Original Article

Development and investigation of *in-vitro* sustained release potential of montmorillonite-chitosan microbeads of cefaclor

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Abstract

The oral drug administration is most appropriate route for drug delivery to patients. But this route is allied with several drawbacks such as frequency of administration as well as gastric distress. To avoid these problems attempt was made to develop the sustained release system by using nanocomposite clay (MMT), polymer chitosan (CS) and crosslinking agent STPP based microbeads for oral administration of Cefaclor (CF). The formulations were optimized and validated by using Box–Behnken design with 3 different levels of MMT, CS and STPP, wherein the %EE and % drug release at 8 h were considered as dependant responses. The prepared formulation was characterized for FT-IR, DSC and XRD. The optimized formulation was evaluated for various studies like % yield, swelling behavior, particle size, *in- vitro* drug release and surface morphology studies. The prepared formulation showed physical interaction due to surface adsorption and intercalation of drug with that of MMT. The optimized formulation showed good yield, %EE and swelling behavior due to high amount of MMT, chitosan polymer and STPP crosslinking agent. The size of the microbeads particle was <500 µm and the drug release takes place in slow and sustained manner up to 8 h. Polymeric cross-linking and MMT stalking were observed in FE-SEM study indicated unique. Drug release followed the non-fickian diffusion pattern coupled with matrix release as indicated by Korsemeyer-Peppas (n) value of 0.3228.

Key words: Sustained release; MMT; STTP; microbeads; Crosslinking

INTRODUCTION:

The most common and recommended form of drug delivery is through oral route. Oral drug delivery effectiveness may be influenced by factors such as gastric emptying, dosage form gastrointestinal transit time, drug release from the dosage formulation, and drug absorption location. Oral sustained drug delivery systems (SDDS) have many benefits over immediate drug release type of dosage forms, including the reduction of overall dose administered; the lesser variations in plasma drug concentrations and at the site of action over long periods of time, ensuing in improved therapeutic concentrations and decreased side effects. Patient compliance will be increased due to reduced dosing frequency.[1] The medication is delivered at a fixed pace for a set duration using oral SDDS. As a result, sustained oral drug delivery system will overcome the drawbacks of traditional dosage forms while also improving a drug's therapeutic efficacy.

Multilayer tablets, matrix tablets, modified capsules and microbeads are some of the different sustained controlled release methods for oral delivery of drug. Because of the ease of planning and administration, microbeads are highly customized. A microbead is a spherical particulate structure having diameter in the range of 0.5-1000 µm. Microbeads capture drug molecules in crosslinked polymeric matrices and the release of drug slowly and in a regulated manner for a prolong period of time.[2] In contemporary era, pharma experts are looking for an alternative carrier system rather than using the conventional tablets, pellets, capsules and microbeads. Other innovative drug carrier systems are being researched in addition to conventional polymeric microbeads. The microbeads formed by blend of modified nanocomposite clay and polymer is the most intriguing cutting-edge technology.[3]

Fusion of inorganic layered silicates with polymer allows for the development of nanocomposite clay-polymer microbeads. Inorganic layered silicates of nanometer size make up nanocomposite clays. Microbeads for sustained or controlled-drug-delivery could be created using a mixture of organic and inorganic materials. Since these clays may be synthesized in a lab, they may be less contaminated. These clays are easily and economically available, and they also have important drug delivery properties.[4,5] Clays can be organically modified to allow drugs to intercalate into the inner space of inter-layered silicates. This might lead to a high level of entrapment. On addition of the polymer to microbeads yields superior results in terms of entrapping the drug and controlling drug delivery. Other than these attractive properties organically modified nanocomposite clays have high levels of safety and biocompatibility. These clays are existed as metal silicates with a thin platelet-like structures with a diameter of '500 – 1000' nm and a thickness of 1 nm.

Generally, clays are hydrated, causing the smectite platelets stalks to swell and form a colloidal gel. These platelets shape three-dimensional structures resembling a house of cards due to electrostatic attraction. Montmorillonite (MMT) and hectorite are the most important members of this nanocomposite clay family.[2]

In previously reported study by 'El-Hamshary H *et. al.,* (2019)', it was observed that MMT-ionene nanocomposite carriers were effectively used for controlled drug delivery.[6] In another study, Lal S *et. al.,* (2015) designed MMT- poly lactic-co-glycolic acid (PLGA) nanocomposites for per oral delivery of Atenolol as a sustained release carrier. Same author reported that the use of the biocompatible of MMT-PLGA nanocomposite for oral drug delivery of the insulin in 2017.[7,8] Iliescu RI *et al.,* (2014) investigated *in-vitro* release of irinotecan from MMT-Alginate nanocomposite beads. All these studies reported the excellent features of nanocomposite such as surface adsorption and intercalation of drugs within the layered silicates.[9] Thus, with these proofs of concept in this study cefaclor (CF) was taken as model drug for development of nanocomposite clay-polymer oral microbeads for SDDS.

Alginate beads have been reported in some studies for the problems during beads preparation. Drug loss and shrinkage of the alginate polymer take place when subjected to an acidic medium, while it dissolves at the higher pH values.[10] On the contrary, chitosan beads dissolve at low pH and are insoluble in alkaline media. Some studies reported that chitosan alone cannot control drug release due to its hydrophilicity.[11] Therefore, the MMT-Chitosan- sodium tripolyphosphate (STPP) complex was considered to be a promising medium to reduce the porosity of alginate beads and decrease the leakage of the encapsulated drug.[12] Furthermore, one approach to obtaining more controlled release of drugs is the formulation of coated drug beads.

CF is a second-generation cephalosporin antibiotic with a wide range of action recommended for the treatment of urinary and respiratory tract infections. CF is sufficiently absorbed in the systemic circulation, with a peak plasma concentration achieved within 30–60 minutes. In the presence of food, the peak serum concentration is greatly decreased, but the exact amount of drug entered in systemic circulation remains unchanged. CF is quickly excreted in urine, with a half-life of around 2 hours. CF is a potential drug candidate for development of sustained release dosage forms due to its short half-life and high dose.[13] Chemically, CF is (6R, 7R)-7-[[(2R) –amino-phenyl acetyl]-amino] - 3-chloro -8-oxo-5-thia 1 Azabicyclo [4.2.0] oct-2-ene- 2-carboxylic acid monohydrate found soluble in water and HCl.[14] CF is effective against *Staphylococcus saprophyticus, Staphylococcus aureus, Streptococcus pyogenes* and *Streptococcus pneumoniae.* Currently, in market variety of CF formulations are available such as conventional tablets, capsules, extended release matrix tablets etc.[15]

In this study attempt has been made to develop a controlled release delivery system of cefaclor using MMT-CS-STPP microbeads for sustained delivery of CF and *in-vitro* investigation of sustained release potential.

MATERIALS AND METHODS:

CFR was collected as a gift sample from Aurobindo Pharma Ltd., Hyderabad, Clay (MMT) was purchased from Platonic Pvt. Ltd. Darbhanga, India. Sodium tripolyphosphate (STPP), Chitosan (CS) were purchased from Sigma Aldrich Ltd. Mumbai, India. All other chemicals used were of analytical grade.

FT-IR analysis of the microbeads formulation:

To check the compatibility between drug and excipients, the analysis of pure CF, clay (MMT), chitosan (CS), STPP physical mixtures of CF with different excipients (mixture of CF+MMT, CF+MMT+CS, CF+MMT+CS+STPP at equal weight ratio) and the optimized formulation were studied by FTIR (8400S, Shimadzu Corporation, Kyoto, Japan). Potassium bromide (KBr) disks were prepared by mixing few milligrams of sample with KBr by compacting in a hydraulic press under the vacuum at pressure of 6–8 torr. The resultant disc was mounted on sample holder in FTIR spectrophotometer and the spectrum was recorded from 4000 cm^{-1} to 40 cm^{-1}. The resultant spectra were compared with that of pure drug for any spectral changes.

Preparation of CF-MMT-CS-STTP microbeads:

Various batches of microbead formulations were prepared by ionotropic gelation technique as earlier reported by Raut *et al.,* (2019) with some modifications.[2] Initially, chitosan was slowly and homogenously dispersed in water (25 mL MilliQ) along with constant stirring at 40 ºC, and 500 rpm for 3 h. Separately, CF was dissolved in this dispersion under stirring. Further, measured quantity of MMT was added to above dispersion with stirring for 2 h. The mixture was observed for homogenous appearance. The entrapped bubbles were removed under vacuum oven overnight at 40 ºC. This homogenous dispersion was dropped into the 100 mL STPP solution. The microbeads formed were kept for curing for 15 min with gentle agitation. Prepared microbeads were filtered and washed multiple times with MilliQ water and then dried at ambient temperature for 24 h, and further in hot air oven for 6 h at 70 ºC. The microbeads obtained were kept in desiccator.

Formulation (CF:CS:STTP), Optimization by Box-Behnken Design for CF microbeads:

The effects of various variables on the formulation of microbeads were examined using the Box–Behnken design. This design was chosen explicitly to investigate the entire design space with less experimental runs and no aliasing of interaction variables.[16] Design-Expert® Software Version 9.0.4.1 (Stat-Ease Inc., Minneapolis, USA) was used to refine the microbead formulation. The most influential factors considered for development of microbeads include the

concentration of MMT, CS and STPP, which may have significant effects on entrapment efficiency (% EE) and drug release.

The independent factors were coded as A: MMT, B: CS and C: STPP, 3 levels were selected, % w/v concentration of coded factors was -1, 0 and +1 with 3 central points. Thus, the present design comprised of concentration of A (10, 15 and 20 % w/v), concentration of B (1, 1.5 and 2 %) and concentration of C (3, 5 and 7 % w/v) respectively. % EE and % drug release at 8 h were selected as dependent variables. Table 1 shows the various independent as well as dependent variables, their levels and constraints. Thus, in the present case 3^3 experimental design was selected without any central points which gives 12 experimental runs (Table 2).

Table No. 1: Different variables, levels and constraints in Box-Behnken Design.

Independent variables (Factors)	**Levels**		
	Low (−1)	Medium (0)	High (+1)
A- MMT % w/v	10	15	20
B- Chitosan % w/v	1	1.5	2
C- STPP %w/v	3	5	7
Dependent Variables (Responses)	**Constraints (In range)**		
R1- % EE	60 – 90 %		
R2 - % Release rate at 8 hr	50 – 90 %		

CF-Cefaclor; **MMT-** Montmorillonite clay; **CS-** Chitosan; **STPP-** Sodium TriPolyPhosphate

Table 2: Compositions of various batches of CF microbeads

Runs	**CF (mg)**	**MMT (%w/v)**	**CS (%w/v)**	**STPP (%w/v)**
1	250	10	1.5	7
2	250	20	1.5	3
3	250	10	1	5
4	250	20	1	5
5	250	15	1	3
6	250	20	2	5
7	250	15	2	3
8	250	10	2	5
9	250	10	1.5	3
10	250	15	1	7
11	250	15	2	7
12	250	20	1.5	7

Differential Scanning Calorimetry (DSC) Analysis:

CF, MMT, CS, STPP and CF-MMT-CS-STPP microbeads were investigated using a DSC instrument (Shimadzu DSC-60, Japan). In the DSC sample pans, the samples were sealed. During the sample analysis, nitrogen gas was purged to remove the moisture. The thermograms were generated by heating the sample to 300 °C at a constant rate of 10 °C/min.

X-ray Diffraction (XRD) Analysis:

XRD analysis was performed to evaluate the solid state of the CF, MMT, CS, STPP and as well as its microbead formulations (CF-MMT-CS-STPP microbeads) by X-ray diffractometer (Miniflex 600, Rigaku Corporation, Japan) at 40 kV and 15 mA. Adequate amount of sample was kept into a holder attached to a goniometer with a 150 mm radius. The samples were scanned over a range 0–100° as 2θ.

Percentage yield of microbeads:

Practical yield of formulations obtained from different batches were calculated on dry weight basis using weight of final product to that of the initial total weight of product.

$$\text{Percentage yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \text{ x } 100$$

Swelling behaviour:

To study the swelling behaviour of microbeads 'water absorption method' was used. Around 100 mg of formulation was soaked in 6.8 pH phosphate buffer (20 mL). After draining the surface water with a filter paper, the beads were weighed after 8 hours. The ratio of the increase in weight of microbeads after swelling to the dry formulation was used to calculate the percent swelling index.

$$\text{Percentage swelling index (\% SI)} = \frac{(\text{Swollen weight} - \text{Initial weight})}{\text{Initial Weight}} \text{x } 100$$

Drug entrapment efficiency:

In a glass mortar, microbeads (50 mg) were precisely weighed and crushed. After complete hydration soaking of the formulation in 6.8 pH phosphate buffer (100 mL) for 24 hours, then the drug was extracted. The mixture was agitated

for 15 minutes the next day, then filtered and diluted with the same buffer. UV spectrophotometric analysis of CFR content in the filtrate was performed at 265 nm against a blank.

$$\text{Percentage drug entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical Drug Content}} \times 100$$

Particle size determination:

An optical microscope (SZX-12, Olympus, Japan) with an accuracy of 0.01 mm and an ocular and stage micrometer was used to quantify the particle size of composite microbeads. At least 100 particles from five distinct fields were inspected in each measurement, and the average particle size was determined.

In-vitro drug release studies:

Amount of CF release from the developed microbead formulations were studied by using USP dissolution apparatus I (Basket type) (TDT-08L, Electrolab, India). Drug release study was carried out initially 900 mL of pH 1.2 HCl for 2 h and then in 6.8 pH phosphate buffer up to 8 h at 37 ± 0.5°C. The rotation speed of basket was kept at 50 rpm. The aliquots (5 mL) were withdrawn at each time intervals between 0 and 12 h and equal volume was replenished with fresh medium. Absorbance of the withdrawn samples were measured by UV spectrophotometer at 265 nm against the blank and the CF drug release was estimated.[17]

Drug release Kinetics:

Korsmeyer *et al*. proposed the investigation of *in-vitro* drug release profile from the formulation fitting as the first 60 % fraction of drug released.[18]

$$M_t/M_\infty = k\, t^n$$

Where, M_t/M_∞ = Drug fraction released at time '*t'*

k = Rate constant

n = Release exponent

The release mechanism was described using the exponential release constant *n*. The intercept and slope of a logarithmic plot of F vs. *t* were used to determine the rate constant *k* and the diffusion exponent.

Field Emission Scanning Electron Microscopy (FEEM):

The surface topography of composite microbeads was observed using a field emission scanning electron microscope (Nova NanoSEM 450). The microbeads were kept in the sample holder after being mounted on the stub and further coated with carbon as well as gold. After that, the coated samples were examined using a FESEM at 5-15 KV.

RESULTS AND DISCUSSION:

FT-IR analysis:

FT-IR analysis clearly revealed the appearance of principle peaks of pure CF. Pure CF showed characteristic peaks for carbonyl groups of β-lactum ring and amide group at 1753.35 cm^{-1}; C-N bond appeared at 2337.80 cm^{-1}; aromatic C-H bond appears at 3039.91 cm^{-1} and –OH and $–NH_2$ groups appeared at 3483.56 cm^{-1}. These peaks are prominently appeared in physical mixtures of CF with different excipients (mixture of CF+MMT, CF+MMT+CS, CF+MMT+CS+STPP) and in the optimized formulation. The results suggested that CFR did not show any interaction with excipients.

Optimization and validation of experimental design for microbeads

By employing Box-Behnken design, software predicted 12 experimental runs with 3 central points as shown in Table 1. The independent factors such as A: MMT, B: CS and C: STPP at 3 levels (-1, 0 and +1) were applied in order to optimize the suitable batch based on output of dependent variables (% EE and % drug release for 8 h). Results of different batches were given in Table 3.

Table 3: Results of various trial batches of Cefaclor

Runs	A*	B*	C*	R1	R2	% Yield	% Swelling Index
1	10	1.5	7	69.51±3.85	79.85±2.34	93.81±0.36	96.24±0.65
2	20	1.5	3	67.85±4.33	78.61±2.96	94.15±0.87	86.13±0.47
3	10	1	5	64.52±2.61	82.36±3.74	91.52±0.94	79.24±0.36
4	20	1	5	71.39±2.84	66.36±2.63	92.37±0.24	71.36±0.21
5	15	1	3	58.86±3.51	84.36±3.51	94.44±0.65	89.37±0.96
6	20	2	5	78.46±2.63	63.21±4.12	**93.34±0.41**	**91.41±0.27**
7	15	2	3	62.85±4.71	76.71±3.45	92.84±0.37	85.74±0.34
8	10	2	5	68.12±3.61	76.36±2.61	93.48±0.28	81.85±0.62
9	10	1.5	3	53.15±2.15	87.86±2.48	94.08±0.31	67.43±0.23
10	15	1	7	69.39±3.64	69.36±3.75	91.82±0.21	62.39±0.81
11	15	2	7	74.96±4.82	63.39±3.69	93.18±0.16	64.85±0.56
12	20	1.5	7	73.85±2.43	72.34±2.67	94.49±0.35	73.61±0.45

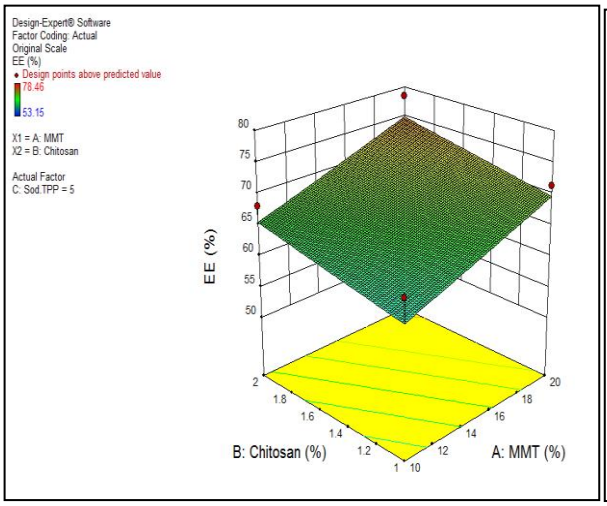
*A- MMT % w/v, B- Chitosan % w/v, C- STPP %w/v; R1- %EE; R2-% Release rate; Note: All the values expressed as Mean±SD; n=3;

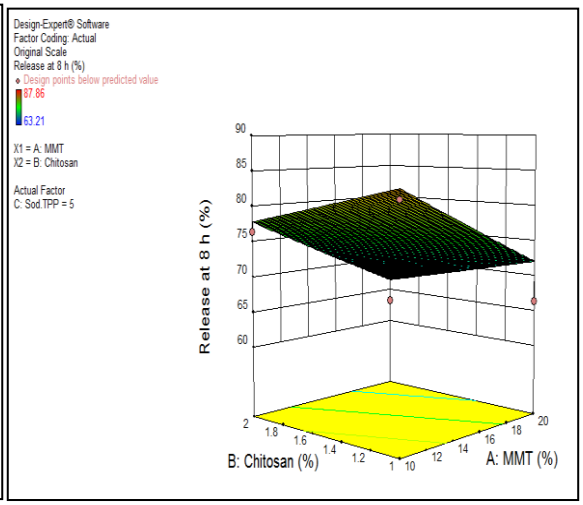
Table 4 − Results of ANOVA of quadratic model

Response	Model	F-Value	p-Value (Prob > F)	R^2 Value	Lack of Fit	Lack of Fit p value
R1 (Entrapment Efficiency)	Quadratic	14.51	0.0013 Significant	0.8447	0.19	0.248
	Model equation (Coded): R1 = 8.22 + 0.28 * A + 0.15 * B + 0.35 * C					
R2 (Release at 8 h %)	Quadratic	7.87	0.0090 significant	0.7469	0.12	0.514
	Model equation (Coded): R2 = 8.65 - 0.33*A - 0.17*B - 0.31* C					

Analysis of variance (ANOVA) was applied and quadratic model was chosen in order to predict the desirability of the factors among the various experimental batches. Significant fit p-values as well as non-significant lack of fit p-values for R1 and R2 responses in all trials were observed which clearly indicated suitability of the applied model. R^2 values in both the cases of R1 and R2 responses evidently complies the applicability of the model. Analysis of the quadratic model with the polynomial equations showed in Table 4. Based on the constraints selected in the model the surface response plots (Figure 1) and corresponding contour plots (Figure 2) defines the influence of various factors on R1 as well as R2. It is found that %EE ranged between 53.15±2.15 to 78.46±2.63, whereas drug release at 8 h (%) ranged between 63.21±4.12 to 87.86±2.48. Increase in concentration of A as well as B increased the %EE. The may be because of high surface adsorption and intercalation due to high amount of MMT and high amount of STPP may have resulted in high cross linking of the microbead system which may load high drug amount. Results showed that the Factor C is the actual factor responsible for increasing the %EE through increased cross linking property of CS by STPP. Increase in concentration of MMT and STPP resulted in reduced drug release at the end of 8 h, which is expected to achieve in case of sustained drug delivery system. This may be achieved due to slow loosening of the polymeric matrix in release medium as well as slow release of drug from intercalated platelets of MMT.

Based on these analysis, we selected system generated solution with desirability value 1 based on desirability plot as shown in Figure 1. The selected solution is A (20% w/v), B (2 %w/v) and C (5 % w/v) predicted %EE value 76.08±1.27 and % drug release at 8 h 66.98±1.42. Whereas, experimental values for %EE and % drug release at 8 h were found to be 78.64±4.67 and 65.42±2.92 along with % error 3.36 and 2.32 respectively (Table 5). These values suggested that the experimental optimized batch of microbeads showed results in accordance with predicted solution generated by the software. The magnitudes for various parameters selected and their experimental results for optimized microbead batch is showed in Table 6.





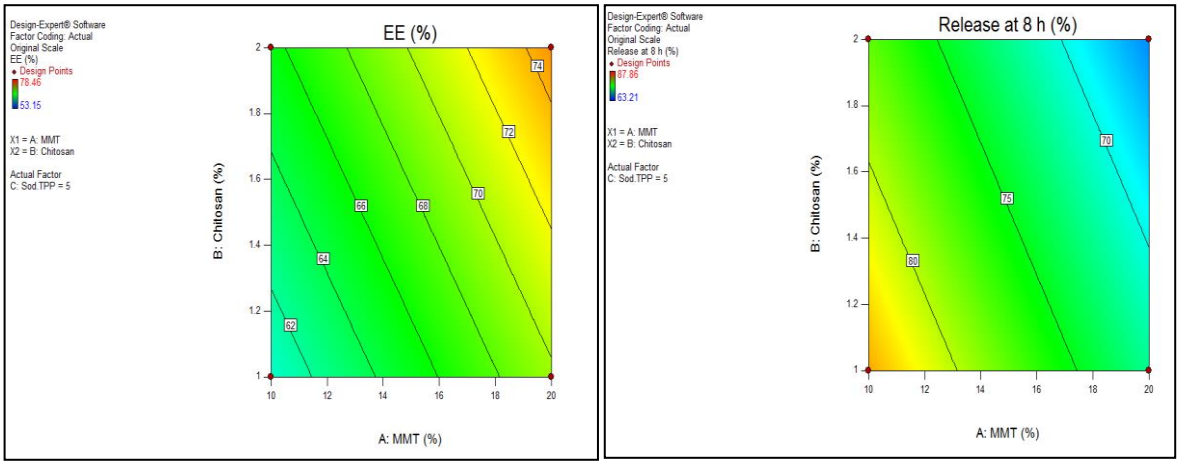


Figure 1: Surface response and contour plot for plot for % entrapment efficacy and % release at 8 hr

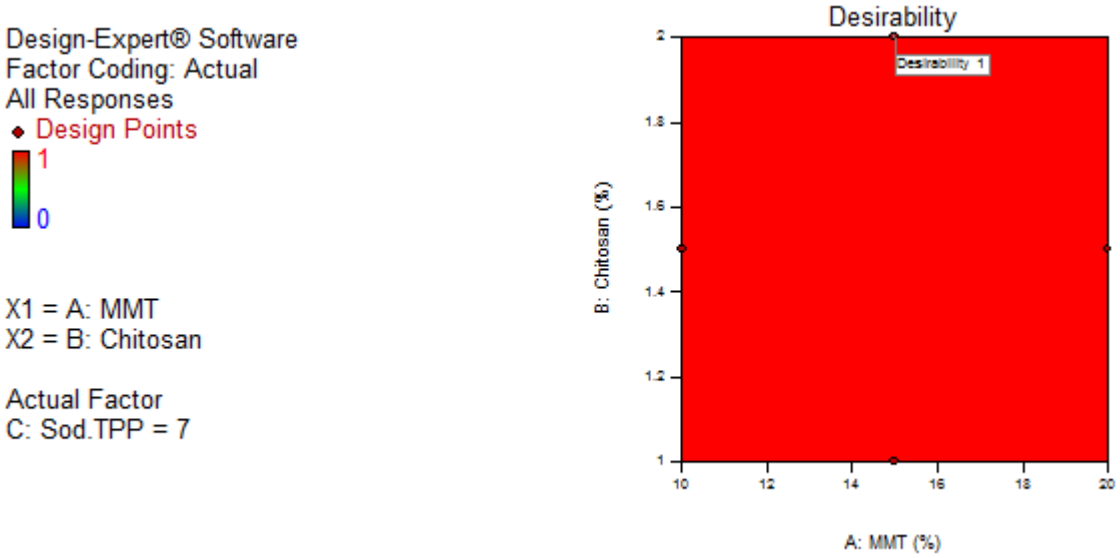


Figure 2: Desirability plot for the software generated solution. Desirability value is 1 which validates the optimization model and process.

Table 5: 'Predicted and observed values of responses for optimized batch'

Responses	**Predicted Value**	**Observed Value**	**% Error***
%EE	76.08±1.27	78.64±4.67	3.36
% Release at 8 h	66.98±1.42	65.42±2.92	2.32

*% error = (observed value – predicted value)/predicted value × 100

Table 6: Optimize batch

A	**B**	**C**	**R1**	**R2**	**Desirability**	
15	2	7	78.64±4.67	65.42±2.92	1	Selected

FT-IR analysis of the microbead formulation:

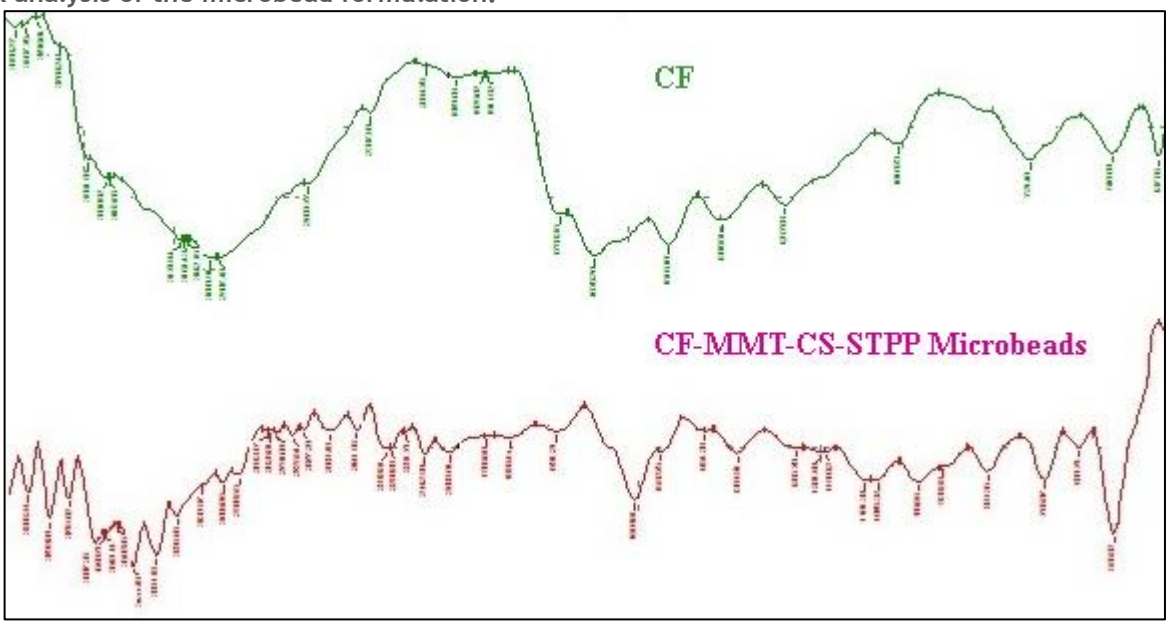


Figure 3: FT-IR spectra of pure CF and CFR-MMT-CS-STPP formulation (Optimized batch)

The FTIR spectrum of CF-MMT-CS-STPP microbead formulation clearly suggested disappearance of principal peaks of CF (C-O-NH: 1753.35 cm^{-1}; C-N bond: 2337.80 cm^{-1}; aromatic C-H bond: 3039.91 cm^{-1} and, –OH and $–NH_2$: 3483.56 cm^{-1}). Similarly, the characteristic bands of MMT found to be disappeared (-OH groups corresponding to the octahedral cations: 3662.94 cm^{-1} and 3778.68 cm^{-1}, including the vibration at 3778.68 cm^{-1} caused by the OH group coupled with Al^{3+} cations.). These disappearances of characteristic bands of CF and MMT revealed the positive interaction among the drug and clay through adsorptive ionic interaction and intercalation between CF and MMT. Also, STPP cross linking within the microbead system may be responsible for holding this system in bounded form (Figure 3).

DSC analysis:

The DSC thermogram of pure CFR, MMT and the optimized batch of microbead is shown in the Figure 4. A sharp exothermic peak at about 202.81°C was observed for pure CFR. It was observed that MMT showed large endothermic peak corresponds to value 97.43 °C. In case of the optimized microbead formulation, the large exothermic peak of pure CFR was broaden and shifted to 204.76 °C. Also, the MMT endothermic peak was disappeared in case of formulation. These results may be due to adsorptive interaction of CFR with MMT along with intercalation and polymer effect. But in this case, the interaction is in favourable side as per mechanism predicted between clay-drug as per reported earlier.

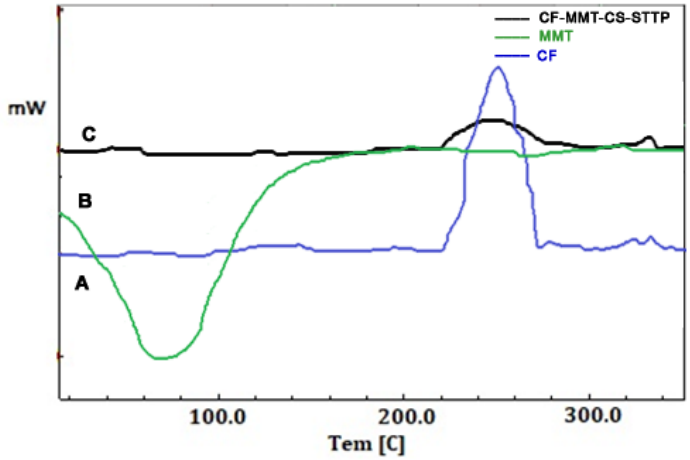


Figure 4: DSC thermograms: [A] CF, [B] MMT and [C] CFR-MMT-CS-STPP microbeads

X-ray Diffraction (XRD) Analysis:

The XRD patterns of CF, MMT, CS and CF-MMT-CS-STPP microbeads are shown in Figure 5. CF showed sharp intense peaks (at 6.88°, 8.71°, 15.45°, 20.09°, 23.88°, 27.31°, 37.84° and 41.07°) which are indicative of the crystalline nature of pure CF. The XRD patterns of MMT, CS and CFR-MMT-CS-STPP microbeads showed the absence of characteristic CFR peaks (Figure 5). These results revealed that CFR is molecularly dispersed or intercalated within the polymer matrix or intercalated within the clay-polymer hybrid system as reported earlier.[19,20]

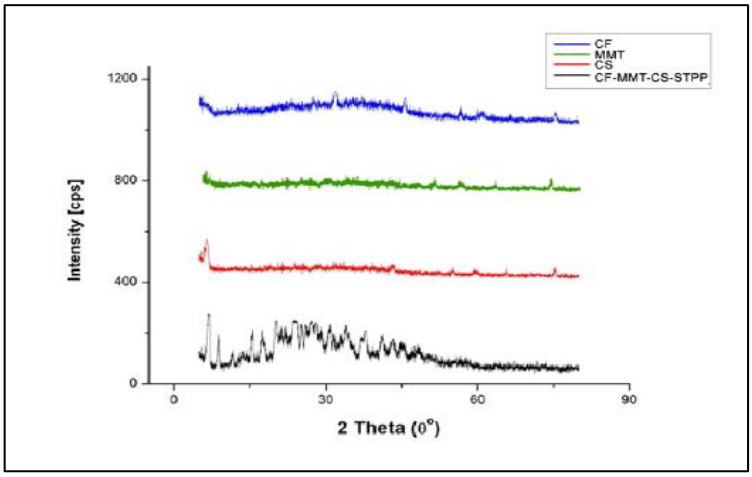


Figure 5: XRD patterns of CF, MMT, CS and CFR-MMT-CS-STTP microbeads

Percentage yield of microbeads:

Percentage yield of microbeads were found to be in the range of 91.52±0.94 to 94.49±0.35, which clearly showed that there are not much variations in the results. Thus, it has been clearly revealed that steps involved in the microbeads preparation were properly executed without much alteration. Results are showed in Table 3.

Swelling study:

The values for % swelling index ranged between 62.39±0.81 to 96.24±0.65 %. It was observed that batches with higher concentration of MMT and STPP showed high swelling index as compared to the batches with lower concentration. This may be due higher water uptake capacity due to presence of ionic groups. Results are showed in Table 3.

Particle size determination:

It was observed that there is increase in particle size with increase in MMT concentration. This may be due to increase in voids between MMT platelets due to stalking when cross linked with STTP. Particle size reduced with the decrease in concentration of MMT due to less voids. The particle size lies within 355.17±0.85 to 481.36±0.17 µm.

In-vitro drug release kinetics:

CFR-MMT-CS-STPP microbeads were formulated to achieve the sustained release of CF. In this formulation, it has been predicted that CF intercalated within the MMT platelets and chitosan polymer as well as dispersed in STPP matrix. The optimized batch of microbeads (MMT: 15 %w/v, CS: 2 % w/v and STTP: 7 % w/v) showed rapid release of CF in initial 2 h (Figure 6). This may be due to initial quick dissolution of CF present in upper layers of cross-linked polymers in pH 1.2 HCl, where CF have higher solubility in that pH. Later, drug release rate slows down due to change in medium to pH 6.8 phosphate buffer. At this stage, drug release rate was sustained till 8 h (Figure 6). This pattern of drug release may be due the microbead matrix created by combining these two constituents has unique characteristics to regulate drug release via a clay-based ion-exchange process and polymeric erosion over time.

Kinetics of drug release from optimized batch was estimated by using zero order release, first order release, Higuchi's and Korsmeyer-Peppas model. The regression coefficient (R^2) values for the optimized formulation by using zero order, first order and Higuchi model were found to be 0.8196, 0.9185 and 0.9639 respectively. Whereas, drug release follows the 'non-fickian diffusion pattern' coupled with matrix release as indicated by Korsemeyer-Peppas (n) value 0.3228. These results clearly suggested that the optimized formulation of CFR exhibit sustained drug delivery.

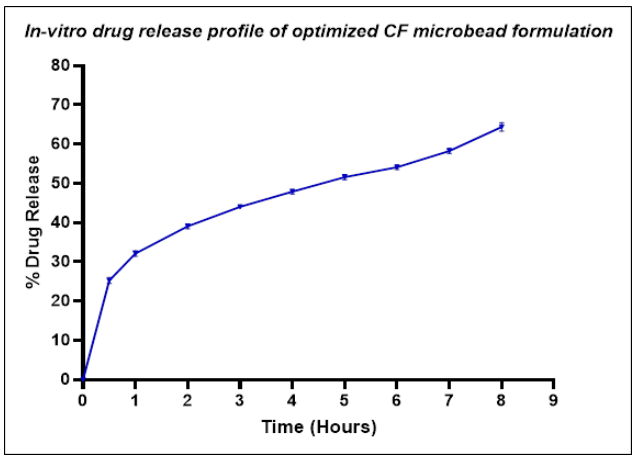
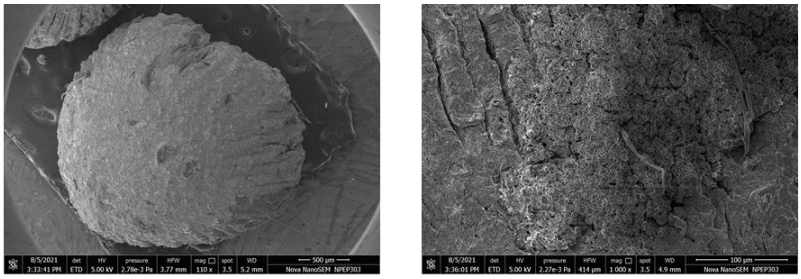


Figure 6: *In vitro* release profile of optimized microbead formulation

Field emission scanning electron microscopy:



Complete bead image Surface texture of bead

Figure 7: Photomicrograph of optimized microbead formulation

The FESEM images of CF-MMT-CS-STPP microbead formulation revealed that the particles are spherical in shape (Figure 7). The surface texture appeared highly cross linked and wrinkled that may be due to collapse of STPP chains after drying step. Stalking strips like structures were observed which may be due to presence of MMT clay and chitosan platelets in between exfoliating STPP chains.

CONCLUSIONS:

CF-MMT-CS-STPP microbead formulations were formulated in order to achieve the sustained delivery of CF. This can be achieved through unique microbeads system by adopting the mechanism of ion-exchange based surface adsorption as well as intercalation within the interspaces of MMT clay molecules and coated by chitosan polymer. Also, the STPP cross-linking made the system distinctive. This system attributed for high drug encapsulation and sustained drug release profile over a period of 8 h with unique swelling properties and surface topography. This study may provide the excellent platform for the development of nanoclay-polymeric system for oral sustained drug delivery.

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