Journal of Applied Pharmaceutical Research
Volume 13 Issue 6, Year of Publication 2025, Page 33 – 46
DOI: https://doi.org/10.69857/joapr.v13i6.1488

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Research Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR
www.japtronline.com *ISSN: 2348 – 0335*

THERMAL SINTERING DRIVEN MODULATION OF DRUG RELEASE AND BUOYANCY CHARACTERISTICS IN DASATINIB GASTRO-RETENTIVE TABLETS

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Article Information
Received: 1st August 2025
Revised: 25th October 2025
Accepted: 1st December 2025
Published: 25th December 2025

Keywords
Thermal sintering, gastroretentive floating tablets, Dasatinib, sustained-release

ABSTRACT

Background: Thermal sintering is emerging as an innovative and cost-effective technique in pharmaceutical formulation design, especially for controlling drug release in oral dosage forms. This study investigates its applicability in the development of gastro-retentive floating tablets for Dasatinib, a tyrosine kinase inhibitor with low solubility and bioavailability. **Methodology**: Floating matrix tablets were developed via direct compression, incorporating carnauba wax and hydroxypropyl methylcellulose as matrix-forming agents, along with sodium bicarbonate as a gas-generating component to impart buoyancy. The tablets were then thermal-sintered at two temperatures for varying durations in a controlled hot-air oven. The effects of thermal sintering conditions were investigated with respect to in vitro dissolution, mechanical strength, percent water uptake, percent erosion**,** total buoyancy duration, floating lag time, and SEM morphology. **Results and Discussion**: Statistical analysis using two-way ANOVA ($\alpha = 0.05$) revealed that sintering condition significantly influenced drug release and buoyancy performance ($p < 0.01$). Formulation DST 02 sintered at 70°C-3 hours exhibited optimal performance, achieving a maximum drug release of 96.3% over 13 hours. Characterization technique methods such as FTIR and DSC have confirmed the absence of chemical interactions and polymorphic transitions. Stability studies conducted in accordance with ICH guidelines indicated that the optimized formulation remained stable throughout the study period. **Conclusion**: Thermal sintering effectively modulated the release characteristics of Dasatinib from floating tablets, thereby increasing gastric retention time and facilitating sustained drug release. This technique holds promise for improving therapeutic efficacy, reducing dosing frequency, and enhancing patient compliance in oral drug delivery.

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INTRODUCTION

An essential objective in dosage form development is to control drug release so that a single daily dose is sufficient to maintain steady-state therapeutic plasma concentrations [1]. Controlled- or extended-release formulations provide significant therapeutic advantages over traditional dosage forms, primarily by reducing dosing frequency and often allowing effective treatment with a single daily dose. These modified-release systems manage or address the conditions by administering the minimum amount of drug over the shortest possible duration, thereby maintaining nearly constant drug levels in the bloodstream. This strategy enhances drug efficacy, reduces systemic and local side effects, and improves patient compliance [2]. In powder metallurgy, "sintering is defined as bonding of adjacent particle surfaces in a mass of powder or in compact, by the application of heat" [3, 4]. Thermal sintering is a simple post-compression technique used to modulate the physicochemical and mechanical properties of polymeric matrices. It involves controlled heating of tablets below the polymer's melting point, thereby causing partial fusion of polymer particles [5,6,7]. Sintering a polymeric matrix in which drug particles are uniformly dispersed is one of several physical methods used to develop controlled- or extended-release dosage forms [8, 9]. Compared with more complex controlled-release methods, sintering offers a simpler and more environmentally sustainable approach, reducing the need for organic solvents and specialized equipment. By fine-tuning the sintering duration and temperature, this method can greatly improve the efficacy of matrix-forming polymers in prolonging drug release [10]. This process enhances inter-particulate bonding, matrix integrity, and hydrophobicity. These bonds entrap the drug particles, enabling a controlled or extended drug release profile. Such modulation allows fine control over both the floating lag time and the sustained drug-release profile of gastroretentive systems [11]. Dasatinib, a potent tyrosine kinase inhibitor used in the treatment of chronic myeloid leukemia and acute lymphoblastic leukemia, poses challenges for oral delivery due to its low aqueous solubility and a pH-dependent dissolution profile. When administered orally, it is rapidly absorbed, with peak plasma levels (Tmax) reached within 0.5 hours (range: 0.25 to 1.5 hours) [12]. With a relatively short half-life of 3-4 hours, Dasatinib is classified as a class II compound under the Biopharmaceutical Classification System (BCS) owing to its low water solubility and high intestinal permeability [13, 14]. The drug demonstrates optimal absorption in the stomach and upper GI (gastrointestinal) tract, owing to its good solubility at low pH. However, its solubility decreases markedly above pH 4, resulting in poor intestinal absorption [15]. As a result, delivering Dasatinib to the stomach via a gastroretentive floating drug delivery system offers a promising strategy to enhance its therapeutic efficacy. In light of the limited studies on thermally sintered tablets, this research focuses on developing stomach-specific floating tablets of Dasatinib and examining the effects of sintering conditions on drug release, physicochemical properties, and other evaluation metrics of the resulting sintered tablets. To date, no gastro-retentive formulation of Dasatinib has been reported, making this study the first systematic investigation to elucidate the influence of thermal sintering on its drug release and buoyancy characteristics.

MATERIALS AND METHODS

Materials

The Dasatinib drug was obtained as a gift sample from Hetero Pharma, Hyderabad. Aurobindo Pharma Ltd. of Hyderabad supplied HPMC K100M and carnauba wax. Magnesium stearate, spray -dried lactose, and sodium bicarbonate were purchased from Loba-chem Private Ltd in Mumbai. All chemicals, reagents, and materials utilized in the investigation were analytical grade.

Methods

Dasatinib dose calculation for the sustained-release tablet

The following pharmacokinetic equations were employed to determine the required loading dose, maintenance dose, desired drug release rate, and total dose necessary for the formulation of a sustained-release Dasatinib tablet [16, 17]: Given parameters include an oral dose (X_0) of 100 mg, a biological half-life ($t_{1/2}$) of 3.5 hours, and a desired duration of sustained action or dosing interval (T) of 12 hours. The peak plasma time (t_p) is 1.5 hours. The K_E (overall elimination rate constant) is determined using the expression: K_E = 0.693/half-life =0.693/3.5 hours = 0.198 h^{-1} The initial dose (Di)can be calculated using the equation:

$$\boldsymbol{Di = \frac{X_0}{KE \times T} = \frac{100}{0.198 \times 12} = 42.08\ mg}$$

To maintain therapeutic plasma concentrations, the desired drug release rate (Ks) is computed as:

$$\boldsymbol{Ks = Di \times KE = 42.08 \times 0.198 = 8.33\ mg/h}$$

Based on this rate, the maintenance dose (D_M) for 12 hours is:

$$\boldsymbol{Ks \times T = 8.33 \times 12 = 99.96\ mg}$$

The loading dose (D_L), which ensures prompt attainment of steady-state concentration, is calculated by:

$$\boldsymbol{Di - (Ks \times tp) = 42.08 - (8.33 \times 1.5) = 42.08 - 12.495 = 29.585\ mg}$$

Consequently, the total drug required (D_T) over the 12 hours is:

$$\textbf{\textit{Total dose}}\ (\textbf{\textit{DT}}) = \textbf{\textit{Loading dose}} + \textbf{\textit{Maintenance dose}}$$
$$= \mathbf{29.585} + \mathbf{99.96} = \mathbf{129.545}\ \textbf{\textit{mg}} \approx \mathbf{130}\ \textbf{\textit{mg}}$$

Accordingly, for a sustained-release formulation with a 12-hour duration, the floating tablet should contain approximately 130 mg of Dasatinib. The release profile should ideally deliver an initial dose of 37.915 mg (comprising the loading dose plus the first hour of maintenance, i.e., 29.585 + 8.33 = 37.915 mg), corresponding to 29.165% of the total dose, within the first hour. The remaining 92.086 mg (130 - 37.915 mg = 92.086 mg) should be released steadily over the subsequent 11 hours at approximately 8.37 mg/hour. This theoretical release profile was utilized to compute the f2 similarity values, as summarized in Table 1.

Table 1: Theoretical Dasatinib drug release profile for 12-hour sustained-release formulation

Time (Hours)	Amount of Dasatinib released from a tablet having 130 mg of the drug	Cumulative amount of drug released (%)
1	37.915	29.165
2	46.286	35.604
3	54.657	42.043
4	63.028	48.483
5	71.399	54.922
6	79.77	61.361
7	88.141	67.800
8	96.512	74.240
9	104.883	80.679
10	113.254	87.118
11	121.625	93.557
12	130	100

Preparation of Dasatinib unsintered GRFTs

The tablets were prepared by direct compression using the method adopted by Mohanty *et al*. [17]. Accurately weighed quantities of the drug, matrix-forming polymers, and other excipients (listed in Table 2) were uniformly blended using a mortar and pestle for 15 minutes, followed by tumbling in a glass bottle to ensure homogeneity. The consequential powder blend was compressed into tablets using a 16-station rotary tablet press having an 8 mm biconcave punch.

Preparation of Dasatinib Sintered GRFTs

The prepared unsintered tablets were wrapped in aluminum foil and subjected to controlled thermal treatment in a hot-air oven at 60°C and 70°C for 1.5 and 3 hours, respectively. The oven temperature was maintained within ±1°C. Following sintering at the specified temperature for the specified duration, the tablets were allowed to cool to room temperature and subsequently stored in covered desiccators for future use [17].

Table 2: Constituents of Dasatinib-based gastro-retentive floating tablet formulation

Ingredients	DST 01	DST 02	DST 03
Dasatinib	130	130	130
Carnauba wax	40	50	60
HPMC K100M	70	60	50
Sodium bicarbonate	50	50	50
Spray-dried Lactose	57	57	57
Magnesium stearate	3	3	3
Total weight (mg)	**350**	**350**	**350**

Each tablet contains ingredients measured in milligrams.

Evaluation of unsintered and sintered forms of Dasatinib GRFTs

Dasatinib floating tablets, both unsintered and sintered, were systematically evaluated for a range of physicochemical properties, including uniformity of drug content, mechanical strength (hardness and friability), water uptake percentage, matrix erosion behavior, *in vitro* buoyancy characteristics, and *in vitro* drug release kinetics.

Tablet hardness

Tablet hardness was assessed with the Monsanto hardness tester by positioning each tablet diagonally between two plungers. Force was applied gradually until the tablet broke completely, and the pressure required for this failure was recorded in kg/cm² [17]. Tests were conducted in triplicate (n=3), and average values were reported.

Friability

The friability of the formulated floating tablets was measured using a Roche-type friabilator to estimate the percentage weight loss. A set of ten accurately weighed tablets was subjected to mechanical attrition at 25 RPM for 4 minutes. Following the test, the tablets were dusted off and reweighed to determine the weight loss. The experiments were performed in triplicate, and friability was calculated as the percentage decrease in tablet weight relative to the initial weight, with the following standard formula [17].

$$\textbf{\textit{Friability}}(\%) = \left[\left(\frac{\boldsymbol{W0 - W}}{\boldsymbol{W0}}\right)\right] \times \mathbf{100}$$

Where 'W0' symbolizes the weight of the tablets before revolution, and 'W' means the weight of the tablets after 100 revolutions.

Drug content estimation

Drug content tests were repeated for three tablets per formulation (n=3). From each batch of formulations, 10 tablets were randomly selected and finely crushed. A precisely

measured portion of this powder, corresponding to the average weight of a tablet, was placed in a 100 mL volumetric flask. To facilitate drug extraction, 10 mL of 0.1N HCL was added, and the mixture was sonicated for about 15 minutes. Following sonication, the volume was adjusted to 100 mL with the same acid medium. The resulting solution was then filtered to remove particulate matter, and appropriate dilutions were prepared in 0.1N HCl [18]. The drug content was quantitatively analyzed spectrophotometrically using a UV-Visible spectrophotometer by measuring the absorbance at 324 nm.

Percent water uptake studies

Tablets were weighed, then placed in 0.1 N hydrochloric acid for 24 hours. After 24 hours, the wet tablets were weighed again and then dried. The following formula was used to calculate percent water uptake [19]. The studies were performed in triplicate (n=3).

$$\%\ \boldsymbol{water\ uptake} = \left[\frac{\boldsymbol{Wet\ weight - Remaining\ dry\ weight}}{\boldsymbol{Remaining\ dry\ weight}}\right] \times \mathbf{100}$$

Percent erosion study

The percent erosion study was performed in triplicate (n=3) using a dissolution apparatus (50 RPM, 900 ml of 0.1 N hydrochloric acid at 37 °C). Pre-weighed tablets were placed in the apparatus, and after 24 hours, the tablets were removed and left to dry. The following formula was used to compute the percent erosion [18, 19]. The experiments were conducted in triplicate (n=3).

$$\%\ \boldsymbol{erosion} = \left[\frac{\boldsymbol{Initial\ Weight - Remaining\ dry\ weight}}{\boldsymbol{Remaining\ dry\ weight}}\right] \times \mathbf{100}$$

Buoyancy test

All formulated unsintered and sintered floating tablet forms were subjected to an in vitro buoyancy test, which included measurements of floating lag time (FLT) and total floating duration (TFD). The study was conducted in triplicate for each tablet batch by placing each tablet in a 1-liter glass beaker containing 900 mL of 0.1 N HCl, maintained at 37 ± 0.5°C. FLT was defined as the interval between tablet immersion and the tablet's rise to the medium's surface. In contrast, TFD was defined as the time during which the tablet remained buoyant without sinking [18].

***In-vitro* drug release (dissolution) studies**

In vitro drug-release experiments were conducted using a USP XXIV Type I (basket-type) dissolution apparatus. These tests were performed in 900 mL of 0.1 N HCl at a controlled temperature of 37 ± 0.5 °C, with the baskets rotating at 50 rpm. At predetermined time intervals, 5 mL aliquots were withdrawn and immediately replaced with an equal volume of fresh dissolution medium to maintain sink conditions. The collected samples were suitably diluted with the dissolution medium and evaluated for drug content at 324 nm using a double-beam UV-Visible spectrophotometer [18]. The *in-vitro* dissolution experiments were conducted in triplicate.

Dissolution profile comparison and $f2$ Similarity factor computation

The comparison of dissolution profiles was performed using the f2 value, as recommended by the SUPAC (Scale-Up and Post-Approval Changes) guidelines for extended-release formulations. The degree of similarity between two profiles can be quantified using the $f2$ statistic. When the two profiles are identical, $f2$=100, whereas a $f2$ value of 50 is obtained when the average difference at all time points is 10%. To indicate that two dissolution profiles are similar, the FDA has established a public standard for an $f2$ value between 50 and 100. The f_2 similarity factor values were estimated by using the formula:

$$\boldsymbol{f2 = 50 \times log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5} \times 100\right\}}$$

Where 'n' indicated the number of sampling points. Whereas Rt and Tt represent the cumulative percentages of drug dissolved from the reference (in this case, the theoretical dissolution profile of Dasatinib) and test formulation, respectively, at a given time point 't' [17].

Drug release kinetics and mechanism

The *in vitro* drug-release profiles of the Dasatinib floating tablets were fitted to kinetic models, including zero-order, first-order, Higuchi, and Hixson–Crowell, to elucidate the underlying release mechanisms and characterize the release profile. For each model, plots were generated, and the model with the highest coefficient of determination (R^2) was considered the best fit. Additionally, the Korsmeyer–Peppas model was applied to investigate the mechanism of drug release. In this model ($Mt/M\infty = Kk \cdot t^n$), *n*, the release exponent, provides insight into the release mechanism and is characteristic of the geometric configuration of the dosage form [17].

Compatibility (FTIR) studies

FT-IR spectroscopy was used to evaluate potential interactions and compatibility between Dasatinib (the pure drug) and combinations of Dasatinib with various polymers and

excipients. The spectra were obtained using the KBr pellet method over the wavenumber range 4000-400 cm^{-1} with an infrared spectrophotometer.

Differential scanning calorimetry (DSC) studies

To assess the thermal properties, DSC analysis was conducted on pure Dasatinib and its physical mixtures with different polymers. Approximately 10 mg of each sample was precisely measured and placed in aluminum pans, then subjected to a controlled heating program from 40°C to 300°C at 5°C/min under a nitrogen atmosphere. Nitrogen gas, used as an inert medium, was kept at a constant flow rate of 25 mL/min throughout the study [17].

Surface morphology studies

SEM at 500× and 1000× magnification was used to examine the surface morphology of the developed Dasatinib floating tablets, both before and after sintering.

Stability studies

Stability studies were conducted in accordance with ICH guidelines to evaluate the stability of the drug and its optimized formulation. For two months, the formulated Dasatinib floating tablets were stored at controlled environmental conditions of 25 ± 2 °C/60 ± 5% RH and 40 ± 2 °C/75 ± 5% RH.

Samples were removed and retested at predetermined time points (0, 30, 40, 50, and 60 days) for several physicochemical properties, including drug content, tablet hardness, friability percentage, floating lag time, total floating duration, and *in vitro* drug release profile [17].

RESULTS AND DISCUSSION

Dasatinib gastroretentive floating tablets were prepared by the sintering technique using carnauba wax and HPMC K1000M as matrix-forming substances, along with sodium bicarbonate as a gas-generating component to add buoyancy, followed by thermal sintering at two different constant sintering temperatures, 60°C and 70°C, for two different sintering durations, 1.5 hr and 3 hr in a hot air oven. Carnauba wax and HPMC K100M were selected for their complementary functions in controlling drug release and enhancing the buoyancy of gastro-retentive tablets. Carnauba wax, a hydrophobic lipid, serves as a thermal sintering agent, providing rigidity to the matrix and creating a dense network that sustains release in acidic environments. Its low permeability and stability help limit water infiltration and matrix erosion. In contrast, HPMC K100M, a high-viscosity hydrophilic polymer, promotes swelling and the formation of a gel layer, slowing drug diffusion and aiding flotation by trapping air within the matrix. The combination of hydrophobic (carnauba wax) and hydrophilic (HPMC K100M) components enables precise control of release kinetics via a dual diffusion-erosion mechanism, ensuring optimal mechanical strength and retention in the stomach. The influence of sintering conditions on the physicochemical parameters of sintered Dasatinib floating tablets was systematically investigated, and the corresponding effects are shown in Table 3.

Table 3: Effect of thermal sintering on physicochemical and floating properties of Dasatinib GRFTs (Unsintered vs. Thermally Sintered) *Mean±S.D (n=3)*

Formulation Code	Sintering Condition	Mechanical strength		Drug content percentage	Percent erosion	Percent Water uptake
		Hardness	Friability			
DST 01 US	Unsintered	3.3±0.16	0.68±0.04	97.73±0.49	79.02±0.68	89.37±0.57
DST 01 SA	60 °C-1.5 h	3.6±0.29	0.60±0.02	98.90±0.38	73.14±0.85	75.21±0.48
DST 01 SB	60 °C-3 h	4.1±0.26	0.56±0.03	99.48±0.87	70.21±1.08	70.23±0.71
DST 01 SC	70 °C-1.5 h	4.3±0.31	0.48±0.02	100.88±0.29	66.02±0.56	68.09±0.24
DST 01 SD	70 °C-3 h	4.6±0.24	0.44±0.02	97.73±0.49	63.16±0.24	66.14±0.21
DST 02 US	Unsintered	3.5±0.31	0.67±0.04	98.12±0.51	75.13±0.84	82.11±0.73
DST 02 SA	60 °C-1.5 h	4.2±0.23	0.58±0.03	99.54±0.84	67.21±0.69	69.21±0.38
DST 02 SB	60 °C-3 h	4.4±0.11	0.53±0.02	97.68±1.08	65.11±0.38	67.18±0.54
DST 02 SC	70 °C-1.5 h	5.2±0.08	0.45±0.03	99.02±0.32	63.28±0.48	64.16±0.47
DST 02 SD	70 °C-3 h	5.4±0.16	0.40±0.04	97.53±0.98	61.13±0.93	60.21±1.08
DST 03 US	Unsintered	3.8±0.22	0.63±0.05	99.16±0.51	70.15±0.51	74.09±1.04
DST 03 SA	60 °C-1.5 h	4.3±0.15	0.46±0.04	98.44±0.84	60.09±0.82	65.19±0.57
DST 03 SB	60 °C-3 h	4.8±0.08	0.41±0.02	97.68±1.08	58.12±0.49	63.14±0.91
DST 03 SC	70 °C-1.5 h	5.2±0.21	0.37±0.03	99.92±0.32	56.21±0.65	61.11±0.74
DST 03 SD	70 °C-3 h	5.6±0.19	0.31±0.02	99.53±0.94	54.27±0.39	59.06±0.53

Effect of thermal sintering on the mechanical strength of tablets

An increase in tablet hardness was observed with increasing sintering temperature and sintering duration, whereas friability decreased with prolonged sintering. The hardness of all Dasatinib floating tablet formulations, including both sintered and unsintered tablets, ranged from 3.3 to 5.6 kg/cm² (Table 3). Hardness increases progressively with increasing sintering temperature (60°C to 70°C) and longer sintering duration (1.5 h to 3 h) across all formulations. For instance, DST 01 hardness increases from 3.3 kg/cm² (unsintered) to 4.6 kg/cm² (70°C, 3 h). This trend was consistently observed across all three formulations. Conversely, tablet friability decreased with increasing temperature and longer sintering durations, indicating improved mechanical strength. For example, DST 03 friability decreased from 0.63% (unsintered) to 0.31% (70°C, 3 h), and the same pattern was observed across all three formulations. This indicates that thermal sintering effectively enhances tablet robustness by reducing friability. Additionally, the friability test showed less than 0.8% weight loss across all formulations, indicating mechanical integrity and compliance with accepted limits. The increase in hardness of sintered tablets is likely attributable to thermal-induced coalescence of polymer particles and molecular rearrangement within the matrix constituents. Carnauba wax, with a melting range of approximately 80–85°C, undergoes surface softening under the sintering conditions, promoting fusion of wax particles at their contact points.

This process yields a continuous hydrophobic network that acts as a binding matrix, enhancing interparticle adhesion and mechanical integrity. Concurrently, thermal exposure increases the mobility of HPMC K100M chains, facilitating partial relaxation and reorganization of the polymeric domains. Upon cooling, these chains undergo physical entanglement and hydrogen bonding, contributing to matrix densification and rigidity. The combined effects of wax fusion and polymer chain rearrangement thus lead to improved mechanical strength and reduced friability.

Effect of thermal sintering on drug content estimation

The drug content of all unsintered and sintered forms of Dasatinib GRFTs was determined to be within the range of 97% and 100% (Table 3), meeting pharmacopeial standards. These findings suggest that the sintering conditions used had no substantial effect on the assay (drug content uniformity) among the different formulations.

Effect of thermal sintering on percent water uptake and percent erosion studies

Table 3 depicts the extent of water uptake and matrix erosion observed in the tablet formulations before and after sintering. It was shown that unsintered tablets exhibited the highest water uptake and erosion rates. However, with increasing sintering temperature and duration, a noticeable reduction in water absorption and erosion was observed, indicating enhanced tablet structural integrity. Water uptake decreases significantly with higher sintering intensity. For instance, DST 03 water uptake decreased from 74.09% (unsintered) to 59.06% (70°C, 3 h). Erosion decreases with increasing temperature and longer sintering times. For example, DST 01 erosion decreased from 79.02% (unsintered) to 63.16% (70 °C, 3 h). This same trend was consistent across all three formulations. Sintering minimizes erosion, likely because it causes polymer and wax particles to bond, creating a stronger matrix that is more resistant to surface wear. The melting of Carnauba wax forms a hydrophobic framework that reduces water absorption, while the reorganization of HPMC K100M chains creates a more compact, physically crosslinked gel layer during hydration. This synergistic restructuring reduces polymer dissolution and surface erosion, producing a denser, less porous matrix that retards swelling and prolongs drug release. These molecular and structural modifications collectively account for the sustained-release behavior observed in the sintered tablets.

Effect of thermal sintering on buoyancy Characteristics

In vitro buoyancy tests revealed that, when immersed in 0.1 N HCl, the formulated tablets exhibited immediate buoyancy and remain*ed* afloat for extended periods. The FLT and TFD values for all formulations ranged from 96 to 224 seconds and from 9 to 16 hours, respectively (summarized in Table 4). DST 01(HPMC-dominant) had the shortest FLT and lowest TFD, indicating a formulation of quick flotation but shorter gastric retention due to its hydrophilic matrix content. Whereas DST 03 (Carnauba wax-rich formulation) exhibited the slowest initial flotation due to its hydrophobic matrix and poor wettability. The values of FLT and TFD for formulation DST 02 were intermediate between DST 01 and DST 03.

Notably, a progressive reduction in FLT was observed with increasing sintering temperature and duration. For instance, in DST 01, the FLT decreased from 138 seconds in the unsintered state to 96 seconds after sintering at 70 °C for 3 hours. An analogous consistent trend was observed in DST 02 and DST 03,

with FLT values decreasing from 175 to 143 seconds and from 224 to 174 seconds, respectively. This behavior could be related to the reduction in tablet porosity generated by heat processing. Elevated sintering temperatures likely promoted partial melting or densification of polymeric components, particularly waxy components such as carnauba wax, thereby reducing voids within the matrix. As a result, the surface area exposed to gastric fluid increased more rapidly, thereby increasing buoyancy by entrapping gas more effectively and accelerating the initiation of flotation. An upward trend in TFD was associated with growing sintering temperatures. TFD increased significantly with more intense sintering conditions. In DST 01, the TFD rose from 9 hours in the unsintered state to 14 hours after sintering at 70 °C for 3 hours. For DST 02 and DST 03, a similar consistent trend was observed, with TFD values improving from 10 to 15 hours and from 11 to 16 hours, respectively. This could be ascribed to enhanced polymer fusion and the formation of strong interparticle bonds under higher thermal exposure, which improved structural integrity and produced a more robust, less soluble matrix that slowed water penetration and tablet erosion, ultimately prolonging their buoyancy.

In summary, FLT showed an inverse relationship with both sintering temperature and duration, whereas TFD was positively correlated with both. The marked reduction in tablet friability, together with SEM observations, suggests the formation of a denser and less porous matrix upon sintering. Such morphological densification has previously been correlated with reduced porosity and improved floating performance. These findings, consistent with those reported by Mohanty *et al.* [20], highlight the pivotal influence of sintering conditions in modulating the buoyancy characteristics of gastro-retentive drug delivery systems. Therefore, thermal sintering appears to be an effective formulation approach for optimizing the buoyancy characteristics of gastro-retentive dosage forms, enabling rapid buoyancy onset and extended gastric retention.

Table 4: Effect of thermal sintering on buoyancy studies

Sintering Condition	DST 01		DST 02		DST03	
	FLT (Sec)	TFD (hr)	FLT (Sec)	TFD (hr)	FLT (Sec)	TFD(hr)
Unsintered	138±3	09±1.0	175±3	10±1.0	224±5	11±0.2
60 °C-1.5 h	126±5	11±1.0	167±4	12±1.0	206±2	12±0.4
60 °C-3 h	110±4	13±0.5	153±3	13±1.0	193±6	14±1.0
70 °C-1.5 h	106±7	13±1.0	150±4	14±0.5	184±7	15±0.8
70 °C-3 h	96±5	14±1.0	143±5	15±0.5	174±1	16±0.5

Mean±S.D (n=3)

***In-vitro* dissolution rate studies**

The *in-vitro* DR profiles of both sintered and unsintered Dasatinib floating tablet formulations are illustrated in Figure 1-3.

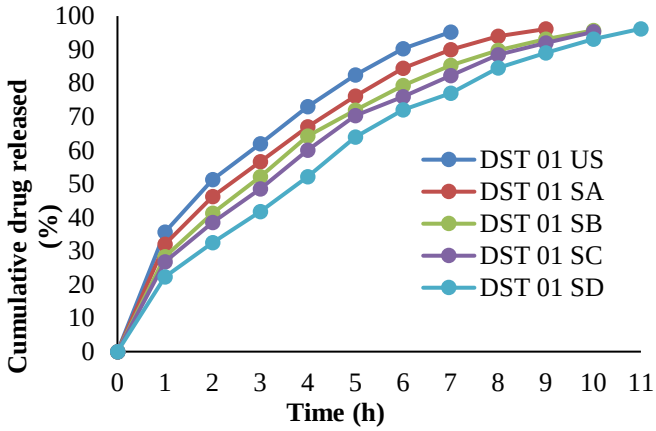


Figure 1: Comparative *In-Vitro* Drug Release Profiles of Unsintered vs. Thermally Sintered Dasatinib Floating Tablets (DST 01)

The unsintered formulation (DST 01 US) demonstrated a sustained drug release for up to 7 hours, achieving a maximum cumulative release of 95.26%. In contrast, tablets sintered at 60°C for 1.5 hours (DST 01 SA) and 3 hours (DST 01 SB) exhibited extended-release durations of 9 and 10 hours, with corresponding drug-release values of 96.14% and 95.70%, respectively. Furthermore, formulations sintered at 70°C for 1.5 hours (DST 01 SC) and 3 hours (DST 01 SD) sustained drug release for 10 and 11 hours, respectively, with cumulative release of 95.3% and 96.22%.

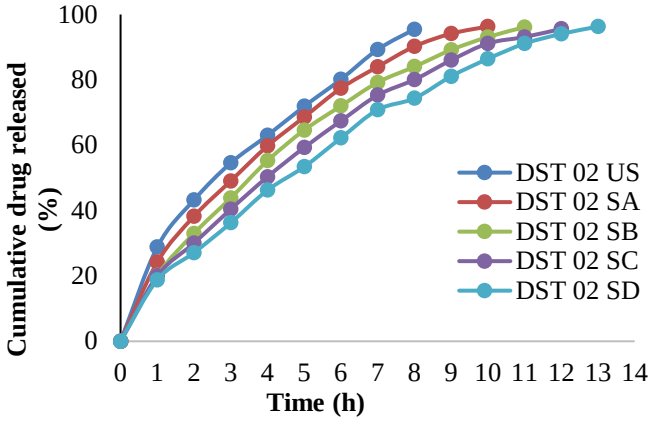


Figure 2: Comparative *In-Vitro* Drug Release Profiles of Unsintered vs. Thermally Sintered Dasatinib Floating Tablets (DST 02)

Likewise, the unsintered formulation DST 02 (DST 02 US) exhibited sustained drug release for up to 8 hours, achieving a maximum of 95.45%. In contrast, when the formulation was sintered at 60°C for 1.5 hours (DST 02 SA) and 3 hours (DST 02 SB), drug release extended to 10 and 11 hours, respectively, with maximum release values of 96.31% and 96.12%. Further sintering at 70°C for 1.5 hours (DST 02 SC) and 3 hours (DST 02 SD) resulted in a prolonged release duration of 12 and 13 hours, with corresponding maximum release percentages of 95.59% and 96.3%.

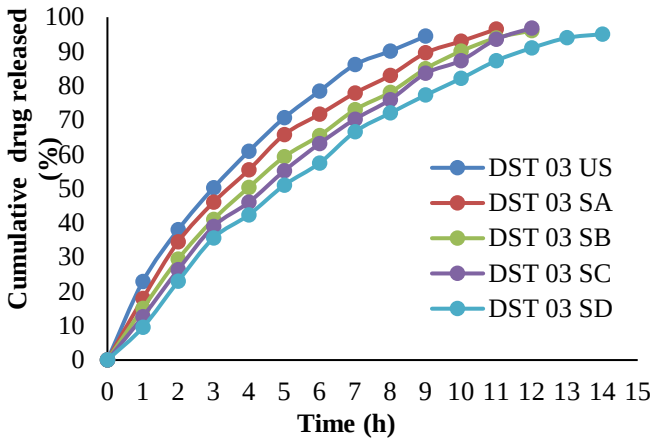


Figure 3: Comparative *In-Vitro* Drug Release Profiles of Unsintered vs. Thermally Sintered Dasatinib Floating Tablets (DST 03)

Similarly, the unsintered formulation DST 03 (denoted as DST 03 US) sustained drug release for up to 9 hours, achieving a maximum cumulative release of 94.46%. Upon sintering the tablets at 60 °C for 1.5 hours (DST 03 SA) and 3 hours (DST 03 SB), the maximum drug release was 96.5% and 96.05%, respectively, with corresponding increases in release duration to 11 and 12 hours. Further sintering at 70 °C for 1.5 hours (DST 03 SC) and 3 hours (DST 03 SD) yielded drug-release maxima of 96.78% and 95.04%, respectively, with prolonged release periods of 13 and 14 hours.

The results of this investigation highlight the substantial influence of both sintering temperature and exposure duration on the drug-release kinetics of Dasatinib from floating-matrix tablets. A clear inverse relationship was seen between drug release rate and sintering conditions; higher temperatures and longer sintering times led to a noticeable decrease in the drug release rate. These findings align with the work of Ramya *et al.* [18] and Akki *et al*. [21], who reported similar outcomes. This sustained-release behavior is likely due to polymer softening and partial fusion under heat, resulting in welded junctions that form a more cohesive matrix. Such thermally induced structural modifications may entrap the drug particles within the polymer network, thereby limiting diffusion and contributing to prolonged drug release. Furthermore, an increase in polymer concentration was also found to reduce the release rate, possibly due to the enhanced formation of air pockets and gel layers at the tablet surface upon hydration. This intensified gel barrier could serve as a diffusion-limiting membrane, thereby contributing to the sustained-release characteristics of the formulation.

Statistical analysis (ANOVA) of thermally sintered formulations on buoyancy properties and dissolution rate

Statistical analysis of experimental data, such as FLT, TFD, and dissolution rate, was performed using Microsoft Excel 2021 (Microsoft Corporation, Redmond, WA, USA). A two-way ANOVA without replication ($\alpha = 0.05$) was conducted to assess the effects of sintering conditions and formulation type on the measured responses. Data are presented as mean ± standard deviation (SD) from three independent experiments.

These ANOVA results (Table 5) highlight the important influence of thermal sintering conditions on the buoyancy performance and dissolution rate of the GRFTs. A two-way ANOVA confirmed that variations in both FLT and TFD under different sintering conditions were statistically significant. For FLT, the p-values for the sintering conditions and DST formulation types (DST01/02/03) were 0.0000036 and 0.0000000012, respectively. Similarly, for TFD, the p-values for the sintering conditions and DST formulations were 0.00000070 and 0.00026, respectively. Since both are less than $\alpha = 0.05$, both factors significantly affected the TFT and TFD.

All formulations showed statistically significant variations in both FLT and TFD across different sintering conditions. This confirms that sintering temperature and duration strongly influence the buoyancy characteristics of the floating tablets. These ANOVA results highlight the important influence of sintering temperature and duration on the buoyancy performance of the floating tablets. Likewise, for dissolution rates, p-values for sintering conditions and DST formulation types were 0.0000058 and 0.00026, respectively. These p-values are less than $\alpha = 0.05$, indicating that both sintering time/temperature and batch variability had statistically significant effects on drug dissolution behavior, independently. This Statistical analysis confirmed that sintering temperature and duration strongly influenced the buoyancy characteristics and dissolution rate of the floating tablets.

Table 5: ANOVA results for FLT, TFD, and dissolution rates across sintering conditions & formulation types (DST 01–03)

Properties	Source of Variation	SS	df	MS	F	P-value	F crit
FLT	**Sintering Conditions**	3223.333	4	805.8333	66.14227	0.0000036233	3.837853
	formulation types	16414.53	2	8207.267	673.6471	0.0000000012	4.45897
	Error	97.46667	8	12.18333			
	Total	19735.33	14				
TFD	**Sintering Conditions**	47.06667	4	11.76667	100.8571	0.0000007036	3.837853
	formulation types	6.4	2	3.2	27.42857	0.0002623864	4.45897
	Error	0.933333	8	0.116667			
	Total	54.4	14				
Dissolution rates	**Sintering Conditions**	33.44283	4	8.360707	58.50467	0.0000058116	3.837853
	formulation types	10.25841	2	5.129207	35.892	0.0001010873	4.45897
	Error	1.143253	8	0.142907			
	Total	44.84449	14				

***SS**: Sum of Squares, **df**: Degrees of Freedom, **MS**: Mean Squares, **F**: F-statistic*

Kinetic modeling and drug release mechanism

Table 6 presents the in vitro dissolution profiles of the formulated tablets using several kinetic models, along with the corresponding correlation coefficients (r^2). The Hixson-Crowell model provided the greatest fit for most formulations, with the highest r^2 values, suggesting a release mechanism governed by erosion. This model is relevant because the matrix's surface area and dimensions decrease gradually during dissolution. As the matrix eroded, the available surface area for drug diffusion diminished, consistent with the Hixson–Crowell premise that the release rate is related to changes in surface area and volume. However, the formulations DST 01 US, DST 01 SA, DST 01 SD, and DST 02 US exhibited higher correlation with the Higuchi model, indicating that diffusion drives release in these formulations. For all unsintered and sintered formulations, the Korsmeyer-Peppas model's release exponents' "n" values were determined to be $0.45 < n < 0.89$. This suggests that a non-Fickian diffusion process (anomalous transport) led to the drug's release from every system. This indicates that the mechanism of drug release is influenced by both diffusion and polymer matrix erosion, rather than relying solely on one process. Thermal sintering increased the matrix rigidity by partially melting and merging carnauba wax, thereby limiting both diffusion pathways and water ingress. At the same time, the gradual hydration and erosion of HPMC enabled controlled matrix erosion. Consequently, the intermediate 'n' values reflect a transition from a release mechanism dominated by diffusion in unsintered tablets to one governed by erosion at greater sintering levels, indicating that both mechani- sms are actively working together to regulate drug release.

Table 6: Kinetic modeling and mechanistic evaluation of drug release from unsintered and sintered Dasatinib floating tablets with correlation coefficients (r^2)

Formulations	Zero Order	First Order	Higuchi	Hixon Crowell	Koresmeyer Peppas (r^2)	Peppas (n)
DST 01 US	0.9157	0.9684	0.9993	0.9932	0.9991	0.5129
DST 01 SA	0.9064	0.9810	0.9962	0.9959	0.9959	0.5174
DST 01 SB	0.9102	0.9860	0.9945	0.9971	0.9934	0.5461
DST 01 SC	0.9304	0.9767	0.9943	0.9974	0.9952	0.5727
DST 01 SD	0.952	0.9596	0.9865	0.9960	0.9939	0.6411
DST 02 US	0.9473	0.9313	0.9954	0.9831	0.9994	0.5735
DST 02 SA	0.9383	0.9680	0.9921	0.9977	0.9957	0.6139
DST 02 SB	0.9440	0.9671	0.9883	0.9985	0.9931	0.6625
DST 02 SC	0.9498	0.9718	0.9866	0.9979	0.9948	0.6580
DST 02 SD	0.9614	0.9528	0.9841	0.9940	0.9951	0.673
DST 03 US	0.9496	0.9765	0.9895	0.9987	0.9946	0.6517
DST 03 SA	0.9402	0.9574	0.9886	0.9960	0.9837	0.6832
DST 03 SB	0.9546	0.0.9560	0.9849	0.9953	0.9868	0.7312
DST 03 SC	0.9697	0.9241	0.9778	0.9862	0.9870	0.7961
DST 03 SD	0.9562	0.9687	0.9778	0.9973	0.9729	0.8318

Selection of Optimised formulation

Table 7 presents key dissolution parameters, including the maximum amount of drug release, the time needed to reach this maximum, the dissolution rate, and the f_2 similarity factor values for all formulations. The f2 values for all formulations were calculated by comparing the dissolution profiles of the test formulations with a theoretical reference profile for Dasatinib. Only formulations DST 02 SC, DST 02 SD, DST 03 SB, DST 03 SC, and DST 03 SD had an f2 value more than 50 (US-FDA considers an f2 value between 50 and 100 to be acceptable). The f_2 values were observed to be 63.59, 65.61, 62.63,61.43, and 53.98 for formulation code DST 02 SC, DST 02 SD, DST 03 SB, DST 03 SC, and DST 03 SD, respectively (shown in Table 7). Among all evaluated formulations, both sintered and unsintered, DST 03 sintered at 70°C for 3 hours (DST 03 SD) and DST 02 sintered under the same conditions (DST 02 SD) maintained drug release for 14 and 13 hours, respectively.

However, DST 02 SD was selected as the best formulation due to its superior performance indicators, including the highest similarity factor (f2 = 65.61), a maximum drug release of 96.3% at a dissolution rate of 7.4% per hour, and buoyancy for 15 ± 0.5 hours. Notably, this formulation achieved these results while using a lower polymer content than DST 03. As a result, DST 02 SD was selected as the optimal formulation, providing a prolonged release profile, efficient drug release, and favorable floating properties.

Compatibility (FTIR) studies

Figure 4 and Figure 5 depict the infrared (IR) spectra of pure Dasatinib and the optimized sintered formulation, respectively. The FT-IR spectrum of the pure Dasatinib exhibited multiple sharp and intense absorption bands, indicative of its characteristic functional groups at 3446.6 cm^{-1} (N-H stretch), at 3058.6 cm^{-1} (=C-H aromatic ring), at 2956.1 cm^{-1} (methyl C-H stretch), at 2900 cm^{-1} (methine C-H stretch), at 2839.7 cm^{-1} (methylene C-H stretch), at 2355 cm^{-1} (C-N stretch), at 1541.7 cm^{-1} (N-H bending), at 1304.1 cm^{-1} (O-H bending), at 1062.5 cm^{-1} (C=O stretch), and the peak at 687.9 cm^{-1} (C-Cl stretch). The IR spectral analysis of the sintered optimized formulation confirmed the presence of all principal characteristic peaks of pure Dasatinib, with only marginal shifts in wavenumber. These minor shifts in characteristic peaks indicate only physical interactions and suggest that no significant chemical incompatibilities exist between Dasatinib and the polymer during formulation or thermal treatment. The mild sintering conditions employed (60°C and 70°C for two different durations of 1.5 hr and 3 hr) are well below the melting point of Dasatinib (283 °C), minimizing the likelihood of thermal degradation or solid-state transformation. Carnauba wax and HPMC K100M are chemically inert and thermally stable within this range; hence, no significant physicochemical interaction is expected. The retention of characteristic peaks in FTIR spectra further supports the compatibility of Dasatinib with the polymer matrix after sintering.

Table 7: Assessment of drug release parameters and f_2 similarity for sintered and non-sintered Dasatinib GRFTs

Formulation Code	f_2 Similarity factor	Maximum percentage of release of the drug	Release Duration (hr)	Dissolution rate (% hr^{-1})
DST 01 US	11.39614	95.26	7	13.60
DST 01 SA	15.36794	96.14	9	10.68
DST 01 SB	19.16548	95.7	10	9.57
DST 01 SC	19.44748	95.3	10	9.5
DST 01 SD	26.36547	96.22	11	8.74
DST 02 US	13.42695	95.45	8	11.93
DST 02 SA	19.3453	96.31	10	9.63
DST 02 SB	26.24895	96.12	11	8.73
DST 02 SC	63.59228	95.59	12	7.96
DST 02 SD	65.61347	96.3	13	7.40
DST 03 US	15.82523	94.46	9	10.49
DST 03 SA	26.21704	96.5	11	8.77
DST 03 SB	62.63959	96.05	12	8.00
DST 03 SC	61.43756	96.78	12	8.06
DST 03 SD	53.98578	95.04	14	6.78

DSC studies

The thermal behavior of pure Dasatinib and its physical mixture with selected polymers and excipients was investigated using differential scanning calorimetry (DSC). The resulting thermograms, shown in Figures 6 & Figure 7, demonstrate the thermal profiles of the unprocessed drug & the optimized

formulation mixture, respectively. The thermogram of pure Dasatinib exhibited a prominent endothermic peak at 258.2°C, corresponding to the melting point. In contrast, the physical mixture exhibited a wider endothermic peak at 217.5°C. A significant decrease in the enthalpy of fusion in the mix suggests possible physical interactions or increased miscibility between the drug and polymer components. Still, no evidence of chemical interaction was identified.

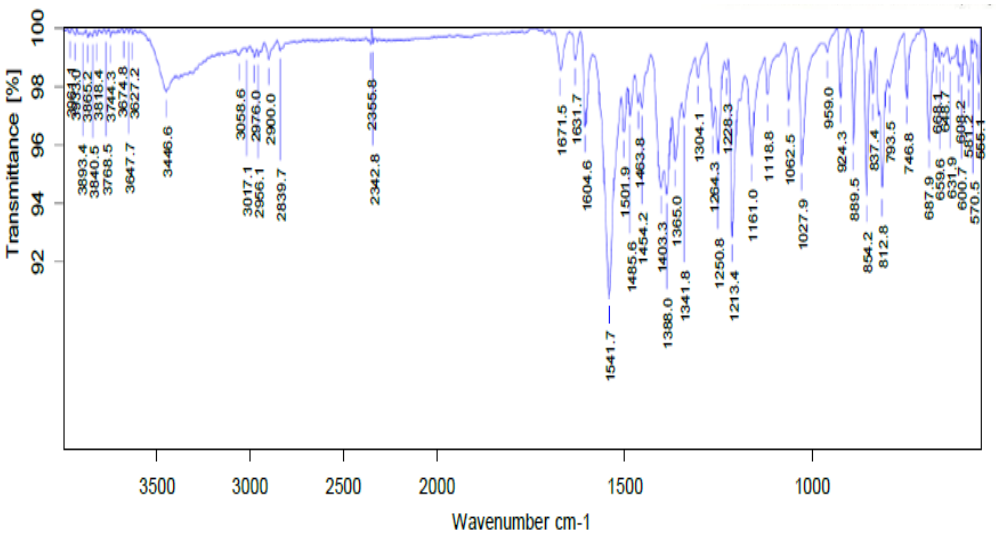


Figure 4: FT-IR Spectrum of pure drug Dasatinib

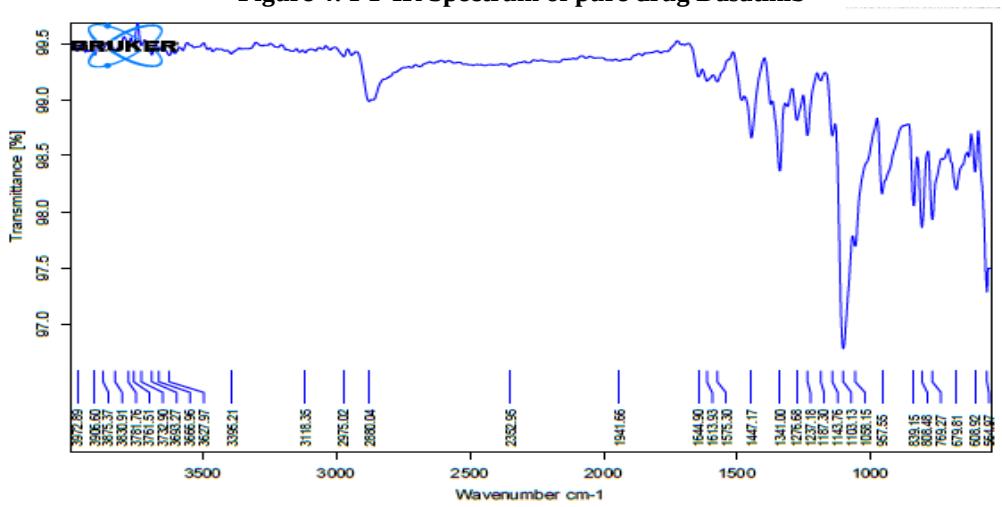


Figure 5: FT-IR Spectrum of sintered optimized formulation

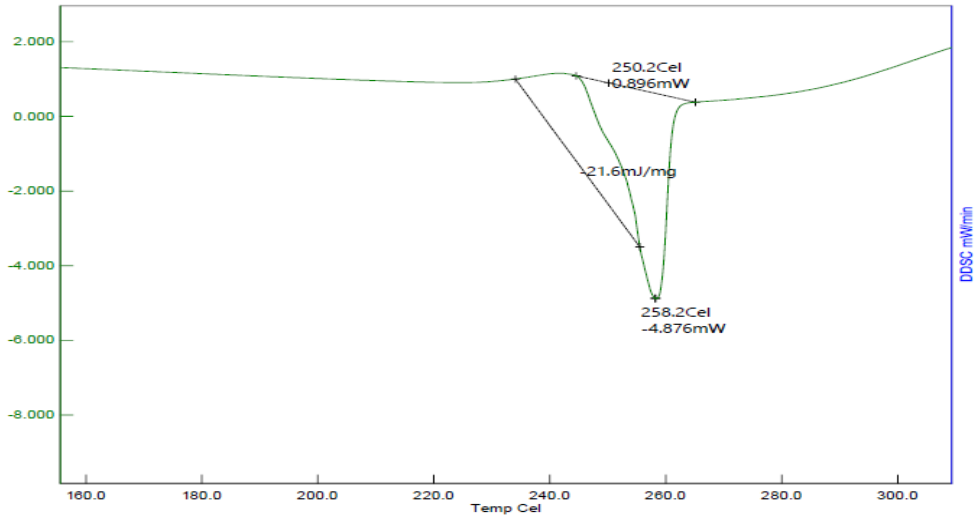


Figure 6: DSC thermogram of the pure drug Dasatinib

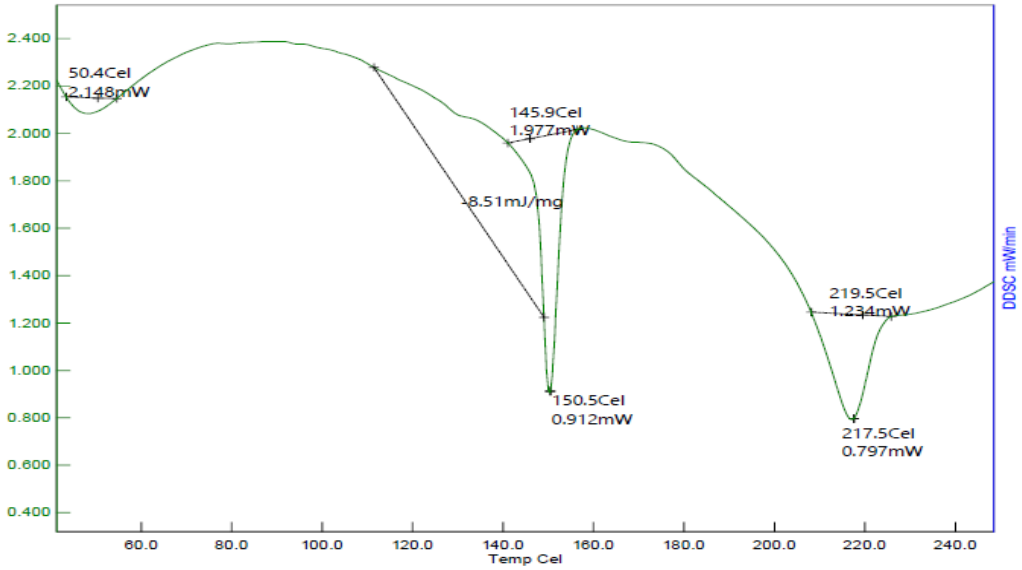
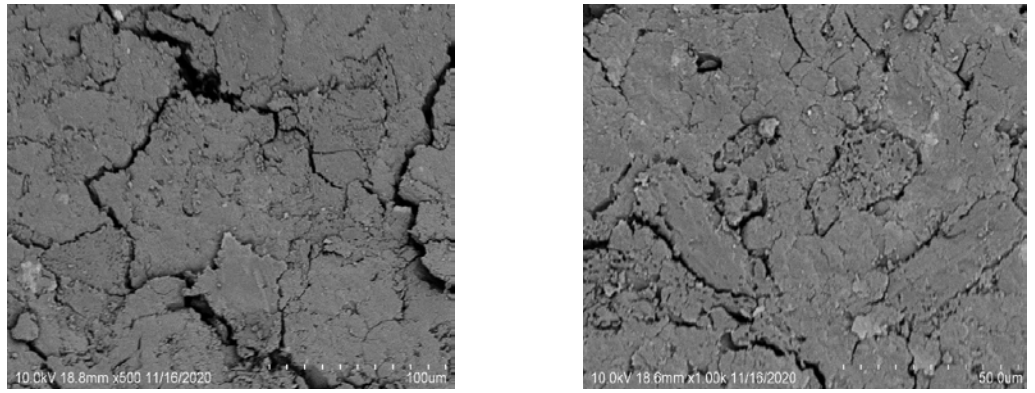


Figure 7: DSC thermogram of drug-polymer-excipient physical mixture

Surface morphology (SEM) analysis

Figure 8 represents the SEM images of the surface morphology of both sintered and unsintered tablets of the optimized formulation DST 02, captured at 500× and 1000× magnifications. Notably, the sintered tablets exhibited a markedly smoother surface than their unsintered counterparts. The sintered tablet surface appeared to be covered by a continuous, film-like layer that reduced surface porosity and wetting properties. These morphological alterations are likely a result of sintering, during which thermal energy induces the fusion of polymeric particles. This fusion facilitates a more homogeneous redistribution of the polymer matrix within the tablet's internal structure, thereby contributing to the observed changes in surface characteristics.

A (Unsintered)



B (Sintered)

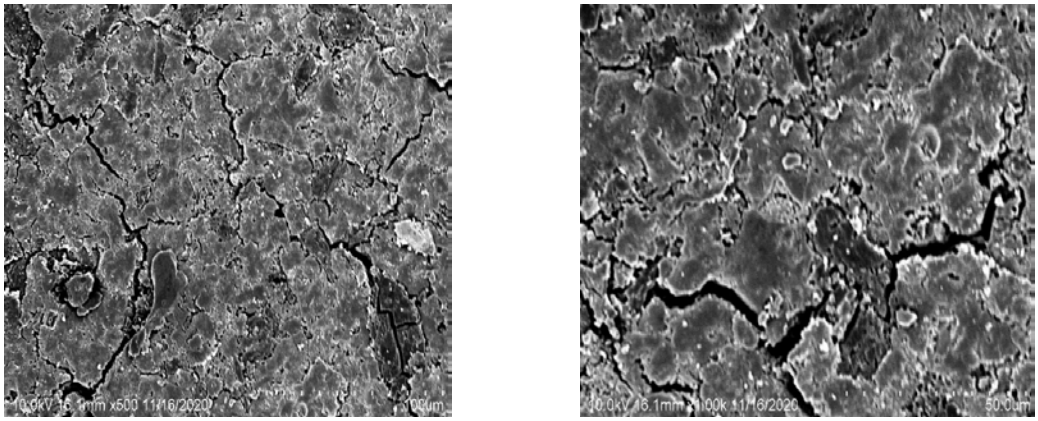


Figure 8: SEM Micrographs Depicting Surface Morphology of Optimized Dasatinib Floating Tablets: (A) Unsintered and (B) Sintered Forms

Stability Assessment of the Optimized Formulation

Stability studies were performed on the optimized formulation DST 02 SD, which was sintered at 70°C for 3 hours, in accordance with ICH guidelines. Tablets were sampled at certain intervals (0, 30, 40, 50, and 60 days) and evaluated for any changes or alterations in their physicochemical properties. The corresponding data are shown in Table 8. The findings showed no significant variation in the evaluated parameters over the study period, indicating that the sintered Dasatinib gastro-retentive floating tablets remained physicochemically stable under the specified storage conditions.

Table 8: Stability assessment of the optimized sintered formulation of Dasatinib floating tablets

Physicochemical Parameters	**Initial (0 Days)** 25 ± 2° C/60 ± 5% RH	**30 days** 25 ± 2° C/60 ± 5% RH	**40 days** 40 ± 2° C/75 ± 5% RH	**50 days** 25 ± 2° C/60 ± 5% RH	**60 days** 40 ± 2°C/75 ± 5% RH
Floating lag time (Sec)	143	140	142	138	141
Total floating time (hr)	15	15 hr 5 min	14 hr 50 min	14 hr 55 min	14 hr 40 min
Percent water uptake (%)	60	60	58	57	59
Percent erosion (%)	61	58	61	59	58
%CDR (After 13 hrs)	96.3	95.13	94.85	94.92	94.76
Drug Content (%)	97.53	97.38	97.32	98.93	97.36
Hardness (Kg/cm^2)	5.4	5	5	5	5
Friability (%)	0.40	0.38	0.42	0.43	0.38

CONCLUSION

In this work, thermally sintered stomach-specific floating tablets of Dasatinib were prepared using carnauba wax and HPMC K100M as matrix-forming agents, along with sodium bicarbonate as a gas-generating agent. Based on the experimental findings, sintered tablets demonstrated superior performance compared with unsintered tablets, exhibiting a longer drug-release profile. The drug release profiles of the sintered formulations were markedly affected by the specific sintering conditions employed. The use of thermal sintering significantly improved the functional properties of the polymers, facilitating prolonged drug release, depending on the sintering duration and temperature. From a manufacturing perspective, this thermal sintering offers a simple, solvent-free, and scalable approach for modulating matrix integrity and drug diffusion. Unlike solvent-based coating or melt-extrusion processes, sintering requires only conventional drying equipment, thereby facilitating process control and enabling cost-effective scale-up. The tunability of matrix rigidity through sintering temperature and duration provides flexibility for large-scale adaptation while maintaining batch uniformity. Furthermore, thermal sintering appears to be a successful formulation strategy for optimizing the floating characteristics of gastro-retentive dosage forms, enabling rapid buoyancy initiation and extended gastric retention. In conclusion, this study establishes thermal sintering as a novel and scalable strategy for developing gastro-retentive Dasatinib tablets that offer controlled release and buoyancy (96.3% release over 13 hours; TFD of 15 h). This approach facilitates modulation of drug-release profiles, minimizes floating lag time, extends overall floating duration and gastric-residence time, increases localized therapeutic efficacy, and ultimately improves the drug's oral bioavailability. Improved matrix buoyancy and prolonged gastric retention achieved through sintering are particularly advantageous for Dasatinib, whose solubility and absorption are pH-dependent and localized in the upper gastrointestinal tract.

The sustained release profile observed suggests the potential for enhanced and more consistent bioavailability, as extended gastric residence ensures longer exposure of the drug to its optimal absorption window. A deeper understanding of the theoretical and technological dimensions of thermal sintering can clarify its role in pharmaceutical production, particularly in the development of controlled or extended-release drug-delivery systems. Furthermore, adopting innovations from other fields may unveil new possibilities for utilizing advanced sintering technologies in drug delivery applications.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Chandan Mohanty conceptualized and supervised the work. Soumya Stuti Patnaik and Jitendra Debata performed the formulation and evaluation studies. Chandan Mohanty, Vakkalagadda Ravi Kumar, and Shaik Harun Rasheed prepared and drafted the manuscript. All authors studied and approved the final manuscript.

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