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APPLICATIONS OF SINTERING TECHNIQUE FOR EXTENDED DRUG DELIVERY-A REVIEW

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ABSTRACT

Sintering is primarily defined in the pharmaceutical sciences as a mechanism for strengthening the mechanical characteristics of pharmaceutical powders at elevated or high temperatures. The drug release characteristics of sintered tablets will be affected by the sintering condition. In terms of sintering, the shaping of solid bonds inside the powder bed during the compression process has also been investigated. In order to investigate the impact of heating on the mechanical properties of various pharmaceutical powders, the concept of sintering was used. The sintering approach has been applied for the production of matrix tablets for sustained release and drug retardation from different systems. This review highlights the mechanism of sintering technique and recent research work reported on sintering technique.

Keywords: Sintering, Heating, Sustained release, matrix tablets, solvent casting method

INTRODUCTION

By applying heat or pressure, or by exposing the adjoining particle surfaces to various solvents, sintering entails bonding of the nearby particle surfaces in a mass of powder, or in a compact [1]. The main principle or mechanism involved in sintering is reduction of total surface area of the compact [2]. This process of sintering is used for production of sustained release matrix tablets for delaying the release of drug [3]. The heating of the powder compact after prepared at ambient temperature without any external pressure applied during the process is known as conventional sintering. This process can be done by either thermal (physical) and solvent casting (chemical) methods, by the implementation of this techniques cross linking will increase between the particles in a polymer. This approach can be modified by heating the compact in the potentiality of transient or stable liquid phases, or even under pressure [4]. The most recent advancements in sintering technology include spark plasma sintering, microwave sintering, and high frequency induction heat sintering [5].

METHODS OF SINTERING: 1. Physical Method - Thermal sintering

2. Chemical Method - Acetone saturation

1. Physical Method:

It is defined as the exposing the dosage form at a different temperature which results in increased cross linking in the dosage form due to rearrangement of polymer molecules at a high temperature [6].

Thermal sintering:

In this technique the dosage form is exposed to above the glass transition temperature of polymers then, the amount of polymer present on the surface of the dosage form will deform, there by the particles of polymer undergo fusion. But, this method is only applicable for the drugs which are thermostable [7].

2. Chemical Method:

This method involves exposing of dosage forms to a cross linking solvents like acetone, glutaraldehyde, formaldehyde for different time intervals [1].

Acetone Saturation:

This sintering technique is applicable for compressed tablets or punched tablets. In this technique acetone is filled in the lower chamber of the desiccator and kept for saturation. Wire mesh is placed on the lower chamber and the punched tablets in a petri plate are placed over it. Then the desiccator is made airtight by closing the lid with help of wax. Acetone vapours from the desiccator penetrate the tablet pores, causing the polymer particles' surfaces to become solubilized. This results in the fusion of particles bringing about sintering. The sintered tablets are removed from the desiccator, kept at room temperature for 24 hours and stored in a vacuum desiccator fused with calcium chloride until further use.

RECENT RESEARCH WORK REPORTED ON SINTERING TECHNIQUES

1. *Chandan Mohanty et.al.* 2021 The objective of their research was to observe how the sintering technique affected the development of a controlled-release dosage form. In healthy male New Zealand rabbits (n=3), the pure atenolol drug solution, as well as designed unsintered and sintered controlled release matrix tablets were examined for in-vivo pharmacokinetics. In comparison to unsintered tablets and pure drug, the elimination half-life ($t_{1/2}$) and elimination rate constant (K_E) of the drug in sintered matrix tablets increased and decreased respectively, demonstrating prolonged and controlled systemic availability of the drug. In rabbits, the examined sintered matrix tablets showed a significant improvement in bioavailability due to prolonged plasma residence and were able to maintain a consistent plasma level of atenolol for up to 24 hours [8].
2. *Chandan Mohanty et.al.* 2021 evaluated in-vivo pharmacokinetics of sintered floating matrix tablets of nicardipine hydrochloride in comparison to pure nicardipine drug and unsintered gastro retentive floating tablets in healthy male New Zealand rabbits. In contrast to unsintered tablets and pure drug, there was an increase in the elimination half-life and a decrease in the elimination rate constant of the drug in sintered matrix tablets, suggesting the drug's prolonged and controlled systemic availability in the biological system [9].
3. *P Madhuri et.al.* 2020 designed thermally sintered sustained-release tablets of bosentan monohydrate by wet granulation and direct compression methods and observed how sintering parameters affect in-vitro dissolution, friability, and hardness. The tablets were sintered at three distinct temperatures: 50°C, 60°C, 70°C for duration of 1 hour, 2 hours, and 3 hours. The drug's release rate was found to be inversely related to both sintering temperature and sintering time. The tablets sintered at 60°C and 70°C had the optimum retardation of drug release. The hardness of sintered tablets increased as the sintering temperature and duration increased, whereas the friability of sintered tablets reduced as the sintering time increased [10].
4. *Rajesh Akki et.al.* 2020 formulated thermally sintered floating tablets of amoxicillin trihydrate using carnauba wax as-sintered polymer and evaluated the effect of sintering on drug release and floating. Sintering at a temperature of 50°C and exposure time of 4 hrs improved the floating characteristics and the floating time. The drug release was retarded and extended by using the sintering technique [11].
5. *Munagala Gayatri Ramya et.al.* 2020 designed and assessed thermally sintered floating tablets of atenolol using and investigated the effect of sintering on PEO polymer. Formulated tablets were exposed to different temperatures i.e. 400, 500 and 600°C at various time intervals of 1, 2, 3 and 4hrs in a hot air oven. Sintering influenced the floating time and dissolution characteristics, according to the results of the study. Polymers' effectiveness in extending the release of drug is influenced by sintering time and temperature [12].
6. *Latha K et.al.* 2018 formulated cefpodoxime proxetil sintered floating tablets using locust bean gum as a release control material. The resulting cefpodoxime proxetil floating tablets were subjected to a sintering technique, which involved exposing the tablets to acetone vapours to promote cross-linking within the polymeric structure. Formulation which contained locust bean gum and drug in the ratio 0.3:1.0 and camphor (10 %w/w) and subjected to acetone vapours for 6 hours, exhibited optimal floating qualities and a better dissolving profile, with 97.3% dissolution in 12 hours. The drug release followed zero-order kinetics with an anomalous transport mechanism [13].
7. *Satish Polshettiwar et.al.* 2018 formulated atenolol floating SR matrix tablets using tragacanth, Eudragit S 100 and evaluated the outcome of microwave sintering on drug release from polymer matrix tablet. The results of in-vitro drug release studies showed that the optimized formulation could extend drug release for 24 hours [14].
8. *Collins O Airemwen et.al.* 2017 formulated and evaluated metronidazole controlled release matrix tablets using *Irvingia gabonesis* gum at 10%w/w concentration as a binder by thermal sintering technique. The tablets were subjected to thermal sintering at 50°C and 60°C for 1, 3 and 5hrs. An increase in sintering temperature and duration increased tablet hardness, and decrease in percentage friability. The optimum drug release retardation was observed in tablets sintered at 60°C for 5 hours, according to the in-vitro dissolution profile of the produced controlled release matrix tablet containing metronidazole [15].
9. *Samra Rumman et.al.* 2017 developed tapentadol hydrochloride extended-release tablets by thermal sintering technique using Eudragit RL-100 as sustaining polymer, sintering waxes-stearic acid and carnauba wax. The prepared tablets were exposed to different temperatures 400°C and 600°C at three different time durations of 1, 2 and 3 hrs. In 12 hours, the drug release from the optimised formulation F17 with stearic acid and carnauba wax, sintered at 600°C for 2 hours was found to be 100.38%, the drug release followed zero-order, the mechanism was found to be super case II transport [16].
10. *Panicker et.al.* 2017 formulated and evaluated sintered matrix tablets of metformin hydrochloride using Eudragit L 10055 and HPMCK 4M. Tablets were sintered by exposing to vapours of acetone for 1.5, 3 and 4.5 hrs. The results

showed that tablets sintered for 4.5 hours were harder and released the drug more slowly than tablets sintered for 3 hours. Eudragit L 100 55 was found to be a more effective rate-controlling polymer than HPMC K4M [17].

11. *Pentewar R S et.al.* 2016 investigated the release characteristic of sotalol hydrochloride matrix tablet prepared by direct compression method using different concentrations of various retarding polymers and sintered at the various time point and temperatures using thermal sintering and microwave sintering techniques. The formulations Fs3, Fs6 were subjected to thermal sintering at 80°C for 5 hrs and microwave sintering at 100 watts for 6 min. showed 96.31%, 95.41 % and 97.21 %, 97.68 % release profiles in 18 hrs respectively [18].
12. *Monica RP Rao et.al.* 2015 sintering technique was applied to matrix tablets of itopride hydrochloride for sustaining the release using Eudragit L-100 and carnauba wax. The effect of sintering on % drug release, porosity and contact angle was studied using a three-factorial design. From the end results, it was observed that the drug release was decreased from the sintered matrix tablets compared to the unsintered tablets [19].
13. *Raju Manda et.al.* 2014 formulated and evaluated non-erodible polymer matrix tablets of isoniazid using the sintering technique. According to the *in-vitro* dissolution results, Eudragit RL 100 exhibited the potential to retard the drug from being released. In comparison to the other formulations, E4 sintered at 4.5hrs showed a higher retardant capacity and followed the Higuchi diffusion model [20].
14. *M V Srikanth et.al.* 2012 developed thermally sintered floating tablets containing propranolol HCl and evaluated the effect of sintering on drug release and buoyancy using an experimental design (Box Behnken). Polymer quantity, sodium bicarbonate concentration, sintering temperature, and sintering duration were used as independent variables, whereas floating lag time, and t95 were used as dependent variables. The end results of the experiments show that as the time of exposure to various temperatures increased, the floating lag time decreased, the overall floating time increased and slowed in vitro drug release [21].
15. *Vaibhav Bhamre et. al.* 2011 designed and evaluate the effect of processing methods, sintering conditions and drug release of stavudine sintered matrix tablet prepared by direct compression method using a combination of (9–13%w/w) Compritol 888 ATO and (22 -33%w/w) Eudragit RS 100. In contrast to the unsintered tablet, the sintered tablet had more strength and the drug release was also prolonged [22].
16. *Patel DM et. al.* 2011 evaluated how sintering conditions affected matrix production and drug release from polymer matrix tablets. The utilization of a microwave oven for the process of sintering to produce more uniform heat distribution while reducing the length of time necessary for sinterings. Compared to conventional hot air oven sintering, effective sintering could be achieved in only 8 minutes. The tablets containing propranolol hydrochloride and the Eudragit S-100 were manufactured and sintered for varied time periods in a microwave oven at 540 watts, 720 watts, and 900 watts power [23].
17. *B. Seshagiri et. al.* 2011 developed hydrodynamically balanced tablets for glipizide using HPMC K4M and HPMC K15M polymers and the solvent casting sintering process. Various batches of glipizide matrix tablets were manufactured utilising the direct compression method with varied polymer concentrations and sintering time periods under a saturated acetone vapour system. In accordance to the results, formulations had a floating lag time of less than 5 minutes and a floating time of more than 22 hours. The matrix tablets containing HPMC K15M, which were exposed to acetone vapours for 4.5 hours, demonstrated 69.17% drug release in 12 hours and better control of drug release than the marketed formulation, according to the *in-vitro* drug release studies (USP XXIII). The data from the in-vitro release was analysed using mathematical equations, and it was determined that glipizide released from the tablet followed the Peppas model with non-Fickian diffusion [24].

Conclusion:

Sintering is reported in pharmaceutical research as a technique for enhancing the mechanical characteristics of pharmaceutical powders at increased temperatures, solid-bond development during compression of tablet, and thermo-curing of polymer-latex coatings. Sintering is not widely used in pharmaceutical manufacturing due to the prolonged time required for sintering, a typical high-temperature and sintering technique is substantially less adapted than a tabletting process for powder consolidation from an economic perspective. Furthermore, prolonged exposure to higher temperature of some compounds may result in thermal degradation. Greater knowledge of the features of the sintering process enables the understanding of its specific requirements in the manufacture of controlled-release matrix systems.

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