

Thermal Sintering: A Novel technique in Formulation of Controlled Release Dosage form

¹P.Madhuri, ²Dr. K.V Ratnamala

Department of Pharmaceutics,
Rbvrr Women's College of Pharmacy, Barkathpura, Hyderabad.

Abstract: Sintering is defined as the thermal treatment of a powder or compact at a temperature below the melting point of the main constituent, for the purpose of increasing its strength by bonding together of particles. The sintering concept in pharmaceutical science is relatively recent, but research interests relating to this process have been growing. 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 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. Controlled release oral dosage forms were developed by sintering the polymer matrix by exposing to temperature above glass transition (T_g) point of the polymer. In the application of thermal sintering technique to the formulation 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.

Keywords: Thermal sintering, Glass transition point, Controlled release, Matrix tablets

Introduction:

Exploration of the Thermal sintering technique in the pharmaceutical sciences is relatively recent, but research interests relating to this process have been growing. Thermal 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. 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 advancements in Thermal sintering technologies (Luk et al., 1996; Chandan Mohanty et al., 2018). The sintering process has been used for the formulation of sustained release matrix tablets and for the stabilization of the drug permeability of film coatings derived from various pharmaceutical lattices (ChandanMohanty, 2011; BhanjaSatyabrata et al., 2010).

SINTERING METHODS

There are two types of sintering methods, namely thermal sintering method (heat treatment) and solvent casting method (acetone saturation method) (Amol R.Bodke et al., 2017).

Acetone saturation method

The punched tablets were exposed to acetone vapour in desiccators. The lower end of the desiccator was filled with acetone, closed and kept aside for saturation. After saturation the punched 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 (Dhiraj G et al., 2013). 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 an ambient temperature to evaporate adhering free acetone for 24hr and were finally dried in a vacuum desiccator over fused calcium chloride for 24hr(B. Sreenivasa Rao et al., 2014). Further stored in desiccators for future studies.

Thermal sintering method

Thermal sintering technique is a method of heating polymer 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 exposure of the polymer matrix to the temperature above the glass transition temperature of the polymer. The entrapment of drug particles in the polymeric matrix leads to controlled release of drug (Amol R. Bodke et al., 2017). As compared to the Acetone saturation method, the thermal sintering method have the following Advantages: Decrease of processing time, no need of solvent removal, elimination of shrinkage and no unwanted effect on the macromolecule because of solvent exposure (Luk et al., 1996).

However this method can be applied 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 high temperatures.

The Sintering of Pharmaceutical Compacts Effect on Microstructures

The alteration in the microstructures of a pharmaceutical compact during sintering is the prevailing factor in determining the release rate of the drug. The structural changes within a compact during sintering can be observed in following stages ChandanMohanty, 2011;BhanjaSatyabrata et al., 2010).

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 bindings 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.1: Three-sphere sintering model (a) Original points of contact; (b) Neck growth; (c) pore channel closure (d) Pore rounding; (e) Pore shrinkage (Tejaswini S Pawatekar et al., 2014).

SINTERING MECHANISM

Sintering in single solid phase

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 (Luk CL et al., 1996; Chandan Mohanty et al., 2018; Amol R. Bodke et al., 2017).

1. Evaporation and condensation

The gradient in the chemical potential ($\mu-\mu_0$) between the convex surface and the adjacent flat surface creates a vapour-pressure gradient that can be described by Gibbs-Thomson equation

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

Where

R is the gas constant.

T is the absolute temperature.

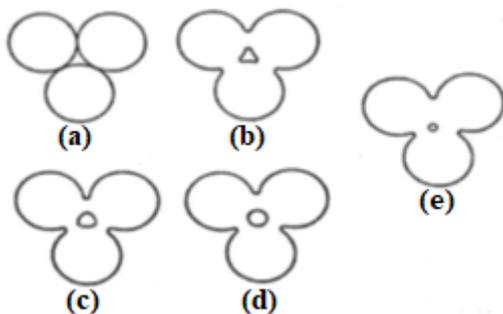
P is vapour pressure over the stressed (curved) surface.

P₀ is the Vapour pressure over the unstressed (flat) surface.

The differences in vapour pressure causes material to evaporate 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, 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

Sintering in liquid phase occurs by the following material transport stages:

1. 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.

2. 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 (Luk CL and Jane HLet al., 1996; Chandan Mohanty et al., 2018; Amol R. Bodke et al., 2017).

3. 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

1. Effect on Hardness:

The increase in points of contact and welded-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 (Kondaiah A et al., 2002). They reported that the hardness increased when the temperature and time increased, this may be due to the strong bonding of EVA particles at higher temperature. The hardness depends on sintering time as well as sintering temperature, this was studied (Sreenivasa B Rao et al., 2014). The studies indicate that as the power of microwave sintering increases hardness increases probably due to the fusion of polymeric granules or formation of a welded bond between particles.

2. Effect on porosity and wettability:

The duration of sintering also affected the porosity, the tablet sintered for less time shows more porosity as compared to the tablet sintered for more time (ChandanMohanty, 2011; Patel DM. et al., 2002) 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 the tablet. This higher contact angle also contributes to the retardation of drug release from matrix tablet.



Fig.2 Photoimages showing contact angle of water with (a) Unsintered tablet. (b) Sintered tablet (Patwekar T S et al., 2014)

3. 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 EudragitRL100 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. 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. 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 (Monica Rao et al., 2009)

4. Effect on stability:

The stability studies shows that there was no effect found on the sintered matrix tablet placed at different storage condition for some period of time (Vaibhav Bhamre et al., 2013).

Controlled release dosage form fabrication

1. 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 (Monica Rao et al., 2009). The method consisted of mixing drug, wax powder (Compritol® 888 ATO), lactose as diluent and talc as lubricant followed by direct compression at room temperature. The compressed tablet 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 observed 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.

2. 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 (Singh R et al., 2007). 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.

3. 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 8hrs sustained drug release (98 %) with desired therapeutic concentration. The drug release followed diffusive mechanism with first order release kinetics (Satyabrata B et al., 2010).

4. 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 (Patwekar T S et al., 2014). 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 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; (Patwekar T S et al., 2014) a decrease in drug-release rate due to curing has also been reported for products coated with acrylic-based polymer latex systems. 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) (Patwekar T S et al., 2014) 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 (Azarmi S. et al., 2005).

RECENT RESEARCH WORK REPORTED ON SINTERING TECHNIQUE

1. Farhadieh. B et al., 1971 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 observed the enhancement of drug release after sintering.
2. Kristofferson. E et al., 1976 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.
3. Carli F and Simioni L et al., 1981 have 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.
4. A. Kondaiah et al., 2002 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.
5. B. Seshagiri et al., 2011 designed Hydrodynamically Balanced Systems for Glipizide with sintering technique. It is an approach to increase the gastric residence time of drugs in stomach. This system is designed for site specific oral drugs with low bulk density than gastric fluids so as to buoyant the dosage form in stomach to increase the residence time of the drug. In the present investigation, HPMC K4M and HPMC K15M polymers were used by solvent casting sintering technique. The study reveals that the formulations of HBS of Glipizide formulated has exhibited a floating lag time of less than 5 minutes and floating time of more than 22 hrs. The results indicate that gas powered Hydrodynamically Balanced Tablets of Glipizide containing HPMC K15M provides a better results for controlled release action and improved bioavailability.

6. Sameer Shafi et al., 2011 prepared the sustained release (SR) sintered matrix tablets of Diltiazem hydrochloride by trituration method using 4% and 8% HPMC K4M and HPMC K15. The drug release study was carried out in USP XXI model. 900ml dissolution medium of 0.1N HCl (pH 1.2) was used for the first 2 hours and pH 6.8 phosphate buffer for remaining 8 hours. The revolutions at 50rpm and temperature at $37\pm 1^\circ\text{C}$ were maintained. Formulations with HPMC K exhibited sustained drug release profiles with maximum sustaining effect when compared with unsintered formulation in about 8 hours by using sintering.

7. Uhumwangho MU et al., 2011 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.

7. Katariya Chaitali Ramesh et al., 2012 have formulated sustained release matrix tablets of lamivudine by using sintering technique. Two hydrophobic polymers Eudragit RL 100 and Eudragit RS 100 were used. In this study the effect of the thermal and solvent treatment on drug release, tensile strength was studied. Increasing the sintering duration increase in the sustained release and also increase in hardness of tablet. During sintering of tablets, polymer particle transform from glassy state to rubbery state and redistributed to entangle the drug particles, leading to drug release retardation. By selecting proper polymer concentration, sintering temperature and duration the effective sustained release formulation of lamivudine were prepared. The drug did not undergo degradation during sintering. The solvent treatment gives more sustained release of drug compare to thermal treatment.

8. Venkata Srikanth Meka et al., 2012 have formulated thermal sintering floating tablets of Propranolol HCL and studied the effect of Sintering conditions on drug release and vitro buoyancy properties. A hydrophilic polymer polyethylene oxide, was selected as a sintered polymer to retard the drug release. The formulations were prepared by a direct compression method. Propranolol HCL, PEO, sodium bicarbonate and magnesium stearate were utilized. As the sintering temperature and time of exposure increased, floating lag time was found to be decreased, total floating time was increased and drug release was retarded. An optimized sintered formulation (sintering temperature 50°C and time of exposure 4 h) was selected, based on their drug retarding properties.

9. Vaibhav Bhamre et al., 2013 have prepared and evaluated sintered matrix tablets of Stavudine by using Eudragit RS100 & Compritol 888ATO with direct compression method. Also studied effect of different three temperatures on stability of sintered tablets. Storage condition & period of storage affect stability Stavudine sintered tablet.

10. M. Parvathi et al., 2013 have formulated and evaluated sintered matrix tablets of Matrix tablets are preferred to sustain drug activity and reduce frequency of administration. Diabetes is a haunting threat for life. So, metformin HCL matrix tablets paves the way to increase the quality of life. The term sintering means fusion of particles or formation of welded bonds between particles of polymer. The SR oral dosage forms can be developed by sintering the polymer matrix by exposing to temperature above glass transition point of the polymer or exposing these matrix systems to solvent vapours.

11. Bhagwat RR et al., 2014 have investigated the release characteristics of matrix granules consisting of hydrophobic (i.e waxy) material and Verapamil hydrochloride for sustained release application using thermal sintering technique. The use of sintering technique causes the polymer to extend the release of drug from formulation depending upon the temperature and time of exposure.

12. Meka Venkata Srikanth et al., 2014 have investigated on the applicability of thermal sintering technique for the development of gastric floating tablets of propranolol HCL. Formulations were prepared using four independent variables, namely (i) polymer quantity, (ii) sodium bicarbonate concentration, (iii) sintering temperature and (iv) sintering time. Floating lag time and t_{95} were taken as dependent variables. From the drug release studies, it was observed that drug retarding property mainly depends upon the sintering temperature and sintering duration. Optimized formulation was stable at accelerated conditions for a period of six months. These tablets were evaluated for in vivo buoyancy studies in humans for both fed and fasted states and found that gastric residence time of the floating tablets were enhanced by fed stage but not in fasted state.

13. Monica RP Rao et al., 2015 have prepared sustained release matrix tablets of Itopride by using hydrophobic polymers and study of sintering technique in modulating drug release. Carnauba wax and Eudragit L 100 were used as release retarding polymers. A 3² optimization design was applied so as to achieve tablets with optimum drug release. Drug release mechanism was found to be diffusion-erosion because of polymer-wax combination. Optimization batches were studied for porosity, contact angle and tensile strength so as to understand effect of sintering on abovementioned properties. Wettability and porosity was decreased with increase in contact angle was evident for sintered tablets.

14. Lakshmi PK et al., 2015 have formulated and evaluated sintered matrix tablets of Lamotrigine using controlled release natural and synthetic polymers such as HPMC K4M, HPMC K15M, HPMC K100M, acacia, guar gum and xanthan gum polymer. Based on the study it can be concluded that sintering technique enhances the extended release of the drug with low concentrations of polymer and it would be a cost effective method.

15. Chandan Mohanty et al., 2015 have formulated Atazanavir Sulphate Gastro Retentive Floating Matrix Tablets using sintering technique. The tablets were prepared by direct compression method using EC N100 and HPMC K100 as polymer. The release rate of the drug decrease with the sintering temperature and the sintering time. The hardness was increased with increase in sintering

temperature and duration of sintering; but friability of tablets was found to be decreased with increasing sintering time. Floating lag time was inversely proportional to the sintering temperature and sintering time, whereas total floating time was directly proportional to the sintering temperature and sintering time. The formulation F2 sintered at 600 for 3 h was selected as an optimized formulation based on the drug release properties and the optimized formulation followed Fickian diffusion mechanism with Korsmeyer-Peppas release kinetics.

16. ChandanMohanty et al., 2016 have prepared thermally sintered floating matrix tablets of Nicardipine HCL and studied the effect of sintering conditions on in-vitro dissolution study, in-vitro buoyancy properties, hardness and friability. The tablets were prepared by direct compression method using HPMC K100M as matrix forming polymer and sodium bicarbonate as gas generating agent. The results revealed that increasing the temperature or time of exposure to a particular temperature often decreased the release rate of the drug. By using sintering technique floating lag time and total floating time of tablets was found to be decreased and increased respectively, with increase in the sintering temperature and sintering time. In addition the hardness of the sintered tablets was increased with increase in sintering temperature and duration of sintering, whereas friability of tablets was found to be decreased with increasing sintering time. An optimised formulation F2 sintered at 70°C for 3hr was selected based on their drug retarding properties and comparatively low proportion of polymer.

17. Satish Polshettiwar et al., 2016 have formulated Carvedilol phosphate matrix tablets by using polymers like HPMC K4M, Eudragit L 100, Guar gum and Sodium bicarbonate, Citric acid were utilized in the formulation. Tablets were prepared by direct compression method. On thermal sintering, it was found that F6, L2, I2 and H4 gave better results compared to other formulations. Their results revealed that sintering caused decrease in drug release as compared to unsintered tablets. Thus stability results prove that the formulation was stable at accelerated condition.

18. Samra Rumman et al., 2017 formulated Tapentadol Hydrochloride sintered tablets were using sustaining polymer-eudragit RL-100, sintering waxes-stearic acid and carnauba wax, disintegrating agent-microcrystalline cellulose, glidant-talc and lubricant-magnesium stearate by direct compression method. The pre compression and post compression parameters results were found to be within the limits. The drug release from optimized formulation (F17-Tapentadol Hydrochloride with stearic acid and carnauba wax sintered at 600C for 2 hours) was found to be 100.38% in 12 hours. Stability studies revealed that optimized formulation was stable at 40±2°C and 75±5% RH for 3 months. Thus, the developed F17 formulation by sintering technique has great future potential to be prepared as sustained release tablets.

19. Collins O Airemwen et al., 2017 formulated sustained release matrix tablets of metronidazole using sintering technique. Controlled release metronidazole matrix tablets were prepared by wet granulation technique using Irvingiagabonesis (IG) gum as binder. Prepared tablets were kept for thermal sintering. There is increase in tablet hardness with increase in sintering temperature and time while the percentage friability decreased. The in-vitro dissolution profile of the prepared controlled release matrix tablet of metronidazole showed that the optimum drug release retardation occurred in tablets sintered at 60 °C for 5hr. The study has revealed that IG gum at a concentration of 10% w/w possesses good binding properties and can be utilized in the formulation of controlled release matrix tablets of metronidazole by thermal sintering.

Future prospective

Day by day there is increase in need of novel technology in drug delivery system. This thermal sintering technology fulfill demand of novel drug delivery system. By exploring the use of sintered technique in various dosage forms it may aids in driving the growth of the pharmaceutical market.

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. Sintering technique adds to the effectiveness of polymers to extend the drug release from the formulation depending upon the temperature time and duration of sintering. The prolonged exposure of some drug molecules to higher temperatures may lead to thermal decomposition. Only the drugs with higher melting points are chosen. Polymer should have higher melting point than main constituent. A better understanding of the theoretical and technical aspects of the sintering process helps in the formulation of controlled-release polymeric matrix systems.

References:

Amol R. Bodke, Smita S. Aher, R. B. Saudagar (2017). A review on sintering technique in Pharmaceutical Sciences; *International Journal of ChemTech research*; **10(5)**: 210-215.

BhanjaSatyabrata, Ellaih P, MohantyChandan, K V R Murthy, P Bibhutibhusan, PadhySudhir Kumar (2010). Design and in Vitro Evaluation of Mucoadhesive Buccal Tablets of Perindopril Prepared by Sintering Technique; *International Journal of Pharma TechResearch*.**2(3)**:1810-1823.

Bhagwat RR, IS Vaidya (2014), Formulation of Verapamil Hydrochloride Matrix Granules by Sintering Technique and its Evaluation. *Global Journal of Medical research*. **14(1)**: 1-4

Carli F and Simioni L (1981). *Int. J. Pharm. Tech Prod. Mfr.* **2**:23-28.

ChandanMohanty (2011). Sintering technique in pharmaceutical sciences: a brief review; *International Journal of Pharmacy and Technology.* **3(1)**:799-806

Chandan Mohanty, K V Subrahmanyam, Tapan Kumar Jena, Devarashetti Sreekanth (2015). Use of Sintering Technique to Sustain the Release of Atazanavir Sulphate from Gastro Retentive Floating Matrix Tablets. *American Journal of Pharmtech Research.* **2(3)**: 498-505.

ChandanMohanty, K V Subrahmanyam, Abdul Saleem Mohammad, Tapan Kumar Jena (2016). Thermal Sintering Technique: A Novel Strategy Used in the Design of Gastro Retentive Floating Matrix Tablets of Nicardipine HCl and Its Evaluation. *International Journal of Pharma Research and Health Sciences.* **6(1)**: 001-021

Collins O Airemwen, Michael U Uhumwangho, Gift E Ofolo (2017). Formulation of Sustained Release Matrix Tablets of Metronidazole using Sintering Technique. *Journal of Science and Practice of Pharmacy.* **4 (1)**: 152-160

Chandan Mohanty, K V Subrahmanyam, Pasupuleti Chandana, Anthati Swathi (2018) Applicability of sintering technique in Fabrication of controlled release dosage forms. *International Journal of Innovative Pharmaceutical Sciences and Research*; **6 (05)**:2347-2154.

Dhiraj G. Savant, Amit S. Patil, Roshan P. Vaishnav, S. H. Majumdar (2013). Formulation and evaluation of matrix tablet of Cefpodoximeproxetil by sintering technique; *American Journal of Pharmtech Research.* **3(5)**: 338-349.

Farhadieh. B, Borodkin. S and Buddenhagen. J. D (1971); *J. Pharma sci.* **60**: 209-212.

Kristoffersson. E, Salomies. H and Rissanen. U (1976). *Farm. Notisbl*; **86**: 45-50.

Kondaiah A, Prakash K (2002). Design of controlled released non-erodible polymeric matrix tablets of Theophylline using sintering technique. *Indian Journal of Pharmaceutical Sciences.* **64**: 239-243.

Katariya Chaitali Ramesh, Goli Ravali, Chaudhari Shilpa Praveen (2012), Formulation development and *In vitro* evaluation of sustained release matrix tablets of Lamivudine. *International Research Journal of Pharmacy.* **3(12)**: 171-174

Luk CL and Jane HL (1996), Sintering in pharmaceuticals; *Encyclopedia of Pharmaceutical Technology.* (In J. Swarbrick and J. C. Boylans eds), Marcel Dekker, New York, **14(2)**: 87-101.

Lakshmi PK, Husnien Ali M (2015), Formulation and Evaluation of Sintered Matrix Tablets of Lamotrigine. *Indo American Journal of Pharmaceutical Sciences.* **2(11)**:1518-1524.

Meka VS, Ambedkar SS, Sreenivasa NR, Janaki BR, VenkataRMK (2013). Thermal sintering: a novel technique used in the design, optimization and biopharmaceutical evaluation of propranolol HCl gastric floating tablets. *Drug Development and Industrial Pharmacy.* **40(1)**: 33-45.

Monica Rao, A Ranpise, Sameer Borate and Kaushik Thanki (2009). Mechanistic Evaluation of the Effect of Sintering on Compritol® 888 ATO Matrices; *AAPS PharmSciTech.* **10(2)**: 355-360.

Parvathi M, Prathyusha P, Raveendra reddy J (2013). Formulation and evaluation of sintered matrix tablets of metformin hydrochloride and its comparison over unsintered matrix tablets. *International Journal of Research in Pharmacy and Chemistry.* **3(3)**: 521-530.

Patwekar T S, Rode R B (2014). A Review on Sintering Method in Pharmaceutical Sciences, *Asian Journal of Pharm.Tech.* **4(2)**: 106-109.

Patel DM, Patel BK, Patel HA, Patel CN (2002). Design of controlled release non-erodible polymeric matrix tablet using microwave oven-assisted sintering technique. *Journal of controlled release.* **84**: 99-114.

RP Rao, Shivpuje S, Godbole R, Shirsath C (2016). Design and Evaluation of Sustained Release Matrix Tablets Using Sintering Technique. *International Journal of Pharmacy and Pharmaceutical Sciences.* **8(2)**: 115-121.

Samra Rumman, T. Vijay Kumar, Md. Munawar Ali Khan, G. Sridhar Babu and Syed Muzammil Afzal (2017). Preparation and *in vitro* evaluation of Tapentadol hydrochloride sustained release matrix tablets of Sintering Technique. *International Journal of Applied Pharmaceutical Sciences and Biological Sciences.* **6(1)**: 001-021

Satish Polshettiwar, Vasudha Arve, Ajinkya Battuwar and Rahul Hajare (2016). Formulation and Evaluation of Gastroretentive Drug delivery System of Carevidelol phosphate by Sintering Technology. *World Journal of Pharmacy and Pharmaceutical Sciences*.**5(4)**: 959-978

Sreenivasa Rao B, Prasana Raju Y, Srinivas L, Seshasayana A; Design and evaluation of Eudragit RL 100 sintered matrix tablet (2014).*Indian Journal of pharmaceutical Sciences*. **64(2)**: 202-207.

Seshagiri B, Chowdary KA, DeepthiPriya Y (2011). Formulation and Evaluation of Sintered Gastro Retentive Tablets of Glizipide, *International Journal of Pharmacy and Pharmaceutical Sciences*, **3(4)**: 128-135

Sameer S, Chowdary K.A., Nagoba S, Nangargekar S (2011), Sintered Matrix Tablets of Diltiazem Hydrochloride. *International Journal of Applied Pharmaceutics*.**3(3)**:16-19

Satyabrata B, Ellaiah P, Chandan M, Murthy KV, Bibhutibhusan P, Padhy SK (2010). Design and in vitro evaluation of mucoadhesive buccal tablets of perindopril prepared by sintering technique. *International Journal of PharmTech Research*. **2(3)**: 1810-1823.

Singh R, Poddar SS, Chivate A (2007). Sintering of wax for controlling release from pellets. *AAPS Pharm Sci Tech*.**8(3)**: E1-E9.

Shirzad Azarmi, Fatemeh Ghaffari, Raimar Lobenberg, Ali Nokhodchi (2005). Mechanistic evaluation of the effect of thermal treating on eudragit RS matrices. *IIFarmaco*. **60**:925-930.

Tejaswini S Pawatekar, Ramdas B. Rode; A review on sintering method in Pharmaceutical Sciences (2014) *Asian Journal of Pharm. Tech*. **4(2)**:106-109.

Uhumwangho MU, Ramana Murthy KV (2011). Release characteristics of Diltiazem hydrochloride wax-matrix granules thermal sintering effect. *J. Appl Sci. Environ Manage*. **15(2)**: 365-370.

Venkata Srikanth Meka, Ambedkar Sunil Songa, Sreenivasa Rao Nali, Janaki Ram Battu, Latha Kukati and Venkata Ramana Murthy Kolapalli(2012). Thermal sintering: a novel technique in the design of Gastroretentive Floating tablets of propranolol HCl and its Evaluation; *Invest Clin*.**53(3)**: 223-236.

Vaibhav Bhamre, Dipika Shekar, Dilip Derle, Minal Narkhede (2013). Stability study of stavudine sintered matrix tablet. *International Research Journal of pharmacy*. **4(1)**: 182-186.