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## Thermal Sintering: A Novel technique in Formulation of Controlled Release Dosage form

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### ABSTRACT

Sintering is defined as the thermal treatment of a powder or compact at a temperature below the melting point of the main constituent, for the purpose of increasing its bond strength. This concept in pharmaceutical science is relatively new, but research works relating to this process have been growing. Sintering has been described as the mechanism for the strengthening of the mechanical properties of consolidated pharmaceutical powders at elevated temperatures, for solid-bond formation during tablet compression, and for thermal curing of polymer-latex film -Coatings. The changes in the microstructures, Hardness, Friability, Wettability, disintegration time and dissolution rate of tablets stored at elevated temperature were also described as a result of sintering. Controlled release oral dosage forms were developed by sintering the polymer matrix by exposing to temperature above glass transition ( $T_g$ ) point of the polymer. In the application of thermal sintering technique to the formulation of controlled release dosage form, the main research focus has been on the influence of sintering on the alteration of the microstructures in a polymeric matrix and the release of the active ingredients from the matrix.

**Keywords:** Thermal sintering, Glass transition point, Controlled release, Matrix

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## INTRODUCTION

Exploration of the Thermal sintering technique in the pharmaceutical sciences is relatively recent, but research interests relating to this process have been growing. Thermal sintering involves the heating of a compact at a temperature below the melting point of the main constituents in a controlled environment under atmospheric pressure. Historically, sintering is a method used to fabricate parts from metals, ceramics and glass. Microwave sintering, plasma-activated sintering and laser sintering are the more recent advancements in Thermal sintering technologies<sup>1</sup>. The sintering process has been used for the formulation of sustained – release matrix tablets and for the stabilization of the drug permeability of film coatings derived from various pharmaceutical lattices<sup>2</sup>.

## SINTERING METHODS

There are two types of sintering methods, namely thermal sintering method (heat treatment) and solvent casting method (acetone saturation method)<sup>3</sup>.

### Acetone saturation method

The punched tablets were exposed to acetone vapour in desiccators. The lower end of the desiccator was filled with acetone, closed and kept aside for saturation. After saturation the punched tablets were taken in petridishes and placed over a wire mesh which is kept above the lower chamber of the desiccator containing acetone. The desiccator is made air tight by closing the lid with the help of wax<sup>4</sup>. The acetone vapours in the saturated desiccator enter the pores of tablets; solubilize the surface of the polymer which results in the fusion of particles, thus bringing about sintering. After exposure for predetermined time intervals, the tablets were removed from the desiccator, dried at an ambient temperature to evaporate adhering free acetone for 24 hr and were finally dried in a vacuum desiccator over fused calcium chloride for 24 hr<sup>5</sup>. Further stored in desiccators for future studies.

### Thermal sintering method

Thermal sintering technique is a method of heating polymer matrix in a sintering furnace below the melting point of the solid constituents until its particles adhere to each other. In this process, polymer particles undergo fusion or formation of welded bonds between each particle. The thermal sintering method involves exposure of the polymer matrix to the temperature above the glass transition temperature of the polymer. The entrapment of drug particles in the polymeric matrix leads to controlled release of drug<sup>3</sup>. As compared to the Acetone saturation method, the thermal sintering method have the following

advantages: Decrease of processing time, no need of solvent removal, elimination of shrinkage and no unwanted effect on the macromolecule because of solvent exposure<sup>1</sup>.

However this method can be applied to only those drugs that are resistant to the temperature of exposure and may be the limiting factor for the drugs that get degraded at elevated temperatures<sup>3</sup>.

### **The Sintering of Pharmaceutical Compacts**

#### **Effect on Microstructures**

The alteration in the microstructures of a pharmaceutical compact during sintering is the prevailing factor in determining the release rate of the drug. The structural changes within a compact during sintering can be observed in following stages<sup>6</sup>.

#### **Inter particle Bonding:**

The transport of molecules at the point of particle contact leads to the formation of physical bandings and grain boundaries. The initial bindings take place rapidly.

#### **Neck Growth:**

Continuing material transport results in the development of a distinct “neck” between particles. The strength of the compact is considerably increased at this stage.

#### **Pore-Channel Closure:**

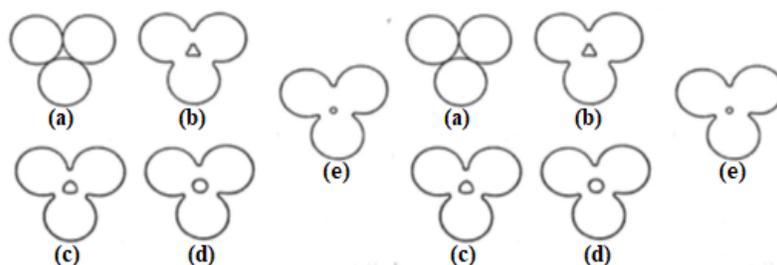
The continuing neck growth leads to the closure of some pore channels within the compact, leading to the isolated pores.

#### **Pore Rounding:**

As the neck growth reaches its final stage, the transport of material from the bulk to the neck regions produces a smoothing effect on the pore wall. At this stage, the toughness of the compact is further strengthened.

#### **Pore Shrinkage:**

With further sintering, the pores in the compact start to shrink in size and decrease in numbers. This facilitates further densification. This stage involves extensive material transport and the annihilation of vacancies in the compact.



**Figure 1: Three-sphere sintering model (a) Original points of contact; (b) Neck growth; (c) pore channel closure (d) Pore rounding; (e) Pore shrinkage<sup>10</sup>.**

## SINTERING MECHANISM

### Sintering in single solid phase

According to Wretbland and Wuff, the process of sintering in solid phases occurs by combination of two or three material-transport mechanisms.

Sintering in solid phases occurs by one of the following material-transport mechanisms:

1. Evaporation and condensation
2. Plastic and viscous flow
3. Volume and surface diffusion flow

According to Wretbland and Wuff, the sintering process is the result of combination of two or three of these mechanisms <sup>7</sup>.

### Evaporation and condensation

The gradient in the chemical potential ( $\mu-\mu_0$ ) between the convex surface and the adjacent flat surface creates a vapour-pressure gradient that can be described by Gibbs-Thomson equation

$$\mu-\mu_0 = RT (\ln P- \ln P_0)$$

Where

R is the gas constant.

T is the absolute temperature.

P is vapour pressure over the stressed (curved) surface.

P<sub>0</sub> is the Vapour pressure over the unstressed (flat) surface.

The differences in vapour pressure causes material to evaporate from the flat surface and condenses on the curved surfaces. This mass transfer mechanism is more significant for a substance with a high vapour pressure, particularly at a temperature close to its melting point.

### Plastic and viscous flow

On a surface of a solid with a sufficiently small radius of curvature, the developed stress becomes sufficiently high to provide dislocation via plastic deformation. In the absence of external pressure, plastic flow may contribute to the material transport phenomenon only in the very large stages of sintering. However, when pressure is applied during sintering, such as in a hot-pressing process, plastic flow becomes the predominant mass-transport mechanism.

### Volume and surface diffusion flow

Diffusional flow as a mass-transport mechanism for sintering is based on the concept that a certain concentration of vacancies exists in the lattice of a crystal. Again, considering the two spheres model, the gradient in chemical potential between the highly curved surface and the adjacent flat surface creates a gradient in vacancy concentration.

### **Sintering in liquid phase**

Sintering in liquid phase occurs by the following material transport stages:

#### **Rearrangement stage**

In the rearrangement stage, densification is brought about by the action of capillary pressure caused by the collapse of melt bridges between particles and by the rearrangement of solid particles sliding over each other.

#### **Accommodation stage**

This stage may be described as the growth of solid particles via a process of dissolution of the smaller particles and their reprecipitation on the larger ones as a result of the differences in solubility of small and large particles in the liquid phase. Since the solubility of the solid phase in the bulk is relatively low, material is transported from the contact region and reprecipitated in the bulk <sup>7</sup>.

#### **The solid-state sintering stage**

Prolonged exposure of the compacts to the sintering temperature may lead to solid-state sintering, which results in further particle growth in the solid phase and formation of a solid skeleton. In some cases, a rigid skeleton in the solid phase may be formed prior to complete densification. The formation of this skeleton may interfere with rapid densification by rearrangement.

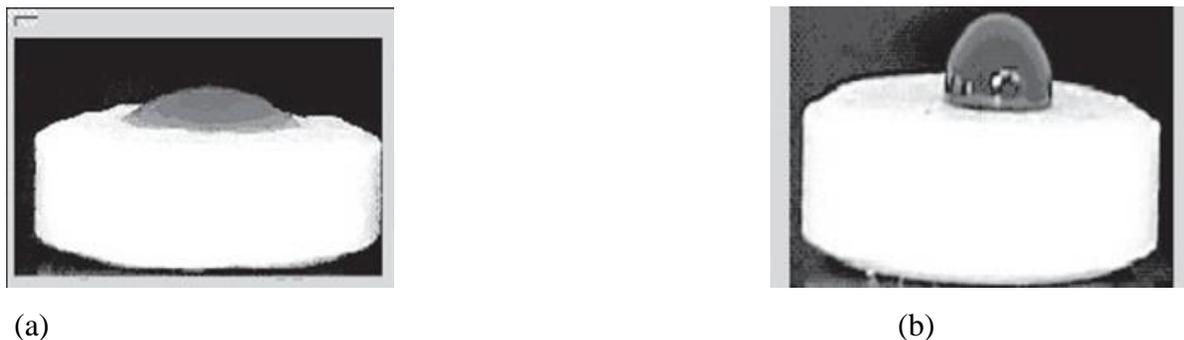
### **Effect of Sintering on Tablet Parameters**

#### **Effect on Hardness:**

The increase in points of contact and welded-bond formation between particles within a compact during sintering enhances its mechanical strength. The effect of sintering on hardness of polymeric matrix tablet of theophylline was investigated by A. Kondaiah et al <sup>8</sup>. They reported that the hardness increased when the temperature and time increased, this may be due to the strong bonding of EVA particles at higher temperature. The hardness depends on sintering time as well as sintering temperature, this was studied by S.B.Rao et al <sup>5</sup>. The studies indicate that as the power of microwave sintering increases hardness increases probably due to the fusion of polymeric granules or formation of a welded bond between particles.

#### **Effect on porosity and wettability:**

The duration of sintering also affected the porosity, the tablet sintered for less time shows more porosity as compared to the tablet sintered for more time <sup>9</sup> They also established that the contact angle of 'sintered tablet was greater than that of the unsintered tablet shown in Fig. 2.. This higher contact angle also contributes to the retardation of drug release from matrix tablet.



**Figure 2: Photoimages showing contact angle of water with (a) Unsintered tablet. (b) Sintered tablet <sup>10</sup>.**

#### **Effect on Dissolution rate:**

The effect of sintering mainly observed on dissolution rate of formulations. The sintering time markedly affected the drug release properties of Eudragit RL100 matrices, it is notable that the release rate of rifampicin from Eudragit RL100 matrices was inversely related to the time of sintering. This may be due to the increase in the extent and firmness of sintering which compacts the mass further so that the drug releases affected. The studies also showed that the drug release prolongation after thermal- treating can be attributed to the polymer chain movement and redistribution of the polymer in the tablet matrix structure. The melting and resolidification of the polymer, due to the thermal treatment resulted in a redistribution of the polymer throughout the matrix and possible changes in the nature of the pores within the matrix. The drug release studies showed that microwave irradiation is potentially useful for the drug release characteristics of polymer beads, without the need for noxious chemical agents <sup>11</sup>.

#### **Effect on stability:**

The stability studies shows that there was no effect found on the sintered matrix tablet placed at different storage condition for some period of time <sup>12</sup>.

#### **Controlled release dosage form fabrication**

##### **Matrix tablet system**

The effect of sintering technique in the development of a controlled release formulation for ketorolac tromethamine was studied by Rao and Ranpise <sup>11</sup>. The method consisted of mixing drug, wax powder (Compritol® 888 ATO), lactose as diluent and talc as lubricant followed by direct compression at room temperature. The compressed tablet matrices were kept at 80°C for 1, 2, and 3 hours for sintering. The sintered tablets were characterized by their physical parameters and in vitro dissolution profile. The sintering time distinctly affected the drug release properties of Compritol® 888 ATO matrices. It is observed that the release rate of ketorolac tromethamine from matrices was inversely related to the time of sintering. This may be due to the increase in the

extent and firmness of sintering which further compact the mass so that drug release is affected. Contact angle measurement and scanning electron microscopy analysis shows that heat treatment caused the sintering wax to melt and redistribute. The redistributed wax formed a network-like structure in which the drug and lactose is entrapped. This particular matrix is responsible for retarding the drug release.

### **Matrix pellet system**

Incorporation of hydrophobic (i.e. waxy) material into pellets using a thermal sintering technique for in vitro controlled drug release was investigated by Singh and Poddar <sup>13</sup>. Matrix pellets of Theophylline prepared with various concentration of carnauba wax were sintered thermally at various time and temperature ranging from 60 seconds to 240 seconds at 90°C to 120°C respectively. The sintering temperature and duration were optimized to allow the controlled release at least for 12 hours.

### **Mucoadhesive Buccal Tablet System**

The sintering time and the sintering temperature markedly affected the drug release properties of Perindopril buccal tablets. It is notable that the release rate of Perindopril from buccal tablets was inversely related to the sintering time and the sintering temperature. This is may be due to increase in extent and firmness of sintering which compact the mass further, so that the drug release is affected. The formulation contains the drug, polyethylene oxide and carnauba wax in the ratio of 1:15:10. The tablets formulation containing 4 mg of Perindopril exhibited 8 hrs sustained drug release (98 %) with desired therapeutic concentration. The drug release followed diffusive mechanism with first order release kinetics <sup>14</sup>.

### **Film-Coating Systems:**

In recent years, aqueous controlled-release film-coating system has gradually gained popularity over the solvent-based film-coating systems because of increasing public concern with environmental pollution from the emitted solvents <sup>10</sup>. The most widely used aqueous controlled-release film-coating systems are acrylate copolymer and ethyl cellulose lattices, which consist of colloidal polymeric particles dispersed in an aqueous medium. Upon the evaporation of water, a latex film or coating is formed as the polymeric particles coalesce. The latex particles continue to coalesce during storage of the coated product. This phenomenon has been shown to be particularly pronounced for products coated with ethyl cellulose latex <sup>10</sup>; A decrease in drug-release rate due to curing has also been reported for products coated with acrylic-based polymer latex systems.<sup>11</sup>In order to shorten the coalescence time, a “heat-curing process” is used to treat the coated product after the coating process. Latex is cured by a post coating heat treatment (e.g. fluidization) <sup>10</sup> in the

coating equipment or by a subsequent oven-heating process. Mechanistically, the curing process is essentially a sintering process with respect to the coalescence of the polymer latex particles in a film matrix. The curing temperature is generally above the glass temperature of the polymer so that sintering of polymer particles is achieved by viscous flow of the polymer as well as by inter diffusion of polymer chains among adjacent particles. The curing temperature was reported to have a stronger effect on the results than the curing time.

### **RECENT RESEARCH WORK REPORTED ON SINTERING TECHNIQUE**

Farhadieh. B et al<sup>15</sup> in 1971, first employed the sintering process, primarily as a means to improve the mechanical properties of drug-loaded methyl acrylate-methyl methacrylate copolymer matrix tablets in order to prevent breakage. They observed the enhancement of drug release after sintering.

Kristoffersson. E et al<sup>16</sup> in 1976 found that sintering was more effective method than compression in slowing the release of acetaminophen from an acrylate plastic (Eudragit RS) matrix tablets, because of decrease in porosity of the tablet due to sintering.

Carli F and Simioni L <sup>17</sup> in 1981 investigated the effect of sintering on drug release from vinyl chloride vinyl acetate copolymer (CPVC) tablets as well as acrylic tablets by using aspirin as model drug. They observed that sintering initially enhanced release of aspirin from CPVC tablets but prolonged sintering decreased the release rate. However, in case of acrylic tablets, the release rate of aspirin decreased drastically upon sintering. They attributed the changes in the release rate of the as the result of sintering to the alteration of the capillary network within the matrix.

A.Kondaiah et al<sup>9</sup> in 2002 prepared and evaluated controlled release polymeric matrix tablets theophylline using sintering technique. They found that irrespective of the drug: polymer ratio in the formulation, with the increase in the time of sintering and/ or temperature of sintering, the percent of theophylline released was reduced. The sintering technique produced non erodible matrix tablets. Hence they concluded that by selecting proper polymer: drug ratio, temperature for sintering and time period of sintering an effective controlled release tablet dosage form can be formulated.

B. Seshagiri et al<sup>18</sup> in 2011 designed Hydrodynamically Balanced Systems for Glipizide with sintering technique. It is an approach to increase the gastric residence time of drugs in stomach. This system is designed for site specific oral drugs with low bulk density than gastric fluids so as to buoyant the dosage form in stomach to increase the residence time of the drug. In the present investigation, HPMC K4M and HPMC K15M polymers were used by solvent casting sintering technique The study reveals that the formulations of HBS of Glipizide formulated has exhibited a

floating lag time of less than 5 minutes and floating time of more than 22 hrs. The results indicate that gas powered Hydrodynamically Balanced Tablets of Glipizide containing HPMC K15M provides a better results for controlled release action and improved bioavailability.

6. Sameer Shafi et al<sup>19</sup> in 2011 prepared the sustained release (SR) sintered matrix tablets of Diltiazem hydrochloride by trituration method using 4% and 8% HPMC K4M and HPMC K15. The drug release study was carried out in USP XXI model. 900ml dissolution medium of 0.1N HCl (pH 1.2) was used for the first 2 hours and pH 6.8 phosphate buffer for remaining 8 hours. The revolutions at 50rpm and temperature at  $37\pm 1^{\circ}\text{C}$  were maintained. Formulations with HPMC K exhibited sustained drug release profiles with maximum sustaining effect when compared with unsintered formulation in about 8 hours by using sintering.

7. Uhumwangho MU. et al<sup>20</sup> 2011 studied the effect of sintering condition on drug release profile of Diltiazem hydrochloride wax-matrix granules for sustained release application using thermal sintering technique. They found that as the temperature and duration of sintering of the matrix granules increased, the drug release rate decreased and the time to attain maximum release increased correspondingly. They concluded that the thermal sintering technique enhanced the extent of retardation of drug release and drug was not affected by the temperature and time period used for sintering.

Katariya Chaitali Ramesh et al<sup>21</sup> in 2012 formulated sustained release matrix tablets of lamivudine by using sintering technique. Two hydrophobic polymers Eudragit RL 100 and Eudragit RS 100 were selected. In this study the effect of the heat and solvent treatment on drug release, tensile strength was studied. Increasing the sintering duration increase in the sustained release and also increase in hardness of tablet. During sintering of tablets, polymer particle transform from glassy state to rubbery state and redistributed to entangle the drug particles, leading to drug release retardation. By selecting proper polymer concentration, sintering temperature and duration the effective sustained release formulation of lamivudine were prepared. The drug did not undergo degradation during sintering. The solvent treatment gives more sustained release of drug compared to Thermal sintering.

Venkata Srikanth Meka et al<sup>22</sup> in 2012, formulated thermal sintering floating tablets of Propranolol HCL and studied the effect of Sintering conditions on drug release and vitro buoyancy properties. A hydrophilic polymer polyethylene oxide, was used as a sintered polymer to retard the drug release. The formulations were prepared by a direct compression method. Propranolol HCl, PEO, sodium bicarbonate and magnesium stearate were utilized. As the sintering temperature and time of exposure increased, floating lag time was found to be decreased, total floating time was

increased and drug release was decreased. An optimized formulation (sintering temperature 50°C and time of exposure 4 h) was selected, based on their drug retarding properties.

Vaibhav Bhamre et al<sup>12</sup> in 2013, prepared and evaluated sintered matrix tablets of Stavudine by using Eudragit RS100 & Compritol 888ATO with direct compression method. Also studied effect of three different temperatures on stability of sintered tablets. Storage condition & period of storage affect stability Stavudine sintered tablet.

M. Parvathi et al<sup>23</sup> 2013, formulated and evaluated sintered matrix tablets of metformin hcl. Matrix tablets are preferred to sustain drug release and reduce frequency of administration. The term sintering means fusion of particles and formation of welded bonds between particles of polymer. The SR oral dosage forms can be developed by sintering the polymer matrix by exposing to temperature above glass transition point of the polymer or exposing the polymer matrix systems to solvent vapours.

Bhagwat RR et al<sup>24</sup> in 2014, investigated the release characteristics of matrix granules consisting of hydrophobic (i.e waxy) material and Verapamil hydrochloride for sustained release application using thermal sintering technique. The use of sintering technique causes the polymer to extend the release of drug from formulation depending upon the temperature and time of exposure.

Meka Venkata Srikanth et al<sup>25</sup> in 2014, investigated on the applicability of thermal sintering technique for the development of gastric floating tablets of propranolol HCl. Formulations were prepared using four independent variables, (i) polymer quantity, (ii) sodium bicarbonate concentration, (iii) sintering temperature and (iv) sintering time. Floating lag time and t<sub>95</sub> were taken as dependent variables. From the drug release studies, it was observed that drug retarding property mainly depends upon the sintering temperature and sintering duration. Optimized formulation was stable at accelerated conditions for a period of six months. These tablets were evaluated for in vivo buoyancy studies in humans for both fed and fasted states and found that gastric residence time of the floating tablets were enhanced by fed stage but not in fasted state.

Monica RP Rao et al<sup>26</sup> in 2015, prepared sustained release matrix tablets of Itopride by using hydrophobic polymers and study of sintering technique in modulating drug release. Carnauba wax and Eudragit L 100 were used as release retarding polymers. A 3<sup>2</sup> optimization design was applied to achieve tablets with optimum drug release. Drug release mechanism was found to be diffusion-erosion due to the polymer-wax combination. Optimization batches were studied for porosity, contact angle and tensile strength so as to analyse the effect of sintering on above mentioned properties. Wettability and porosity was decreased with increase in contact angle was evident for sintered tablets.

Lakshmi PK et al<sup>27</sup> 2015, formulated and evaluated sintered matrix tablets of Lamotrigine using controlled release natural and synthetic polymers such as HPMC K4M, HPMC K15M, HPMC K100M, acacia, guar gum and xanthan gum polymer. Based on the study it can be concluded that sintering technique enhances the extended release of the drug with low concentrations of polymer and it would be a cost effective method.

Chandan Mohanty et al<sup>28</sup> in 2015, formulated Atazanavir Sulphate Gastro Retentive Floating Matrix Tablets using sintering technique. The tablets were prepared by direct compression method using EC N100 and HPMC K100 as polymers. The release rate of the drug decrease with the sintering temperature and the sintering time. The hardness was increased with increase in sintering temperature and duration of sintering; but friability of tablets was found to be decreased with increasing sintering time. Floating lag time was inversely proportional to the sintering temperature and sintering time, whereas total floating time was directly proportional to the sintering temperature and sintering time. The formulation F2 sintered at 600 for 3 h was selected as an optimized formulation based on the drug release properties and the optimized formulation followed Fickian diffusion mechanism with Korsmeyer-Peppas release kinetics.

ChandanMohanty et al<sup>29</sup> in 2016, prepared thermally sintered floating matrix tablets of Nicardipine HCL and studied the effect of sintering conditions on in-vitro dissolution study, in-vitro buoyancy properties, hardness and friability. The tablets were prepared by direct compression method using HPMC K100M as matrix forming polymer and sodium bicarbonate as gas generating agent. The results revealed that increase in temperature or time of exposure to a particular temperature often decreased the release rate of the drug. By using sintering technique floating lag time and total floating time of tablets was found to be decreased and increased respectively, with increase in the sintering temperature and sintering time. In addition the hardness of the sintered tablets was increased with increase in sintering temperature and duration of sintering, whereas friability of tablets was found to be decreased with increasing sintering time. An optimised formulation F2 sintered at 70<sup>0</sup>C for 3 hr was selected based on their drug retarding properties and comparatively low proportion of polymer.

Satish Polshettiwar et al<sup>30</sup> in 2016, formulated Carvidilol phosphate matrix tablets by using polymers like HPMC K4M, Eudragit L 100, Guar gum and Sodium bicarbonate, Citric acid were utilized in the formulation. Tablets were prepared by direct compression method. On thermal sintering, it was found that F6, L2, I2 and H4 gave better results compared to other formulations. Results revealed that the sintering caused decrease in drug release as compared to unsintered tablets. Thus stability studies prove that the formulation was stable at accelerated condition.

Samra Rumman et al<sup>31</sup> in 2017, formulated Tapentadol Hydrochloride sintered tablets using sustaining polymer-eudragit RL-100, sintering waxes-stearic acid and carnauba wax, disintegrating agent-microcrystalline cellulose, glidant-talc and lubricant-magnesium stearate by direct compression method. The pre compression and post compression parameters results were found to be within the limits. The drug release from optimized formulation (F17-Tapentadol Hydrochloride with stearic acid and carnauba wax sintered at 600C for 2 hours) was found to be 100.38% in 12 hours. Stability studies proved that optimized formulation was stable at 40±2°C and 75±5% RH for 3 months. Thus, the F17 formulation developed by sintering technique has great future potential to be prepared as sustained release tablets.

Collins O Airemwen et al<sup>32</sup> in 2017, formulated sustained release matrix tablets of metronidazole using sintering technique. Controlled release metronidazole matrix tablets were prepared by wet granulation technique using Irvingia gabonensis (IG) gum as binder. Prepared tablets were kept for thermal sintering. There is increase in tablet hardness with increase in sintering temperature and time while the percentage friability decreased. The in-vitro dissolution profile of the prepared controlled release matrix tablet of metronidazole showed that the optimum drug release retardation occurred in tablets sintered at 60 °C for 5 h. The study has revealed that IG gum at a concentration of 10% w/w possesses good binding properties and can be utilized in the formulation of controlled release matrix tablets of metronidazole by thermal sintering.

### **Future prospective**

Day by day there is increase in need of novel technology in drug delivery system. This thermal sintered technology fulfil demand of novel drug delivery system. By exploring the use of sintered technique in various dosage forms it may aids in driving the growth of the pharmaceutical market.

### **CONCLUSION:**

In the pharmaceutical science, sintering has been described as the mechanism for the strengthening of the mechanical properties of consolidated pharmaceutical powders at increased temperatures, for solid-bond formation during tablet compression, and for thermal curing of polymer-latex film coatings. Sintering technique adds to the effectiveness of polymers to extend the drug release from the formulation depending upon the temperature time and duration of sintering. The prolonged exposure of some drug molecules to higher temperatures may lead to thermal decomposition. Only the drugs with higher melting points are chosen. Polymer should have higher melting point than main constituent. A better understanding of the theoretical and technical aspects of the sintering process helps in the formulation of controlled-release polymeric matrix systems.

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