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APPLICABILITY OF SINTERING TECHNIQUE IN FABRICATION OF CONTROLLED RELEASE DOSAGE FORM

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Abstract

The concept of sintering in pharmaceutical sciences is relatively new, but the research interests related to this process have been growing continuously. Sintering means fusion of particles of polymer. Sintering has been described as the mechanism for solid bond formation during tablet compression, for thermal curing of polymer latex film coatings and for strengthening of the mechanical properties of consolidated pharmaceutical powders at elevated temperatures. 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. In the application of this sintering technique to the fabrication 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. Controlled release oral dosage forms were developed by sintering the polymer matrix by exposing to temperature above glass transition (Tg) point of the polymer.

Keywords: Sintering, Glass transition, Controlled release, Matrix, Film coating.

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INTRODUCTION

In powder metallurgy, sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in compact, by the application of heat. 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. 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 advances in sintering technologies [1, 2].

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 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 [3,4].

SINTERING METHODS

Sintering means fusion of particles of polymer. There are two types of sintering methods, namely thermal sintering method (heat treatment) and solvent casting method (acetone saturation method) [5].

Acetone saturation method

This method involves exposure of compressed tablets to acetone vapour in desiccators. The lower chamber of the desiccator 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 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 [6].

The acetone vapours in the saturated desiccator enter the pores of tablets; solubilise 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 a 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. [7].

Thermal sintering method

Thermal sintering technique is a method of heating polymeric 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 fusion of polymer particles or formation of

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welded bond between particles by exposing the polymer matrix to the temperature above the glass transition temperature of the polymer. The entrapment of drug particles in the welded bond leads to controlled release of drug [5].

As compared to the solvent casting method, the thermal sintering method have the following advantages: reduction of processing time, no need of solvent removal, elimination of shrinkage and no adverse effect on the macromolecule because of solvent exposure [1]. However this method is applicable 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 temperature [5].

THEORY OF SINTERING

Driving forces for sintering

The principal driving force for sintering is the reduction of total free energy in the system as a result of the bonding of particles, void-space shrinkage and the consequent decrease in total surface area of the compact. Hence, from the thermodynamic point of view, sintering is a spontaneous process.

A simple two sphere sintering model (fig.1) was described, based on Laplace's equation, to examine the chemical-potential gradients of the surface of a solid in regard to the driving forces for sintering. The stress distributed around the neck area is expressed by the following equation (1).

$$\sigma = \gamma (-1/r + 1/x) \quad (1)$$

Where γ = Surface energy of the solid.

As x>>r, the term of 1/x can be neglected and stress is taken as equation (2).

$$\sigma = - \gamma / r \quad (2)$$

The negative sign indicates a tensile stress. The corresponding gradient in chemical potential may be as equation (3).

$$\mu - \mu_0 = \sigma \Omega = - \gamma \Omega / r \quad (3)$$

Where μ = the chemical potential over the convex side of curvature with radius 'r'.

μ_0 = the chemical potential at adjacent flat surface which is not under stress.

Ω = Atomic volume.

The chemical potential gradients ($\mu - \mu_0$) for the surfaces of the two spheres become the driving force for sintering [1,2].

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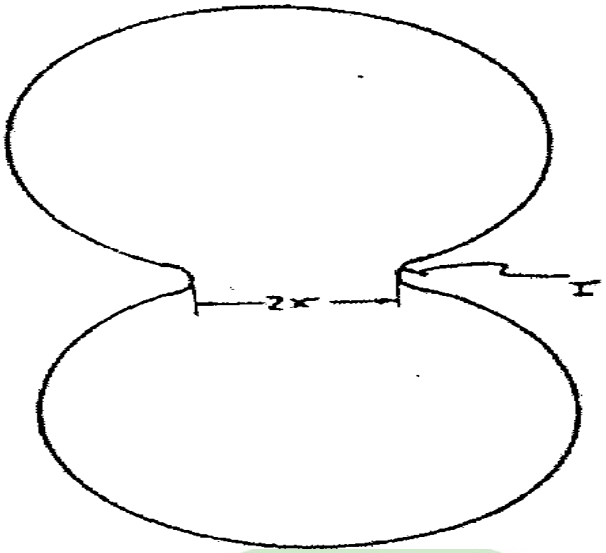

Fig. 1: Two-sphere sintering model, showing the diameter (2 x) of the neck between the particles and the radius (r) at the end of the neck [1]

SINTERING MECHANISM

Sintering in single solid phase [1,2,5]

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.

1. Evaporation and condensation

The gradient in the chemical potential (μ-μ_0) between the convex surface and the adjacent flat surface (Fig. 1) creates a vapour-pressure gradient that can be described by Gibbs-Thomson equation (Equation 4).

$$\mu - \mu_0 = RT (\ln P - \ln P_0) \quad (4)$$

Where

R is the gas constant.

T is the absolute temperature.

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

P_0 is the Vapour pressure over the unstressed (flat) surface.

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Because of these differences in vapour pressure, material evaporates 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.

2. 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.

3. 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 (Fig. 1), 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 [1,2,5]

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.

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.

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SINTERING TECHNIQUE IN FABRICATION OF CONTROLLED RELEASE DOSAGE FORM

Matrix system

The alteration of the microstructures within a pharmaceutical compat during sintering is the prevailing factor in determining the release rate of the drug. In the application of this sintering technique to the fabrication 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.

The structural changes within a compact during sintering can be broken down into several stages. Some of which may occur virtually simultaneously. Five different stages[1, 3] of sintering are illustrated in figure 2, as detailed below

1. **Interparticle Bonding.** The transport of molecules at the point of particle contact leads to the formation of physical bondings and grain boundaries. The initial bondings take place rapidly.

2. **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.

3. **Pore-Channel Closure.** The continuing neck growth leads to the closure of some pore channels within the compact, giving rise to isolated pores.

4. **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.

5. **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.

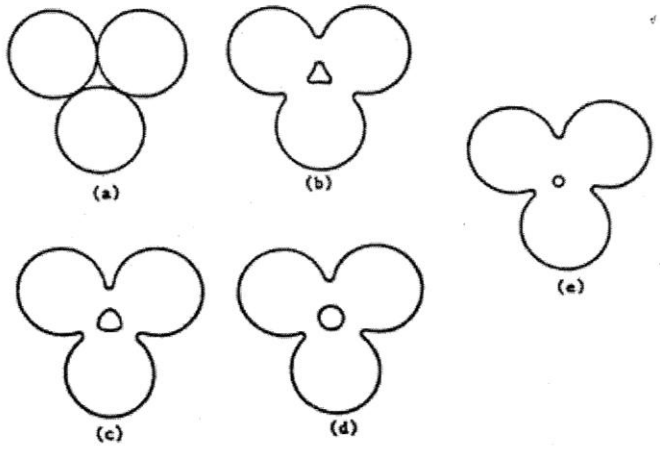

Fig.2: Three-sphere sintering model (a) Original points of contact; (b) Neck growth; (c) and (d) Pore rounding; (e) Pore shrinkage.

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Farhadieh *et al* [8] 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 pointed out the enhancement of drug release after sintering.

Kristoffersson and co-workers [9] in their work 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 and Simioni [10] 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 and K Prakash [11] 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 Sreenivasa Rao et al [12] prepared sintered matrix tablets of rifampicin with Ethylene vinyl acetate (EVA) copolymer for controlling the drug release rate. They observed that the sintering time significantly affected the rifampicin release properties from the sintered matrices. The drug release rate from EVA 1408 matrices was inversely related to the sintering time. They concluded that among the different strategies employed in designing the controlled-release systems, sintering technique is an alternative technique in the preparation of polymeric matrices for the oral controlled release dosage form.

Monica Rao et al [13] in their work investigated the effect of sintering in the development of controlled release dosage formulation of ketorolac tromethamine from compritol 888ATO matrix. They reported that on sintering, the hydrophobic wax is more uniformly dispersed through the compact and hence there is a decrease in the wettability of the tablet surface, which in turn resulted in the retardation of drug release from matrix tablet.

Satyabrata Bhanja et al [4] in their study used sintering technique to prepare mucoadhesive buccal tablets of Perindopril to avoid extensive first pass metabolism, to improve

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bioavailability and to prolong the drug action. They data indicated that the release rate of Perindopril from buccal tablets prepared by thermal sintering technique was inversely related to the duration of sintering and the sintering temperature. They proposed that sintering technique can be a good approach for the design of mucoadhesive buccal tablets for the controlled release of the drug.

A Hussein and Ahmed [14] investigated the feasibility of use of sintering technique to control the highly water soluble trifluoperazine Hcl release from carnauba wax matrix. They found that sintering condition increased hydrophobicity of the tablet surface, which in turn hinder the water penetration into the tablet and hence retarded the release of the drug. They concluded that sintering is a simple and low cost technique in the preparation of wax based controlled release tablet since by controlling the time and temperature of sintering the release of the drug can be controlled.

DM Patel et al [15] studied the effect of sintering condition on the formation of matrix and subsequent drug release from the polymeric matrix tablet for control release, using propranolol Hcl and Eudragit S-100 as model drug and sintering polymer respectively. The prepared tablets were irradiated in microwave oven at three different power 540 watt, 720 watt and 900 watt for different time duration. During dissolution study they found that the release of the drug was sustained more from the sintered tablet matrices than the non-sintered tablets. They concluded that polymeric matrices sintered at microwave oven resulted in a greater extent of sintering due to firmness among Eudragit S-100 particle and as compared to conventional hot air oven; microwave oven sintering gave more uniform heat distribution with less time.

M U Uhumwangho and K V Ramanamurthy [16] 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.

Venkata Sikanth M et al [17] in their study prepared gastro retentive floating tablets of propranolol Hcl using sintering technique and studied the effect of sintering conditions on drug release and buoyancy properties of prepared floating tablets. From the data obtained they observed that as sintering temperature and time of exposure increased, floating lag time were found to be decreased, total floating time were increased and the release of the drug was retarded. The drug release retarding properties directly related to the sintering temperature and

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sintering time. They concluded that the thermal sintering technique can be employed in the design of gastro retentive floating tablets for controlled release of drug.

C S Praveen et al [18] developed sustained release sintered matrix tablets of lamivudine and investigated the impact of sintering technique on release of lamivudine from the polymeric matrix tablet. They found that during the sintering, polymer particles transform from glassy state to rubbery state and redistributed to entangle the drug particle, which in result sustained the drug release from sintered matrix tablets. Hence an effective sustained release formulation of lamivudine can be developed by selecting proper polymer concentration, sintering duration and sintering temperature.

R R Bhagwat and I S Vaidya [19] in their study formulated verapamil hydrochloride matrix granules for sustained release containing carnauba wax and glyceryl behenate as wax matrix forming polymer using sintering technique. Their data indicated that the time to attain maximum drug release increased as the sintering temperature and duration of sintering of the prepared matrix granule increased correspondingly. They concluded that the sintering condition markedly affected the drug release properties of sintered matrix granules and use of this sintering technique adds to the effectiveness of polymers to extend the drug release from the formulation depending upon the duration and temperature of sintering.

Chandan Mohanty et al [20] in their study prepared thermally sintered floating matrix tablets of Nicardipine HCL to sustain the drug release and investigated the effect of sintering condition on mechanical strength, buoyancy properties and drug release. They observed that, compared to the non-sintered tablet, more sustained release of the drug was observed from sintered tablet matrices,. Floating lag times of the thermally sintered tablets were found to be decreased with increase in sintering time, whereas total floating times were increased with sintering. Friability of tablet was found to decrease with increasing sintering time and hardness was increased with increasing sintering time. Hene a simple technique of thermal sintering may be used in the development of floating tablets of Nicardipine HCL to sustain the drug release.

C Mohanty and K V Subhrahmanyam [21] evaluated the effect of sintering condition in the development of matrix tablet of atenolol for controlled release by using Eudragit RS 100 as sintering polymer. They observed that percent erosion of and percent water uptake of tablets found to be decreased with sintering condition. Drug release characteristics from the sintered matrix tablets were inversely related to the sintering temperature and sintering duration. As temperature of sintering and duration of sintering increased, the time required to attain maximum release from tablets also increased accordingly.

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Film-Coating Systems

Recently, aqueous controlled-release film-coating system has slowly gained popularity over the solvent-based film-coating systems because of increasing public concern with environmental pollution from the emitted solvents. 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 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 ethycellulose latex; [22] a decrease in drug-release rate due to curing has also been reported for products coated with acrylic-based polymer latex systems [23]. 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) [24] 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 interdiffusion of polymer chains among adjacent particles. The curing temperature was reported to have a stronger effect on the results than the curing time.

CONCLUSION

Among the different strategies employed in designing the controlled-release systems, sintering technique is an alternative technique in the preparation of oral controlled release dosage form. Sintering condition markedly affected the drug release properties and use of this sintering technique adds to the effectiveness of polymers to extend the drug release from the formulation depending upon the duration and temperature of sintering. Thermal sintering is a simple and low cost technique in the preparation of controlled release dosage form since by selecting proper polymer concentration and by controlling the time and temperature of sintering the release of the drug can be controlled. However, sintering technique has not experienced a broad application in manufacturing of pharmaceuticals. From the economic point of view, 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 lead to 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

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pharmaceutical manufacturing such as the fabrication of controlled-release polymeric matrix systems. More importantly, an understanding of the ever-growing advancements in new technologies relating to sintering as used in other technical fields may lead to new applications of modern sintering processes to pharmaceutical systems.

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