ABSTRACT
Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder or in a compact by application of heat. This concept in pharmaceutical science is relatively recent, but research interests relating to this process have been growing. The principal driving force for sintering is reduction of total free energy in the system as a result of this bonding of particles, void-space shrinkage, and the consequent decrease in total surface area of the compact. Historically, sintering is process employed to fabricate parts from metals, ceramics and glass. In the pharmaceutical sciences, sintering has been described as the consolidated pharmaceutical powders at elevated temperatures, solid- bond formation during tablet compression. However, a better understanding of theoretical and technical aspects of sintering process may allow the identification of its specific needs for pharmaceutical manufacturing such as a fabrication of controlled release polymeric matrix system.

KEYWORDS: Sintering, Controlled release, Novel technique, Solid state sintering, Effect of temperature.

INTRODUCTION
In the pharmaceutical sciences sintering concept is relatively recent, but research interests relating to this process have been growing. Sintering is defined as bonding of adjacent particle surfaces in a mass of powder, or in a compact by application of heat. The principal driving force for sintering is 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. The formation of solid bonds within a powder bed during tablet compression was also studied in terms of sintering. The changes in hardness and disintegration time of the compact were investigated.
tablets stored at elevated temperature were described as result of sintering. Furthermore, the sintering process has been used for fabrication of sustained release matrix tablets.\textsuperscript{[1,2]}

Conventional sintering involves the heating of a compact at a temperature below the melting point of the solid constituents in a controlled environment under atmospheric pressure. Variations in this method include heating in the presence of transient or stable liquid phases and/or under pressure (hot-pressing). Plasma-activated sintering, microwave sintering and laser sintering are the more recent advances in sintering technologies. Historically, sintering is process employed to fabricate parts from metals, ceramics and glass. In the pharmaceutical sciences, sintering has been described as the consolidated pharmaceutical powders at elevated temperatures, for solid-bond formation during tablet compression. However, a better understanding of theoretical and technical aspects of sintering process may allow the identification of its specific needs for pharmaceutical manufacturing such as a fabrication of controlled release polymeric matrix systems, more importantly an understanding of the ever-growing advancements in new technologies relating to sintering processes pharmaceutical systems.\textsuperscript{[2]}

**Sintering mechanisms**

According to the classical theory of sintering one can distinguish four stages of this process: adhesion, initial stage, intermediate stage and final stage. Adhesion occurs almost immediately after mechanical contact between particles. So the starting point is an assembly of contacting particles. The initial stage of sintering corresponds to the period during which the inter-particle contact area increases from 0 to 0.2 of the cross-sectional area of the particle and neck size ratio \(X/D\) increases from 0 to 0.1 (Figure 1).

\[D = \text{cross-sectional area of the particle}; \ X = \text{neck size}.\]

The main driving force for sintering is the reduction of surface energy of the particles as result void-space shrinkage, and the consequent decrease in total surface area of the compact.

\[\text{Figure 1: Sketch of a model of the sintering of two particles.}\]
Therefore, from the thermodynamic point of view, sintering is a spontaneous process.\cite{3,4} If the melting points of the components of system are different, sintering may be facilitated at temperature above the melting point of the constituent with the lowest melting point. The presence of a liquid phase considerably increases the rate of diffusion. The major material-transport mechanism is called the heavy-alloy mechanism; it can be divided into three stages.

1) **The Rearrangement Stage**- In the rearrangement stage, densification is brought about by action of capillary pressure caused by the collapse of melt bridges between particles and by the rearrangement of solid particles sliding over each other.

2) **Accommodation Stage**- This stage is characterized by the solution reprecipitation process, commonly known as Ostwald ripening. It may be described as the growth of solid particles via a process of dissolution of smaller particles and their reprecipitation on the larger one as a result of the difference in solubility of small and large particles in the liquid phase. Densifications arising from the presence of pores produce very high stresses at the point of particle contact, which causes a marked increase in the solubility of the solid phase in the melt. Since the solubility of solid phase in the bulk is relatively low, material is transported away from the contact regions and reprecipitated in the bulk.

3) **The Solid-State Sintering Stage**- In many cases of liquid-phase sintering by the heavy-alloy mechanism, complete densification is achieved during the first two sintering stages. However, prolonged exposure of compacts to the sintering temperature may lead to solid-state sintering, which result 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.\cite{2}

Effect of sintering on pharmaceutical compacts

**Effect on Microstructures**

The structural changes within a compact during sintering can be broken down into several stages, some of which may occur simultaneously. Figure 2. Illustrate five different stages.\cite{5}
1. **Interparticle Bonding.** The transport of molecule at the point of particle contact leads to formation of physical bonding and grain boundaries. The initial bonding takes place rapidly.

2. **Neck Growth.** Continuing material transport result in the development of a distinct “neck” between particles. The strength of 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 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.

The effect of sintering on microstructure changes in Compritol®888 ATO matrices was investigated by Rao. Compact prepared by direct compression at room temperature and heated at 80°C for 1, 2 and 3 hours for sintering. As seen in Figure 3, the surface of the tablet is smoother after sintering. SEM micrographs of the surface of tablets after sintering show that a thin film-like structure cover the entire surface, indicating that heat treatment causes wax to melt, redistribute and coat drug and excipient particles, which result in pore rounding and pore shrinkage.^[6]
Figure 3: Scanning electron microscope images of a) unsintered and b) sintered tablet surfaces.

Scanning electron microscopy (SEM) provides valuable direct visual evidence of microstructural changes during sintering, although these results are only descriptive. Porosimetry allows quantitative measurement of structural changes in terms of mean pore size, total pore volume, and pore volume size distribution.[2]

Helium pycnometer (Ultra pycnometer 1000, Quantachrome Instruments, USA) used to evaluate changes in pore-size distribution of Eudragit RS matrices after heat treatment at 70°C. The result showed that the porosity of tablet before and after heat treating were 19 ± 6 and 12 ± 5 % respectively.[7]

Effects on mechanical strength
Rao BS[8] studied the effect of sintering on ethylene-vinyl acetate copolymer matrices, it shows that hardness of the tablet enhances with increase in temperature of sintering, these is probably due to the fusion of polymer granules or formation of welded bonds between the polymer particles. The effect of sintering on the tensile strength of ibuprofen compacts was investigated by Li[9] Table 1. shows the tensile strength of ibuprofen compacts with different initial apparent porosities before and after sintering for 24 hours at four different temperatures. Tensile strength of compacts increases with increasing temperature and this effect was more pronounced for compacts with a relative high apparent porosity.
Table 1: The tensile strength of Ibuprofen Compact after sintering for 24h.

<table>
<thead>
<tr>
<th>Packing Fraction</th>
<th>Initial Tensile Strength ($kgf/cm^2$)</th>
<th>Temperature (°C)</th>
<th>Final Tensile Strength ($kgf/cm^2$)</th>
<th>Change (%)</th>
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$1\ kgf/cm^2 = 9.8\times10^4\ Pa.$

Singh and poddar[3] studied the effect of sintering on wax for controlling release from matrix pellet of Theophylline prepared with various concentration of carnauba wax were sintered thermally at various temperature and durations ranging from 90°C to 120°C for 60 seconds to 240 seconds respectively in an oven. Sintered pellets had a packing property superior to that of unsintered pellet. The average percent hardness index of sintered pellet was 93 and 71 respectively which indicate that sintered pellet were harder than unsintered ones. Increasing the temperature and/or time of exposure to a particular degree during sintering boosted the hardness, because of fusion of wax particle or formation of welded bonds among the particles.

Effect on Dissolution Rate

Drug and polymer powder (ethylene-vinyl acetate copolymer) were mixed and compressed at room temperature The compressed fluffy matrices were kept at 60°, 70° and 80° for 1.5, 3 and 4.5 hours for sintering. The sintered tablet were characterized for their physical characteristic and evaluated for in vitro dissolution studies. The sintering time markedly affected the drug release properties from the matrices the release rate of Rifampicin from EVA 1408 matrices was inversely related to the time of sintering due to the increase in extent and firmness of sintering which compacts the mass further so that the drug release is affected. The drug release followed diffusive mechanism with first-order release kinetics. [5] Also Rao[8,10] reported the dissolution profiles of Rifampicin from Eudragit RL100 sintered matrix tablets for various times indicate that sintering time markedly affected the drug release.
properties of Eudragit RL100 matrices. This may be due to the increase in the extent and firmness of sintering which compacts the mass further so that the drug release is affected.

**Sintering in 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.[6] The method consisted of mixing drug and wax powder (Compritol® 888 ATO) along with lactose as diluent and talc as lubricant followed by direct compression at room temperature. The compressed fluffy 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 markedly affected the drug release properties of Compritol® 888 ATO matrices. It is notable 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 indicated that heat treatment caused the wax to melt and redistribute. This redistributed wax formed a network-like structure in which the drug along with lactose is entrapped. This particular formed 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.[3] 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 for controlled release at least 12 hours.

**Mucoadhesive Buccal Tablet System**

The sintering times 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 time of sintering 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.\textsuperscript{[11]}

**CONCLUSION**

In Pharmaceutical sciences, sintering has been described as the mechanism for the strengthening of the mechanical properties of consolidated pharmaceutical powder at elevated temperatures, for solid- bond formation during tablet compression. However, sintering has not experienced a broad application in pharmaceutical manufacturing, from the viewpoint of economy, a conventional high temperature sintering process 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 molecule to higher temperatures may cause thermal decomposition. However, a better understanding of theoretical and technical aspect of sintering process may allow the identification of its specific needs for pharmaceutical manufacturing such as the fabrication of controlled release polymeric matrix system. An understanding of the ever-growing advancements in sintering may lead to development of modern sintering processes to pharmaceutical system.

**REFERENCES**


