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Review Article

SINTERING TECHNIQUE IN PHARMACEUTICAL SCIENCES: A BRIEF REVIEW

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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.

KEY WORDS: 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.[1] 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[13], microwave

sintering[14], and laser sintering[15] are the more recent advances in sintering technologies. Historically, sintering is a process employed to fabricate parts for metals, ceramics, and glass.

THE SINTERING OF 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 virtually simultaneously. Five different stages[1] of sintering are illustrated in figure 1, 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.

The effect of sintering on the micro structural changes in ibuprofen (mp, 75-77.5°c) compacts was investigated by Li[2]. Compacts were prepared at a compression pressure of 215 kgf/cm^2(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.

Effects on Mechanical Strength

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 the tensile strength of ibuprofen compacts was investigated by Li [2] and the results are shown in table 1. The results show the tensile strength of ibuprofen compacts with different initial apparent porosities before and after sintering for 24h at four different temperatures. Tensile strength increased with increasing temperature and this effect was more pronounced for compacts with a relatively high apparent porosity.

Effect on Disintegration Time and Dissolution Rate

A tablet disintegrates in water when the forces exerted by the disintegrate overcome the binding forces within the tablet. The relative magnitude of these two forces determines how fast a tablet disintegrates (disintegration time). Pilpel and Esczobo [3] studied the effect of sintering on the disintegration time of acetaminophen and oxytetracycline tablets. They reported that tablets produced at a higher temperature exhibited greater tensile strength and longer disintegration time. The prolongation of disintegration time for tablets after sintering was also confirmed for ethyl amino benzoate by Ando et al.[4] They attributed this Increase to the enhanced tensile strength of the tablet after sintering.

Li investigated the effect of sintering on the tensile strength and disintegration time of ibuprofen tablets containing a "super-disintegrate," Ac-DI-Sol. Both the tensile strength of the tablets and their disintegration time increased after sintering. Comparison of the time courses for changes in these two properties during sintering showed that the increase in tensile strength leveled off in the early stages of sintering, but the prolongation of the disintegration of tablet disintegration after sintering could not be solely attributed to solid-bond formation between ibuprofen particles within the tablet. She postulated rather that the evaporation-condensation and sublimation-deposition of ibuprofen within the tablet during sintering may lead to the coating of Ac-Di-Sol particles with a hydrophobic layer of ibuprofen, thus interfering with the ability of this disintegrate to absorb water and effect fast disintegration.

The impact of sintering on the dissolution rate for single-component compacts was investigated by Danjo and Otsuka.[5] They reported that the dissolution rate for the 8-phenylbutazone compact decreased, but that for the barbital compact increased at sintering temperatures above 70^0C. They pointed out that the reduction in the specific surface area was responsible for the decrease in the dissolution rate for 8-phenylbutazone. Whereas crack formation in the compact as a result of crystalline-structure transition was given as the cause for the increase in the dissolution rate for barbital. This was further confirmed by the increase in the specific permeability of air into the barbital compacts after sinter

SINTERING IN CONTROLLED-RELEASE DOSAGE-FROM 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.[6] 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.[7] 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.

Kristoffersson and co-workers [8] 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 (37^0C) sintering technique was used to prepare ethylene-vinyl acetate copolymer matrices containing macromolecules, bovine serum albumin and tyrosine.[9] 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.

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. 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; [10] a decrease in drug-release rate due to curing has also been reported for products coated with acrylic-based polymer latex systems.[11]

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[12]) 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 for the design of controlled release dosage forms, sintering technique is one of them[16].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. More importantly, an understanding of the ever-growing advancements in new technologies relating to sintering as used in other technical fields [13-15] may lead to new applications of modern sintering processes to pharmaceutical systems.

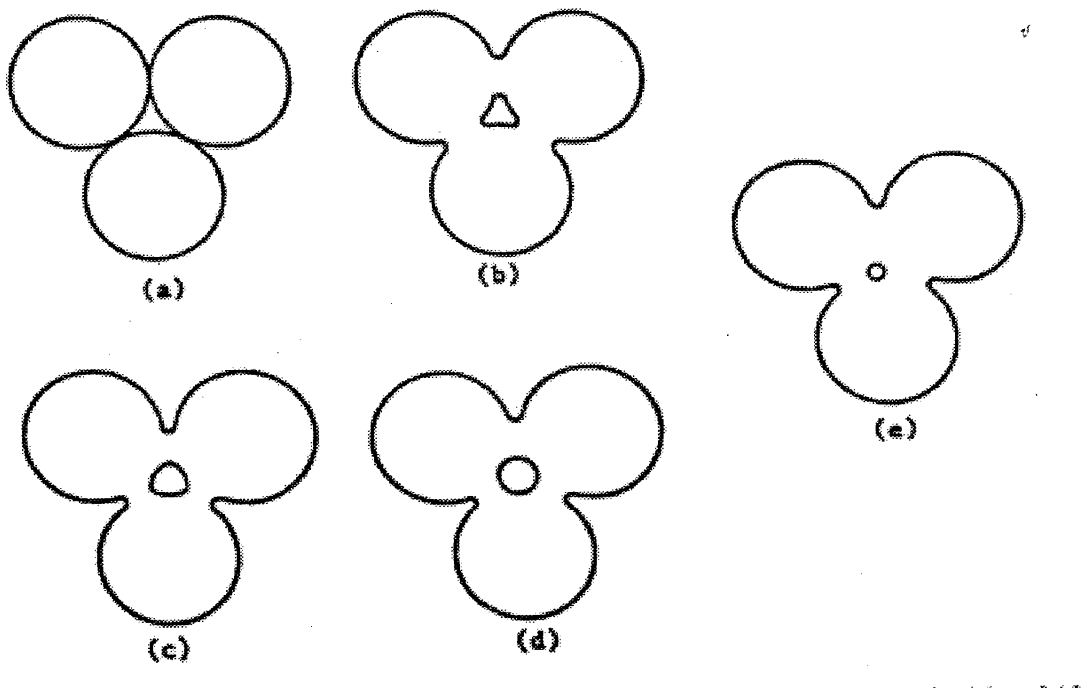

Figure-1: Three-sphere sintering model (a) Original points of contact; (b) Neck growth; (c) and (d) Pore rounding; (e) Pore shrinkage

Table-1: The Tensile Strength of Ibuprofen Compacts after Sintering for 24h.

Packing Fraction	Initial Tensile Strength (kgf/cm^2)*	Temperature (^0C)	Final Tensile Strength (kgf/cm^2)*	Change (%)
0.78	1.58	40	2.35	48.7
		50	3.33	110.8
		60	4.84	206.3
		70	6.48	310.1
0.84	4.73	40	6.03	27.5
		50	7.23	52.9
		60	8.97	89.6
		70	10.84	129.2
0.90	14.13	40	15.47	9.5
		50	15.67	10.9
		60	16.65	17.8
		70	18.14	28.4

*$1kgf/cm^2 = 9.8 \times 10^4$ Pa.

REFERENCES

1. Klar, E., Powder Mettalurgy, Applications,Advantages, and Limitations, American society for Metals, Metal park, OH, 1983
2. Li, J. H. The Sintering of Ibuprofen, Ph.D. Dissertation, Purduc University, west Lafayette, IN, 1990
3. Pilpel, N., and esezobo, S., J., Pharmacol., 29;389-392(1977).
4. Ando, T., Kanaya, Y., and Asahina. K., Chem. Pharma. Bull., 33:3440-3446(1985).
5. Danjo, K., and otuska, a., chem... Pharma. Bull., 36:763-768(1988).
6. Farhadieh, B., Bordkin, S. and Buddenhagen.J.D., J. Pharma. Sci., 60:209-212(1971).
7. Rowe. R. C., Elworthy. P. H. and Ganderton. D., J. Phrm. Pharmacol., 25;12P-16P(1973).
8. Kristoffersson, E., Salomies. H., and Rissanen, U., Farm.Notisbol. 86:45-50(1976).
9. Eaves, T., Walker, S. E., and Ganley, J. Pharm. Sci ., 73:1034-1037(1984).
10. Aquacoat Handbook, FMC Corporation, Philadelphia, 1982.
11. McPhillips. A. M., and Sakr,A. A., Pharm. Res.,11:S-168(1994).
12. Harris. M., Ghebre-Sellassie. I., and Nesbitt, R. U. Pharm. TECHNOL., 10:102-107(1986).

13. Kong, P. C., Heat Transfer Div.Proc(Am. Soc. Mech. Eng.), 161:9-149(1991).

14. Katz, J. D.,Annu. Rev. Mater. Sci., 22:153-170(1992).

15. Bourell, D. L., Mareus, H. L., Barlow,J. J., Int. J. Powder Metall., 28:369-381 (1992).

16. Bhanja Satyabrata, Mohanty Chandan; Design and in vitro evaluation of mucoadhesive buccal tablets of perindopril by sintering technique; IJPRF; vol.2, no.3, pp1810-1823, july-sept 2010.

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