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A STUDY ON EFFECT OF THERMAL SINTERING ON GASTRIC FLOATING TABLETS

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Keywords:

Carnauba wax, Sintering, Time of exposure, Bioavailability

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ABSTRACT: The purpose of this study was to develop a gastroretentive controlled release drug delivery system using sintering for enhanced oral bioavailability using carnauba wax polymer. Formulations (CC1-CC3) were prepared by wet granulation method and then exposed to sintering temperature at different time intervals. The optimized formula showed zero-order drug release kinetics for the period of 12 h. The results revealed that sintering temperature and time of exposure significantly affected the *in-vitro* drug release and floating character. FTIR Spectra showed no noticeable incompatibility between drug and polymers in both physical mixtures and in the formulation.

INTRODUCTION: Annealing is processed to heat the polymer at a certain temperature for a specified period of time. Because of this treatment, it influences the mechanical properties of polymers with the association of time-dependent nature of glass transition [1-2]. Thermal treatment effects the drug release by decreasing the release rate. This may be due to increase in tensile strength [3]. Gastric residence time (GRT) is most important for formulation to design stomach specific dosage forms but efficacy of oral drug delivery was reduced due to gastric emptying [4-6]. Gastro retentive drug delivery systems help to retain the dosage form in the stomach and improve oral bioavailability of drugs that have absorption windows at upper GIT [7-8]. In the present study captopril was selected as a model drug candidate. Captopril is an angiotensin-converting enzyme inhibitor and widely used for the treatment of hypertension. Half-life of the oral drug dose is 2 h [9].

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It is stable at acidic pH 1.2, and it is unstable as the drug shows degradation at higher pH along the GIT [10-11]. BCS classification of captopril was class III. The present study effectively utilized polymer carnauba wax for the preparation and evaluation of floating tablets of captopril using carnauba wax by employing the annealing process.

MATERIALS AND METHODS:

Materials: The active ingredient used in the study was captopril (Astra lifecare, India) Pvt. ltd, carnauba wax used as a polymer (SD fine chemicals, Mumbai India). All other materials used were of analytical grade.

Drug-Excipients Compatibility Studies:

Fourier Transform Infrared (FTIR) Spectroscopy: Compatibility studies were carried out to know the interactions between drug and excipients used in the formulation. Physical mixtures of drugs and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FTIR spectroscopy.IR spectrum of pure drug and excipients was seen in between 500-4000 cm^{-1}.

DSC Studies: For thermal analysis of drug and drug excipient mixtures, a differential scanning

calorimeter (DSC 821, mettle Toledo, Switzerland) was used. Individual samples, as well as optimized formulation, were taken in the pierced DSC aluminum pan and scanned in the temperature range of 25-300 °C at the heating rate of 10 °C min^{-1} under an atmosphere of dry nitrogen.

Preparation of Floating Tablets of Captopril: All the ingredients are weighed according to **Table 1**. Tablets are prepared by wet granulation method. PVPk30 was mixed with Isopropyl alcohol. Drug Polymer gas generating agent and diluent was passed through sieve #40 and then mixed to this add a granulating agent to get wet mass and passed through sieve # 10. Granules are dried for at 45 °C for 45 min and then passed through 22# sieve. Dried granules are lubricated with magnesium stearate and talc and compressed using 9 mm punches. Compressed tablets were exposed to 40 °C, 50 °C and 60 °C for 1 h, 2 h, 3 h, and 4 h, respectively. After annealing, tablets are cooled to room temperature and placed in a controlled environment.

***In-vitro* Evaluation of the Prepared Tablets:** Weight variation and tablet friability test were carried according to USP, respectively.

TABLE 1: FORMULAE OF CAPTOPRIL FLOATING TABLETS

Ingredients	CC1	CC2	CC3
Captopril	50	50	50
Carnauba wax	50	100	150
HPMCK100M	10	12.5	15
Microcrystalline cellulose 101	185	152.5	80
Sodium Bicarbonate	50	50	50
Mg Stearate	5	5	5
PVPK30	qs	qs	qs
IPA	qs	qs	qs
Total weight	350	350	350

Drug Content Uniformity: Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet was dissolved in 100 ml of 0.1 N HCl. After filtration through a cellulose acetate membrane (45 µm) Then drug content was determined by UV spectroscopy (UV-1650 PC Double beam spectrometer, Shimadzu, Kyoto, Japan) at a wavelength of 202 nm after suitable dilution with 0.1 N HCl [12].

Tablet Floating Behaviour: *In-vitro* buoyancy studies were studied by placing the tablet in a beaker containing 900 ml of 0.1N HCl maintained in a water bath at 37 ± 0.5 °C. The floating lag time and total floating duration were recorded [13].

***In-vitro* Dissolution Studies:** Dissolution profiles of gastric floating tablets were determined by using USP XXIII paddle method. Tablets were placed into 900 ml of 0.1N HCl solution (pH 1.2) with 37 ± 0.5 °C and 50 rpm. 5 ml samples were withdrawn with replacement at a fixed time of intervals. Samples were diluted with medium when necessary and absorbance was measured at 202 nm[14].

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 (hour). First-order kinetics First order as log cumulative percentage of drug remaining versus time, $\text{Log } C = \text{Log } C_0 - k t / 2.303$ Where, C0 = initial concentration of a 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, $Mt/M\infty$ = 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 [15-17].

RESULTS AND DISCUSSION:

FTIR: The IR spectra of the pure drug showed characteristic bands C-H stretching at 2874-2972/cm. SH stretch prominent peak observed at 2770/cm. A peak at 1741/cm indicated C=O of –COOH, 1582/cm indicates C=O of amide.1305-1375/cm peaks were shown indicating OH bending, 1227.5/cm indicating C-O stretching, 1192/cm indicating CN stretching. From the spectra, it is evident that all the characteristic peaks of drug replicated in the same region in the spectra of physical mixture indicating there is no significant interaction between the drugs and polymers.

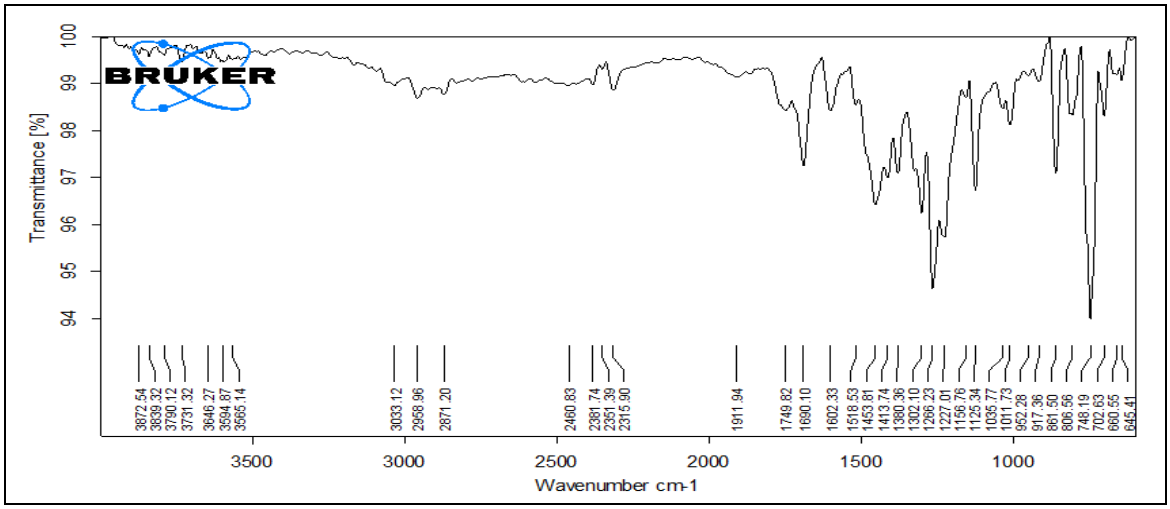

FIG. 1: INFRARED SPECTRA OF PURE DRUG

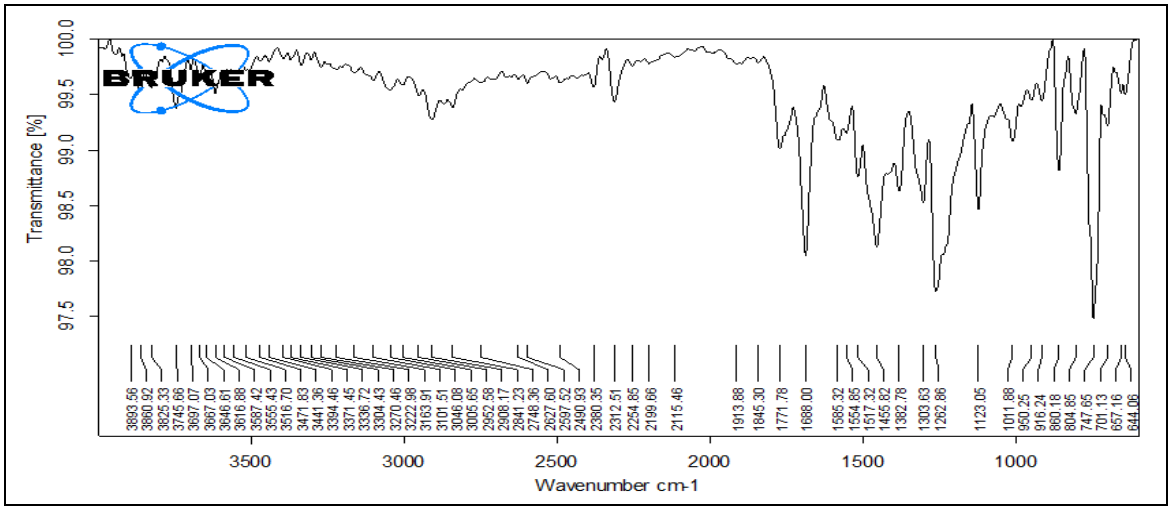

FIG. 2: INFRARED SPECTRA OF PURE DRUG+POLYMER

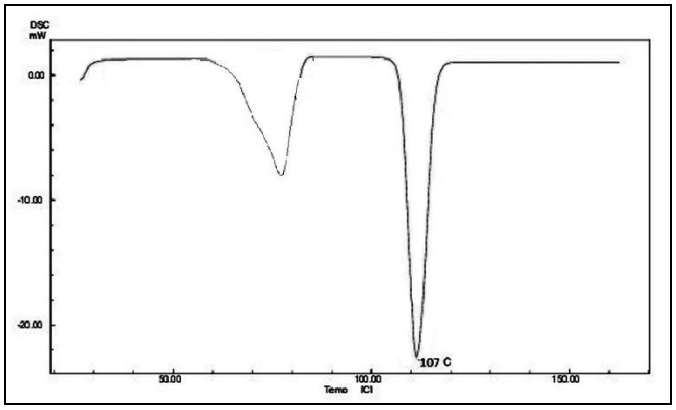

FIG. 3: DSC THERMOGRAM OF DRUG AND POLYMER

DSC: The DSC thermogram showed the endothermic peak at 107 °C, which is the melting point of the drug. In the DSC thermogram of tablet, the peaks were obtained nearly at same temperature of pure drug, which indicates no significant interaction between the drug and other excipients.

Physical Parameters of Unsintered and Sintered Tablets: All the unsintered and sintered formulated tablets had hardness 4-5 kg/cm^2. The friability percentage was below 0.5%, the weight variation of tablets was within ±5%. Drug content uniformity of all the tablets were in the range of 98% to 101%. So, all the tablets have good physical characteristics.

TABLE 2: TABLETTING PROPERTIES AND *IN-VITRO* FLOATING BEHAVIOUR OF UNSINTERED FLOATING TABLETS

Sintering temp. and time	Weight (mg)	Assay (%)	Hardness (Kg/cm^2)	Friability (%)	Floating lag time (sec)	Total floating time (h)
CC1	350.1	99.4	4-6	0.32	58	>6
CC2	349.2	100.2	4-6	0.41	68	>7
CC3	351.1	100.3	4-6	0.35	74	>8

***In-vitro* Floating Behaviour and *in-vitro* Drug Release:** The results of *in-vitro* buoyancy are shown in **Table 3**. The formulations had floating lag time between 74 to 18 sec. Floating lag time was affected by the concentration of polymer used in the formulation. Prolonged exposure of tablets to different temperature floating was improved. Total floating time also improved with annealing of tablets. Unsintered tablets of CC1, CC2, and CC3 drug release were 97.4%, 97.2%, and 99.4% at 6 h, 7 h, and 8 h, respectively. CC1, CC2 and CC3 sintered tablets drug release was unchanged when exposed to 40 °C at 1 h, 2 h, 3 h and 4 h respectively. CC1 sintered tablets when exposed to 50 °C drug release was 98.9%, 99.2%, 98.9% and 99.6% in 8 h, 9 h, 10 h, and 11 h respectively, at 60 °C drug release was 97.8%, 98.4%, 97.4% and 98.4% in 10 h, 11 h, 12 h, and 13 h respectively. *In-vitro* drug release was shown 99.4%, 98.6%, 99.4%, and 99.7% in 11 h, 12 h, 13 h, and 14 h when sintered tablets of CC2 exposed to 50 °C. Same batch sintered tablets at 60 °C for 1, 2, 3, and 4 h retarded the drug up to 12, 13, 13, and 14 h.

TABLE 3: FLOATING, BUOYANCY TIME

Sintering temp and time	CC1		CC2		CC3	
	Floating lag time (sec)	Total floating (time)	Floating lag time (sec)	Total floating time (h)	Floating lag time (sec)	Total floating time (h)
Unsintered	59	6	68	7	74	8
40 °C 1 h	55	6	56	7	68	8
40 °C 2 h	51	6	52	7	60	8
40 °C 3 h	48	6	47	7	57	8
40 °C 4 h	42	6	41	7	52	8
50 °C 1 h	41	8	53	11	58	13
50 °C 2 h	38	9	46	12	50	14
50 °C 3 h	26	10	39	13	44	14
50 °C 4 h	23	11	31	14	36	15
60 °C 1 h	35	10	43	12	53	13
60 °C 2 h	28	11	35	13	46	15
60 °C 3 h	22	12	29	13	37	15
60 °C 4 h	18	13	21	14	28	15

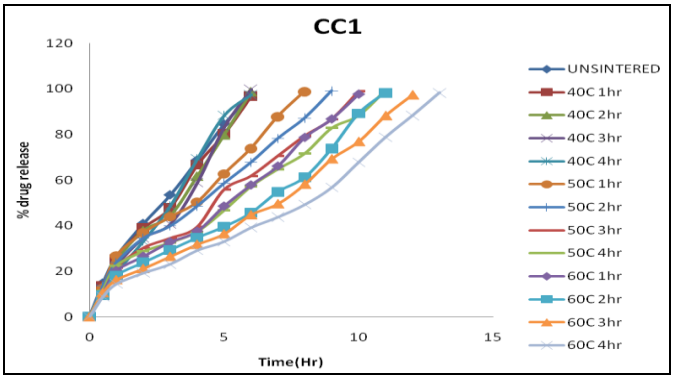

FIG. 4: *IN-VITRO* DRUG RELEASE OF CC1

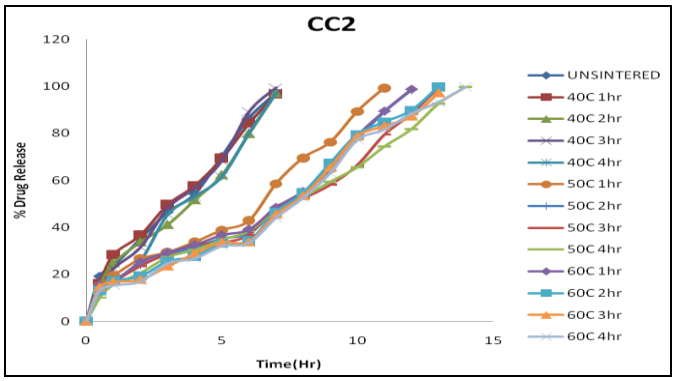

FIG. 5: *IN-VITRO* DRUG RELEASE OF CC2

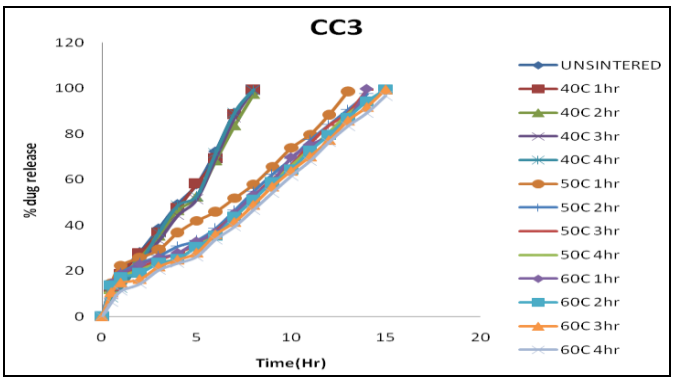

FIG. 6: *IN-VITRO* DRUG RELEASE OF CC3

The formulation CC3 tablets at 50 °C for 1, 2, 3 and 4 h retarded the drug up to 13, 14, 14 and 15 h respectively and at 60 °C for 1, 2, 3 and 4 h retarded the drug up to 14, 15, 15 and 15 h. Results data observed that drug release was decreased with the increase of time of exposure and temperature. Thermal treatment of the tablet matrix promoting a better distribution of waxy polymer throughout the matrix and increasing strength of the polymer network. While sintering the polymer can move through the matrix of the tablet and fill between the gaps and coats the drug particles. This may be the reason which decreases the floating lag time and prolongs the drug release.

TABLE 4: RELEASE KINETICS OF CC1

Sintering temp and time	Zero order	First order	Higuchi	Peppas	
	r	r	r	r	n
Unsintered	0.9903	0.8377	0.9187	0.9968	0.741
40 °C 1 h	0.9908	0.8136	0.8967	0.9915	0.761
40 °C 2 h	0.9860	0.7016	0.8599	0.9827	0.760
40 °C 3 h	0.9807	0.5981	0.8246	0.9734	0.797
40 °C 4 h	0.9948	0.8551	0.8860	0.9924	0.872
50 °C 1 h	0.9804	0.7273	0.8779	0.9768	0.680
50 °C 2 h	0.9857	0.6986	0.8779	0.9878	0.653
50 °C 3 h	0.9830	0.9455	0.8785	0.9782	0.689
50 °C 4 h	0.9788	0.9324	0.8504	0.9678	0.623
60 °C 1 h	0.9872	0.9109	0.8435	0.9760	0.693
60 °C 2 h	0.9781	0.9359	0.8492	0.9775	0.645
60 °C 3 h	0.9808	0.9443	0.8279	0.9715	0.613
60 °C 4 h	0.9827	0.9821	0.8731	0.9851	0.610

TABLE 5: RELEASE KINETICS OF CC2

Sintering temp and time	Zero-order	First-order	Higuchi	Peppas	
	r	r	r	r	n
Unsintered	0.9848	0.8127	0.8486	0.9651	0.626
40 °C 1 h	0.9811	0.8206	0.8911	0.9862	0.641
40 °C 2 h	0.9786	0.7356	0.8276	0.9708	0.655
40 °C 3 h	0.9911	0.7091	0.8721	0.98852	0.750
40 °C 4 h	0.9888	0.7511	0.8462	0.9736	0.782
50 °C 1 h	0.9555	0.9008	0.7590	0.9199	0.533
50 °C 2 h	0.9489	0.9167	0.7891	0.9399	0.495
50 °C 3 h	0.9523	0.9610	0.8609	0.9717	0.513
50 °C 4 h	0.9757	0.9747	0.8690	0.9834	0.582
60 °C 1 h	0.9536	0.9438	0.8187	0.9418	0.482
60 °C 2 h	0.9436	0.8883	0.7255	0.8967	0.519
60 °C 3 h	0.9443	0.8973	0.7156	0.8632	0.495
60 °C 4 h	0.9520	0.9105	0.7359	0.8902	0.521

TABLE 6: RELEASE KINETICS OF CC3

Sintering temp and time	Zero-order	First-order	Higuchi	Peppas	
	r	r	r	r	n
Unsintered	0.9930	0.6853	0.8502	0.9894	0.785
40 °C 1 h	0.9910	0.6430	0.8315	0.9822	0.758
40 °C 2 h	0.9880	0.7389	0.8140	0.9695	0.742
40 °C 3 h	0.9863	0.6272	0.8052	0.9781	0.843
40 °C 4 h	0.9913	0.6797	0.8388	0.9882	0.914
50 °C 1 h	0.9575	0.9711	0.8717	0.9676	0.489
50 °C 2 h	0.9557	0.9421	0.8085	0.9472	0.504
50 °C 3 h	0.9587	0.9433	0.7948	0.9373	0.513
50 °C 4 h	0.9614	0.9439	0.7922	0.9377	0.544
60 °C 1 h	0.9481	0.9398	0.7776	0.9159	0.457
60 °C 2 h	0.9532	0.9330	0.7440	0.8864	0.478
60 °C 3 h	0.9702	0.9483	0.7770	0.9260	0.554
60 °C 4 h	0.9843	0.9625	0.8199	0.9747	0.700

Drug Release Mechanism: Knowledge of drug release kinetics provides to understand drug release mechanism and a basis for predicting release profiles from different systems studied. 4 mathematical models for drug release considered were zero order, first order, Higuchi, as well as Korsmeyer and Peppas model. Values of the correlation coefficients (r) and the release rate constants are presented in **Table 4, 5, 6**.

The r values ranged from 0.9436 to 0.9948 (zero-order), 0.5981 to 0.9821 (first-order), 0.7156 to 0.9187 (Higuchi) and 0.8632 to 0.9968 (Korsmeyer and Peppas). All formulations are showing that they fit well into the Korsmeyer and Peppas model. This indicates that the release of captopril floating tablets from these formulations followed Fickian diffusion mechanism with zero order.

CONCLUSION: Here in this research, thermal sintering was studied to reduce the concentration of polymer and to achieve the desired dissolution profile. Experimental data concludes that floating lag time was decreased with annealing time of exposure. The dissolution profile shows that drug release was retarded with an increase in thermal treatment duration. Hence, the design of gastric floating tablets of captopril using carnauba wax can be prepared by the thermal sintering method.

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CONFLICTS OF INTEREST: Nil

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