

## A Review on Sintering Technique in Pharmaceutical Sciences

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### ABSTRACT

In the pharmaceutical science, 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 concept of sintering was applied in the investigation of the effect of heating on the mechanical properties of pharmaceutical powders. The formation of solid bonds within a powder bed during tablet compression was also studied in terms of sintering. The changes in the hardness and Disintegration time of tablets stored at elevated temperatures were described as a result of sintering. Furthermore, the sintering process has been used for the fabrication of sustained – release matrix tablets and for the stabilization of the drug permeability of film coatings derived from various pharmaceutical lattices.

**Keywords:** Sintering, Sustained release, Disintegration, Film coating.

### INTRODUCTION

Exploration of the sintering concept in the pharmaceutical sciences is relatively recent, but research interests relating to this process have been growing. Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in compact, by the application of heat<sup>1</sup>. Conventional sintering technique involves the heating of compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure. Variation in this method include heating in the presence of transient or stable liquid phases and/or under pressure(hot-pressing). Plasma activated sintering<sup>1,3</sup>, microwave sintering<sup>1,4</sup>, and laser sintering<sup>1,5</sup> are the more recent advances in sintering technologies. Historically, sintering is a process employed to fabricate parts for metals, ceramics, and glass.

#### *Sintering method*

There are two types of sintering methods

Heat treatment

Acetone saturation

#### *Heat treatment*

Thermal sintering is a method of heating a polymer in a sintering furnace below its melting point (solid state sintering) until its particles adhere to each other. In this process, polymer particles will undergo fusion or formation of welded bonds between each particle. The thermal sintering method involves the exposure of the formulation to a polymer transition temperature in which the polymer forming the matrix slowly softens and welded

bonds are formed. The drug particles will be entrapped in the formed matrix, resulting in the controlled release of the active ingredient. However, this method may be applied to only those drugs that are resistant to the temperature of exposure and this may be the limiting factor for many drugs that get degraded at elevated temperatures.

#### *Acetone Saturation*

The punched tablets were subjected to sintering process. The lower of the desiccators was filled with acetone, closed and kept aside for saturation. After saturation the compressed tablets were taken in petridishes and placed over a wire mesh which was kept above the lower chamber of the desiccator containing acetone. The desiccator was made air tight by closing the lid with the help of wax. The acetone vapors in the saturated dessicator enter the pores of tablets solubilize the surface of the polymer particles which results in fusion of particles, thus bringing about sintering. Tablets of each formulation were divided into 3batches and exposed to3 different duration of sintering time (1.5 hr, 3.0 hr, 4.5 hr). After sintering, the tablet were removed from the desiccator, and dried at room temperature for 24 hr to evaporate the adhering acetone and were finally dried in vacuum desiccator at 300C over fused calcium chloride to remove the residual acetone from the tablet for 24 hr and stored in desiccator for further studies.

#### *The Sintering of Pharmaceutical Compacts*

#### *Effect on Microstructures*

The structural changes within a compact during sintering can be broken down into several stages<sup>2,4</sup>. Some of which may occur virtually simultaneously. Five different stages of sintering are illustrated in as detailed below.

#### *Interparticle 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 enhanced at this stage.

#### *Pore-Channel Closure*

The continuing neck growth leads to the closure of some pore channels within the compact, giving rise to 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.

#### *Example*

The effect of sintering on the micro structural changes in ibuprofen (mp, 75-77.5°C) compacts was investigated by Li<sup>2</sup>. Compacts were prepared at a compression pressure of 215 gf/cm<sup>2</sup> (21MPa) and heated at 70°C for 24 hr. The most noticeable change on the surface of compact is coalescence of the deformed particle, resulting in pore rounding and pore shrinkage. The fusion of adjacent ibuprofen particles in the interior of compact resulted in an even more dramatic reduction in the internal void volumes of sintered compact.

#### *Sintering Mechanism*

##### *Solid Phase<sup>1</sup>*

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

**Evaporation and condensation:** The gradient in the chemical potential ( $\mu - \mu_0$ ) between the convex surface and the adjacent flat surface (Fig.1) creates a vapor-pressure gradient that can be described by the Gibbs-Thomson equation (Eq.4).

$$\mu - \mu_0 = RT (\ln P - \ln P_0) \quad (3)$$

Where, P and P<sub>0</sub> are the vapour pressures over the stressed (curved) and the unstressed (flat) surfaces, resp. R is the gas constant, and T is the absolute temperature. Because of this difference in vapour pressure, material evaporates from the flat surfaces and condenses on the curved surface. This mass-transfer mechanism is more significant for a substance with a high vapor 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 stresses become sufficiently high to produce dislocation via plastic deformation. In the absence of external

pressure, plastic flow may contribute to the material-transport phenomenon only in the very early 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 diffusional 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 (Fig.1), the gradient in chemical potential between the highly curved surface and the adjacent flat surface creates a gradient in vacancy concentration.

##### *Liquid phase<sup>1</sup>*

Sintering in liquid phases occurs by one of 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 difference 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 precipitated in the bulk.

##### *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 solid-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>5</sup> They reported that the hardness increased when the sintering temperature and time increased, this may be due to the firm 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>6</sup> The studies indicate that as the power of microwave sintering increases hardness increases probably due to the fusion of polymer granules or formation of a welded bond between particles<sup>7</sup>.

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

The duration of sintering also affected the porosity<sup>2</sup>, the tablet sintered at less time shows more porosity as compared to the tablet sintered at more time was studied by M. Rao et al.<sup>8</sup>. They also established that the contact angle of sintered tablet was greater than that of the unsintered tablet shown in Fig. 2. This clearly indicates that sintering decreases the wettability of tablet surfaces.

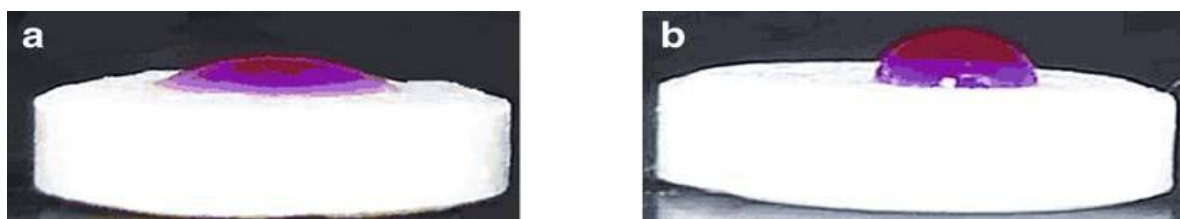


Figure 2: Photo images showing contact angle of water with (a) Un sintered tablet. (b) Sintered tablet<sup>2</sup>.

This higher contact angle also contributes to the retardation of drug release from matrix tablet.

#### *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<sup>10</sup>. 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<sup>11</sup>. 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>12</sup>.

#### *Effect on stability*

The stability studies show that there was no effect found on the sintered matrix tablet placed at different storage condition for some period of time.<sup>1,3</sup>

#### *Sintering in Controlled Released Doses from and Fabrication*

##### *Matrix Systems*

The alteration of the microstructures within a compact during sintering is the predominant factor in determining the release rate of the active ingredient. In the application of this technique to the fabrication of controlled-release systems, the research focus has been on the influence of sintering on the micro structural changes in a polymeric matrix and the release of active ingredient from the matrix. A sintering process was first employed by Farhadieh et.al<sup>16</sup> 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. The effect of sintering on the release of potassium chloride from a matrix tablet prepared from a vinyl acetate-vinyl chloride copolymer was investigated by Rowe et al<sup>7</sup> The matrix showed a pronounced initial increase in release rate of potassium chloride. Followed by a gradual decline; the final release rate still exceeded that for the unsintered compact. Porosity data and the alteration of the matrix microstructure, as evidenced by SEM photomicrographs, demonstrated that sintering caused axial expansion of the tablets because of elastic recovery of the polymer particles. This resulted in an increase in

matrix porosity as well as in the drug release rate. Kristofferson and co-workers<sup>8</sup> found that sintering was more effective method than compression in showing the release of acetaminophen from an acrylate plastic (Eudragit RS) matrix table.

A low-temperature (370.C) sintering technique was used to prepare ethylene-vinyl acetate co polymer matrices containing macromolecules, bovine serum albumin and tyrosine<sup>9</sup>. In contrast with the solvent-casting methods, the sintering method was credited with the following advantages: elimination of shrinkage, no need for solvent removal, reduction of processing time, and no adverse effect on the macromolecule because of solvent exposure<sup>12</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 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>1,2</sup>. The most widely used aqueous controlled-release film-coating systems are acrylate co polymer 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 degree of coalescence affects 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>1,2</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<sup>1,4</sup>.

## **CONCLUSION**

In the pharmaceutical science, 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. However, sintering has not experienced a broad application in pharmaceutical manufacturing. From the viewpoint of economy, a conventional high-temperature sintering process is much less efficient than a tableting process for powder consolidation because of the long time required for sintering. Furthermore, the prolonged exposure of some drug molecules to higher temperatures may cause thermal decomposition. However, a better understanding of the theoretical and technical aspects of the sintering process may allow the identification of its specific needs for pharmaceutical manufacturing such as the fabrication of controlled-release polymeric matrix systems. Sintering of the matrix tablets results in melting and redistribution of the wax throughout the matrix and a possible change in the nature of the pores within the matrix.

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