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DESIGN AND EVALUATION OF CIPROFLOXACIN FLOATING TABLETS USING THERMAL SINTERING TECHNIQUE

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Keywords:

Ciprofloxacin, Floating matrix tablets, Sintering, Total floating time

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ABSTRACT: The main of this study was production of floating tablets to maintain the drug stay in its absorption area. Ciprofloxacin is better absorbed in the stomach because of this reason floating matrix tablet was prepared using novel sintering technique with sodium bicarbonate as gas generating agent and a polymer eudragit robust formulation was decided on the basis of floating time and *in-vitro* drug release with possible less polymer concentration, time of exposure and at low temperature. Three batches were prepared with hardness between 4-6 kg/cm^2 based on time of exposure at particular sintering temperature desired total floating time, and drug release was retarded up to 12 h. Hence, it is evident from this investigation that a floating matrix tablet using the sintering technique could be promising delivery with improved sustained release action and drug availability.

INTRODUCTION: Sintering is characterized as the bonding between particles by the application of heat. The conventional sintering technique involves heating at a temperature below the melting point of solid constituents in a controlled environment [1, 2]. The process of sintering may affect the pore structure and strength of matrix tablets [3]. Controlled gastric retention of solid dosage forms may be achieved by the mechanism of floating systems. The principle of buoyant preparation offered a residence time for the dosage form and sustained drug release [4]. The significant problem may arise due to there may be a narrow absorption window, local action, or poorly soluble in the intestine.

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Thus, the main issue in the development of a floating tablet is not just to prolong the delivery of drugs more than 12 h but to maintain the presence of dosage form in the stomach over a desired period of time [5]. Ciprofloxacin is a fluoroquinolone antibacterial which is widely absorbed from the stomach and upper GIT. 70% of oral bioavailability with peak plasma concentration is within 1-2 h. Absorption becomes less as the drug passes beyond this [6-8]. The main objective of this investigation was to formulate a floating tablet using a gas generating agent component with set limits of dissolution profile and minimum floating ability for 8h and tablets were placed in thermal sintering temperature to improve floating ability and dissolution profile.

MATERIALS AND METHODS: Ciprofloxacin and eudragit were procured from yarrow chem products (Ghatkopar West Mumbai). Sodium bicarbonate (Merck, Germany) was used. Materials and excipients used were USP grades. All other ingredients were of analytical grades.

Formulation of Floating Tablets: All the ingredients are weighed according to the formulae shown in **Table 1**. Weighed ingredients were passed through sieve number 40#. All the ingredients were mixed except lubricant magnesium stearate and aerosil; granules were prepared by wet granulation using a binding agent mixture of PVP K30 and IPA.

The wet mass was passed through 10#, then dried for half an hour at 45 °C and then dried granules are passed through 20# sieve. Dried granules were lubricated with magnesium stearate 60# for 2 min. The blend was compressed into tablets using 12 mm punches.

TABLE 1: COMPOSITION OF CIPROFLOXACIN FLOATING TABLETS

INGREDIENTS	CE1	CE2	CE3
ciprofloxacin	500	500	500
Eudragit RS 100	90	120	150
HPMCK 100M	20	40	60
Sodium bicarbonate	40	40	40
Microcrystalline cellulose	60	50	40
Magnesium stearate	7.5	7.5	7.5
Aerosil	7.5	7.5	7.5
PVP K30	Q. s	Q. s	Q. s
IPA	Q. s	Q. s	Q. s
Tablet weight	725	765	805

Preparation of Thermally Sintered Floating Tablets of Ciprofloxacin: The formulations CE1 and CE2 tablets were exposed to 50 °C, 55 °C and 60 °C for 1 h, 2.5 h and 4 h in a hot air oven. After exposure to the respective temperature at different time, tablets were removed and cooled to room temperature.

Evaluation of Floating Tablets: The prepared tablets were evaluated for hardness, weight variation, thickness, buoyancy, and *in-vitro* drug release characteristics.

Floating Behavior of Tablets: *In-vitro* floating behavior of the tablets was studied in 900 ml of 0.1 N HCl. The duration of floating is the time the tablet floats in the dissolution medium, including buoyancy lag time [9].

***In-vitro* Drug Release:** Drug release studies were done using the USP paddle method by placing the tablets in 900 ml of 0.1N HCl buffer solution pH 1.2 at 37 °C. Samples were withdrawn, and concentration was estimated using a UV spectro-photometer at 278 nm[10].

Evaluation of Mechanism of Release: The drug release mechanism was determined by fitting the release data to the various kinetic equations such as zero-order, first-order, and Korsmeyer-Peppas and finding the regression values of the release profile corresponding to each model. Zero-order kinetics zero order as the cumulative amount of drug released versus time,

$$C = C_0 - K_0 t$$

Where K_0 = zero-order rate constant and is expressed in units of concentration/time (h). First-order kinetics First order as cumulative log percentage of drug remaining versus time,

$$\text{Log } C = \text{Log } C_0 - kt / 2.303$$

Where, C_0 = initial concentration of the drug, K = first-order constant and T = time Korsmayer Peppas equations log cumulative percentage of drug released versus log time, and the exponent n will be calculated;

$$M_t / M_\infty = K t^n$$

Where, M_t / M_∞ = fractional solute release, T = time, K = kinetic constant characteristics of the drug/polymer system and n = exponent, which characterizes the mechanism f release of tracers. If the exponent N = 0.45, then drug release mechanism is fickian diffusion and if $0.45 < n < 0.89$, then it is non-fickian or anomalous diffusion.

Drug Polymer Interaction FTIR Study: The pellets of the drug were prepared using potassium bromide by compressing at 20 psi for 10 min on KBr press, and the spectra were scanned in the wavenumber range 600 cm^{-1} - 4000 cm^{-1}. FTIR study was carried on a drug and physical mixture of drug and polymer.

RESULTS AND DISCUSSION: Table 2, 3, and **4** depicts the physical parameters and floating time of all the fabricated unsintered and sintered tablets. **Fig. 1, 2,** and **3** reflect the *in-vitro* release of the drug from these tablets. Hardness was maintained in the range of 4-6 kg/cm^2. All batches were very much within the designated assay range of 99-101%. The percentage weight variation test for all the formulation batches is under 5%. The floating lag time of all unsintered and sintered tablets was within range of 58 to 153 sec. The *in-vitro* drug

release of unsintered tablets of CE1, CE2, and CE3 was more than 98% retarded up to 6 h, 8 h, and 10 h, respectively. The CE2 was selected because the desired drug release was maintained up to 8 h.

TABLE 2: CHARACTERISTICS OF UNSINTERED TABLET AND *IN-VITRO* FLOATING BEHAVIOUR

Formula	Weight (mg)	Assay (%)	Hardness (kg/cm^2)	Friability (%)	Floating lag time (sec)	Total floating time (h)
CE1	735	99.9	4-6	0.43	123	6
CE2	765	99.8	4-6	0.38	138	8
CE3	805	99.7	4-6	0.41	153	10

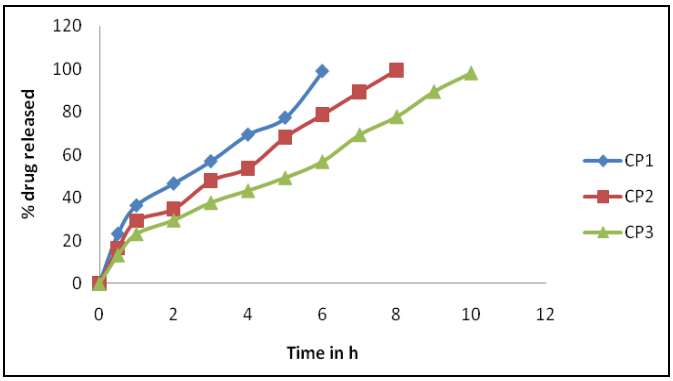

FIG. 1: *IN-VITRO* DRUG RELEASE OF UNSINTERED TABLET

CE1 tablets were exposed to 50 °C for 1 h, 2.5 h, and 4 h more than 97% drug released in 7 h, 8 h and 9 h. The same batch tablets were exposed to 55 °C for 1 h, 2.5 h, and 4 h more than 99% drug released in 8 h, 9 h, and 10 h. CE1 tablets were exposed to 60 °C for 1 h, 2.5 h, and 4 h more than 98% drug released in 8 h, 9 h, and 10 h, respectively. When CE2 tablets were exposed to 50 °C for 1 h, 2.5 h, and 4 h, more than 98% drug released in 9 h, 10 h, and 12 h, respectively. Tablets of the same batch exposed to 55 °C for 1 h, 2.5 h and 4 h more than 98% drug released in 11 h 12 h and 13 h respectively and when exposed to 60 °C for 1 h, 2.5 h and 4 h more than 98% drug released in 12 h, 13 h, and 13 h respectively.

TABLE 3: CHARACTERISTICS OF TABLET AND *IN-VITRO* FLOATING BEHAVIOUR OF CE1

Sintering temp and time	Weight (mg)	Assay (%)	Hardness (kg/cm^2)	Friability (%)	Floating lag time (sec)	Total floating time (h)
unsintered	725.8 ± 1.43	99.8 ± 1.03	4-6	0.44	123	6
50 °C 1 h	725.4 ± 1.62	99.3 ± 1.94	4-6	0.35	119	7
50 °C 2.5 h	725.1 ± 1.24	99.6 ± 1.45	4-6	0.34	112	8
50 °C 4 h	725.3 ± 1.83	99.7 ± 1.59	4-6	0.35	101	9
55 °C 1 h	726.7 ± 1.34	99.3 ± 1.85	4-6	0.36	115	8
55 °C 2.5 h	725.8 ± 1.83	99.8 ± 1.75	4-6	0.24	109	9
55 °C 4 h	726.3 ± 1.39	99.7 ± 1.64	4-6	0.38	105	10
60 °C 1 h	725.1 ± 1.93	99.9 ± 1.75	4-6	0.33	107	9
60 °C 2.5 h	724.2 ± 1.38	99.9 ± 1.74	4-6	0.45	98	10
60 °C 4 h	723.7 ± 1.03	99.5 ± 1.53	4-6	0.32	83	11

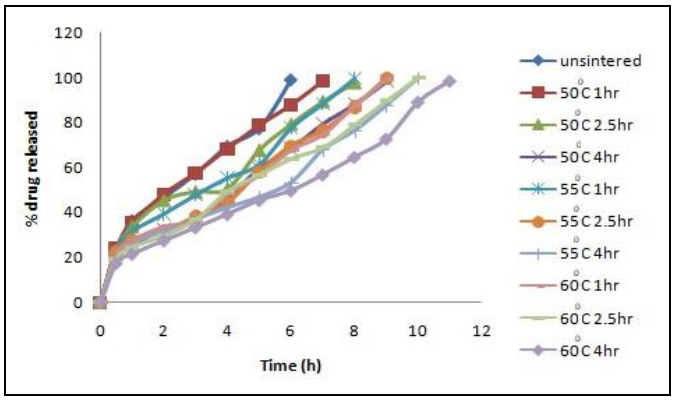

FIG. 2: *IN-VITRO* DRUG RELEASE OF CE1

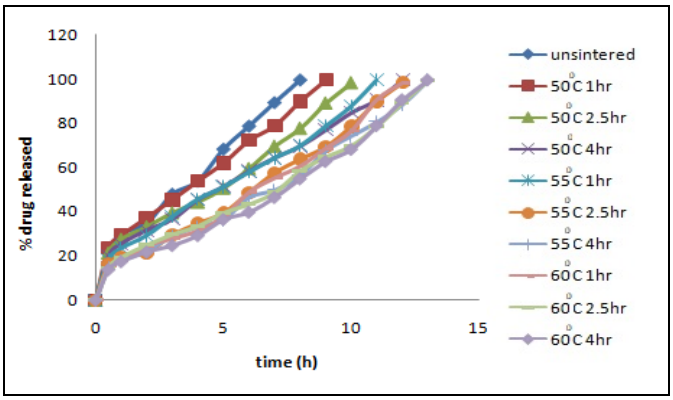

FIG. 3: *IN-VITRO* DRUG RELEASE OF CE2

The dissolution profiles of ciprofloxacin from eudragit sintered matrix tablet for various times are shown in **Fig. 2-3**. The sintering time and temperature markedly affected the drug release characteristics and *in-vitro* floating behavior. As the sintering temperature and time of exposure, floating lag time was decreased, and drug release was prolonged.

Because of the thermal treatment of the tablet matrix, it promotes the better distribution of polymer throughout the matrix at the same time, increases the bond strength and thus strengthened the polymer network by ensuring complete coalescence of the particles inside the matrix. When the tablets are exposed to the temperature, the polymer may move through the matrix of the tablet and fill between the pores and coat the drug particles. These types of changes in tablets result in a matrix structure that decreases the drug release and increases entrapment of gas generated from the gas generating agent results decrease in floating lag time. The optimized formula CE2 tablets of sintered at 55 °C 2.5 h with lag time 90 sec and drug release retarded up to desired 12 h, which follows zero-order with non-fickian diffusion mechanism. The curve fitting method of zero order, first order, Higuchi model, and Peppas for analysis of drug release kinetics are given in **Tables 5** and **6**. Formulation CE1 and CE2 drug release kinetic data shows zero order follows with non-fickian diffusion mechanism.

TABLE 4: CHARACTERISTICS OF TABLET AND *IN-VITRO* FLOATING BEHAVIOUR OF CE2

Sintering temp and time	Weight (mg)	Assay (%)	Hardness (kg/cm^2)	Friability (%)	Floating lag time (sec)	Total floating time (h)
Unsintered	765.8 ± 1.83	99.1 ± 1.02	4-6	0.41	138	8
50 °C 1 h	765.4 ± 0.74	99.2 ± 1.52	4-6	0.45	127	9
50 °C 2.5 h	765.5 ± 1.76	99.3 ± 1.44	4-6	0.34	113	10
50 °C 4 h	765.2 ± 1.63	100.6 ± 1.05	4-6	0.34	92	12
55 °C 1 h	766.3 ± 1.37	99.3 ± 1.84	4-6	0.38	105	11
55 °C 2.5 h	765.8 ± 1.45	99.4 ± 1.65	4-6	0.24	90	12
55 °C 4 h	766.2 ± 1.72	99.3 ± 1.74	4-6	0.38	83	13
60 °C 1 h	765.8 ± 1.24	99.5 ± 1.82	4-6	0.43	89	12
60 °C 2.5 h	764.1 ± 1.54	99.9 ± 1.34	4-6	0.45	64	13
60 °C 4 h	763.1 ± 1.63	99.6 ± 1.55	4-6	0.42	58	13

TABLE 5: DRUG RELEASE KINETICS OF CE1

Sintering temp and time	Zero r	First r	Higuchi r	Pappas	
				r	n
Unsintered	0.9513	0.6921	0.8972	0.9811	0.536
50 °C 1 h	0.9492	0.8148	0.9378	0.9958	0.519
50 °C 2.5 h	0.9469	0.8171	0.8556	0.9546	0.489
50 °C 4 h	0.9789	0.7709	0.8165	0.9311	0.5411
55 °C 1 h	0.9629	0.6721	0.8454	0.9604	0.505
55 °C 2.5 h	0.9726	0.5893	0.7962	0.9152	0.518
55 °C 4 h	0.9541	0.8712	0.7812	0.9214	0.475
60 °C 1 h	0.9730	0.6621	0.8061	0.9305	0.522
60 °C 2.5 h	0.9746	0.9168	0.8590	0.9590	0.536
60 °C 4 h	0.9651	0.9633	0.8573	0.9645	0.488

TABLE 6: DRUG RELEASE KINETICS OF CE2

Sintering temp and time	Zero r	First r	Higuchi r	Pappas	
				r	n
Unsintered	0.9799	0.7277	0.8845	0.9793	0.617
50 °C 1 h	0.9687	0.7085	0.8623	0.9644	0.497
50 °C 2.5 h	0.9605	0.8875	0.8177	0.9415	0.472
50 °C 4 h	0.9745	0.9582	0.8847	0.9695	0.464
55 °C 1h	0.9647	0.9739	0.8911	0.9773	0.505
55 °C 2.5 h	0.9736	0.9645	0.8082	0.9185	0.516
55 °C 4 h	0.9702	0.9506	0.8251	0.9515	0.523
60 °C 1 h	0.9728	0.9595	0.8090	0.9322	0.527
60 °C 2.5 h	0.9624	0.9610	0.8461	0.9649	0.494
60 °C 4 h	0.9678	0.9524	0.8003	0.9339	0.506

FTIR Study: In FTIR spectra characteristic peak was observed between 3,350 and 3300 cm^{-1}, which was assigned to stretching vibration of OH groups and intermolecular hydrogen bonding. The 1,000 to 1,750 cm^{-1} region exhibited absorption from a variety of double-bonded functional groups. The band at 1,750 to 1,700 cm^{-1} represented the carbonyl C=O stretching. The peak was observed

1,650, and 1600 cm^{-1} was assigned to quinolones. C-O band observed between 1400 to 1350 cm^{-1}. Bending vibration of the O-H group observed at 1200 cm^{-1} to 1250 $cm^{-1,}$ which proved the presence of carboxylic acid. C-F group observed between 1050 and 1000 cm^{-1}. From FTIR spectra, it is evident that there is no interaction between drug and polymer.

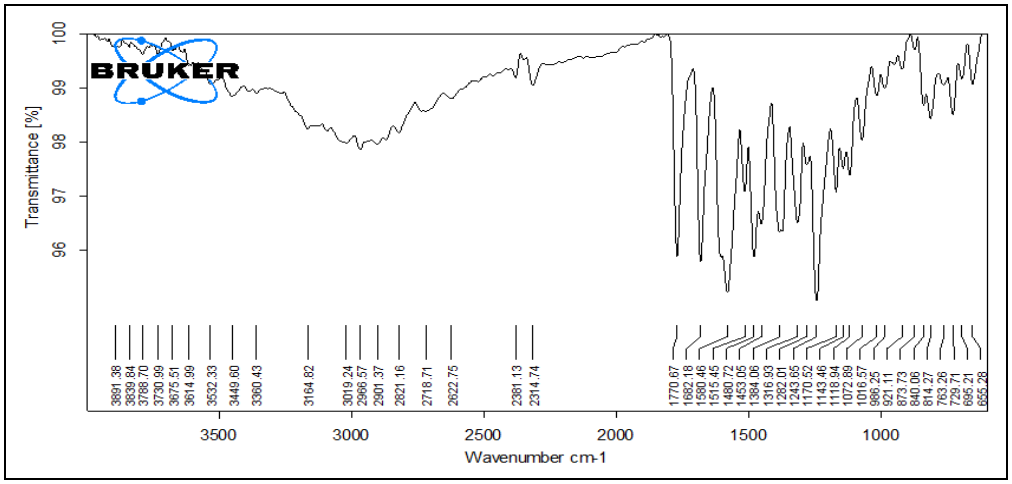

FIG. 4: FTIR SPECTRUM OF PURE DRUG

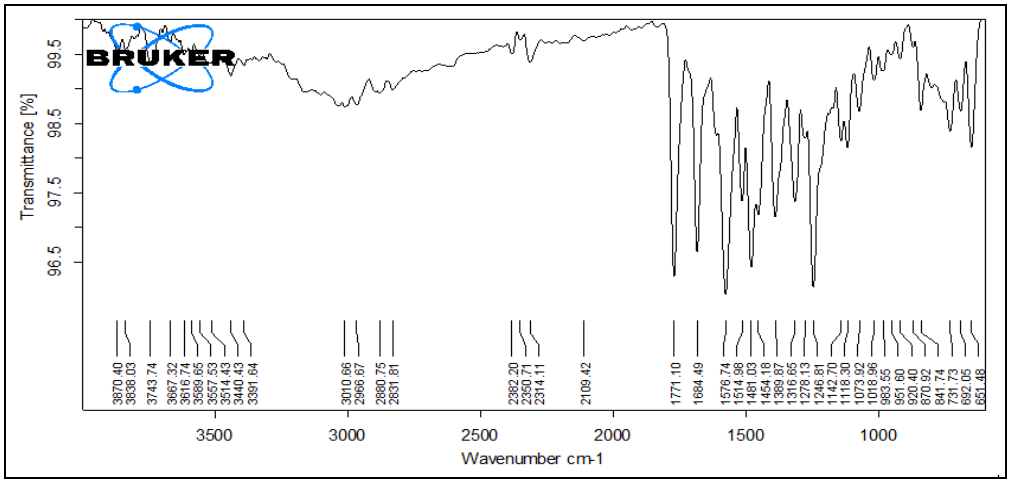

FIG. 5: FTIR SPECTRUM OF OPTIMIZED FORMULATION

CONCLUSION: The present study was showed that drug release prolongation after thermal sintering attributed the polymer chain movement and redistribution of the polymer matrix structure. Because of this, floating lag time was decreased with the thermal treating and time of exposure. So, it concluded that floating tablets with thermal treating could be used.

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CONFLICTS OF INTEREST: Nil

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