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Review Article

An Innovative Sintering Technique in Pharmaceutical Industry

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Abstract:
The pharmaceutical dosage form is the dosage form by which active pharmaceutical ingredients are supplied to the patient as a unite dose, to provide a pharmaceutical effect in the body with minimum undesirable side effects. The most common dosage forms are solid dosage form (tablets, capsules, powders and granules in sachet, etc.) due to their excellent physical and chemical stability, cost effectiveness and are easy of manufacturing. Solid dosage form contains a unit dose of one or more APIs with an inert excipient. The tablets are formulated by traditionally either compression methods (Direct/ Wet/ Dry granulation) or an innovative sintering method after compression. The sintering is expressed as the joining of adjacent particles in a mass of powder, or in tablets, by the heat application. Conventional sintering technique involves heating of compact mass at a temperature below the melting point of the available solid constituents in a controlled environment. The sintering technique has manifold advantages over traditional dry or wet granulation method like minimum quantity of drug polymer ratio, easy tailoring of drug release profile, cost effective, high mechanical strength and less disintegration time for the manufacturing of modified release dosage forms. Sintering concept not only improves mechanical strength of dosage form, but it also controls the release of medicament on over an extended time period.

Keywords: *Pharmaceutical dosage form, Modified Release, Controlled Release, Sustained Release, Tablets, Sintering Technique*

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Introduction

The oral route is be more partial to oral route of drug delivery due to its diverse superiority including cost effective, ease in ingestion, non-invasiveness, inventiveness, flexibility of dosage form design and most important high patient compliance.[1,2] The United States Pharmacopeia (USP43NF38) define tablets as "oral solid dosage forms in which the drug substance is generally blended with excipients and compressed into the final dosage form" Tablet dosage forms can be immediate release or modified release or specialized tablet. Specialized tablet can

sustain or modify or extend the release of the drug substance(s) or help in separation of incompatible drug substances. Modified-release tablet are categorized in two separate categories in USP. [3] These are:

Delayed-release tablets: "Tablets are sometimes formulated with acid-resistant or enteric (also called "gastro-resistant") coatings to protect acid-labile drug substances from the gastric environment or to prevent adverse events such as irritation".

Extended-release tablets: "Extended-release tablets are formulated in such a manner as to make the drug substance available over an extended period of time following ingestion".

Modified release dosage forms are classified on the basis of release mechanism, are as follows: [4,5]

- Diffusion based products,
- Dissolution based products,
- Erosion based products and
- A Combination approaches

In general, Pharmaceutical Industry can adopt two manufacturing method for the development of Modified release dosage forms:

a. Commercial Manufacturing Method involves Polymer Matrix System

In this method, manufacturing is carried out by either Dry or Wet granulation method. It is a widely used method for the development of modified release dosage forms. [4,5].

b. Sintering Technology - Polymer Matrix system with heat treatment

Sintering Technology is generally and widely used in powder metallurgy. Now a day, sintering concept is growing in the Pharma Industry to modified release patterns of API's.

Sintering Technology

Sintering can be expressed as the joining of particles (adjacent to each) surfaces in a powder compacts, or in tablets, by the application of thermal effect. Traditional sintering technique imply, heating of compact at a temperature below the melting point of the solid constituents present in compact, in a controlled environment [105-108].

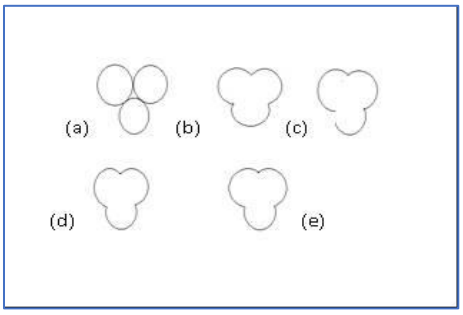

Fig. 1: Schematic representation of Sintering Concept in a pharmaceutical compact. (a) Interparticles Bonding (b) Neck growth, (c) and (d) Pore Uniformity, (e) shrinkage of Pore

Polymer Matrix Sintering Technique in Pharmaceutical Industry

Sintering concept describes the impact of heat on a pharmaceutical compacts preparation to improve the product performance and its applicability in the manufacturing of modified release products, to alter their release profile. The sintering concept consists of following properties [105-108]:

(I) Impact on Powder/ Polymer Microstructure

The effect of sintering causes different structural changes in microstructure of compacts. Polymer microstructure during sintering can be easily studied by Scanning Electron Microscopy (SEM), Mercury intrusion and Nitrogen adsorption porosimeter. The change in microstructure can be divided in following five stages (Figure-1).

Stages in Sintering Process:

a) Bonding of Interparticle: - The particles come in closure at their boundaries by physical bonding. This type of bonding happens rapidly on heat application.

b) Neck growth: - Continuing application of heat, resulting formation of easily distinguishable "neck" development leads to enhancement of compact strength.

c) Closeness of Pore: - The pores in compact become more closure and forms isolated pore.

d) Pore Uniformity: - Continuous closeness of pore, produces much more uniform size of pores. Hence, this stage enhances smoothing effect on the pore wall and ultimately improves toughness and strengths.

e) Shrinkage of Pore: - On continuation of Sintering (heating), the number of pores and their sizes are reduced. A shrinkage phenomenon causes densification of powder compacts.

(II). Impact on Powder mechanical strength

The overall mechanical strength of powder or compact is improved as the particle comes in closure to each other.

(III) Impact on disintegration time and dissolution rate

The sintering concept increase onset and duration of disintegration time for powder compacts as the mechanical strength is increased.

Sintering Method

There are two methods for the application of sintering concept in tablet dosage form:

1. Heat treatment method or Thermal Sintering or Solid State Sintering

i. Microwave sintering Method
ii. Laser Sintering Method

2. Acetone saturation methods

1. Heat treatment Method or Thermal Sintering or Solid State Sintering

Heat treatment method involves heating a drug-polymer in a sintering heating system (thermal or microwave or any other) until its particles start to adhere/fuse to each other and forms a amalgamated bonds. The API's particles are entangling in the matrix, resulting in slow release of the active ingredient from a tablets. Thermal sintering can also be provided by Microwave irradiation or by laser technique. [6-9]

3. Acetone Saturation Method

Acetone saturation method imply by holding of tablets in a prefilled saturated non-aqueous solvent based closed chamber for sufficient time durations. The prefilled saturated chamber can be prepared by using desiccators with a volatile solvent like acetone. The solvent vapors move to center of tablets thru capillary and polymer particles solubilize outer surface of particles and resulting joining or sintering of particles. Tablets can expose to different duration of sintering time. After sintering, the tablets are further dried at room temperature or in a closed camber containing calcium chloride to remove the entrapped residual solvent. Final sintered tablets are finally air tightly packed for further evaluation. [6-9]

Some of the critical research work based on polymer sintering techniques are highlighted in Table-1.

Table-1: Highlights of research work based on Polymer Sintering Techniques

S. No.	Drug Candidate	Sintering Polymer	Tablet Manufacturing Method & Sintering Method	References
1.	Amoxicillin Trihydrate	Carnauba Wax	• Wet granulation with IPA solvent • Thermal Sintering in Hot air oven	10
2.	Atenolol	Eudragit RS 100	• Direct compression method • Thermal Sintering in Hot air oven • Evaluate In-vivo performance	11
		Tragacanth, Eudragit S-100	• Wet granulation method • Thermal Method by microwave irradiation in microwave oven	12
3.	Bosentan Monohydrate	Stearic Acid, Carnauba Wax, EVA 1802 polymer	• Direct compression & Wet Granulation method • Thermal Sintering in Hot air oven	13
4.	Carevedilol Phosphate	Hydroxypropyl methyl cellulose (K4M), Methacrylic acic and methyl methacrylate copolymer (L 100), Guar Gum	• Direct compression Method • Thermal Sintering in Hot air oven	14
5.	Cefpodoxime Proxetil	Locust Bean Gum	• Wet granulation method using a sublimating agent • Sintering by solvent (acetone) saturation method	15
6.	Diltiazem Hydrochloride	HPMC K4M and HPMC K15M	• Direct compression Method • Sintering by solvent (acetone) saturation	16
7.	Glipizide	HPMC K4M and HPMC K15M	• Direct Compression Method • Sintering by solvent (acetone) saturation method	17
8.	Itopride Hydrochloride	Methacrylic acic and methyl methacrylate copolymer (L 100), Carnauba Wax, Xanthan Gum	• Wet granulation with PVPk30 and hydroalcoholic solvent • Thermal Sintering in Hot air oven	18
9.	Lamotrigine	HPMC K4M, HPMC K15M, HPMC K100M, Acacia, Guar Gum and Xanthan Gum.	• Direct compression Method • Solvent Sintering method	19
10.	Losartan Potassium	Natural polymer Pullulan	• Direct compression method • Thermal Sintering in Hot air oven.	20
11.		Eudragit L 10055 and HPMC K4M	• Direct compression Method • Solvent Sintering method	21

	Metformin Hydrocloride	Xanthan Gum and Guar Gum, Methocel-K4M, Ethocel.	• Wet granulation Method • Sintering by solvent (acetone) saturation method	22
12.	Metronidazole	Arvingiagabonesis Gum	• Sublimation and sintering technique • Sintering performed in Hot air oven at 40°C & 60°C gfor 1,2 &3 hr.	23
13.	Nicardipine	HPMC K100M	• Direct compression method • Thermal Sintering in Hot air oven • Evaluate In-vivo performance	24
			• Direct compression Method • Sintering performed in Hot air oven at 60°C and 70°C for two different time periods 1.5 hr and 3 hr.	25
14.	Paracetamol	Powder Charcoal	• Selective laser sintering Method	26
15.	Propranolol HCl	Polyethylene Oxide (PEO)	• Direct compression Method Thermal Sintering in Hot air oven	27
		Polyethylene oxide (PEO) & sod. bicarbonate	• Direct compression Method • Thermal Sintering in Hot air oven	28
16.	Sotalol Hcl	Eudragit RS100, HPMC K4M, Gum Acacia, Xanthan Gum	• Direct compression Method • Thermal Sintering in Hot air oven & in microwave	29
17.	Stavudine	Eudragit RS 100 and Compritol 888 ATO	• Direct compression Method • Sintering by solvent (acetone) for varying time period.	30
18.	Tapentadol Hydrochloride	Eudragit RL-100, Carnauba Waxes & Stearic Acid	• Direct compression method • Thermal Sintering in Hot air oven	31
19.	Verapamil Hydrochloride	Glyceryl Behenate and Carnauba Wax	• Melt granulation Method • Thermal Sintering in Hot air oven	32

Conclusion & Future prospective of Sintering Technology:

Now a day, Sintering technologies play a unique importance in the development and production of advanced drug delivery, to satisfy market need of novel drug delivery system. By exploring the use of sintered technique like sintering temperature, sintering method with current techniques in a modified release tablet form, may become a key role in the growth of the pharmaceutical field. Recent research is also going on the development of temper resistant dosage form by the use of sintering technique.

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