Research Article

DEVELOPMENT OF DIRECTLY COMPRESSIBLE METFORMIN HYDROCHLORIDE TABLETS

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ABSTRACT

Metformin hydrochloride (MH) is an oral hypoglycemic agent and a high-dose drug that has poor flow and compression properties and thus presents formulation problems. In this study the tabletting properties of MH agglomerates prepared by spherical crystallization techniques, i.e a spherically agglomeration method was investigated. The flow and packing properties of agglomerates, represented in terms of the angle of repose and change in tapping density, were much improved by this technique compared with those of conventional crystals due to the spherical shape and smooth surface. Furthermore, spherical agglomerates possessed superior strength characteristics to conventional crystals and were compressed into compacts having considerable hardness without capping at high compaction pressure. From the calculated Heckel's parameter, it was demonstrated that the spherical agglomerates of the drug showed better particle arrangement in the compression stages. Kawakita analysis revealed better packability of the agglomerated drug compared to the conventional drug.

Keywords: Metformin hydrochloride**,** Spherical crystallization technique, Direct compression, Flowability, Packability, Compactibility.

INTRODUCTION

Solid dosage forms, especially tablets, offer many advantages for industrial production. For the manufacture of tablets, good flowability of the blend, i.e. the mixture of excipients and drug, and good compressibility are critical properties. One way to produce tablets of drugs that show bad flow and compression in the pure form is by wet granulation. Heat and moisture sensitive drugs cannot usually be manufactured using wet granulation. Further, it involves large number of processing steps and processing time are problems due to high level manufacturing costs. In recent past newer agglomeration technique, termed spherical crystallization process, has been developed that can transform directly into the fine crystals produced in the crystallization or the reaction process into a spherical shape that are reported to possess free flowing and directly compressible properties.

Spherical crystallization can be achieved by various methods such as simple spherical crystallization using solvent change method, emulsion solvent diffusion, ammonia diffusion, and neutralization[1,2]. In the solvent change method the solution of the drug in a good solvent is poured in a poor solvent under controlled condition of temperature and speed to obtain fine crystals. These crystals are agglomerated in the presence of bridging liquid. The poor solvent has miscibility with good solvent but low solubility with solvent mixture so during agitation of the solvent system the crystals formed. The Drawback of this system is that it provide low yield because the drug shows significant solubility in the crystallization solvent due to co solvency effect. This method is not applicable for water insoluble drugs[3].

Flowability is the ability of solids and powders to flow. Flow behavior is multi-dimensional in nature and it depends on many physical characteristic[4]. Particle size and particle size distribution, bulk density, angle of repose and compressibility play significant role in flowability of bulk solids. A study was carried out using Hausners ratio and angle of repose as indicator to determine powder flowability of two types of powders-spherical and angular by Geldart et al[5]. It was revealed that increase in the particle size of a powder results in decrease in cohesiveness. The same trends were observed for the angle of repose, which increased for both the materials as the mean particle size decreased.

Compressibility and compactibility of a powder are influenced by the flow properties and in the microscale by the adhesion forces between the particles. Compressibility is the ability to reduce the volume under pressure and compactibility is the ability to build the solid agglomerate under pressure with sufficient strength and stability[6]. The two most commonly used measures of the relative importance of interparticulate interactions are the compressibility index often referred as Carrs index and Hausners ratio.

In this study, solvent change method was employed to form agglomerated crystals of metformin HCl (MH-AG). Additionally, result of a study of the effect of shape and size of solvent change agglomerated powder on powder flow and compressibility properties is presented. These properties were evaluated by comparing the MH and wet granules of the drug (MH-Wet).

MATERIAL AND METHODS

Materials

Metformin HCl was obtained from Sain Medicaments Pvt Ltd, Hyderabad, India. Acetone, chloroform was purchased from E. Merc, (Mumbai, India) and starch and

other materials were purchased from S. D. Fine chemicals (Mumbai, India).

Solvent change Agglomeration Method (MH-AG)

Preparation of spherical agglomerates of metformin HCl

Metformin HCl (300 mg/ml) was dissolved in water and saturated solution was obtained. The drug solution was poured quickly in to acetone (1:20 proportion) at room temperature, under continuous stirring at 500 rpm with a propeller. When fine crystals of ketoprofen begun to precipitate (5-10 min), 10 ml of chloroform (bridging liquid) was added. The stirring was continues for about half hour, spherical agglomerates were formed and were separated from the solution by filtration. Spherical agglomerates were dried at 45^0C for overnight. The dried agglomerate powder was stored in plastic bag.

Wet granulation method (MH-Wet)

Metformin HCl powder was granulated using 5 % soluble starch as binder solution. The granules were dried in a laboratory tray dryer, passed through 500 µm screen using a sieve shaker and stored in plastic bag.

Powder characterization

Particle size distribution

Particle size distribution of the powders was determined by sieve (mesh) analysis using laboratory sifter equipped with series of 6 screens and a pan. An approximate 10 gm sample was tested for total sifting time of 5 min. The method was carried out in triplicate (*n*=3).

Determination of particle shape parameters

The particle shape in the present work was measured by using Motic (optical) microscope with an attached digital camera (Olympus). The microscope was used to create 10 images, at a magnification of 10X or 40X. From the microscope images, approximately 100 particles were analyzed using the Image-Pro Plus software to determine the particle descriptors of major and minor axis length and perimeter. Aspect ratio and irregularity were calculated from these particle descriptors using equations

$$\text{Aspect Ratio} = b/l \quad (1)$$

$$\text{Irregularity} = P/l \quad (2)$$

In these equations *b* represents the length of the minor axis, *l* is the length of the major axis, and *P* is the perimeter.

Static Angle of Repose

The static angle of repose flowability test was performed following the procedure described in literature[7]. A conical funnel was mounted with its stem 6 cm from the horizontal surface. Between 50 and 100 grams of powder were poured through the funnel, enough that the top of the resulting pile reached the funnel outlet. The angle measured on the right and left hand sides of the pile were averaged to give a single static angle of repose. The angle of repose can be obtained from equation

$$\tan\theta = h/0.5d \quad (3)$$

Where h- height of the cone and d- diameter of the cone. The method was carried out in triplicate (*n* = 3).

Hausners Ratio and Carrs Index

The Hausners Ratio and Carrs Index are both calculated from compressibility data[8]. The test powder is gently loaded through a funnel into a 100 ml cylinder and weighed to calculate its bulk density. Next, the cylinder is tapped in a single platform tapped density meter till no change in the volume of powder is observed. The Hausner ratio is calculated from equation (4) and the Carr Index from equation (5), where BD is the powder bulk density and TD is the powder tapped density[9]. The method was carried out in triplicate (*n*=3).

$$HR = TD/BD \quad (4)$$

$$CI = TD-BD/TD \times 100 \quad (5)$$

Porosity

The porosities of the MSA, MSA-AG and MSA-Wet powder were calculated from their bulk and true densities. The porosity of the powder was calculated from true density of the powder using the following equation:

$$\text{Total Porosity (E)} = 1 - \text{Bulk density}/\text{True density} \quad (6)$$

Packability

Sample packability was assessed by analysis of the tapping process with the Kawakita[10] (Eq. 7) and Kuno[11] (Eq. 8) methods, and using the parameters a, b, and k in the equations.

$$n/C = 1/(ab) + n/a. \quad (7)$$

$$C = (V_o - V_n)/V_o, a = (V_o - V_\infty)/V_o . \rho_f - \rho_n = (\rho_f - \rho_o) . \exp.(-kn) \quad (8)$$

Where: a is the degree of volume reduction when the tap number is infinity, b and k are constants for the apparent packing rate, V0 and Vn are the volume in the initial loosely packed and the nth tapped state, and ρ0, ρ n, and ρ f are the apparent density in the initial state, the nth tapped state, and the most densely packed state.

Compact Preparation of Powder

Compact compression was performed on R&D tablet press tablet (model M/C-12 STN, Cemach Machineries Ltd, India). Six different compaction forces (from 1 ton to 6 ton) were used for MH, MH-AG and MH-Wet powders. The compact mass was of 500 mg metformin HCl and 40% w/w microcrystalline cellulose. The powder mass was compacted into tablet using flat-faced punch with a diameter of half inch (D-tooling). The punch and die were lubricated with magnesium stearate before punching. Each compact was weighed accurately, and its dimensions (diameter and thickness) were measured with vernier caliper apparatus.

Compact characterization of MH, MH-Wet, MH-AG

Heckel Analysis

The following Heckel's equation[12] was used to analyze the compression process of agglomerated crystals and wet granules, and assessed their compactibility.

$$\ln [1/(1-D)]=KP+A \quad (9)$$

Where, D is the relative density of the tablets under compression Pressure, K is the slope of the straight portion of the Heckel Plot. The following equation gives the intercept obtained by extrapolating the straight portion of the plots.

$$A=1n [1/(1-D_0)]+B \quad (10)$$

Where, D_0 is the relative density of the powder bed when P=0. The following equation gives the relative densities corresponding to A and B.

$$D_A=1-e^{-A} \quad (11)$$

$$D_B=D_A-D_0 \quad (12)$$

Tablet Elastic Recovery Test

Each powder was placed, 550 mg, in a die with 12 mm diameter and compressed under 6 tons (Hc) pressure. The thickness and diameter of each tablet at initial and after 24 h of ejection (He) was measured. Following equation was used to calculate the elastic recovery ratio (ER).

$$ER=[(He – Hc)/Hc]x100 \quad (13)$$

About 24 h after the tablet was ejected, its weight, diameter, and thickness were measured, and its apparent density ρa calculated.

Compact Hardness, Tensile strength, Friability and Disintegration time

Tablet hardness was determined using a Monsanto hardness tester. The tensile strength (*T*) of the compact was calculated using the following equation:

$$T = 2F/ \pi Dt \quad (14)$$

in which *D* and *t* are the diameter and thickness of the compact, respectively, and *F* is the force fracturing the compact.

The friability values of the tablets were determined using a Roche-type friabilator. It was rotated at 25 rpm for 4 min. Percent friability was calculated using the following equation:

$$\text{Friability} = ([W0 – W]/ W0) \times 100 \quad (15)$$

in which *W*0 is the weight of the tablets at time zero before revolution, and *W* is the weight of the tablets after 100 revolutions.

The disintegration times of the tablet formulations were determined using a tablet disintegration test apparatus (Veego, Mumbai).

Content Uniformity

Metformin HCL was estimated by using U.V. Spectrophotometer at 232 nm formulation Quantity equivalent to 100mg of metformin HCL was taken for assay and dissolved in 70ml p/w, sonicated and volume was made to 100ml. After filtration 10ml was diluted to 100ml with p/w and further 10ml was diluted with 100ml with p/w and drug content was analyzed spectrophotometrically at about 232 nm. Each sample was assayed to triplicate (*n*=3).

RESULTS AND DISCUSSION

Preparations of agglomerates

It was found that crystal agglomeration was possible with solvent change method. The MH consisted of single, small crystals and with an unfavorable habit for direct compression [Figure 1(a)]. The structure and particle size distribution of the agglomerated powder were determined by the parameters that depended on the stirring rate and the time of stirring. It was observed that less the initial time of stirring and larger stirring rate resulted in no or smaller size agglomerates. More time of stirring and slower stirring rate was favorable in the building-up of crystal agglomerates with a closed structure [Figure 1(b)]. On the basis of above results the agglomerates preparation was optimized considering stirring rate of 100 rpm and stirring time of 1 h and this agglomerate powder now onwards would be named as MH-AG for further characterization. The agglomerates of wet granulation showed irregular structure [Figure 1 (c)] with relatively larger sizes than MH.

Powder characterization of MH, MH-Wet, MH-AG

The physical properties of the MH, MH-AG and MH-Wet are summarized in Table 1. The mean diameters of the agglomerated particles were approximately 4 times higher than those of the untreated MH crystals.

The flow properties of particulate solids are known to depend on the size, shape and size distribution of particles[2]. Aspect ratio varies between 0 and 1, with a low value indicative of an elongated particle; a perfect circle has an aspect ratio of 1. Irregularity measures the surface area compared to the size of the particle; in this case, a perfect circle has an irregularity of π. Table 1 showed that the aspect ratio of MH-AG powder was close to 1, indicating spherical shape while that of MSA-Wet had slightly higher aspect ratio than agglomerated crystals. Similarly MH- AG was less irregular while MH-Wet exhibited higher irregularities. The aspect ratio for MH could not be calculated as they were small and needle shaped.

According to Cain[8], a static angle of repose greater than 40° indicates a cohesive powder, whereas an angle greater than 50° indicates a very cohesive powder. The angle of repose of MH crystals clearly shows that they form very cohesive powder.

The bulk density and tapped density of MH is lower than those of the MH-AG and MH-Wet indicating more porous nature of powder. The MH had a Hausner ratio of 1.7 and a Carr index of 26.7 %. Both of these measurements are indicative of slightly cohesive powder [8]. MH-AG and MH-Wet had Hausner ratio of 1.16 and 1.28 whereas a Carr index of 14.51 % and 22.82 % respectively. These measurements indicate increased or good flow property.

The equations of Kawakita and Kuno were used to analyze the tapping process. The value 'a' in Kawakita equation was lower for MH-AG compared to that of the MH-Wet and MH crystals, while 'b' in Kawatika equation and 'k' in Kuno equation were both higher for MH-AG and MH-Wet than MH. This indicates that both MH-AG and MH-Wet had excellent flowability and packability.

Compact characterization of MH, MH-Wet, MH-AG

In order to achieve uniformity in tablet weight, the feed powder crystals must flow and pack smoothly into the die cavity of the tablet machine. The MH granules were poorly compressible. The Heckel plots for the MH-AG and MH-Wet are shown in Figure 2 and Table 1, shows the Heckel constants derived from the plots. The plots for the MH-AG and MH-Wet were similar, showing linearity over the compression range of 2-4 tons, indicating that the mechanism of consolidation of the material were similar, predominantly plastic deformation**.** The slope of the linear portion, K, can be correlated to the crushing strength of compacts; larger values of K usually indicate harder compacts[12]. The K values for the MH-AG and MH-Wet are comparable and would be expected to form harder compacts. On the basis of these findings, it could be concluded that good flowability and packability for agglomerates (MH-AG) may be attributed to the spherical shape and the bigger particle size.

A hardness study of tablets showed that the tablets prepared from MH-AG and MH-Wet had similar mechanical strength (see Table 2). As expected, the tensile strength of the MH-AG compact was more than the MH- Wet compacts. This may be a result of the stronger bonds formed between newly formed crystals of agglomerates. A friability study showed lower friability of the tablets prepared from the MH-AG, possibly owing to the better compaction of the spherical crystals. Disintegration tests showed that the tablets of MH-AG and MH-Wet were comparable and disintegrated within the prescribed official limits.

Table 1: Physical property of the MH, MH-AG and MH-Wet powder

Sr. No.	Property (n=3)	Formulations		
		Original Crystals of Meformin HCl (MH)	Agglomerated Metformin HCl (MH- AG)	Wet Granules of Metformin HCl (MH- Wet)
1	Mean particle diameter (µm)	229± 12	807± 22	680± 20
2	Aspect ratio	1.99± 0.01	1.003± 0.012	1.053± 0. 011
3	Irregularity	-	0.416± 0.016	2.98± 0.013
4	Angle of repose(^{0})	40.81± 1.40	22.78± 0.67	34.82± 0.85
5	Bulk Density gm/cm^3	0.7043± 0.14	0.8064± 0.1	0.7844± 0.2
6	Tapped Density gm/cm^3	0.9617± 0.12	0.9433± 0.18	0.9568± 0.13
7	True Density gm/cm^3	1.8± 0.13	1.52± 0.10	1.29± 0.15
8	Carr's Index %	26.76± 0.91	14.51± 0. 15	22.82± 0.67
9	Hausner's ratio	1.36± 0.14	1.169± 0.12	1.28± 0.11
10	Porosity	0.61± 0.09	0.392± 0.012	0.392± 0.013
11	a	0.375	0.294	0.32
12	b	0.9618	0.9787	0.9688
13	k	0.703	0.719	0.712
14	1/b	1.039	1.0217	1.03
15	Content Uniformity	99± 0.58	98± 0.54	98± 0.32

Table 2: Compact property of the MH, MH-AG and MH-Wet powder

Sr. No.	Property (n=3)	Formulations		
		Original Crystals of Meformin HCl (MH)	Agglomerated Metformin HCl (MH- AG)	Wet Granules of Metformin HCl (MH- Wet)
1	Tablet Elastic Recovery Test (%)	0.2339	0.2506± 0.013	0.2414± 0.012
2	Hardness (kg/cm^2)	2± 0.013	4± 0.12	4± 0.13
3	Tensile strength (at 6 tons)	0.03159	0.04644	0.3868
4	Friability (%)	1.15%± 0.013	0.4% ± 0.11	0.8% ± 0.14
5	Disintegration time (min)	6± 0.013	10± 0.24	12± 0.26
6	A	0.061	0.119	0.160
7	slope	0.127	0.102	0.102

(a) (b) (c)

Figure 1: Motic images of – (a) original bulk powder MH; (b) Solvent change agglomerate powder MH-AG and (c) Wet granules powder MH-Wet

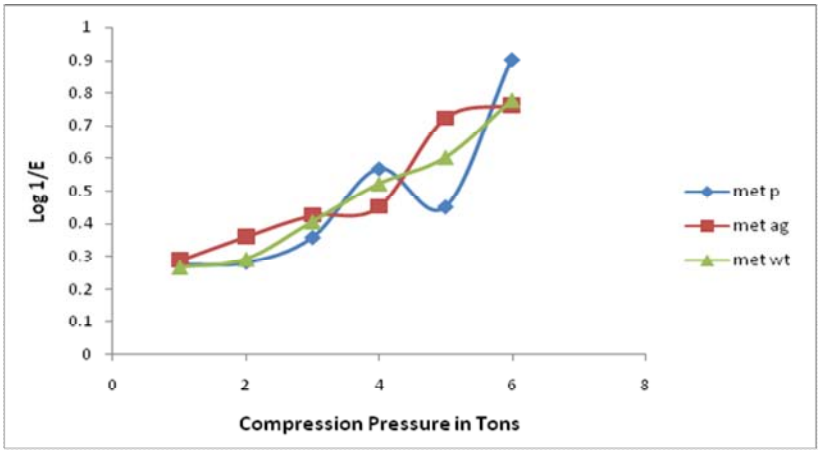

Figure 2: Heckel plots for Solvent change agglomerate powder MH(♦); Wet granules powder MH-AG(■) and MH-Wet(▲)

CONCLUSION

It was concluded that the selected solvent change method for the formation of agglomerates of model drug improved the powder functionality properties of the of MH drug powder such as flowability, packability and compactibility. Compacts by direct compression method could be formed successfully of agglomerated powder (MH-AG) that was comparable with the wet granules (MH-Wet). The original powder of model drug (MH) was poorly compressed by direct compression method. Thus MH-AG provided the requirements needed to convert wet granulated formulations to direct compression formulations, thus avoiding labor and energy intensive of wet granulation processes and is an alternative to develop cost effective formulations.

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