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Original Article

Formulation and evaluation of Microspheres for Colon targeted delivery of Ondansetron

Saurav Kumar, Rajwinder Kaur and Rakesh Kumar Sharma*

Guru Nanak Institute of Pharmacy, Dalewal, Distt. Hoshiarpur, India

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ABSTRACT: Objective: The main objective of the present study was to evolve and characterize the microspheres for colon specific target delivery of Ondansetron HCl for the treatment of Inflammatory Bowel Disease.
Methods: Ondansetron HCl loaded microspheres were devised by using emulsion solvent evaporation method. HPMC and Ethyl cellulose were used as polymers.
Results and Discussion: The preformulation compatibility studies between drug, excipients and microsphere formulations were carried out by Fourier transform infra-red spectroscopy (FTIR). The optimization of the process and formulation was done with respect to the different parameters like drug-polymer ratio, stirring speed, volume of internal phase and amount of emulsifying agent. The microspheres were filled into hard gelatin capsule shells which are sealed and coated with ethanolic solutions of ethyl cellulose and shellac. Drug release profile of microspheres was investigated in GIT pH specific media (0.1M HCl & Phosphate buffer pH 6.8). The FTIR spectra showed that no chemical interaction or changes take place during perpetration of formulations. The drug was stable in all the formulations. The process parameter modulation results showed that the production yields and particle size was decreased with increased stirring speed and increasing the volume of internal phase.
Conclusion: *In-vitro* drug release study of all ondansetron HCl loaded microsphere formulations OF1-OF4 show the release of drug released by non-Fickian diffusion n<0.85.

⇑ Corresponding author at:
Rakesh Kumar Sharma, Guru Nanak Institute of Pharmacy, Dalewal, Distt. Hoshiarpur, India
E-mail: rks19761@gmail.com

INTRODUCTION

Targeted drug delivery implies selective and effective localization of drug into the target at therapeutic concentrations with limited access to non-target sites [1]. A targeted drug delivery system is favored in drugs having instability, low solubility and short half-life, large volume of distribution, poor absorption, low specificity and low therapeutic index [2,3,4].

The colon targeted or specific drug delivery system (CSDDS) is beneficial for the localized treatment of several colonic diseases mainly inflammatory bowel diseases (IBD) [5], irritable bowel syndrome and colonic cancer as well as prolonged release dosage form for once a day medications [6-10].

Gastroenteric micro flora of the colon has a determined number of implications in health and the treatment of diseases such as IBD [11]. The convergence of gut micro-flora rises significantly in the terminal ileum to achieve surprisingly high levels in the colon. The gut microbes are fit for catalyzing an extensive variety of metabolic occasions. Numerous colon-particular medication delivery frameworks depend on enzymes engrossing to gut microflora to discharge dynamic specialists in the colon [12]. In any case, just a few catalyst frameworks to be specific; namely azoreductases and glycosidase including glucuronidase have been investigated around there [13]. An extensive number of polysaccharides are effectively hydrolyzed by gut micro-flora prompting the likelihood of utilizing naturally occurring biopolymers as carriers for the drugs [14].

The drug delivery system should surpass the barriers in the stomach and small intestine so as to reach and release the drug in the colon. The major factors which need to be addressed include variation in the GIT pH that varies from 1.5 to 7.5, food, fasting, and disease state [15-18]. Regularly the small intestinal travel isn't impacted by the physical state, size of the dose and shape [19]. The mean travel time of the dose shape is around 3-4 hour to come to the ileocecal intersection. Amid this period the dosage form is exposed to different pH levels as well as enzymes present throughout in the entire GIT.

Ondansetron HCl (ODN) is a selective serotonin 5-HT3 receptor antagonist that is regularly used for the prevention of vomiting [20]. The literature search indicated that it is also prescribed for treatment of IBS (Irritable Bowel Syndrome). ODN has half-life 3-5 h and bioavailability ~60%. It is very well absorbed in whole GIT. The conventional oral formulations of ODN were orally administered in t.i.d or q.d dosage regimen. ODN affect the mucosal membrane and produce burning sensation on local anal/rectal following insertion of suppositories [21]. Therefore, the microsphere drug delivery system in the form of appropriate solid dosage form preferably in hard gelatin capsules for once a day medication was envisaged & investigated in the present research.

Ethyl cellulose (EC), Hydroxy Propyl Methyl cellulose (HPMC) and other excipients that were used in the present study was selected based on vis a vis biocompatibility, biodegradability, stability in GIT environment and non-toxicity [22,23,24].

MATERIALS AND METHODS

Ondansetron HCl (ODN) was a gift sample from Torrent Pharma, Ahmadabad. Ethyl cellulose (EC), Hydroxy Propyl Methyl cellulose (HPMC) were purchased from CDH Delhi, Pectinex Ultra SPL purchased from Himedia, Mumbai; Shellac purchased from KEE GAD Biogen (P) Ltd, Delhi. All the other chemicals used in the study were of analytical grade and used as received.

Determination of absorption maxima (λmax)

10 mg of ODN was accurately weighed and transferred to 100 ml of volumetric flask. The drug was dissolved in 100 ml distilled water to obtain a stock solution 100 µg/ml. One ml of this stock solution was again diluted with distilled water up to 10 ml to obtain a solution of 10 µg/ml. The resulting solution was scanned between 200 nm to 350 nm using Systronics 2205 double beam UV/ visible spectrophotometer [25].

Preparation of standard calibration curve

Accurately weighed 10 mg of ODN was transferred to 10 ml volumetric flask. The drug was dissolved in 10 ml distilled water (stock solution-I) to make a solution 1000 µg/ml. 5 ml of stock solutions-I diluted to 100 ml with distilled water to give a stock solution of concentration 50 µg/ml (Stock solution-II). From stock solution II aliquots of 1, 2, 3, 4, 5, & 6 ml were transferred to a series of 10 ml volumetric flasks and the volume was made up to the mark with 0.1 N hydrochloric acid to prepare the concentration from 5 to 30 µg/ml.

The absorbance of standard solutions was measured at 310 nm. Mean absorbance of three determinations was taken to check the reproducibility. The observed absorbance was subjected to regression analysis, to study the linearity and optical characteristics. The same procedure was followed & standard calibration curve of ODN was prepared in phthalate buffer pH 4.5, phosphate buffer 6.8 & 7.4.

Fourier Transformation Infra-red Spectroscopy (FT-IR)

The infrared spectroscopy of the sample was carried out to ascertain the preformulation compatibility of ODN with formulation excipients (British Pharmacopoeia, 2009). A pellet of approximately 1 mm diameter of each drug was prepared by compressing 3 - 5 mg of the drug with 100-150 mg of potassium bromide in KBr press (Model M-15, Techno Search Instruments). The pellet was mounted in IR compartment and scanned between wave number 4000–450 cm-1 using a Shimadzu 8400 FT-IR [26, 27].

Preparation of ODN Microspheres

The ODN microspheres were prepared by emulsion-solvent evaporation technique. Accurately weighed quantities of the polymers were (HPMC and EC) dissolved in 10 ml dichloromethane and isopropyl alcohol mixture (1:1). Weighed quantity of ODN; previously passed through the sieve # 150 was then dissolved in 0.1N HCl. Then polymer solution adds drop by drop to the drug solution by using syringe.

The drug- polymer solution then is emulsified with 0.5%w/v tween 80 by continuous stirring at 1000 rpm on mechanical stirrer (REMI MORTOR RQT-124A). The stirring was continued for 2 hours to ensure complete evaporation of solvent. The microspheres were then separated using Whatman filter paper No. 44, air dried for 12 hours, filled in clear glass screw capped bottles and stored in a desiccator [28, 29, 30].

Production Yield, Drug contents and entrapment efficiency

Production yield of the microsphere was determined by applying the following formula:

$$Production\ Yield\ (\%) = \frac{Final\ Mass\ of\ Microspheres}{Mass\ of\ Raw\ Materials}\ X\ 100$$

The 10 mg accurate weighted amount of drug loaded microsphere was keep in 10 ml pH 6.8 phosphate buffer for 12 hours at 37°C with constant shaking. After 12 hours sample was filtered and measure the absorbance (Ab_m) at 310 nm against blank using UV spectrophotometer (UV 2205, Systronics).

The drug contents were determined by repeating the same procedure using pure ODN reference standard (A_t) and entrapment efficiency were calculated using the following formula [31, 32]:

$$Drug\ content\ \% = \frac{Ab\ (m)}{Ab(s)}\ X100$$

$$\text{Entrapment efficiency}(\%) = \frac{\text{Actual drug Content in Microspheres}}{\text{Amount of drug added in formulation}} \text{ X } 100$$

Particle size and surface morphology

Particle size of the microsphere was determined by using optical microscopic method. The calibrated micrometer was fitted in eye piece and measures the particle size. 100 microspheres were measured randomly and the mean particle size was calculated by Edmondson's equation [33]:

$$d = \left\{ \frac{(\sum nd^{p+f})}{(\sum nd^{f})} \right\}^{1/p}$$

Where n; no. of particles in size range, d; average diameter, p; index related to the particle size (p=1) and f; is the frequency index (f=2).

Derived Properties

The flow properties of the ODN formulations were assessed by determination of angle of repose, Carr's index and Hausner's ratio.

Formulation of colon Targeted Hard gelatin capsules

Hard gelatin capsules of Size '0' were filled by hand with 500 mg of microspheres of ODN containing varying amount of HPMC. After filling the capsules were sealed with 5% (w/w) ethanolic solution of Ethyl cellulose. The capsules obtained were coated with three layers of shellac of different concentration (5, 10 and 15%) by dipping method. The capsule was dipped into the shellac coating solution for 3-5 sec, removed from the solution and air dried followed by again dipping in to the shellac solution & dried. This process of shellac coating was done 3 times with each concentration of shellac solution. The shellac coated capsules were evaluated for weight variation, drug contents, disintegration and dissolution pattern.

***In-vitro* drug release**

In-vitro dissolution test was conducted in USP 2 apparatus at 75 rpm and a temperature of 37±0.5ºC. Sampling was done at predetermined time intervals and the same were estimated for drug content after suitable dilution by using double beam UV-VIS spectrophotometer. Initial drug release studies were conducted in 900 ml of 0.1N HCI for 2 hours followed by 900 ml of 7.4 potassium phosphate buffer solution for next 3 hours. Then, 900 ml of 6.8 potassium phosphate buffer solution for rest of the time [34,35].

RESULTS AND DISCUSSION

An absorption maximum (λ max) of ODN was found 310 nm which was in confirmation to the value reported in the literature. The calibration curve of ODN in 0.1N HCl was prepared in the concentration range 5 – 30 µm/ml in 0.1N HCl, phthalate buffer pH 4.5, phosphate buffer 6.8 & 7.4, represented in figure.

The calibration curve obtained followed Beer's – Lambert's law with r^2 value less than 1.0.The recorded FT-IR spectra of ODN show in Figure 1. The characteristic ODN spectra showed H_2O peak at 3487.06 cm-1, C-H deformations at 1471.59 cm-1, C-N at 1282.57 cm-1 and carbonyl stretching band at 1632.54 cm-1 were noted. HPMC showed an ester C=O stretching peak around 1671.67 cm-1, C-H stretching at 2995.25 cm-1 and bond characteristic to carboxylic group in the range 2437-3473 cm-1 as reported in the literature. The presence of all characteristic peaks of ODN was observed in the FT-IR spectra of physical mixture of drug and HPMC, physical mixture of drug and ethyl cellulose, physical mixture of drug, Ethyl cellulose and HPMC. The above study showed that no chemical interaction and changes took place in FT-IR spectra of the drug and other excipients alone or in combination exhibiting compatibility of the drugs with all excipients.

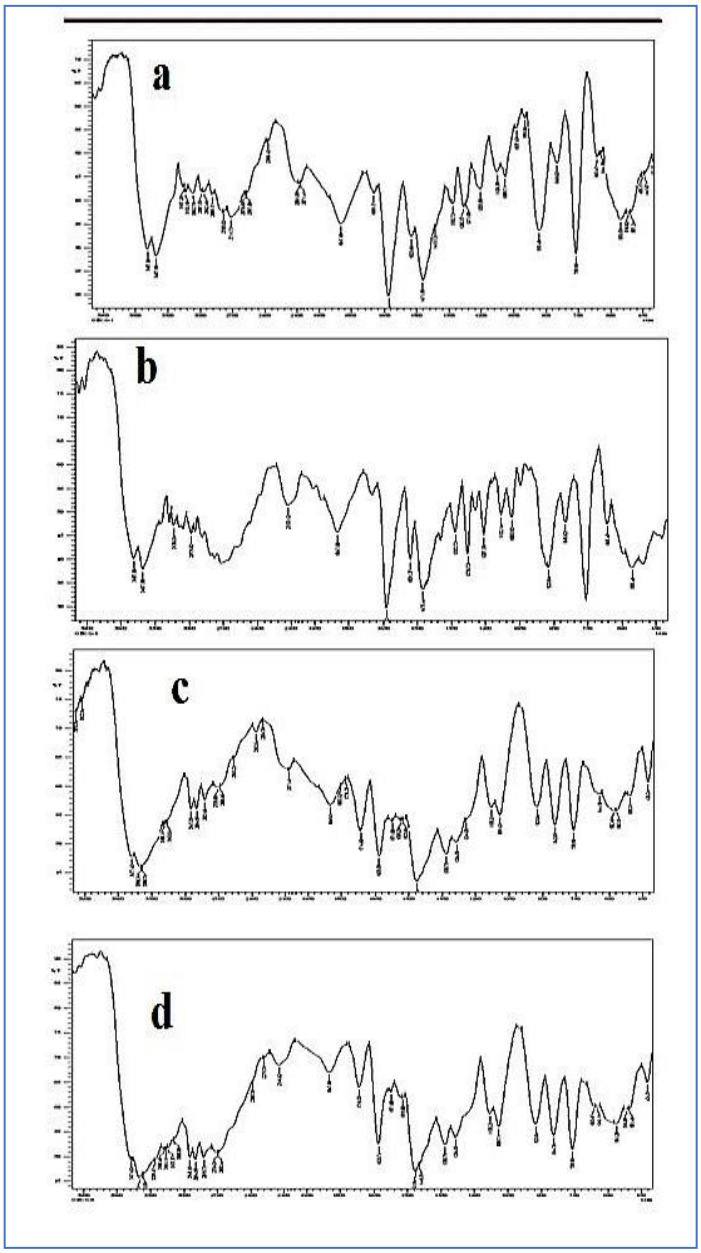


Fig. 1: FT-IR spectra of ODN & excipients a) ODN b) ODN+ HPMC c) ODN+ EC d) ODN+ HPMC+ EC

Emulsion solvent evaporation method was adopted to prepare ODN loaded microsphere because of its simplicity and reproducibility, low cost, the production of microspheres of relatively high drug loading and having low solvent toxicity.

In this process, the drug-polymer (ODN: EC: HPMC) in the ratios 1:0.5:0.5, 1:1:0.5, 1:0.5:1, 1:1:1, were taken for preparation of microsphere formulations. OF1, OF2, OF3, OF4 respectively. The amount of emulsifying agent (tween 80), dichloromethane and volume of isopropyl alcohol were kept constant for each formulation. The agitating speed was selected 1000 rpm.

The production yield, theoretical and actual drug content, encapsulation efficiency and mean particle size of microspheres is presented in Table 1.

The production yield of all microsphere formulation was found to be in range 67 - 75%. The microsphere formulations (OF1, OF2, OF3 and OF4) were assayed for estimation of actual drug content and percentage encapsulation efficiency. The actual drug content was observed 54.61 – 68.46% for OF1-OF4 and encapsulation efficiency 81.92 – 82.15% for OF1-OF4. The microsphere formulation (OF4) exhibit highest drug loading and percent entrapment efficiency value of 68.46% and 82.15% respectively.

Table1: Production yield, theoretical and actual drug content, encapsulation efficiency and mean particle size of microspheres

Formulation	Drug: Polymer	Production yield (% ± SD)	Theoretical drug content (% ± SD)	Actual Drug Content (% ± SD)	Encapsulation efficiency (% ± SD)	Mean Particle Size (µm± SD)
OF1	1:0.5:0.5	74.88± 0.173	66.66	54.61± 0.391	81.92±0.584	37.97±0.552
OF2	1:1:0.5	72.08± 0.172	75	57.43± 0.148	76.57±0.202	46.81±0.820
OF3	1:0.5:1	67.26± 0.080	80.0	63.33± 0.391	79.16±0.481	55.38±0.756
OF4	1:1:1	75.05± 0.141	83.33	68.46± 0.256	82.15±0.305	58.79±0.330

Mean (**n=3)**

The drug-polymer ratio has considerable effect on the morphology and size of microspheres. In the various microsphere formulations were observed that when the ratio of drug to polymer was increased, the production yield increased. The reason for increased production yield at high drug-polymer ratios could be due to reduce dichloromethane diffusion from concentrated solution into aqueous phase. This provide more time for the droplet formation. The drug entrapment efficiency increased progressively with increasing polymer concentration. An increase in the polymer concentration resulted in the formation of larger microspheres entrapping greater amount of drug. The effect of internal phase volume, agitation rate (stirring) and conc. of tween 80 on the size of microspheres and production yield of microspheres was studied, depicted in figure 2a & 2b.

The formulation with the lower drug to polymer ratio (OF1) was selected for optimization. It was observed that the viscosity of the inner phase is an important factor for the preparation of microspheres. The average mean particle size 53 – 39 µm of microspheres was formed by decreasing the volume of dichloromethane 3 to 5 ml. The volumes of dichloromethane 5 to 10 ml, microsphere was formed very tiny having particle size between 38 – 13 µm. The production yield of microspheres decreased sharply with increase in amount of dichloromethane. This is due to the lower concentration of drug in the higher volume of dichloromethane.

The different agitating speeds (300, 400, 500 and 600 rpm) were selected for this study. The dispersion of the drug and polymer into the aqueous phase and the formulation of microspheres were found to be dependent on the agitation speed. It was observed that particle size of microspheres decreased with the increasing of the stirring speed. When the rate of agitation was increased 300 - 500 rpm, the spherical microspheres were formed with mean particle size range from 56.24 µm to 37.02 µm and production yields found to be 78.08 – 73.95 %.

However, at 600 rpm, the polymer adhered to paddle due to the turbulence created within the external phase hence production yield was decreased 69.32 % and particle size also decreased. Therefore, agitation at 500 rpm for the preparation of microsphere was suitable. Tween 80 a non-ionic surfactant was widely accepted and preferred emulsifying agent in the formulation of various dosage forms therefore was used in the preparation of microspheres. The presence of tween 80 significantly prevented aggregation of the droplets with solidified outer shells during the process. The dispersion of the inner phase into droplets in the medium depended on the concentration of tween 80 in the medium. An increased amount of emulsifying agent was decreased the production yield of microsphere formulations from 75.53% to 52.45% while increased the mean particle size due to increased viscosity, wherein larger emulsion droplets formed resulting in larger microspheres. An increased amount of emulsifying agent increased the mean particle size from 36.47 µm to 44.65 µm.

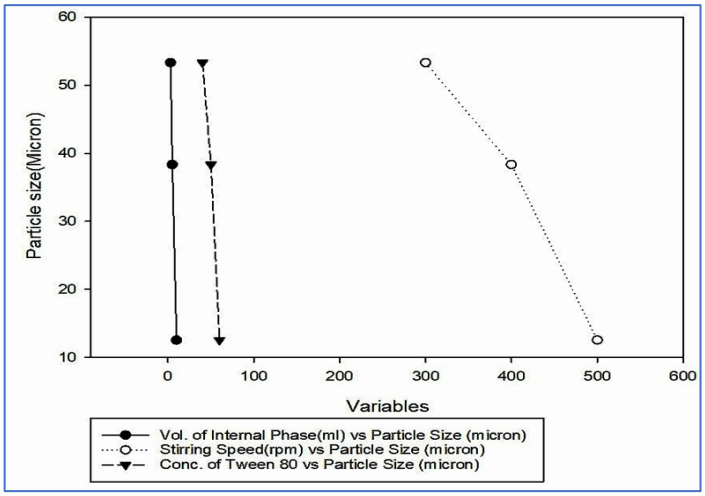


Fig. 2a: Effect of Process variables on size

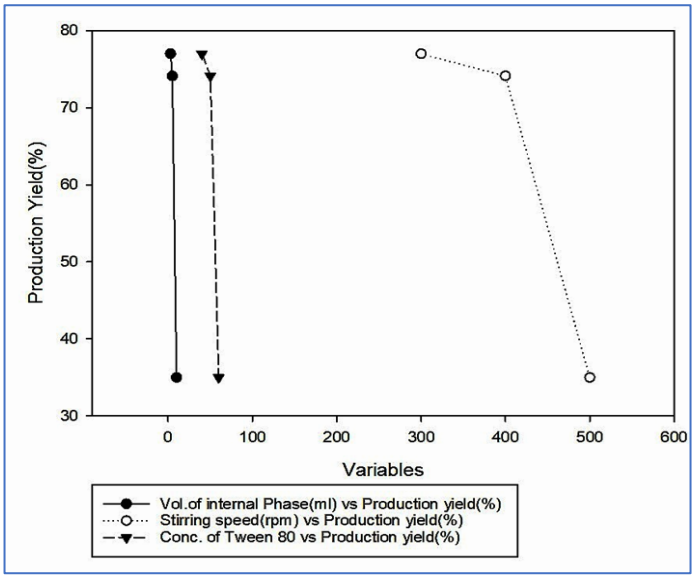
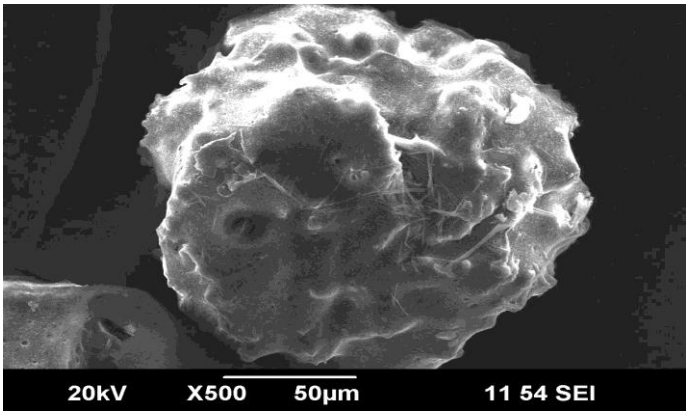
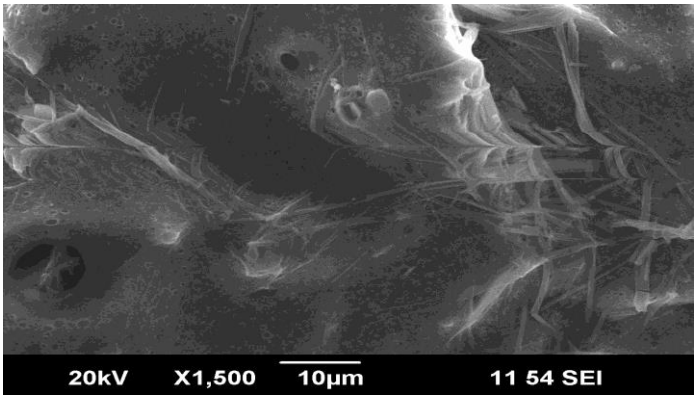


Fig. 2: Effect of process variables on production yield

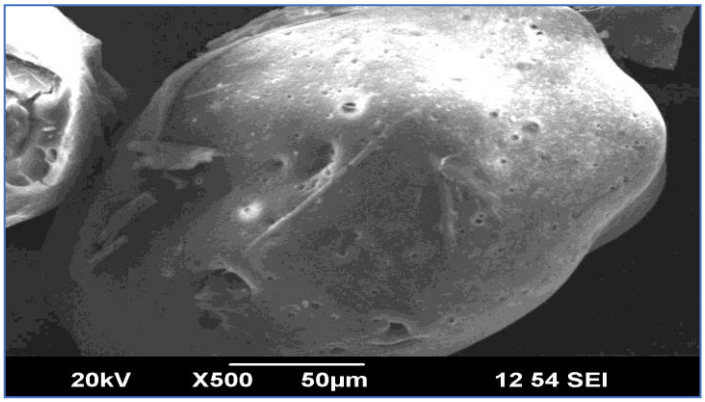
The mean particle size was found to be 37.97 – 58.79 µm for OF1-OF4. The surface morphology of microspheres analyzed by Scanning electron microscope (SEM) is depicted in figure 3. The SEM photograph showed uniform and spherical microsphere for formulation OF1, OF2 and OF3. The formulation OF4 microsphere morphology was not found in spherical shape. It was observed that the drug-polymer ratio increases the morphology of microsphere was change into irregular.



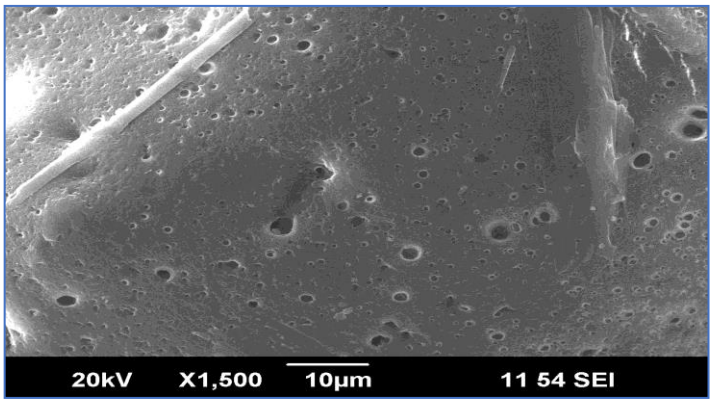
OF1 (A)



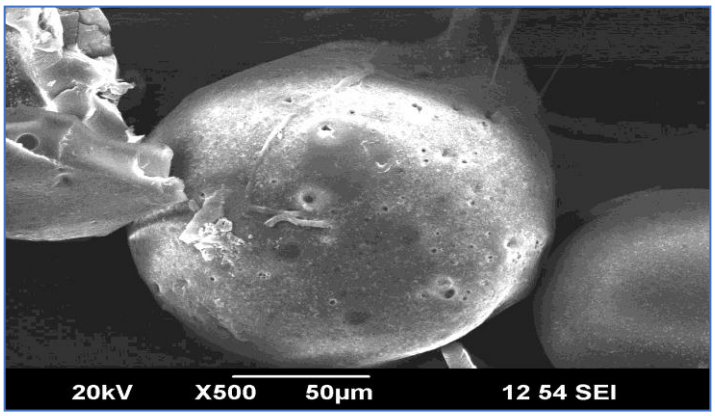
OF1 (B)



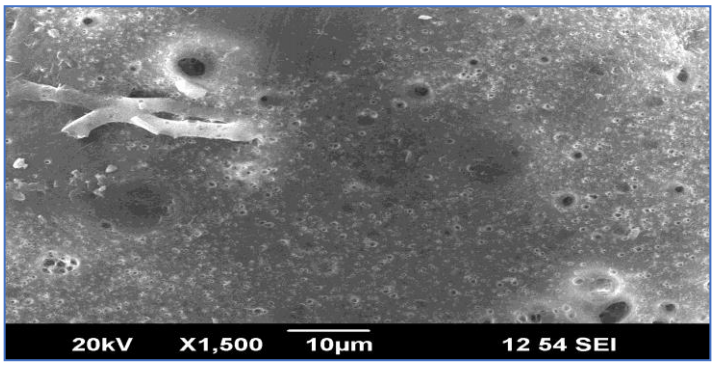
OF2(A)



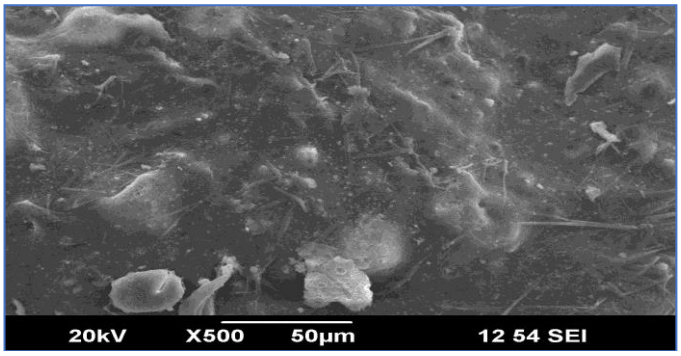
OF2(B)



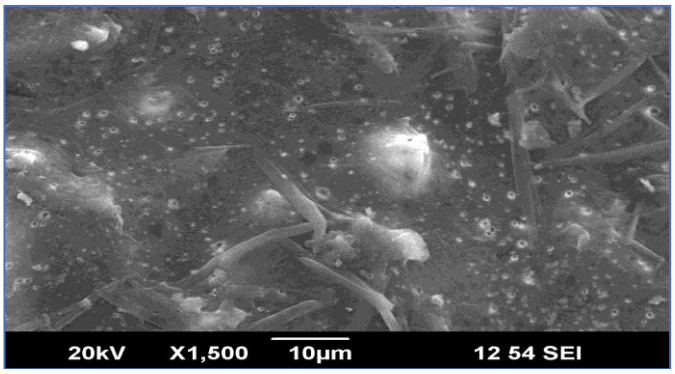
OF3(A)



OF3(B)



OF4(A)



OF4(B)

Fig. 3: Morphology of different microsphere formulations (OF1-OF4) showing whole image (A) and Surface image (B)

The angle of repose, percentage compressibility index and Hausner's ratio of microsphere formulations were determined in order to find out the flow properties. The formulation OF1, OF3, OF4 exhibited good flow properties with an angle of repose to be greater than 20 while formulation OF2 showed excellent flow with angle of repose < 20. The value of percentage compressibility index for microsphere formulations OF1-OF4 was found in the range of 15.47 % to 8.35%, suggesting excellent flow properties of all microsphere formulations.

Hausner's ratio is another mean of defining the flow properties. The numerical values of microsphere formulations (OF1 – OF4) were representing the Hausner's ratio 1.17 – 1.09, this indicates that all microsphere formulations exhibited low inter-particle friction and good flow property.

Formulation OF1-OF4 filled in hard gelatin capsules and sealed with 5% ethyl cellulose solution coated with 5%, 10% & 15% shellac solution was coded as C1–C4, C5-C8 & C9-C12 respectively.

The quality control tests carried on sealed coated capsules loaded with ODN microspheres complied with the pharmacopoeial standards for hard gelatin capsule. QC data was presented in Table 2.

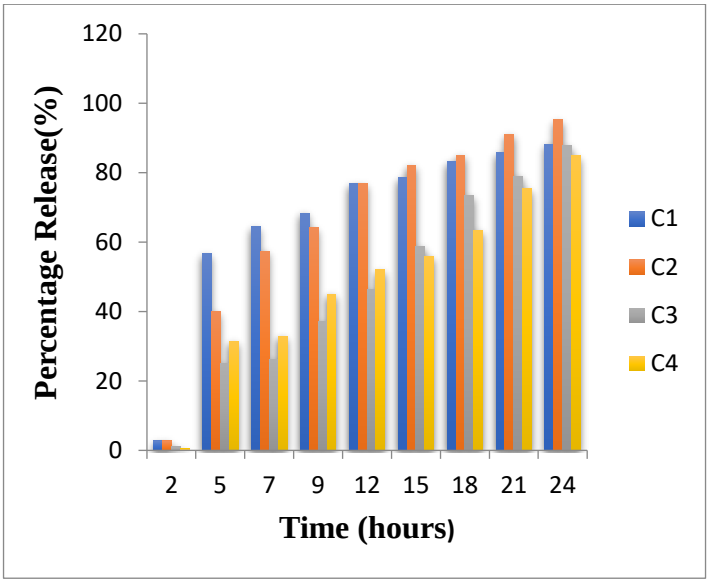
Table 2: Quality control tests of Coated Capsules of ODN Containing Varying Concentration of Coated Hydroxypropyl Methyl Cellulose (HPMC) and Ethyl Cellulose with Different Percent Shellac Solution Coating.

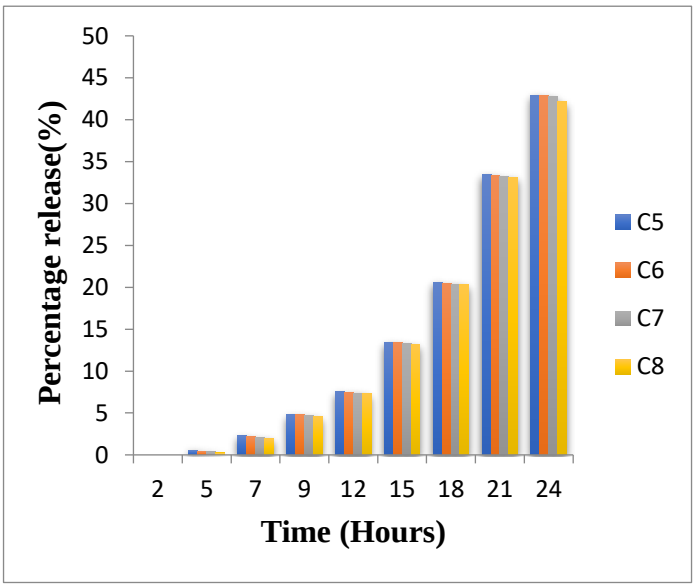
Formulation code	Average weight (mg)*	[1]Percentage weight variation (%)	% Drug content[2]	[2]Disintegration time (hrs)
C1	575.67	- 1.35 to + 1.71	95.08 ± 1.33	3.4 ± 0.13
C2	577.85	- 2.74 to + 2.68	98.56 ± 0.86	3.3 ± 0.09
C3	582.34	- 1.13 to + 1.56	100.23 ± 1.34	3.4 ± 0.06
C4	583.77	- 2.48 to + 2.62	98.04 ± 1.06	3.5 ± 0.10
C5	597.24	- 1.25 to + 2.89	101.2 ± 3.89	3.8 ± 0.09
C6	592.55	- 1.74 to +2.68	95.99 ± 3.96	3.6 ± 0.08
C7	603.43	- 1.63 to + 1.66	97.04 ± 2.33	3.9 ± 0.10
C8	598.29	- 2.48 to + 3.52	96.66 ± 1.83	3.8 ± 0.15
C9	611.75	- 2.35 to + 2.71	96.59 ± 3.93	4.2 ± 0.20
C10	609.31	- 1.68 to + 1.73	98.76 ± 3.32	4.2 ± 0.19
C11	613.24	- 2.63 to + 2.66	100.15 ± 1.73	4.3 ± 0.14
C12	610.87	- 2.28 to + 3.59	96.82 ± 2.78	4.1 ± 0.12

[1]Number of determinations = 10; [2]Values are mean ± S.D, Number of determinations=3

In-vitro drug release studies for all microsphere formulations filled in hard gelatin capsules (without sealing with shellac) were carried outby using buffer change method to mimic the GIT environment conditions. The dissolution medium was used 900 ml 0.1 N HCl (pH 1.2) as simulated gastric fluid for the first 2 h, followed by phosphate buffer as simulated intestinal fluid (900 ml, pH 6.8) for the rest of 6 h. The *in-vitro* release data for ODN formulations was depicted in Figure 4. It was observed that for each formulation the drug release decreased with increase in the amount of polymer because the release of drug from the polymer matrix takes place after complete swelling of the polymer.

The amount of polymer in the formulations increases the time required to swell the polymer also increases. The drug release from microsphere formulations OF1, OF2, OF3, and OF4 was noted to be 18.35%, 22.10%, 25.54% and 27.42% respectively in the first hour. This may be due to the drug present in the surface and pores of the microsphere. All microsphere formulations OF1, OF2, OF3, OF4 show percent drug release at the end of eight hours was found to be 58.92%, 66.70%, 75.07%, and 81.99%, respectively.





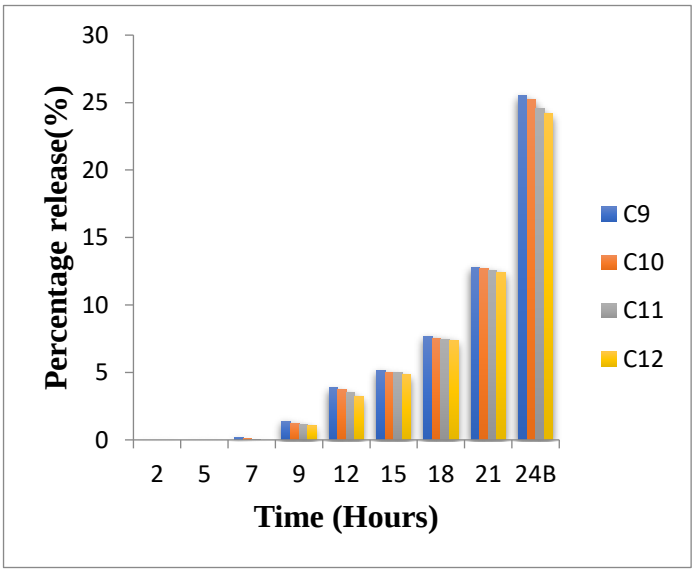


Fig. 4: Comparative *In-vitro* release profile of ODN Capsule formulations

The drug release data fitted in to Higuchi and Korsemeyer equation and coefficient of correlation were computed for all formulations [36,37,38]. The R^2 values were much closer to one for the Higuchi kinetics. Higuchi model explained the matrix diffusion mechanism of drug release. The correlation coefficient values for Higuchi model confirmed that drug release followed matrix diffusion mechanism or Higuchi pattern release. The mechanism of drug release of the all formulations was studied by fitting the release data to Korsemeyer equation. The n values with Korsemeyer-Peppas model for formulations OF1 - OF4 was found to be between 0.6162 - 0.5834. Since the n value from 0.45 to 0.85 is for Korsemeyer-Peppas model is an indicative of non-Fickian diffusion, the drug released from microspheres follow concentration independent non-Fickian diffusion [39, 40].

The drug release pattern of ODN formulations filled in hard gelatin capsules sealed with 5% ethyl cellulose and 5-15% shellac solution was investigated in same dissolution media for the same duration of time. It was found that after 9 hr of dissolution testing 41% to 65% ODN release was observed for formulations C4 to C1. Maximum 80% drug release was found with C1 after 18 hr and 70% was found with C4. All other shellac coated formulations from C5 to C12; maximum 20% drug release was found after 18 hr. *In-vitro* drug release pattern from shellac coated hard gelatin capsules it was found that the maximum drug release was found in the formulations coated with 5% shellac (C1-C4) after 18 hr proved the fact the sealing with ethyl cellulose and coating with shellac sufficiently protect the capsules from the intestinal environment and release the drug in the colon.

CONCLUSION

This study presented a novel colon specific drug delivery system containing ODN microspheres for the treatment of IBS. Preformulation study results showed the ODN was compatible with HPMC and Ethyl cellulose. The production method was optimized for particle size and production yield. The volume of internal phase, rate of agitation and concentration of emulsifying agent significantly influence the particle size and production yield of ODN microspheres. The prepared ODN microspheres exhibits good flow properties. *In-vitro* drug release study of all ODN loaded microsphere formulations OF1-OF4 show the release of drug from the microspheres was by diffusion which is well confirmed by Higuchi kinetic model. The n value of 0.62 from Korsemeyer- Peppas model showed the drug released follow non-Fickian diffusion.

The sealing and coating of hard gelatin capsules done with solutions of ethyl cellulose and shellac provide excellent protection for capsules in the GIT environment and avoided the drug release into the stomach and small intestine. The ODN capsules complied with pharmacopoeial standards for hard gelatin capsules. The colon specific capsule formulation C1 was best for colonic delivery of drug from other colon specific capsule formulations. The maximum drug release 80% & 70% was found in the formulations coated with 5% shellac C1 & C4 formulations after 18 hr an increase in the thickness of shellac coating influence inhibitory effect on drug release in the colon. In future, *in-vivo* microsphere based ODN delivery into the colon for treatment of IBS may be show good results.

REFERENCES

1. Lee WJ, Park HJ, Robinson JR. Bioadhesive-based dosage forms: the next generation. J Pharm Sci. 2000; 89:850-866.
2. Chourasia MK & Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems, *J. Pharm. Pharmaceutical Science* 2003; 6:33-66.
3. Mukherjee B, Mahapatra S, Guptab R, Patra B, Tiwari A, & Arora PA. Comparison between povidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrix patches based on in vitro skin permeation, *Eur. J. Pharm. Biopharm*., 2005;59(3):475–483.
4. Asghar L & Chandran S. Multiparticulate Formulation Approach to Colon Specific Drug Delivery, Current Perspectives, Journal of Pharmaceutical Science, 2006; 9(3):327-338.
5. Devrim B & Canefe K. Preparation and evaluation of modified release ibuprofen microspheres with acrylic polymers (eudragit) by quasi emulsion Solvent diffusion method: effect of variables, *Acta Poloniae Pharmaceutica & Drug Res*., 2006; 63(6):521-534.
6. Jelvehgari M, Siahi-Shadbad MR, Azarmi, S, Martin, GP & Nokhodchi, A. The microsponge delivery system of benzoyl peroxide: Preparation, characterization and release studies. *Int. J. Pharm*., 2006; 308(1-2):124-132.
7. Orlu M, Cevher E & Araman A. Design and evaluation of colon specific drug delivery system containing flurbiprofen microsponges. *Int. J. Pharm*., 2006; 318(1-2):103-117Johnson J & Mukhtar, H. Curcumin for Chemoprevention of colon cancer, *J. Pharm. Science*, 2007; 23:170–181.
8. Patra S, Choudhary AA, Khar RK, & Barik BB. Spectrophotometric method for ondansetron hydrochloride, *Ind. J. Pharm. Sci.* 2007;69(6): 840-841.
9. Chandra D, Kumar I, Jaiswal D, Ghosh, N, Singh H, Mishra A, Bhattacharya A, Bajpai M, & Jain D. Formulation and Evaluation of Satranidazole Microspheres for Colon Targeted Drug Delivery, *Journal of Pharmacy Research*, 2009; *2 (7*):1230-1233.
10. Hagger FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival and risk factors. *Clinical Colon Rectal Surg*. 2009; 22:191-197.
11. Dhawale SC, Bankar A & Patro M. Formulation and Evaluation Porous Microspheres of 5- Fluorouracil for Colon Targeting, *International Journal of Pharm Tech Research* 2010; 2(2):1112-1118.
12. Philip AK & Philip B. Colon targeted drug delivery systems: A Review on primary and novel approaches. *Oman Med. J*., 2010; 25:70-78.
13. Jose S, Dhanya K, Cinu, TA & Aleykutty NA. Design and formulate multiparticulate system containing chitosan microspheres for the colon targeted delivery of ondansetron for the treatment of irritable bowel syndrome, *Indian J Pharm Sci*, 2010;72 (1): 58-64.
14. Kajale AD, Kamble RS, Giradkar, KP, Bakde BV, Channawar MA, & Chandewar AV. Colon targeted drug delivery using natural polymers, *Int. J. Pharm. Res*., 2010; 2:1-5.
15. Kumar SB, Kumar S, Anand P, Saravanakumar M, Thirumurthy B. Formulation and Evaluation of Celecoxib Microspheres by Using Ethylcelluose and Eudragit S-100 in Colon Drug Delivery, *Der Pharma Chemica*, 2010;2(5), 322-328.
16. Philip A, & Philip B. Colon Targeted drug delivery systems: A review on primary and novel approaches, *Oman Medical Journal*, 2010;25(2):143-146.
17. Simi SP. Formulation and evaluation of Albendazole microcapsules for colon drug delivery system, *Asian Pacific Journal of tropical medicine, 2010;* 2:374-378.
18. Sunitha S, Amareshwar P & Kumar S. Preparation and Characterization of Ondansetron Hydrochloride Microspheres Using Various Cellulose Polymers, *International Journal of current Pharmaceutical Research*, 2010;2(2):44-49.
19. Kumar KV, Kumar T, & Math T. Colon targeting drug delivery system. A review on recent approaches. *J. Pharm. Biomed. Sci*., 2011; 2:11-19.
20. Patel A, Patel D, Solanki, T, Bharadia PD, Pandya VM, & Modi DA. Novel approaches for colon targeted drug delivery system. *IJPI's J. Pharm. Cosmetol*, 2011; 1:86-87.
21. Kulkarni P, Mudit D, Selvam P, & Singh D. Formulation and evaluation of Indomethacin microspheres for colon drug delivery system, *International research journal of Pharmacy*, 2011;2(8):181-184.
22. Swapna A, Mohammad A, Wamorkar V & Swathimutyam P. Formulation and Evaluation of Mesalamine Microspheres for Colon Targeted Drug Delivery System, *Journal of Pharmacy Research*, 2011;4(6):1670-1672.
23. Vajpayee A, Fartyal S, Singh A & Kumar S. Formulation and Evaluation of Colon Targeted Curcumin Microspheres Using Natural Polymers, *Journal of Pharmaceutical Research and Opinion*, 2011;4:108 – 112.
24. Modasiya MK, & Patel VM. Design of colon specific drug delivery using Sodium alginate and HPMC, *Journal of Pharmacy Research 2012;5(4): 2253-2258*.
25. Rajput S, Aggrawal P, Pathak A, Shrivasatava N, & Singh S. A Review on Microspheres: Methods of Preparation and Evaluation, *World Journal of Pharmacy and Pharmaceutical Sciences*, 1, 2012 ;(1):422-438.
26. Ramteke H, & Nath, LK. Formulation, Evaluation and Optimization of Controlled Release Hydrogel Microspheres for Colon Targeted Drug Delivery, *J. Pharm. Sci. & Res.*, 2012;4(2): 1739-1747.
27. Singh S, Singh A, Mahajan A, Pathak N, Upadhyay S & Pratap V. Formulation and Evaluation of Colon Targeted Drug Delivery of an Anti-Amoebic Drug, *International journal of pharmaceutical Innovations*, 2012;2(2): 138-152.
28. Sreelatha D & Kumar C. Colon Targeted Drug Delivery – A Review on Primary and Novel Approaches, *Journal of Global Trends in Pharmaceutical Sciences*, 2013; 4(3):1174-1183.
29. Kumar KGB, & Yadav NS. Design and Evaluation of a new Capsule-type Dosage form for Colon-Targeted Delivery of Etoricoxib. hit *J Pharma Sci*., 2013;3(1):147-151.
30. Kumar KG, & Yadav S. Design and Evaluation of a new Capsule-type Dosage form for Colon-Targeted Delivery of Etoricoxib. *J Pharma Sci*., 2013;3(1):147-151.

31. Raj S, Shanthi, Sreedharan, R, Samraj P. Formulation and Evaluation of Coated Microspheres for Colon Targeting, *Journal of Applied Pharmaceutical Science*, 2013; 3(4): S68-S74.
32. Sharma N & Harikumar SL. Formulation and Evaluation of Enteric Coated Microspheres of Ketoprofen Using Natural Polymers for Colon Drug Delivery, *International Journal of Pharmacy and Pharmaceutical sciences*, 2014;6(2): 886-892.
33. Prathap M, Gulshan MD & Rao R. Colon: Targeted Drug Delivery System – A Review, *J. Pharm science*, 2014; 3(5):429 - 437.
34. Filho TJ, Andreazza F, Sato ME & Murakami F. Development of a multiparticulate system containing enteric-release mini-tablets of omeprazole *Brazilian Journal of Pharmaceutical Sciences*, 2014; 50(3):505-511.
35. Dang T, Cui Y, Chen Y, Meng B, Tang B, & Bao B. Preparation and Characterization of Colon-Specific Microspheres of Diclofenac for Colorectal Cancer, *European Journal of Pharmaceutical Sciences*, 2015;14(9):1541-1548.
36. Saxena A, & Kitawat **S.** Formulation, Development and Evaluation of Microspheres of Ketoprofen by Using Different Polymers, *ASIO Journal of Pharmaceutical & Herbal Medicines Research*, 2015;1(1):41-47.
37. Lei J, Ding Y, Feng M, & Cao Q. Preparation of oral levofloxacin colon-specific microspheres delivery: *in vitro* and *in vivo* studies, *J. Pharm Biopharm*, 2016;2(3): 982-988.
38. Rai G, Awesh K, Yadav, Narendra K, Jain & Agrawal, Eudragit-coated dextran microspheres of 5-fluorouracil for site-specific delivery to colon, *J. Pharm. Science*, 2016;23(1): 328-337.
39. Katta R, Deveswaran R, Bharath S, Basavaraj B. Development of Mesalazine Microspheres for Colon Targeting, *Journal of Pharmacy Research* 2017;9(4):1-9.
40. Sharma RK and Midda AK. Preparation of Sustained Release Microspheres of Aceclofenac: Characterization &in-vivo studies. *Int. J. Res. Dev. Pharm. L. Sci*. 2017; 6(7):2862-2866.

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