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Optimization and fabrication of the nanosponge carriers of on dansetron using one-factor design

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Abstract: The current studies were aimed to formulate ethyl cellulose (EC), beta-cyclodextrin (β–CD facilitated EC based Ondansetron nanosponges (NS) using Response Surface Methodology (RSM) by employing One Factor Design. The NS were fabricated by Emulsion Solvent Diffusion method, followed by characterizations including, drug-polymer compatibility, entrapment efficiency, percentage yield, zeta size, zeta potential and *in-vitro* release of drug and Scanning Electron Microscopy (SEM) and X-Ray Diffractometry (XRD). The outcomes of Fourier Transformed Infra-Red Spectroscopy (FTIR) have confirmed the compatibility of the drug and excipients. It was found that NS have good entrapment efficiency along with their satisfactory percentage yield. Particle size analysis has confirmed the synthesis of nanosized NS (87.8nm to 108.2nm), having spongy surface, that was described by SEM results. Furthermore, the drug release studies have described a good sustained release of ondansetron for the period of 8 hours. The kinetic modeling has predicted that drug would follow the non fickian type of diffusion mechanism. The application of statistical approach was found helpful in designing and evaluating the NS, avoiding the laborious work, needs to be conducted while using hit and trial method.

Keywords: Ondansetron, nanosponges, response surface methodology, β-cyclodextrin.

INTRODUCTION

Cancer is the disease is one of the fatal disease with alarming mortality rate in the world (Saginala *et al.*, 2020). Due to its prevalence and the complications, it is the area of focus for research nowadays. Chemo and radio therapy are associated with the side effects of nausea and vomiting leading to concomitant administration of the ondansetron (a highly selective 5-HT3 receptor antagonist) as palliative treatment. As the chemotherapeutic agents trigger the release of 5-hydroxy tryptamine leading to increased gastroesophageal reflex (Heckroth *et al.*, 2021), so ondansetron act by antagonizing its action on the receptor. It is short acting drug with 3.1 hours of half-life, for which concomitant doses are required.

The frequent dosage can reduce the patient compliance. Thus, with the objective to increase patient compliance by dose reduction and reduction in the frequency of dose administration, the prolonged release formulation design utilizing nanotechnology is one of the favorable approach. Its frequent used in drug delivery and medicine industry has gained significant importance (Selvamuthukumar *et al.*, 2012), that may offers decrease in side effects of the medicines, while increasing therapeutic index, tolerability and efficient delivery of the corresponding medicine (Shivani *et al.*, 2015). Thus, nano medicines are replacing the traditional drugs in the area of therapeutic impact, targeted delivery and controlled release.

Nanosponges (NS) is a novel drug delivery design with a particle size under 1 μm. NS can entrap wide range of drug molecules by forming additional and non-inclusion multiplexes (Patel *et al.*, 2012). They are considerable for more exact delivery and drug targeting, reducing toxicity while maintaining the beneficial effects such as, better safety and greater biocompatibility (Arnum, 2011).

The purpose of present work was to formulate ondansetron nanosponges using EC with and without β-CD, by design expert software. The current formulation would help to reduce dosing frequency and increase patient compliance by sustained release drug delivery.

MATERIALS AND METHODS

Material

For the preparation of Nanosponges, Ondansetron was gifted generously by Pharmedic laboratories, Lahore,

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Pakistan. Ethyl cellulose (EC) was purchased from China N.10CP.S lab chemical, Polyvinyl Alcohol (PVA), Beta-Cyclodextrin (β–CD), Dimethyl sulfoxide (DMSO) and Ethanol were purchased from Merck Darmstadt Germany. Distilled water and other chemicals were taken from M.Phil. Research lab, The University of Lahore, Lahore, Pakistan. All other chemicals used were of Pharmaceutical grade.

Method

Synthesis of ethyl cellulose based nanosponges

Ethyl Cellulose based Ondansetron Nanosponges were prepared by solvent diffusion method. Different formulations of these nanosponges were formulated using different proportions of drug-to-polymer (table 1). The weighed quantity of drug and EC was added gradually into the continuously stirring 8 ml of Ethanol for each preparation to form organic phase (Internal Phase). The aqueous phase (External Phase) was consisted of 1% PVA and tween 80. The organic phase was added dropwise in to the aqueous phase under continuous stirring at very high-speed of 1000 rpm using the GUO-HUA multi-functional overhead stirrer for 2 hours, followed by filtration through the whatman filter paper No-1. The resultant residue that was obtained afterwards was then dried, weighed and stored for the further analysis

Table 1: Composition of the EC based Nanosponges according to One-Factor design

Serial Number	Formulations Code	Amount of EC (gm)
1	F1	0.75
2	F2	2.06
3	F3	1.63
4	F4	2.5
5	F5	0.75
6	F6	1.19
7	F7	2.5

Constant quantities of Ondansetron (750 mg), PVA (50mg) and Tween 80 (50mg) and Ethanol (20ml) were used in each formulation batch

Synthesis of β-CD facilitated EC based nanosponges

Emulsification technique was used to formulate β-CD facilitated EC based Ondansetron Nanosponges. Initially, an inclusion complex Ondansetron-β-CD (1:1) was prepared by the co-grinding method in the china dish. The grinding was continued for 30 minutes. The measured quantity of EC was dissolved in Ethanol and DMSO (1:1) mixture to form an organic phase, followed by addition of the inclusion complex in it. The mixture of organic phase and inclusion complex was added rapidly to aqueous phase that contains the 1% w/v, each of PVA and tween 80, under continuous speed at 1200 rpm for 2 hours to form the oil in water emulsion. Afterwards, the mixture was stirred at the variable rpm that ranges from 1000-2000 rpm for 3 hours to evaporate he of solvent through the reaction system in the flask. This was resulted in the formation of Nanosponges, which were obtained by filtration through whattman filter paper No-1. The obtained mass was then dried at the room temperature and stored for further analysis (table 2).

Development and optimization of formulation by one-factor design of response surface methodology (RSM)

Formulations of nanosponges were developed and optimized by one-factor experimental design of Response Surface Methodology (RSM) with the help of Design-Expert software (7.01version). Seven (7) formulations by selecting EC as variable and after initial evaluation, 3 formulations were selected for further studies. Formulations were developed with and without β-CD as presented in table 1 and **2** respectively.

Table 2: Composition of the β-CD facilitated EC Nanosponges according to One-Factor design

Serial Number	Formulations Code	Amount of EC (gm)
1	CF1	0.75
2	CF2	2.06
3	CF3	1.63
4	CF4	2.5
5	CF5	0.75
6	CF6	1.19
7	CF7	2.5

Constant quantities of Ondansetron (750 mg), β-CD (750mg) and Ethanol+DMSO (5:1) and PVA (50mg) Tween 80 (50mg) were used in each formulation batch

Characterization drug excipients compatibility studies

Fourier transform infrared spectroscopy (FTIR) was done to confirm the drug-excipients compatibilities. It was conducted for β-CD, EC and for PVA individually as well as for the prepared nanosponges (Sohail *et al.*, 2014).

X-Ray diffraction (XRD)

The X-ray diffraction (XRD) was performed to identify the nature of drug, that whether it was amorphous or crystalline, both in pure form as well as in nanosponges (Sohail *et al.*, 2014).

Scanning electron microscopy (SEM)

The surface morphology of nanosponges could be determined observing it under the scanning SEM. The SEM of the pure drug as well as prepared formulations had been conducted at 2500X.

Percentage yield

Percentage yield is the percentage of total mass of product obtained as a result of process as compared to total mass used, which can be calculated from following formula;

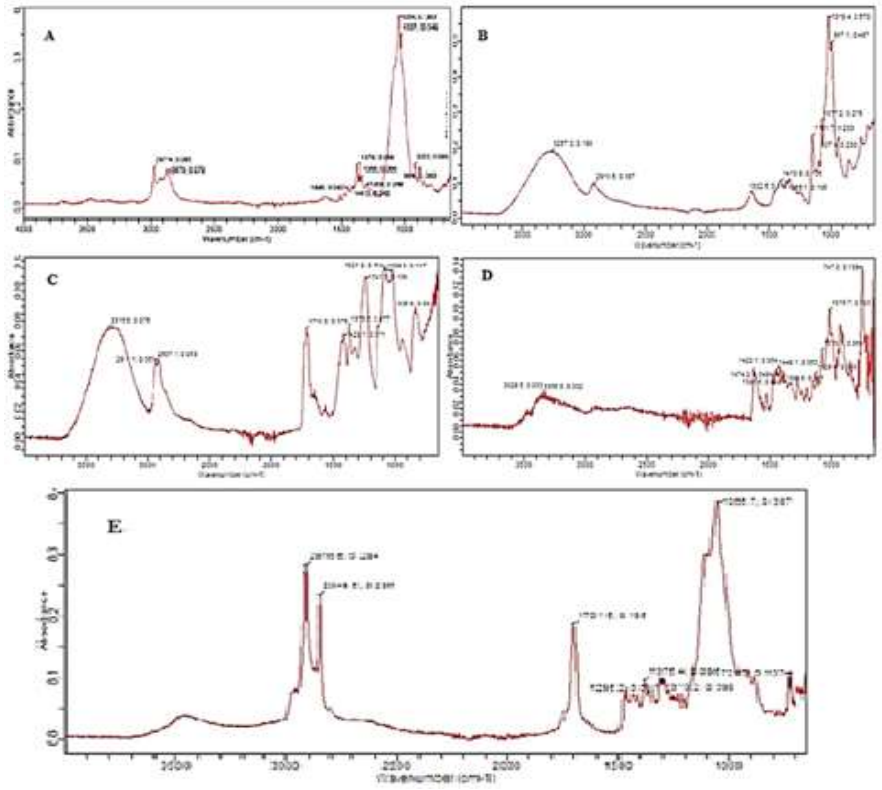

Fig. 1: FTIR scan of ethyl cellulose (A), β-Cyclodextrin (B), Polyvinyl Alcohol (C), Ondansetron (D) and prepared nanosponges (E)

$$\text{Production yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100 \quad \text{Eq. 1}$$

Percentage yield

The results showed that the percentage yield of EC based and β-CD facilitated EC based nanosponges has been increased with increase in the polymeric contents. The findings have been tabulated in table 3.

Entrapment efficiency

Entrapment efficiency gave us an idea that how much percentage of drug is entrapped or taken up into the prepared nanosponges. For this purpose, the weighed amount of nanosponges was triturated in the pestle and mortar with ethanol, this was then washed with water and filtered. The solution thus obtained was analyzed for amount of drug entrapped through UV-spectrophotometer and calculated as (Sherje *et al.*, 2017);

$$\text{Entrapment effciency} = \frac{\text{Drug entrapped}}{\text{Total drug}} \times 100 \quad \text{Eq. 2}$$

In-Vitro drug release studies

In-vitro dissolution studies were performed using 900ml of neutralized phthalate buffer solution of pH 4.6 as a dissolution media for 8 hours. The apparatus was set to constant conditions of temperature (37°C±0.5°C) and paddle speed (50 RPM). The calculated amount of nanosponges were taken and placed in cellophane membrane and sub merged in 900ml of dissolution medium. The first sample of 5ml was taken, after 30 minutes and afterward, after every hour, till the 8th hour of the studies. The same volume of dissolution medium was added after every sample to maintain the constant volume of the dissolution medium. These samples are then analyzed using double beam UV/VIS-Spectrophotometer at 310nm wavelength (Tanveer *et al.*, 2021).

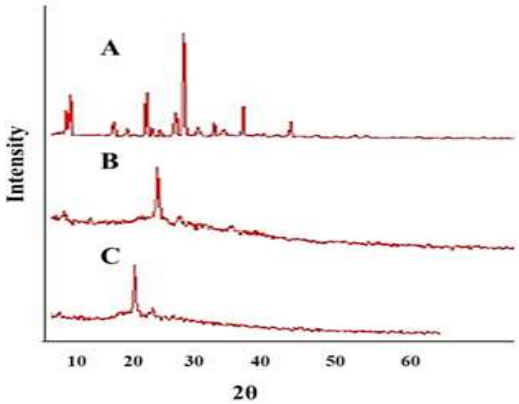

Fig.2: XRD studies indicating the behavior of drug in pure form (A) and after incorporation in EC based nanosponges (B) and β-CD facilitated EC based nanosponges (C)

Table 3: Percentage yield and Encapsulation efficiency (%) of EC based and β-CD facilitated EC based nanosponges

Formulation	Percentage Yield (%)	Encapsulation Efficiency (%)
F1	22.81±3.8	65±0.03
F2	40.02±8.2	32±0.01
F3	50.24±2.1	47.68±0.02
CF1	19.01±5.9	55.98±0.02
CF2	48.89±8.9	97.38±0.03
CF3	73.80±3.3	93.15±0.08

Table 4: Release kinetics of EC based (F1-F3) and β-CD facilitated EC based nanosponges (CF1-CF3)

Kinetic Models	Variables	F1	F2	F3	CF1	CF2	CF3
Zero Order	k_0	0.61	1.224	1.266	1.843	2.271	2.233
	R^2	0.96	0.379	0.7962	0.9406	0.8548	0.9585
First Order	k_1	0.006	0.013	0.013	0.02	0.025	0.024
	R^2	0.958	0.418	0.8158	0.9505	0.8667	0.97
Higuchi Model	k_H	1.412	2.991	3.027	4.316	5.309	5.225
	R^2	0.773	0.884	0.8968	0.8614	0.7774	0.8741
Korsmeyer-Peppas Model	k_{KP}	0.474	3.254	2.435	2.519	3.066	3.021
	R^2	0.966	0.892	0.9233	0.9587	0.8702	0.9756
	N	1.143	0.448	0.634	0.826	0.833	0.831
Hixson-Crowell Model	k_{HC}	0.002	0.004	0.004	0.006	0.008	0.008
	R^2	0.959	0.406	0.8094	0.9475	0.8631	0.9666
Best fit Model		Korsmeyer-Peppas	Korsmeyer-Peppas	Korsmeyer-Peppas	Korsmeyer-Peppas	Korsmeyer-Peppas	Korsmeyer-Peppas

Table 5: Statistical outcomes of applied model on release data of EC based and β-CD facilitated EC based nanosponges

Quadratic Model						
Response	F-Value	Prob>F	R^2	Predicted R^2	Adequate Precision	C.V (%)
% Drug Release in EC based nanosponges	899.08	0.0001	0.9979	0.9967	59.384	1.15
% Drug Release β-CD facilitated EC based nanosponges	130.95	0.0002	0.9850	0.9626	23.280	1.72

Table 6: Zeta Size and Zeta Potential of EC based (F1-F3) and β-CD facilitated EC based nanosponges (CF1-CF3)

Formulation	Zeta size (nm)	Zeta potential (mV)
F1	108.2±0.5	-23.5±0.5
F2	101.4±0.27	-27.3±1.0
F3	99.5±.2	-16.9±0.15
CF1	93.9±0.5	-7.1±0.5
CF2	97.2±.4	-11.5±0.8
CF3	87.8±1.0	-15.7±0.5

STATISTICAL ANALYSIS

One-way Analysis of Variances (ANOVA) has been employed to evaluate the release data statistically. The level of confidence interval was set to 95%.

Release kinetics

The *in-vitro* release data was subjected to release kinetic modeling, where different kinetic models including first order, zero order, higuchi model and korsmeyer peppas model were applied to find out the mechanism and behavior of drug release form the prepared nanosponges (Tai *et al.*, 2019).

Zeta potential

Zeta potential determination is done for the estimation of the product surface charge which owes its stability. The particles will not adhere to one another, when its zeta potential is above +30 and below -30 (Instruments, 2012).

Zeta sizer

Zeta sizer is used for the estimation of size of the particle range of the sample fed. The Malvern software installed in the system gives the intensity distribution data of the particles on different size ranges as well as the graphical representation is obtained. Peak on graph tells the actual size of which most particles are present (Instruments, 2012).

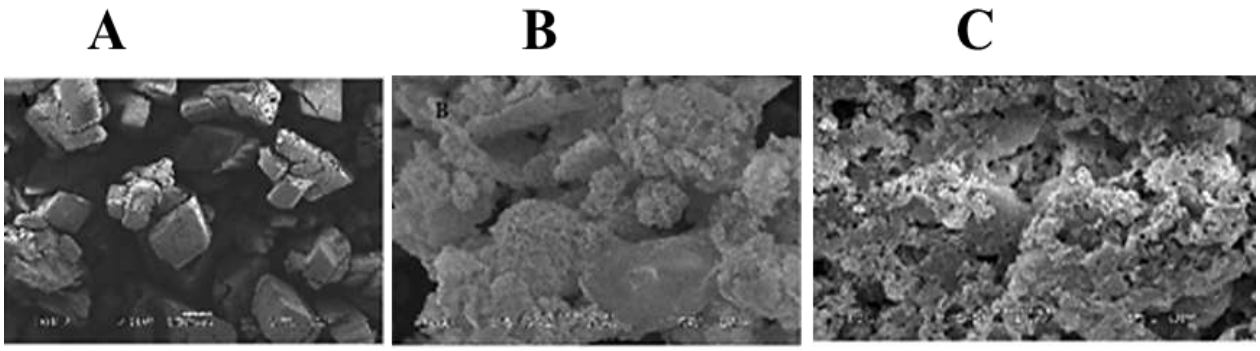

Fig. 3: SEM of pure drug (A) indicating crystalline nature and spongy surface of EC based nanosponges (B) and of β-CD facilitated EC based nanosponges (C)

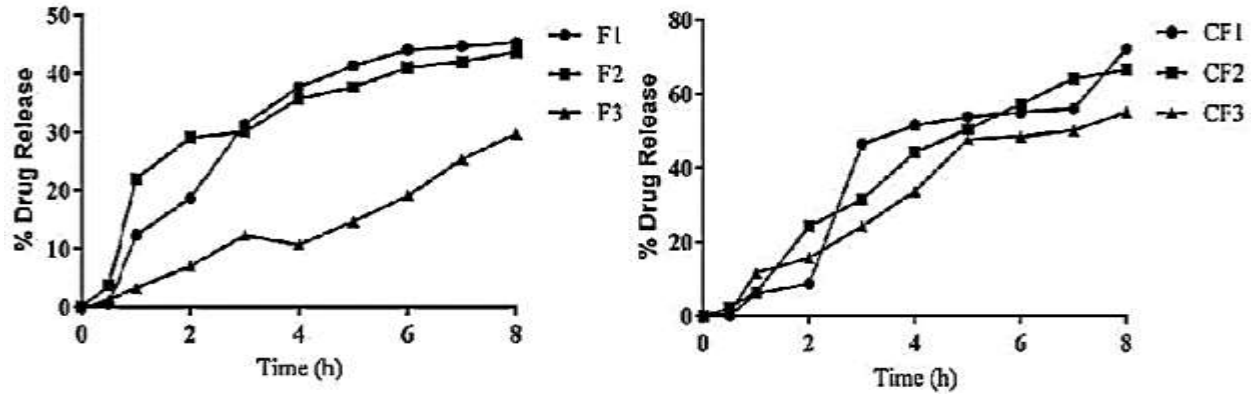

Fig. 4: *In-vitro* drug release studies describing polymeric concentration dependent sustained release behavior from both EC based (F1-F3) and β-CD facilitated EC based nanosponges (CF1-CF3)

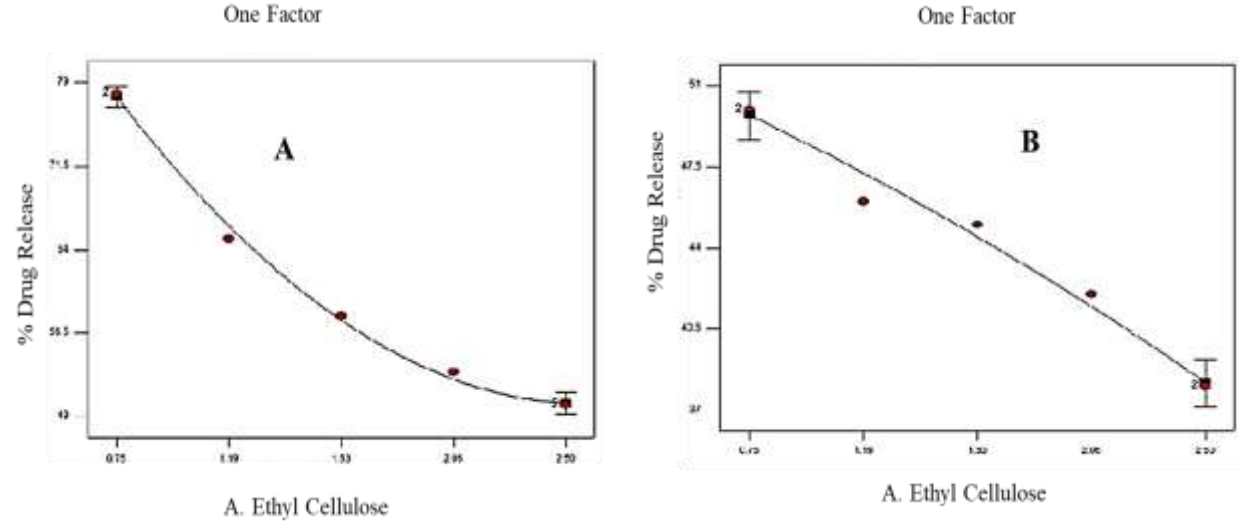

Fig. 5: Effect of variable concentrations of EC on drug release from EC based (A) and β-CD facilitated EC based nanosponges (B)

RESULTS

Fourier transform infrared (FTIR) spectroscopy

FTIR scan of Ondansetron, EC, PVA and β-CD as well as for prepared formulation was run between 4000-500cm^{-1}. The presence of characteristic peeks of the drug in the formulation has provided the evidence of physicochemical compatibility of the used ingredients. The results showed that in the IR spectrum of EC, the peaks at 1037 and 1054cm^{-1} reviled the presence of C-O stretches for alcoholic groups and at 1445 cm^{-1}, there was C-C stretches for the presence of aromatic group. O-H stretch was described by peek at 2974 cm^{-1} (Sadashivaiah *et al.*, 2014). In IR of β-CD, OH stretching was observed at 3267 cm^{-1} (Abarca *et al.*, 2016; Dardeer *et al.*, 2017). The hydroxyl groups (O-H) PVA, in the IR scan displayed a wide and intense band at 3315 cm^{-1}. The band at 2911cm^{-1} corresponded to the (-CH2-) asymmetric and the symmetric stretching. Where, the peak observed at 1420 cm^{-1} can be recognized for C–H and O-H bending. Absorption bands at 1718 cm^{-1} was due to symmetric stretching of the carboxylate anion (-COO-) (Srinivasa *et al.*, 2003). The spectra for ondansetron has shown the peaks observed at 747 cm^{-1}, indicated the presence of O-di-substituted benzene and peaks at 1448cm^{-1} and 1474 cm^{-1} indicated the existence of CH_3 group (Khan *et al.*, 2007). All the characteristic peaks were observed in the FTIR scan of ondansetron nanosponges, indicating the compatibilities of the used ingredients (fig.1).

XRD studies

XRD studies indicated the crystalline nature of the drug by showing characteristic intense peaks at angles ranging from 7 to 36.5º and the maximum intensity of the peak, appeared at 26.4º (fig.2A). However, in figure 2B and 2C, it was observed that, except one prominent peak in both diffractogram, at about 25º and 20º, respectively, all other peaks were masked in the form of nanosponges.

Scanning electron microscopy (SEM)

The outcomes of the SEM studies were also supporting the XRD findings, as the crystalline structure of the pure drug has been observed in the fig. 3A, while a spongy surface of the particles was evident from 3B and 3C (Kharb *et al.*, 2016; Kumria *et al.*, 2013).

Entrapment efficiency

The data observed for the entrapment efficiency for the weighed amount of nanosponges, shown in table 3. The tabulated results have disclosed that the encapsulation efficiency of the formulations decreased with increase in the polymer content in formulation F1 to F3.

In vitro drug release studies

The formulated nanosponges were subjected to *in-vitro* drug release studies using USP dissolution apparatus type-II. The rate of drug release was found to be decreasing with increase in concentration of the polymer and vice versa (fig. 4).

Drug release kinetics

The drug release data was subjected to drug release kinetics, which has reviled that the korsmeyer peppas model was the best fit model, explaining the diffusion type of drug release mechanism (table 4).

The results shown in table 4 were describing the dominancy of korsmeyer peppas model for all the selected formulations. Formulations have followed the korsmeyer-Peppas model, showing the exponential release of drug from the formulations. The values observed for formulation have strong correlation, as R^2 values for all formulations are close to 1. The value of $n \leq 0.45$ correspond to the fickian type of diffusion, while, $n \leq 0.89$ show transport through non-fickian diffusion while $n > 0.89$ describes the super case II transport. Thus, the formulation F1 showed super case II transport mechanism, while all other showed non-fickian transport predicting that the release of drug is coupled with relaxation of polymer and can be affected by various variables.

Numerical optimization of data

Total 7 formulations were design by using design-expert software and optimized by One-Factor RSM. Studied response was the release of the drug from prepared nanosponges. Statistical evaluation was done by applying quadratic model, followed by analysis of variances (ANOVA). The positive values 57.65 and 44.48 were the indication that the overall response was constructive while negative values of X_1 and X_1^2 were advocating that negative impact of increase in the concentrations of selected variable (EC). Outcomes of the applied models were tabulated in table 5.

The F-value in Model, of 899.08, inferred that the model was significant. The value of *P* ($0.0001 < 0.05$) had also indicated the significance of the applied model terms (table 5). The Predicted value of R^2 (0.9946) was also supported the findings. Similarly, in case of β-CD facilitated EC based nanosponges, the F-value 130.95 pointed out towards the significance of model, along with the *P* value ($0.0002 < 0.05$). The prediction of strong correlation (Pred R^2 =0.9626) has also indicated that the applied model is significant and valuable in studying the selected response (Drug release).

Graphical illustrations in fig. 5 were the evident of sustained release effect that was directly linked with the concentration of the EC. The results of the current study were in compliance to the findings of many researchers, available in the literature (Khairnar *et al.*, 2014; Phadke *et al.*, 2014; Tsunashima *et al.*, 2016).

Zeta potential and zeta size analysis

The Zetasizer Nano-ZS was used for zeta size analysis of EC based and β-CD facilitated EC based nanosponges. The zeta potential was measured for defining the velocity of particle motion in the particle charge and electric field. The particle size determination has confirmed that the prepared particles were of nano size (table 6) hence; Confirming the suitability of adopted method and selected ingredients for the preparation of nanosponges. The suitable value of negative zeta potential (F1 and F2) has described the satisfactory stability and segregation of prepared nanosponges (table 6)**.**

DISCUSSIONS

The prepared NS were evaluated for different physicochemical parameters and it was observed that these particles were of satisfactory quality and capable of delivering the drug with desired characteristics.

According to FTIR, the characteristic peaks of the individual ingredients have been emerged in the IR scan of prepared NS formulation, confirming the chemical compatibility of the selected ingredients. When the pure drug and NS were subjected to XRD, it has been reviled that drug was crystalline in nature but, in NS formulation the intensity of crystallinity had been decreased. The claim that drug was crystalline, has been strengthen by the findings of SEM, where a clear crystalline structure of the drug has been observed. However, the formulated NS were of spongy nature, assuring the successful synthesis of NS. In the preparation of NS, the facilitation of β-CD was proved to be fruitful, as the studied parameters were the explanation of pronounced effects of stated excipient. EC it-self has a good repute of being effective in formulating micro as well as nano particulate drug delivery systems but its combination with β-CD was even more effective. The fact has been observed in percentage yield of NS, where the yield was greater in the case, where β-CD has been used. Although, the entrapment efficiency was found to be decreasing with increase in polymeric contents, however, the inclusion of β-CD has shown a positive influence over the entrapment of the drug in the core of nanosponges, indicating the beneficial effect of β-CD to capture and hold the drug. The prepared NS have also been evaluated for the drug release studies, where a burst effect was noticed in the case of F1, while other formulations gave a good sustained effect throughout the study duration. However, greater amount of drug has been released in β-CD facilitated NS. It might be due to the fact that β-CD could improve the dissolution profile of the drug (Badshah *et al.*, 2021). All the formulations have guaranteed a satisfactory drug retardation property, but this effect was towards lesser side in those formulation prepared with the addition of β-CD, as it is famous for facilitating in prompt release of the drug. The cyclodextrins are well known for their ability to enhance the dissolution profile of the drugs (Wei *et al.*, 2017). In current study, it might be the reason that sustained effect was more promising in the formulation having EC alone. It is of great importance to evaluate the pattern and mechanism drug release form the prepared formulations. In the current studies, the koremeyer peppas model was found to be dominating with non-fickian type of diffusion mechanism.

The studies have been assisted by One Factor statistical approach, which described that variation in the concentration of polymer could influence the rate of drug release. The EC, being the hydrophobic polymer, has the great potential to impart sustained effect. Similar observations have been made in the current studies, where increasing concentration of the polymer, causing decrease in the rate of drug release and vice versa (Qiao *et al.*, 2021).

CONCLUSION

The Ondansetron was efficiently entrapped in both EC based nanosponges as well as β-CD facilitated EC based nanosponges. The application of statistical approach proved to be efficient in designing, evaluating the formulation and found helpful in saving the time and ingredient, that is very much difficult in tedious hit and trial approach.

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