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Study of particle rearrangement, compression behavior and dissolution properties after melt dispersion of ibuprofen, Avicel and Aerosil

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ABSTRACT

Particle rearrangements, compaction under pressure and in vitro dissolution have been evaluated after melt dispersion of ibuprofen, Avicel and Aerosil. The Cooper–Eaton and Kuno equations were utilized for the determination of particle rearrangement and compression behavior from tap density and compact data. Particle rearrangement could be divided into two stages as primary and secondary rearrangement. Transitional tapping between the stages was found to be 20–25 taps in ibuprofen crystalline powder, which was increased up to 45 taps with all formulated powders. Compaction in the rearrangement stages was increased in all the formulations with respect to pure ibuprofen. Significantly increased compaction of ibuprofen under pressure can be achieved using Avicel by melt dispersion technique, which could be beneficial in ibuprofen tablet manufacturing by direct compression. SEM, FTIR and DSC have been utilized for physicochemical characterization of the melt dispersion powder materials. Dissolution of ibuprofen from compacted tablet of physical mixture and melt dispersion particles has also been improved greatly in the following order: $Ibc < Ibsmd_1 < Ibsmd_2 < Ibsmp_{10} < Ibsmd_5 < Ibsmd_{10}$.

1. Introduction

In die compaction of powders, materials are subjected to compressive forces, which lead to volume reduction and tablet is produced. The volume reduction process is generally divided into three different stages: (i) die filling, (ii) particle rearrangement and (iii) deformation and bonding of discrete particles [1,2]. Particle rearrangement is the particle motion without deformation or fracturing of the particles. It is a critical process for densification during the initial compression phase [2–6] at low applied pressures. Rearrangement of particles becomes insignificant with increasing pressure and the next phase proceeds by elastic deformation, plastic flow or fragmentation of the particles. The compression ability and the dissolution rate of ibuprofen are poor and several efforts have been made in past for their improvement. Crystal engineering [7] and also spherical agglomeration [8] were developed for producing directly compressible ibuprofen. There are many reports on solid matrix systems prepared by melting or fusion [9–11] for specific pharmaceutical processing and improvement of drug dissolution. Hot-melt granules of drug (BAY 12-9566)—Gelucire 50/13—Neusilin dispersion can be compressed easily into tablets with up to 30% w/w drug loading [12]. Many reports are already published on techniques of melt dispersion [13,14] and melt solidification [15,16] of ibuprofen. Melt granulation technique was also adopted in ibuprofen tablet formulations [17].

The present study has been explored to evaluate the particle rearrangement under tapping and compression under applied pressure of the hot-melt ibuprofen dispersion with Avicel containing Aerosil and in vitro dissolution of the compact. Melt dispersion powder mix has been tableted by direct compression, which is supposed to bring about improvement in both mechanical behavior and dissolution of drug. Cooper and Eaton [18] described the compaction process of powders under applied pressure and introduced a biexponential equation. This equation has also been applied here in describing the densification of powder under tapping process. Kuno [19] developed his equation under tapping only to describe the powder packing process. Kawakita and co-workers [20,21] have described the densification process both by tapping and applied pressure. Therefore, the Cooper–Eaton compaction parameters under tapping process could be of importance. Kuno described the powder packing process and developed the equation based on the relationships between the change in apparent density and the number of tappings. The early stage of compaction process as a function of pressure due to slippage of particles

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or rearrangement has been explained in different ways in the literature although it is difficult to characterize and quantify [1,2,6,18,22,23]. An attempt has been made here to characterize the early stages of compaction behavior by tapping process. Characterization of particle rearrangements before deformation and compression during deformation with increasing pressure has been studied applying two different mathematical models, namely Cooper–Eaton and Kuno. Physicochemical characterization of the melt dispersion powder materials has also been carried out by SEM, FTIR and DSC.

2. Materials and methods

2.1. Preparation of powder materials by melt dispersion method

Ibuprofen (native crystalline powder: IOL Chemicals and Pharmaceuticals Ltd., India), microcrystalline cellulose (Avicel PH 101, average particle size 50 μm, mess size 60/200: Lupin Pharmaceuticals, Mumbai, India) and colloidal silicone dioxide (Aerosil 200, average particle size 15 nm: Lupin Pharmaceuticals, Mumbai, India) were used in this study. Avicel has been lubricated with Aerosil (1%, 2%, 5% and 10%) by simple blending using mortar and spatula without triturating for 5 min and thereafter named as $Smcc_1$, $Smcc_2$, $Smcc_5$ and $Smcc_{10}$, respectively.

In this process 5 g of ibuprofen was placed in a beaker for 45 min at ~80 °C in an incubator. Each silicified sample was incorporated into the completely melted ibuprofen and kneaded for few minutes to a homogeneous mass. The mass was cooled to laboratory ambient temperature and passed through mesh 30. In this way four powdered samples were prepared and named as $Ibsmd_1$, $Ibsmd_2$, $Ibsmd_5$ and $Ibsmd_{10}$ and preserved in screw cap bottles. The formulation detail of melt dispersion ibuprofen powder has been tabulated in Table 1.

2.2. Density measurement

Bulk density is the ratio of weight of powder to its volume before tapping. The bulk density of powder is dependent on particle packing. The bulk density was measured by pouring powder sample into a graduated 50 ml cylinder (stoppered) and the volume of the powder sample was recorded directly from the cylinder. The measurement was repeated five times varying the amount (15–20 g) and the value was reported. The tapped volume was measured up to 200 taps using a bulk density measurement apparatus (Koshiash Instruments bulk India) and the height of the powder was determined visually. The true density was determined by helium pycnometer (Pycno 30, Smart Instruments, India) without replication.

Table 1
Ibuprofen powder samples prepared by melt dispersion technique.

Powder formulation	Aerosil added to Avicel[a] (%)	Ibc:Smcc ratio	Technique used	Aerosil in final mix (%)
Ibc	–	Crystalline ibuprofen alone	–	–
$Ibsmp_{10}$[b]	10 ($Smcc_{10}$)	1:1	Physical mixture	5.0
$Ibsmd_1$[c]	1 ($Smcc_1$)	1:1	Melt dispersion	0.5
$Ibsmd_2$[c]	2 ($Smcc_2$)	1:1	Melt dispersion	1.0
$Ibsmd_5$[c]	5 ($Smcc_5$)	1:1	Melt dispersion	2.5
$Ibsmd_{10}$[c]	10 ($Smcc_{10}$)	1:1	Melt dispersion	5.0

[a] Lubrication was done by physical mixing of Aerosil with Avicel (mcc) in a mortar with spatula before use and named as Smcc.
[b] Prepared by blending crystalline ibuprofen and Smcc in a mortar with spatula and not crushed.
[c] Kneaded mass was prepared after incorporating Smcc into the completely melted ibuprofen (Ibc) at ~80 °C and cooled to laboratory ambient temperature and passed through mesh 30.

2.3. Compaction of powder

Ibuprofen pure and other formulated powders were compacted on a hydraulic pellet press (Kimaya Engineers, India) over a compression pressure ranging from 245 to 2942 MPa, using a 10 mm diameter die and flat faced punches. Materials for each pellet were weighed accurately (400 mg) and poured manually into the die and pellets of each formulation were prepared. Maximum upper punch pressure at each load with a dwelling time of 60 s was recorded for compaction of each tablet in the laboratory ambient condition (~27 °C, ~60% RH). The thickness of each pellet was measured with a digital micrometer (Mitutoyo, Japan). This data was used for the calculation of apparent density, porosity and degree of volume reduction. Tablets were preserved in a wide mouth tightly closed container immediately after compression.

2.4. Characterization of particle rearrangement and compression behavior

2.4.1. Application of Cooper–Eaton equation

Cooper and Eaton developed a biexponential equation for describing the compaction of powders as a function of applied pressure and adopted from other fields of industry for research in pharmaceutical compression process. The equation is

$$((1/D_0)-(1/D))/((1/D_0)-1) = a\exp(-K_a/P)+b\exp(-K_b/P) \quad (1)$$

where D_0 and D are the relative density at zero pressure and at pressure P, respectively, a indicates the fraction of the theoretical maximal densification, which could be achieved in the first stage by filling large voids by interparticulate slippage and b indicates small voids by deformation or fragmentation at a higher pressure in the second stage of densification. K_a and K_b describe the magnitude of pressure at which the respective compaction process would occur with the greatest probability of density. Tablets were produced on a hydraulic pellet press and the parameters of the second stage due to particle deformation were determined from the graphical plot of $\mathrm{Ln}((1/D_0)-(1/D))/(1/D_0)-1$ versus $1/P$, where the slope of the linear region is K_b and the ordinate intercept of that linear region of the second stage compaction measures $(a+b)$.

Rearrangement of discrete particles could be described by two major steps [24,25] based on cohesiveness of the powdered material as (i) primary rearrangements of fine discrete particles and (ii) secondary rearrangements. Replacing pressure, P, by the tapping number, N, in the Cooper–Eaton equation we get

$$((1/D_0)-(1/D))/((1/D_0)-1) = a_1\exp(-K_1/N)+a_2\exp(-K_2/N) \quad (2)$$

where D_0 and D are the relative density before tapping obtained by poured density divided by equilibrium tapped density and the relative density at Nth tapped obtained by apparent density of a powder column divided by equilibrium tapped density, respectively. The coefficient K_1 represents the tapping required to induce densification by primary particle rearrangements, which has the greatest probability of density, whereas K_2 represents the tapping required to induce densification through secondary particle rearrangements. a_1 and a_2 are the dimensionless constants that indicate the fraction of the theoretical maximum densification of tapping, which could be achieved by filling voids by primary rearrangements (a_1) and secondary rearrangements (a_2). Above parameters were determined from the graphical plot