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Research Article

Formulation development and in-vitro evaluation of floating sintered matrix tablets of Cefpodoxime Proxetil using carnauba wax

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Abstract

The current study is centered on the development of floating sintered matrix tablets of Cefpodoxime proxetil for gastro-retentive delivery, employing carnauba wax as a release retardant. The hot melt granulation method was employed for the preparation of floating tablets. Carnauba wax was employed as a rate-controlling polymer and found to be well-suited for physical sintering. Menthol served as a buoyant agent. The compatibility between Cefpodoxime and carnauba wax was determined through Fourier Transform Infrared Spectroscopy and Differential Scanning Calorimetry studies. The tablets exhibited floating without lag time due to the evaporation of menthol during sublimation, and the floating duration exceeded > 24 h. The F3 formulation was optimized based on in-vitro dissolution studies of 97.09 ± 0.29% over 8 h. The F2, F3, and F4 formulations underwent physical sintering at temperatures of 50, 60, and 70 ºC for varying durations. The physicochemical parameters and in-vitro dissolution studies were evaluated for the sintered tablets. The F3S formulation includes carnauba wax and drug in a ratio of 0.6:1 with 8% w/w menthol, was subjected to a temperature of 70 ºC for 2 h, exhibited favorable floating properties, and improved dissolution profile of 81.05 ± 0.15% within a 12 h timeframe. Model-dependent kinetics demonstrated that drug release exhibited zero-order kinetics and Higuchi Fickian diffusion mechanism, suggesting that drug release was governed by diffusion through the matrix. The successful preparation of floating sintered matrix tablets of cefpodoxime proxetil was achieved through the process of physical sintering with sustained drug release.

Keywords: Cefpodoxime proxetil; gastroretentive; floating tablets; physical sintering; sustained release

Introduction

Controlled drug delivery systems refer to pharmaceutical formulations designed to administer drugs in a controlled manner, ensuring a consistent release rate over a specified period of treatment. These systems can be utilized to achieve either local or systemic effects. Osmotic pressure-activated drug delivery systems, which represent a novel generation of pharmaceuticals, have obtained regulatory approval for commercialization owing to their clinical benefits in comparison to sustained-release and quick-release products [1,2].

Certain drugs exhibit site-specific release upon oral administration. Pharmaceutical substances characterized by brief half-lives and efficient absorption from the gastrointestinal tract (GIT) are rapidly eliminated from the body. It is imperative that the medication remains within the gastric region and is released in a controlled and gradual manner. Consequently, the drug will persistently reside at gastrointestinal absorption sites [3]. Prolonged gastric retention has the potential to enhance bioavailability by extending the duration of substance retention within the stomach. The advantages include enhanced drug release, improved solubility, and minimal degradation in an alkaline pH

environment. The objective of gastro-retentive drug delivery is to achieve site-specific drug release in the upper GIT in order to produce local or systemic effects while also prolonging the residence time in the gastrointestinal tract. There exist various approaches for administering gastro-retentive medications, such as high density/sinking, low density/floating, mucoadhesive systems that remain at the bottom of the stomach, buoyant gastric fluid, and adherence to the mucosa. Unfoldable, extendable, or swellable systems, such as super porous hydrogel systems and magnetic systems, can impede the rapid emptying of dosage forms through the pyloric sphincter of the stomach.

In the realm of pharmacy, sintering is defined as a process by which bonding occurs during compression, resulting in enhanced mechanical properties at higher temperatures. The sintering process is employed in the production of matrix tablets designed for controlled-release applications.

Sintering refers to the process of heat-induced bonding between adjacent particles of powder or compacted material. In the conventional sintering process, a compact is subjected to controlled heating in an environment with atmospheric pressure, wherein the temperature remains below the material's melting point. Examples of method variations in the context of heating include the application of pressure and the presence of passing or stable liquid phases, as observed in the process known as hot-pressing. The latest advancements in sintering techniques encompass spark plasma sintering, microwave sintering, and high-frequency induction heat sintering [4]. Both physical and chemical processes can be employed for sintering materials. The sintering of solid phases involves the utilization of the following processes. Evaporation and condensation, plastic and viscous flow, volume and surface diffusional flow, among others, represent various mechanisms [5]. Uhumwangho et al., investigated the release characteristics of diltiazem hydrochloride matrix in glyceryl behenate for sustained release using a thermal sintering technique [6].

The Gibbs-Thomson equation is a mathematical expression that characterizes the vapor pressure gradient arising from the chemical potential difference between adjacent planar and curved surfaces during the processes of evaporation and condensation. The evaporation of material from planar surfaces and its subsequent condensation on curved surfaces can be attributed to disparities in vapor pressure. When a solid surface with a small radius of curvature experiences viscous and plastic flow, the stress exerted on the surface increases to a magnitude that can lead to plastic deformation and the formation of dislocations. Plastic flow may potentially contribute to the material-transport phenomenon during the initial stages of sintering, even in the absence of external pressure. However, during the sintering process in hot pressing, the application of pressure results in the dominance of plastic flow. The mass transport mechanism for sintering is facilitated by volume and surface diffusional flow, which relies on the presence of vacancies within a crystal's lattice [6,7].

The administration of an orally extended-release formulation of cefpodoxime proxetil, a semi-synthetic cephalosporin antibiotic, was initiated due to its favorable characteristics, such as high solubility, chemical stability, and enzymatic stability at low pH. Additionally, this formulation is designed to take advantage of the absorption window in the stomach. The formulation of a gastro-retentive dosage form is feasible due to the compound's brief elimination half-life and efficient absorption in an acidic pH environment [8]. Latha Kukati et al. formulated and evaluated sintered floating tablets of cefpodoxime proxetil for gastro-retentive application using a chemical sintering technique with acetone [1].

Materials and Methods

Materials

Cefpodoxime proxetil (CP) was received as a gift sample from Micro Labs, Bengaluru, India. Carnauba wax, magnesium stearate, hydrochloric acid, and menthol were acquired from S.D-fine Chemical Ltd., Mumbai, India. Purified talc purchased from Accord- labs, Mumbai, India.

Pre-formulation studies

Pre-formulation studies were performed to test the physical and chemical properties of a drug alone and with a combination of excipients. FTIR, DSC, and pre-compression parameters for the granules (angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio) were carried [9-11].

Formulation of CP floating tablets

Hot melt granulation method using non-effervescent agent

All the ingredients were accurately weighed, and the carnauba wax was transferred to a china dish and melted. Drugs and other ingredients were added to it and mixed properly to form granules. The granules were passed through a nominal mesh aperture of 355 μm (Sieve No. 44). Magnesium stearate was added and mixed thoroughly. The final mixture was compacted into tablets using a "Rimek-1 rotary tablet machine" 11.9 mm punch (Table 1) [12].

Table 1. Formulation of floating tablets containing menthol.

Formulations	CP (mg)	Carnauba wax (mg)	Menthol (mg)	Mg. Stearate (mg)	Talc (mg)
F1	330	66	52.5	3.75	3.75
F2	330	132	52.5	3.75	3.75
F3	330	198	52.5	3.75	3.75
F4	330	264	52.5	3.75	3.75
F5	330	330	52.5	3.75	3.75
F6	330	396	52.5	3.75	3.75
F7	330	462	52.5	3.75	3.75

Evaluation of CP floating tablets

Evaluation tests such as weight variation, thickness, hardness, friability, assay/drug content, and buoyancy/floating tests were performed. By application of floating CP tablet exposed to 40 ºC in a hot air oven for evaporation of menthol, *in-vitro* dissolution was conducted for the prepared tablets [1,13,14].

Weight variation

A sample of twenty tablets was selected at random, and the mean weight of the tablets was calculated. The percentage deviation of each tablet from the average was computed.

Thickness

The tablet's thickness was measured using a screw gauge. There exists a correlation between the thickness of a tablet and its hardness. It is recommended to maintain tablet thickness within a range of ± 5% deviation from a predetermined standard value. The thickness of 10 pre-weighed tablets was individually measured in millimeters (mm) using a screw gauge. The researchers provided information regarding the mean thickness and standard deviation.

Hardness

The hardness of a tablet is typically quantified in terms of its tensile strength, measured in kilograms per square centimeter (Kg/cm^2). The tablet crushing load refers to the amount of force necessary to fracture a tablet into multiple fragments. The tablet hardness was assessed utilizing a Monsanto hardness tester, specifically the Cintex Ind. The corporation model is located in Mumbai. Three tablets were randomly selected from each batch, and their average reading was recorded.

Friability

The determination of tablet friability was conducted using the Roche Friabilator (Electrolab, India). A preweighed sample consisting of 20 tablets was introduced into the friabilator and subsequently exposed to 100 revolutions. The tablets underwent a dusting process utilizing a gentle muslin cloth, followed by subsequent reweighing. The friability, expressed as a percentage (F %), can be calculated using the following formula:

F % = (1-W0 /W) x 100 -------- (1)

Where, W0 is weight of the tablet before the test and W is the weight of the tablets after test.

Assay

The assay involved the precise measurement of a tablet powder mixture, specifically 100 mg of cefpodoxime proxetil. This mixture was placed in a 100 ml volumetric flask and combined with methanol. The resulting solution was then diluted with a 0.1 N HCl solution. The sample was subjected to mechanical agitation for one hour. The liquid portion of the sample underwent filtration. A 1 ml portion of the sample was transferred into a separate 10 ml volumetric flask, and the volume was adjusted by adding 0.1 N HCl solution. The concentration of the dilution was determined to be 10 µg/ml by measuring its absorbance at 264.2 nm using a double-beam UV spectrophotometer, with a blank solution of 0.1 N HCl serving as the reference. The quantification of drug content was determined through the utilization of a standard calibration curve for comparison.

Buoyancy or floating test

The buoyancy or floating test involves placing a tablet into a 100 ml beaker filled with 0.1 N HCl. The time it takes for the tablet to rise to the surface of the medium after being introduced into the beaker is referred to as the floating lag time. The total duration for which the dosage form remains buoyant is known as the total floating time (TFT).

Dissolution

A dissolution study was conducted using USP type II apparatus at a rotation speed of 50 rpm (paddle) in 900 ml of 0.1 N HCl at a temperature of 37 ± 0.5 °C. The equipment used for the study was the Electro lab TDT08L, Mumbai. During each sampling time interval, a volume of 5 ml of sample was collected and subsequently substituted with an equal volume of fresh media.

Physical sintering of prepared floating tablets

By applying heat or exposure to solvents, sintering is the bonding of neighboring particles in a mass of powder/ in a compact form. In order to stabilize and delay the release of the drug, matrix tablets have been made using sintering methods. The tablets were thermally treated by being placed on aluminum foil and then sintered at 50°, 60°, and 70 °C for 6,12,18, and 24 h in a hot air oven [15].

Evaluation of sintered floating tablets

Sintered floating tablets were subjected to various evaluation tests like hardness, friability, buoyancy studies, and dissolution studies, which were conducted in 0.1 N HCl solution as discussed in the evaluation of CP floating tablets.

Model-dependent kinetic assessment of dissolution data

The in-vitro release data was fitted into various kinetic models (zero-order rate, first-order rate, Higuchi, Korsmeyer plots) to describe the system's drug release order and mechanism.

Stability studies

Optimized formulation F3S was subjected to stability studies at 40 ± 2°C/ 75 ± 5% RH analyzed for its physical characteristics, drug content, and dissolution studies for one month.

Results and Discussion

Pre-formulation studies

Drug-Excipient compatibility study by FTIR

FTIR study was done, and spectra of CP and physical mixture blends are shown in Figure 1. From the IR spectra, the peaks signifying the pure drug were similar to a combination of drug and wax, suggesting that there are no interactions. It was found that the functional peaks were retained after the addition of carnauba wax to the drug. Hence, there is no interaction between drugs and wax [16].

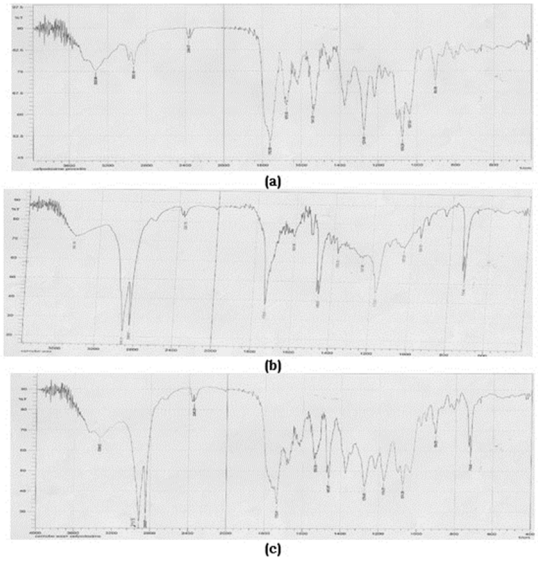

Figure 1. FT-IR spectra (a) Cefpodoxime proxetil (b) Carnauba wax (c) Cefpodoxime proxetil+carnauba wax.

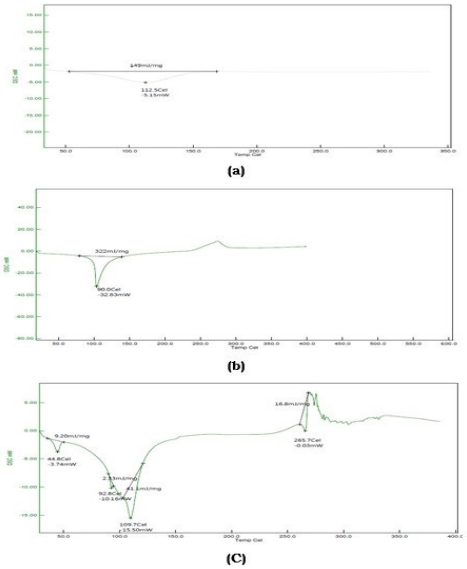

Figure 2. DSC thermogram of (a) cefpodoxime proxetil, (b) carnauba wax and (c) F3 formulation.

Differential scanning calorimetry studies

DSC thermograms of floating tablets of CP, along with those of drug and polymer, are depicted in Figure 2. DSC of pure drug showed a sharp endo-thermic peak at 112.5 °C, and the polymer showed a sharp endo-thermic peak corresponding to its melting point. Thermal traces of the prepared tablet showed peaks at 109.7 °C and 92.8 °C, respectively. The thermal behavior of CP in the form of a tablet suggests that the drug is still in amorphous form [17].

Precompression parameters

Pre-compression parameters are given in Table 2. The angle of repose of all the formulations ranged between 33.72 ± 1.2 and 26.78 ± 0.64, showing excellent flow or good flow properties (25-35 IP limits). Carr's index calculated from bulk density and tapped density ranged from 8.3 ± 0.6 to 14.28 ± 0.3, which means good or fair flow property (1-15 IP limits). Hausner's ratios ranged from 1.11 ± 0.45 to 1.2 ± 0.59, which explained excellent or good flow properties (1.05 - 1.20 IP limits) and were within the compendial limits of Indian Pharmacopoeia (IP). Therefore, the tablets were prepared by the hot melt granulation method [18-20].

Table 2. Precompression parameters of the granules.

Formulations	Angle of repose (Θ) *	Bulk density (gm/cm3) *	Tapped density (gm/cm3) *	Hausner's ratio*	Carr's index (%)*
F1	33.72±1.2	0.424±0.31	0.497±0.33	1.17±0.2	14.28±0.3
F2	33.29±0.83	0.427±0.12	0.51±0.13	1.19±0.1	16.27±1
F3	27.15±0.84	0.53±0.91	0.6±0.88	1.13±0.5	11.66±0.5
F4	29.6±0.3	0.415±0.75	0.498±0.88	1.2±0.59	8.3±0.6
F5	30.7±0.79	0.44±0.68	0.508±0.58	1.15±0.62	13.38±0.29
F6	31.73±1.6	0.396±0.64	0.451±0.69	1.13±0.27	12.19±0.27
F7	26.78±0.64	0.389±0.54	0.432±0.67	1.11±0.45	9.95±0.45

*Mean ± SD, n=3

The reason for the increase in tablet weight, friability, and decrease in drug content in Tables 3 and 4 is that the total weight was not constant and varied from 450 mg to 850 mg (approx). The reduction in density by an increase in volume leads to porosity (due to air gap formation), and friability was observed as an increase.

Table 3. Physicochemical evaluation of tablets.

Formulations	Weight variation (mg) *	Friability (%) *	Assay (%) *	Hardness (kg/cm2) *	Thickness (mm) *
F1	451.6±0.23	0.71±0.81	101.03±0.99	5.8±0.23	4.5±0.01
F2	518.21±0.77	0.85±0.02	96.42±0.40	6.9±0.06	4.7±0.02
F3	590.83±0.39	0.44±0.07	99.01±0.77	6.4±0.09	4.6±0.09
F4	652.24±0.84	0.60±0.01	94.64±0.20	5.6±0.45	5.0±0.03
F5	718.36±0.69	0.39±0.41	89.24±0.23	6.6±0.01	4.8±0.21
F6	787.36±0.24	0.55±0.23	91.47±0.50	6.8±0.14	4.3±0.48
F7	851.02±0.07	0.42±0.13	98.02±0.22	7.1±0.69	4.9±0.07

*Mean±SD, n=3;

Buoyancy/Floating test

The tablets containing menthol were placed in oven for 40 °C for 1 h i.e., for sublimation. When the tablets were placed in 0.1 N HCl solution, tablet were floating > 24 h (Figure 3) without floating lag time because menthol evaporates during sublimation.

Figure 3. Floating ability (without lag time) of tablets containing menthol.

Table 4. Comparison of physical parameters before and after sublimation.

Formulations	Before sublimation		After sublimation	
	Hardness (kg/cm²) *	Thickness (mm) *	Hardness (kg/cm²) *	Thickness (mm) *
F1	5.8±0.23	4.5±0.01	5.2±0.03	4.7±0.02
F2	6.9±0.06	4.7±0.02	6.1±0.01	5.2±0.49
F3	6.4±0.09	4.6±0.09	5.8±0.23	4.9±0.1
F4	5.6±0.45	5.0±0.03	5.5±0.09	5.5±0.09
F5	6.6±0.01	4.8±0.21	5.9±0.01	5.9±0.06
F6	6.8±0.14	4.3±0.48	6.1±0.8	5.1±0.66
F7	7.1±0.69	4.9±0.07	6.4±0.12	5.5±0.80

*Mean±SD, n=3;

Dissolution studies

Evaluation of prepared tablets was done in 0.1 N HCl solution for 12 h according to the specifications of USP. The obtained values were compared with the standard USP values for the extended release of the drug. Based on the result, it was observed that the F1 and F2 formulations were released up to 6 h, F4 to F7 were release up to 12 h while F3 formulation was released in 8 h. Therefore, F3 formulation was chosen for further sintering process (Figure 4). Formulation F1released the drug faster within 2 h for about >50%. These can't be controlled by simple thermal sintering. In case of F4 and F7 were having self release control due to high concentration of carnauba wax, sintering may further increase may be up to 18 h. In the current work drug release was aimed up to 12 h and administration of two doses per day.

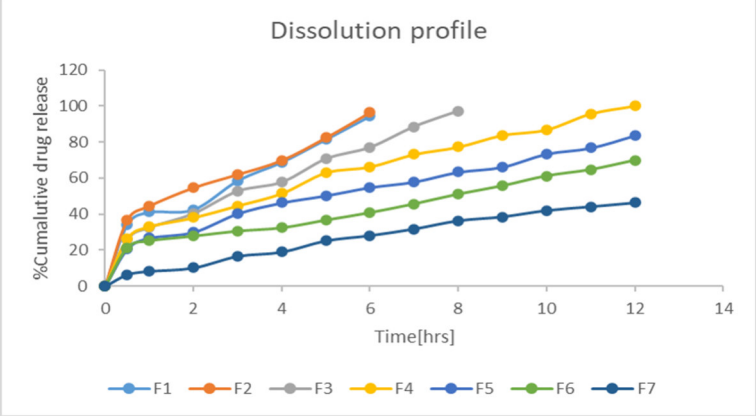

Figure 4. Dissolution profiles of floating tablet.

Hence F3 was considered for further studies as the release was controlled up to 8 h. thermal sintering might be useful for extending the drug release up to 12 h due to crosslinking the bonds and reducing the pore size on the surface structure of tablet.

Model dependent kinetics for floating tablets

Based on the percentage of drug release profiles, model-dependent kinetic parameters were calculated to understand the kinetic model and release profile. Among all the formulations, F1 and F6 demonstrated first-order release kinetics (r^2 = 0.9727 & 0.9268) and the Higuchi model (r^2 = 0.9408 & 0.9268), and they followed Fickian diffusion. Formulation F3 showed zero-order release kinetics (r^2 = 0.995) and the Korsmeyer-Peppas model (r^2 = 0.9713), and they followed Fickian diffusion. Formulations F2, F4, and F5 exhibited to show zero-order release kinetics (r^2 = 0.9892, 0.9924, and 0.9868), and the Higuchi model (r2 = 0.9582, 0.9800, and 0.9849) and followed Fickian diffusion. Formulation F7 was found to show zero-order release kinetics (r^2 = 0.9893) and Higuchi model (r^2 = 0.9777) and followed anomalous transport (Table 5).

Table 5. Model dependent kinetic for floating tablets.

Formulation	Zero order	First order	Higuchi	Korsmeyer-Peppas		Release Mechanism
	R^2	R^2	R^2	R^2	n	
F1	0.9245	0.9727	0.9408	0.9242	0.4255	Fickian diffusion
F2	0.9892	0.9799	0.9582	0.958	0.3643	Fickian diffusion
F3	0.995	0.9645	0.8948	0.9713	0.4594	Fickian diffusion
F4	0.9924	0.9423	0.9800	0.9663	0.432	Fickian diffusion
F5	0.9868	0.9186	0.9849	0.979	0.4394	Fickian diffusion
F6	0.9884	0.9906	0.9268	0.8927	0.3718	Fickian diffusion
F7	0.9893	0.9056	0.9777	0.9727	0.6754	Anomalous transport

Evaluation of sintered floating tablets of CP

Tablets containing the polymer formula F2 'S' is sintered (0.4 ratio), F3 'S' is sintered (0.6 ratio), F4 'S'is sintered (0.8 ratio) were compressed, subjected to physical sintering for 2, 4, 6, 8, 10, 12 h and evaluated for various parameters (Table 6).

All the post-compression parameters of the sintered tablets were found to be within the IP limits, and there was no remarkable change in the post-compression parameters as a result of sintering. However, the hardness and friability were slightly increased as compared with the unsintered floating tablet formulations (Table 7).

Table 6. Evaluation of sintered tablets.

Parameters	F2S*	F3S*	F4S*
Weight variation (mg)	521.04±0.26	595.15±0.98	657.48±0.37
Hardness (Kg/cm²)	7.1±0.43	6.9±0.01	6.6±0.65
Thickness (mm)	4.9±0.67	5.4±0.17	5.9±0.39
Friability (%)	0.95±0.01	0.65±0.28	0.72±0.03
Assay (%)	92.34±0.29	89.62±0.16	96.88±0.83

* Mean ± SD, n=3

In-vitro dissolution of sintered tablets (Tablets sintered at 50 °C)

The tablets were placed in a hot-air oven at 50 °C for thermal sintering. The samples were withdrawn every 2 h up to 12 h.

Table 7. Comparison of unsintered (floating tablets) and sintered tablets.

Formulation	Hardness (Kg/cm²) *	Friability (%)*
F2	6.1±0.01	0.85±0.02
F3	5.8±0.23	0.44±0.07
F4	5.5±0.09	0.60±0.01
F2S	7.1±0.43	0.95±0.01
F3S	6.9±0.01	0.65±0.28
F4S	6.6±0.65	0.72±0.03

*Mean ± SD, n=3

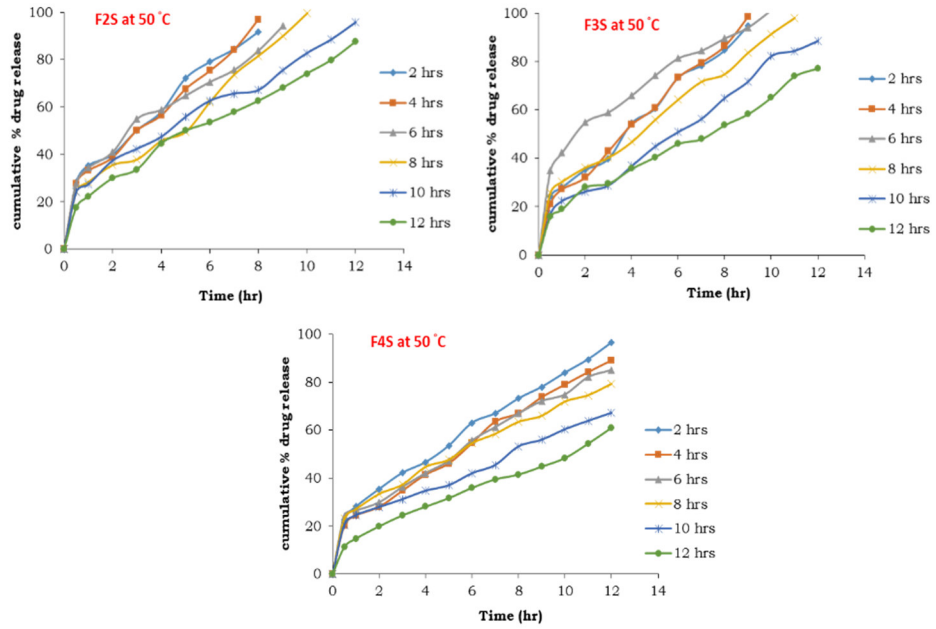

Figure 5. Dissolution profiles of sintered tablets at 50 °C for (a) F2S (b) F3S and (c) F4S.

These samples were tested for dissolution studies for 12 h using 0.1 N HCl solution shows the effect of sintering on F2S formulation (Figure 5a). Based on the results, it was found that release of the drug retarded up to 8 h when tablets were exposed to 4 h of physical sintering. While unsintered tablets (floating tablets) retarded for 6 h, which implies the cross-linking was increased and the process of sintering was initiated, drug release was further prolonged by increasing the sintering time. Tablets exposed to 10 h of physical sintering the drug release was retarded up to 12 h. Further sintering, i.e., for 12 h, there was no significant difference in the drug release (prolonged for 10 h only) as the sintering process was saturated due to the unavailability of molecules for further sintering [19]. Unsintered F3 tablets retarded the drug release up to 8 h. After 4 h of physical sintering, the drug release was prolonged up to 9 h. F3S formulation at 8 h of physical sintering has shown an optimum dissolution profile compared to the different periods of physical sintering, i.e., F3S at 8 h of exposure showed 98.03 ± 0.12% drug release in 11 h (Figure 5b). F4S on exposure to physical sintering had slightly prolonged the drug release. The reason might be due to a minor increase in the polymer concentration (Figure 5c). Hence, based on the results of dissolution studies, it can be concluded that F3S, on exposure to 8 h of physical sintering, has better-sustained drug release (98.03 ± 0.12%). Therefore, F3S was selected as the optimized formulation.

Tablets sintered at 60 °C

Figure 6a shows the effect of sintering on F2 formulation. Based on the results, it was found that the drug release was retarded up to 9 h when tablets were exposed to 2 h of physical sintering. While unsintered tablets (floating tablets) retarded the drug release for 6 h, which implies the cross-linking was increased and the process of sintering was initiated, drug release was further prolonged by increasing the sintering time. Tablets, when exposed to 6 h of physical sintering, the drug release was retarded up to 12 h. Further sintering, i.e., for 8 to 12 h, there were no significant differences for the drug release (drug release was prolonged for 6 h only). Unsintered F3 tablets retarded the drug release up to 8 h.

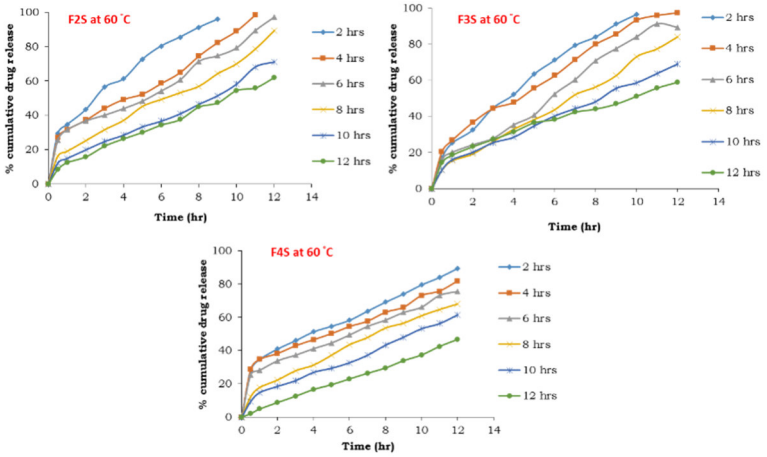

Figure 6. Dissolution profiles of sintered tablets at 60°C for (a) F2S (b) F3S and (c) F4S.

The F3 formulation at 4 h of physical sintering has shown an optimum dissolution profile compared to the different periods of physical sintering, i.e., F3 at 4 h of exposure has shown 97.31 ± 0.47% drug release in 12 h (Figure 6b). Formulation F4 on exposure to physical sintering had slightly prolonged the drug release. The reason might be due to a minor increase in the polymer concentration (Figure 6c). It can be concluded that F3 on exposure to 4 h of physical sintering has sustained the drug release (97.31 ± 0.47%) for 12 h. Hence, F3 was selected as the optimized formulation.

Tablets sintered at 70 °C

Figure 7a shows the effect of sintering on F2 formulation. Based on the results, tablets, when exposed to 2 h of physical sintering, the drug release was retarded up to 12 h. Further sintering, i.e., for 4 to 8 h, there was no significant difference in the drug release (prolonged for 2 h only).

Unsintered F3 tablets retarded the drug release up to 8 h. After 4 of physical sintering, the drug release was prolonged up to 12 h. The F3 formulation at 2 h of physical sintering has shown an optimum dissolution profile compared to the different periods of physical sintering, i.e., F3 at 2 h of exposure has shown 81.08 ± 0.15% drug release in 12 h (Figure 7b).

F4 on exposure to physical sintering had slightly prolonged the drug release. This might be due to a minor increase in the polymer concentration (Figure 7c)**.** Hence, based on the results of dissolution studies, it can be concluded that F3 on exposure to 8 h of physical sintering has sustained the drug release (81.08 ± 0.15%). Therefore, F3 was selected as the optimized formulation.

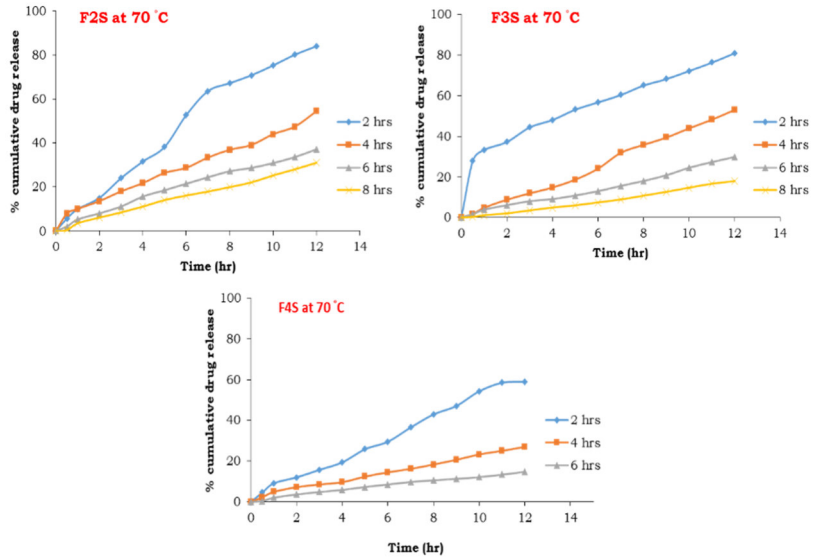

Figure 7. Dissolution profiles of sintered tablets at 70 °C for (a) F2S (b) F3S and (c) F4.

Comparative dissolution studies of optimized formulations

A comparative study was conducted for the optimized formulation (F3) at different temperatures, i.e., 50, 60 & 70 °C. This is to observe the effect of temperature on the time taken for the sintering of tablets.

In comparative dissolution studies, it was found that F3 formulation showed better sustained drug release when exposed to 70 °C for 2 h, compared to other temperatures such as 60 °C and 50 °C, which had shown 4 h and 8 h, respectively. Hence, it can be inferred that as the sintering temperature increases, the time taken for sintering decreases, and the time taken for drug release increases, i.e., the temperature is inversely proportional to sintering time (Figure 8).

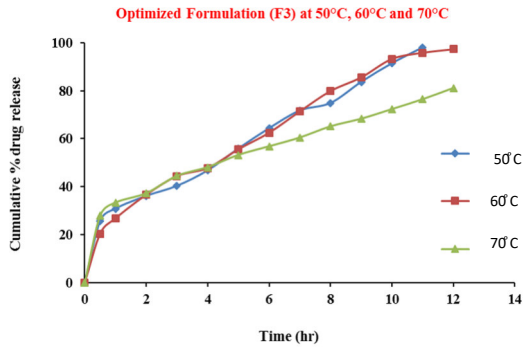

Figure 8. Comparative dissolution studies of optimized formulation (F3) at 50, 60 and 70 °C.

Model dependent kinetic for sintered tablets

As mentioned above, the release data was analysed by fitting the drug release profiles into different model-dependent kinetics like zero-order, first-order, Higuchi and Korsmeyer-Peppas model" for formulations F2S, F3S and F4S, which were subjected to physical sintering at different temperatures such as 50, 60 & 70 °C for different periods (sampling was done for every 2 h up to 12 h). Based on the results, the optimized formulation F3 was found to follow zero-order kinetics (r^2 = 0.991), Higuchi model (r^2 = 0.948) and mechanism of release was found to be Fickian diffusion (n = 0.336).

Stability studies

During the stability studies, optimized tablets were stable with insignificant changes in floating lag time, floating time, drug content, and *in vitro* drug release characteristics. The optimized formulation was subjected to stability studies and the results are given in Table 8.

Table 8. Model dependent kinetic for sintered tablets of F3S at 50°C, 60°C, and 70°C.

Parameters	0 [initial] *	1st week*	2nd week*	1st month*
Floating lag time	No lag time	No lag time	No lag time	No lag time
Floating time	>12 h	>12 h	> 12 h	>12 h
Thickness [mm]	5.4±0.17	5.4±0.22	5.38±0.27	5.36±0.32
Hardness [kg/cm2]	6.9±0.01	6.88±0.11	6.88±0.11	6.88±0.11
Drug content [%]	89.62±0.16	89.62±0.16	89.62±0.16	87.72±0.31
Drug release [%]	81.08±0.15	81.07±0.16	81.07±0.16	81.06±0.17

* Mean ± SD, n=3

Conclusion

Formulating and evaluating the floating sintered matrix tablets of CP by hot melt granulation method using carnauba wax as a rate-controlling polymer has been achieved successfully. It is evident from drug excipient compatibility studies such as FTIR and DSC that there is no interaction between CP and carnauba wax. F2, F3, and F4 formulations were compared and subjected to physical sintering at 50, 60, and 70 °C for different time intervals. In comparison to other formulations and temperatures, it was found that the F3 formulation, when exposed to 70 °C for 2 h (F3S), showed sustained drug release for up to 12 h due to physical sintering by hot melt granulation. In conclusion, the objective of the study was achieved by formulating CP floating sintered matrix tablets using low polymeric concentration at low hardness by sintering at high temperatures (much below the melting point of CP). Therefore, the sintering method can be used as an alternative technique for the preparation of sustained-release matrix tablets with less amount of retardant and compression force for greater strength and extended-release.

Future Scope

To perform in vivo studies to determine the pharmacokinetic parameters of the drug.

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Authors contribution

All the authors have contributed equally.

Declaration of interest

The authors declare no conflict of interest.

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