entrapment efficiency as batch F1, F4, F7 show % EE 89.52%,81.30%,85.50% have more polymer content.

Drug release profile (In-vitro) of optimized batches

The drug release profile was also performed on optimized batches (Batch F1, F4 and F7). Release profile

was studied for twelve hours. The release curve is shown in Figure 11.

Above data clearly show that the batch F1 and F7 show good value of In-Vitro Drug Release and entrapment efficiency so, two batches F1 & F7 were taken for further evaluation for determination of particle size and zeta potential.

Determination of particle size

Particle size analysis of nanoparticles for the optimized batches F1, F7 is 318.8 nm and 523.4 nm shown in Figures 12 and 13 respectively.

Zeta Potential Determination

Zeta potential of Nanoparticles from optimized batches F1 and F7 is shown in Figures 14 and 15 respectively.

Filling of Nanoparticles in capsules

On the basis of experimental design and evaluation of the Nanoparticles optimized batch i.e. F1 batch Nanoparticles were filled in capsule i.e. final dosage form and these filled capsules drug release profile were tested up to 12 hours in triplicate. Drug release data of capsule containing nanoparticles is shown in Figure 16.

From the dissolution study it was clear that batch F1 shows the good drug release in colonic region.

The batch F1 A, F1 B and F1 C contains Eudragit S100 in 100mg. The result was good because it shows less than 11% drug release in stomach i.e. 9.01%, 9.88% and 9.11% respectively which is advantageous and achieves our objective to target colon.

Scanning Electron Microscopy

The Scanning Electron Microscopy analysis of optimized batch (batch F1) demonstrates that nanoparticles are round in shape. The Budesonide entrapped Nanoparticles do not show presence of cavities. The results of Scanning in Electron Microscopy are shown in Figure 17.

Stability study

The capsule containing Nanoparticles were stored in a container at 25ºC ±5ºC and flooded solution of sodium chloride to attain relative humidity of 60% ±5%. Study was continued for a duration of 6 month and time points for testing were 1 month, 3 months and 6 months. This optimized formulation was tested to determine whether there is any significant change in appearance and other evaluation parameters like drug release.

Appearance and in-vitro drug release shows there is no significant change in the results comparable with initial results of optimized batch i.e. Batch F1.

CONCLUSIONS

In the treatment of IBD targeted delivery to site of action is advisable, so in this regard considerable progress has been made and novel technologies like nanoparticles were approached. In current study we developed polymeric nanoparticles of Budesonide to target colon in the treatment of colitis. The optimized nanoparticles formulated to minimize drug release in the stomach and release at site of treatment i.e. in colon in treatment of IBD. In vitro release profile demonstrated maximum release of budesonide from the formulated polymeric Nanoparticles. The present study has brought our potential of polymeric Nanoparticles formulation (Nanoparticles in capsule) in ulcerative Colitis. Extensive clinical studies will further substantiate the merit of this novel formulation.

REFERENCES

Colombel, J. F., Sandborn, W. J., Reinisch, W., Mantzaris, G. J., Kornbluth, A., Rachmilewitz, D., Lichtiger, S., D'Haens, G., Diamond, R. H., Broussard, D. L., Tang, K. L., van der Woude, C. J., Rutgeerts, P. 2010. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. *New England Journal of Medicine*, 362(15):1383–1395.

Frank, D. N., Amand, A. L. S., Feldman, R. A., Boedeker, E. C., Harpaz, N., Pace, N. R. 2007. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proceedings of the National Academy of Sciences*, 104(34):13780–13785.

Hua, S., Marks, E., Schneider, J. J., Keely, S. 2015. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: Selective targeting to diseased versus healthy tissue. *Nanomedicine: Nanotechnology, Biology and Medicine*, 11(5):1117–1132.

Kadian, S. S., Harikumar, S. L. 2009. Eudragit and its Pharmaceutical Significance. *Pharmainfo Net*, pages 1–16.

Lathaeswari, R., Prasad, G. S., Prabhu, S. 2013. Preparation and evaluation of capecitabine loaded eudragit nanoparticles for colon targeting. *International Journal of Pharmacology and Biological Sciences*, 7(2):33–42.

Lautenschläger, C., Schmidt, C., Fischer, D., Stallmach, A. 2014. Drug delivery strategies in the therapy of inflammatory bowel disease. *Advanced Drug Delivery Reviews*, 71:58–76.

Leonard, F. 2012. Screening of budesonide nanoformulations for treatment of inflammatory bowel

disease in an inflamed 3D cell-culture model. *ALTEX*, 29(3):275–285.

Nikam, A. P., Ratnaparkhiand, M. P., Chaudhari, S. P. 2014. Nanoparticles - An overview. *International Journal of Research and Development in Pharmacy and Life Sciences*, 3(5):1121–1127.

Paharia, A., Yadav, A. K., Rai, G., Jain, S. K., Pancholi, S. S., Agrawal, G. P. 2007. Eudragit-coated pectin microspheres of 5-fluorouracil for colon targeting. *AAPS PharmSciTech*, 8(1):E87–E93.

Radhika, R., Sasikanth, Sivakumar, T. 2011. Nanocapsules: A new approach in drug delivery. International journal of pharmaceutical science and research. pages 1426–1429.

Sanjay, J., Kshirsagar, Naresh, C., Bingi, Jaydeep, N., Dusane 2016. Formulation and evaluation of nanocapsules for colon targeted drug delivery. *Journal of Science and Technology Advances*, 1(1):33–52.

Tiruwa, R. 2016. A review on nanoparticles - preparation and evaluation parameters. *Indian J. Pharm. Biol. Res*, 4(2):27–31.

Xavier, R. J., Podolsky, D. K. 2007. Unravelling the pathogenesis of inflammatory bowel disease. *Nature*, 448(7152):427–434.

Xiao, B., Laroui, H., Viennois, E., Ayyadurai, S., Charania, M. A., Zhang, Y., Zhang, Z., Baker, M. T., Zhang, B., Gewirtz, A. T., Merlin, D. 2014. Nanoparticles With Surface Antibody Against CD98 and Carrying CD98 Small Interfering RNA Reduce Colitis in Mice. *Gastroenterology*, 146(5):1289–1300.e19.

Yoo, J. W., Naeem, M., Choi, M., Cao, J., Yoon, S., Kim, M. S., Lee, Y. 2015. Colon-targeted delivery of budesonide using dual pH- and time-dependent polymeric nanoparticles for colitis therapy. . *Drug Design Development and Therapy*, 2015:3789–3799.