International Research Journal of Pharmaceutical and Applied Sciences (IRJPAS)
Available online at **www.irjpas.com**
Int. Res J Pharm. App Sci., 2013; 3(5):127-134

Research Article

CONTRIBUTION OF WAXES ON GRANULATION AND COMPRESSION OF NONCOMPRESSABLE DRUG (1)PARTICLE SIZE DISTRIBUTION AS A TOOL FOR STUDYING THE GRANULATION PROCESS.

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Abstract: Granulation of noncompressible drug is essential for tabletting process. Known granulation techniques are dry ganulation, wet granulation and melt granulation technique (thermoplastic granulation). Melt granulation is obtained through the addition of a binder which melts or softens at relatively low temperature. After melting, the binder acts as a binding liquid. The binders used for melt granulation are stearic acid and glyceryl monostearate. Different concentrations of the granulating substances were mixed with paracetamol powder (Non compressible model drug) at room temperature using Hobart's mixer. The temperature was increased gradually to 80 C and then decreased again to room temperature while stirring. The products were spherical granules with some concentrations of the granulating agent added. To clear the pure effect of the added granulating agents, the same procedure was also carried out using paracetamol alone. Sieve analysis of all products was carried out as a tool to compare the granulating agent efficacy of the added waxy substances. Different physical parameters (Bulk density, True density, Compressibility % and Flowability) were measured. The results indicated that there are changes in the powder characters as a result of addition either SA or GMS. The physical parameters indcated that the folwability of all products is not improved as a result of addition of the granulating agent but the products are, in most cases, granules with either irregular or smoth surfaces. The results encourage trying to apply this technique for large-scale process for compression of noncompressable drug. Also preparation of tablets and studying the drug release are the subject of the next work.
Keywords: Paracetamol, Stearic acid, Glyceryl mono stearate, granulation

INTRODUCTION

For tabletting prcess there are three main methods, they are diect compression, slugging and wet method. The main aim for slugging and wet methods is to change the noncompressable powder to compressable granules. Accodringly, granulation is frequantly used process in tableting production. In addition, tablets compressed from granules are knowen to be stronger than that those compressed from powders. Also granules have better flowability which led to homogeneity of tablet mass.

Paracetamol is known as the poor tabletting drug. It has been used as standered referance for the determination of the capacity of direct compression excipients for drugs with poor tabletting characterstics [1,2]. It was reported that, it is very difficult to produce tablets with sufficient mechanical properties, with a high content of crystalline paracetamol because of its high capping tendency. It was related to an elastic component of the mainly brittle material [3,4]. This leads to stress inside the tablet which is not released by plastic deformation but by elastic recovery which in turn destroy the bonds formed during the compression process [4]. The remaining stress which is not released weakness the tablet. Furthermore, crystalline paracetamol shows anisotropic properties which also causes stress which weakens the tablet [5].

There are different ways to improve the tabletting properties of paracetamol. The most widly used one is the grnaulation process. Barlow et all [6], diclosed the preparation of free-flowing granular paracetamol containing PVP, soluble starch and potassium sorbate by continously slurrying the components in water and spray drying. Vogel et al [7], introduces a product containing 90% paracetamol by spray granulating a blend of paracetamol and CMC with an aqueous dispersion of pregelatinzied starch.

Melt granulation (thermoplastic granulation) process is a process in which granulation is obtained through the addition of a binder which melts or softnes at a relatively low temperature. After melting, the binder acts like a binding liquid [8]. The binder usually used for melt granulation are polyethylene glycol [9] and different waxes [10,11]. Rbuenstein et all [11], prepared paracetamol tablets using a direct wet granulation method which empolys a low metling point binding agent (stearic acid). They melted stearic acid and coats the powder particles which forming granules directly as the powder cools.

Glyceryl mono stearate (GMS) is a mono ester of stearic acid with glycerol. It is a mixture of stearic, palmatic acid together with variable quantities of di and triglycerides. GMS is a poor W/O emulsifying agent but usefull stabilizer of W/O and O/W emulsions preparations for internal and external use. It is also used in the food and cosmotic

industeries [12]. GMS is widly used as a sustained release matrix.
The aim of this work is studying the contribution of the waxy substnces on the granulation of noncomprisable drug which is mixed with the pure drug as an excipient then the temperature elivated to start the granulation process.

MATERIALS AND METHODS

1. **Materials:**

Acetaminophan (Sgma, USA), Stearci acid (SA) (ADWIC, Egypt), Glyceryl mon stearate (GMS)(BDH chemicals Ltd Poole, England).

2. **Equipment:**

Mechanical stirrer supports with hobart's shaft (Heidolph,RZR-2000,Germany), Sieve set (Web MLW Labortechnik, Germany), Vibreting set sieve (VEB, Metalweberei, neuatatt Drla, Germany), Electron microscop (leitz 10000, Wetzlar, Germany).

3. **Manufacture and characterization of granules:**

3.1. Preparation of paracetamol granules:

Acetaminophan (50 gm) containing different concentratons of either SA or GMS was mixed for 5 minutes using hobart's mixer. The concentrations of the waxy matrices used, were (5%, 10%, 15% or 20%) of the total powder mixture. The stirring rate was 200 r.p.m. The temperature of the mixture was raised while stirring and granulation occurred by sintering of the mixture using water path at 80°C. The granules were cooled while stirring to room temerature. The same procedure was conducted to pure acetaminphin without any additive of waxy substance.

3.2. Characterization of the granules:

A. Particle size analysis:

The geometric mean (P.S.) of different samples was determined by sieves analysis. The amount of samples placed on the top sieve of the sieve set and subjected to vibration for 10 minutes. The amount of granules (%) which passed from oversize and retained on the undersize was plotted a linear function of sieve size on probability scale and the characteristic parameters were read. The mean particle size of the granules was calculated using the following formula [13]:

$$\text{Geometric mean} = \frac{\sum[\text{Mean particle size of the fraction} \times \text{ \% weight fraction}]}{\text{\% weight fraction}}$$

B. Electron scanning microscope examination:

The morphology of the products was studied using an electron microscope with different magnifications. The magnification used was depending on the shape of the product and also the best vision.

C. Flow prperties:

The flow properties of different products was carried out using angle of repose method. The samples were passed through a funnel at an even rate to form a stable cone. The funnel was maintained at a fixed hight in all experiments. The angle of repose (θ) was calculated using the following equation:

$$\theta = \tan^{-}(h/r) \ldots\ldots\ldots\ldots\ldots\ldots \ldots\ldots\ldots\ldots\ldots(1)$$

where, θ = angle of repose h = height of cone, r = radius of the cone base

D. Density measurements:

The bulk density (Fluff density) of different samples was measured as the following. A sample of 10 gm was carfully introduced into a 100 ml grauated cylinder. The bulk volume (V_0) was measured in cm^3. The fixed cylinder was dropped from a hight of 2.5 cm at one second intervales. The tapping was contiuned until no further change in volume was noted. the tapped volume (V_t) was measured cm^3. The different parameters of the granules were calculated according the following formule:

Bulk density(ρ_μ) = [weight of the sample in gm / volume in cm^3 (V_0)]…… (2).

Tapped density (ρ_t) = [weight of the sample in gm / volume in cm^3 (V_t)]…….(3).

Compressability % (carr`s indes) = [(ρ_{t} - ρ_{μ}) / ρ_t] × 100…………… (4).

Hausner`s ratio = V_0 / V …(5).

RESULTS AND DISCUSSION

Granulation is a subset of size enlargement, which involves any process whereby small particles are agglomerated, compacted, or otherwise brought together into larger, relatively permanent structures in which the original particles can still be distinguished [14]. Melt agglomeration is a process by which agglomeration - or size enlargement by which fine particles are bound together to agglomerates or granulates - is obtained through the addition of either a molten binder liquid or a solid binder which melts during the process. To obtain a stable, dry granule, a cooling to ambient temperature is necessary to solidify the binder.

During the granulation process it was noticed that there is no remarkable change in the appearance of the products prepared on using SA except that prepared on using 20% SA. On contrary, there is a remarkable change of the products prepared on using GMS.
Granules size distributions were used as a function of the quality of the granulation process of the products prepared on using either SA or GMS as granulating agents. Figure (1) represents the frequency distribution curve of paracetamol using different concentrations of SA. From the figure, it can be noticed that, paracetamol frequency distribution curve is a bell shape one (unimodal) with a narrow size range indicating there is no change in the drug powder form after heating. At the same time the effect of the addition of SA on the drug powder can be noticed from the change of the frequency distribution curves of all products from unimodal to bimodal form. It can be also noticed that, there is a clear cut between the two peaks of bimodal for all products with different intensity and starts. For all products prepared on using SA, the first one peak of bimodal has the same start of the particle size range of the pure drug with different end, different mean particle size and intensity (table 1). These results indicated that although the first part of the product

has the nearly same start of the particle size range of the drug but there is a change in the particle size as a result of increasing of the mean particle size and decreasing the amount of powder in this range which could be noticed from the peak intensity.

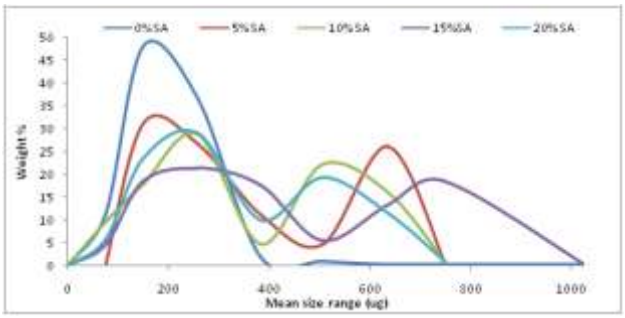


Figure (1): Frequency distribution curve of paracetamol granules using different concentrations of SA

The second peak of bimodal for all products has different size range and different mean particle size. Also there is no regular correlation between the concentration of SA used and either size range or mean particle size (table 1). On contrary, studying the effect of GMS, from figure (2), it can be noticed that, all products have also bimodal frequency distribution curve with a clear cut between the two parts of bimodal for all products.

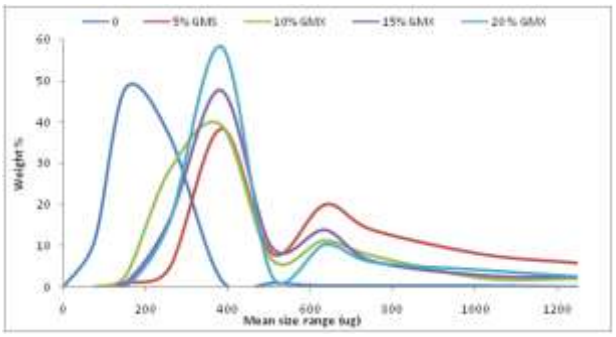


Figure (2): Frequency distribution curve of paracetamol granules using different concentrations of GMS:

Table (1): The size range and mean particle size on using stearic acid:

	Size range	Mean particle size	Size range	Mean particle size
0 % Stearic acid	0-400	195	0	0
5% Stearic acid	75-505	246.5	505-750	614.9
10% Stearic acid	0-382	207.2	382-750	542.4
15% Stearic acid	0-505	268.43	505-1024	673.99
20% Stearic acid	0-383	223.6	383-750	515.14

Table (2): The size range and mean particle size on using GMS:

	Size range	Mean particle size	Size range	Mean particle size
0 % GMS	0-400	195	0	0
5% GMS	75-505	385.62	505-1025	763.18
10% GMS	75-505	338,91	383-1250	707.83
15% GMS	75-505	368.31	635-1250	696.02
20% GMS	75-505	361.54	505-1250	771.17

The first part of bimodal size range of all products is shifted from that of the drug with different mean particle size indicating the effect of GMS on the granulation of the drug is not only from increasing the mean particle size but also from the value of particle size range (table 2). Also from figure (2), it can be notice that, the highest peak intensity of the first part of bimodal has the lowest peak intensity in the second part of bimodal which means there is a regular order of intensity arrangment which is correlated to the percent of GMS concentration used. For the same GMS concentration used, the concentration which has highest peak in the first part of bimodal has lowest peak in the second part of bimodal and vise versa. This observations were not found in case of using different concentrations of stearic acid as a granulating agent. Comparing the effect of the same binding agents concentration on the frequency distribution curve of paracetamol was also studied (figure 3,A-D).

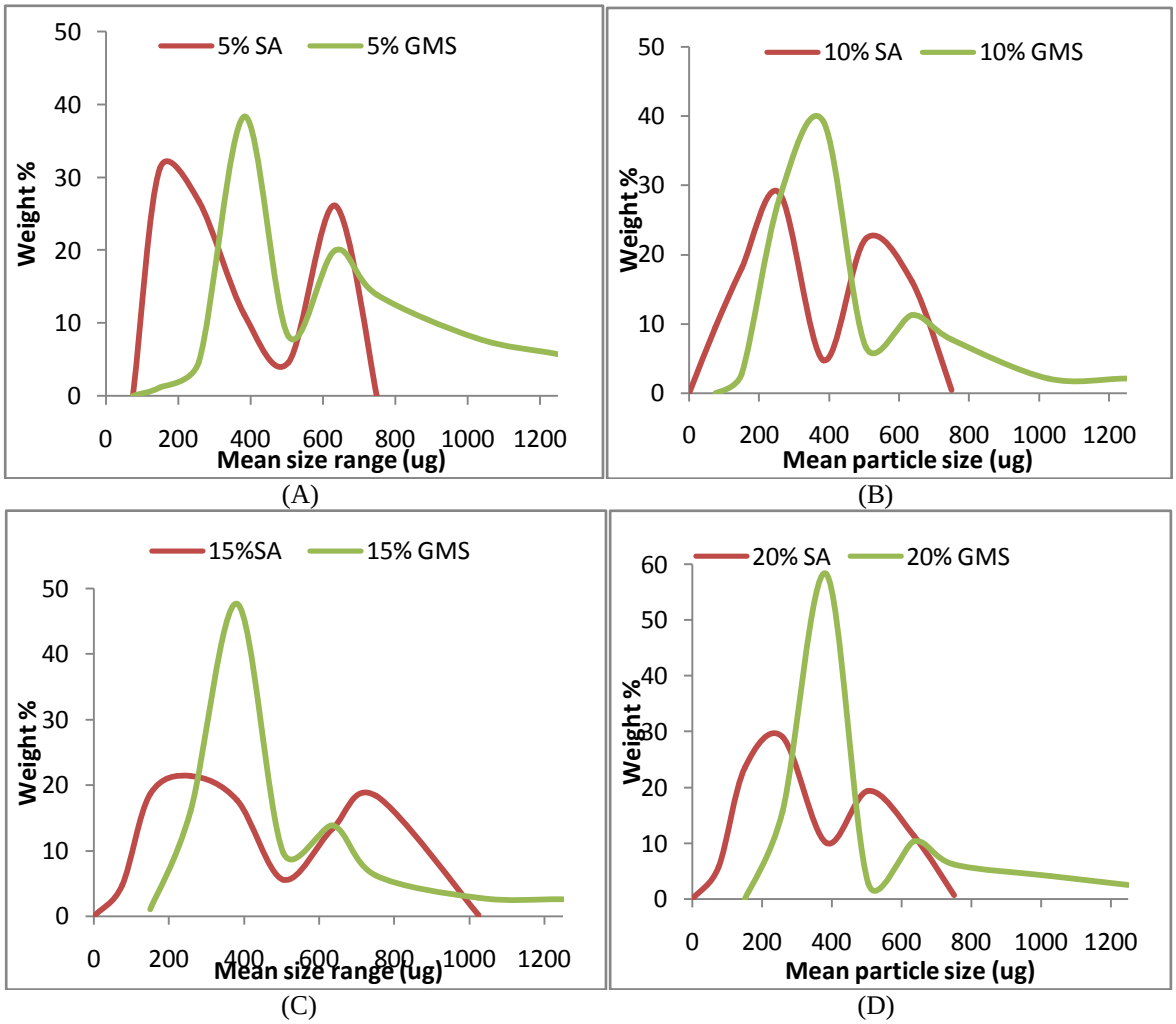


Figure (3): Comparing the effect of the same concentration of binding agent on the frequency distribution curve of paracetamol.

From the figure it can be noticed that the frequency distribution curve of the product prepared by using GMS showed a symmytrical peak of the first one of the bimodal curve which increased with increase the concnetration of GMS used. The best one is that obtained on using 20% GMS indicating there is the possibility to get more better product with better frequancy distribution curve on using higher concentration of GMS but this may be lead to formulation of sustained release dosage form which is not the aim of this work. Also in every case the second peak of bimodal shows a positive skewed. These findings are not observed on using stearic acid as a graulating agent but it can easly noticed the symmetry of the two bimodal peaks will be better with an increase the concentration of stearic acid. From above it can be concludede that, the granules prepared on using GMS as a granulating agent have better frequancy distribution than that prepared on using SA.

A normal distribution curve may occur when a apopulation sonsists of one group with the same attribute. It was noticed that after the heating of paracetamol powder, the frequency distribution curve is unimodal with high singl hump that is may be due to the high melting point of the drug. The addition of either SA or GMS as a powder to the drug powder, mixing and then heating led to a frequancy distribution curves with two humps called bimodal. The bimodal distribution may occur when a population consisits of two groups with different attributes. The first peak in the bimodal in case of using stearic acid as a granulating agent located nearly in the same range of that of the drug and has a positive shifting in case of using GMS. Accordingly it can be concluded that the bimodal distribution occurred as a result of the drug powder consists of two groups with different particle size granules.

The process of granulation consists of a combination of three phases (figure 4) [15]: (1) Wetting and nucleation, (2) Coalescence step and (3) Attrition and breakage.

(1) Wetting and nucleation step: During the nucleation step the binder comes into contact with the powder bed and some liquid bridges are formed, leading to the formation of small agglomerates. Two nucleation mechanisms are proposed by Schafer and Mathiesen [16] which are immersion and Distribution.

(a) Immersion: Nucleation by immersion occurs when the size of the molten binder droplets is greater than that of the fine solid particles. Immersion proceeds by the deposition of fine solid particles onto the surfaces of molten binder droplets.

(b) Distribution: In the distribution method a molten binding liquid is distributed onto the surfaces of fine solid particles. The nuclei are formed by the collision between the wetted particles. Generally, small binder droplet size, low binder viscosity, and high shearing forces are favorable conditions for nucleation by the distribution method.

(2) Coalescence step: It involves nuclei that have residual surface liquid to promote successful fusion of nuclei. The surface liquid imparts plasticity to the nuclei and is essential for enabling the deformation of nuclei surface for coalescence as well as promoting the rounding of granulation.

(3) Attrition-breakage step : Attrition and breakage refer to the phenomenon of granulation fragmentation in that are solidified by tray cooling to ambient temperature without the need for drying by a tumbling process. Consequently, breakage is known to have a more essential role in affecting the resultant properties of the melt granulation during the granulation phase.

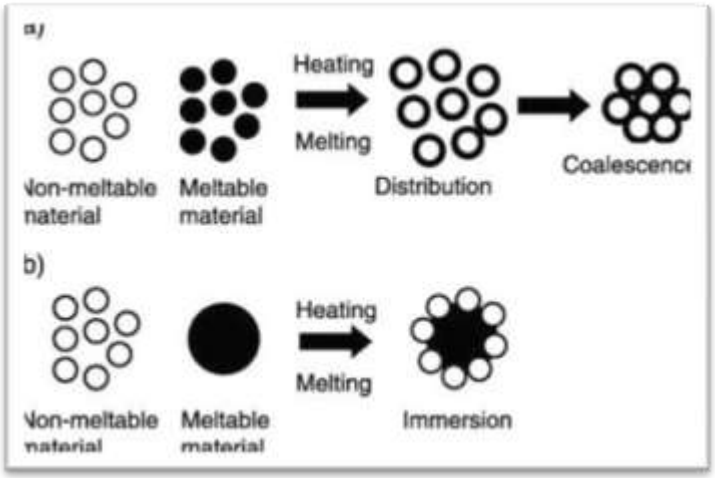
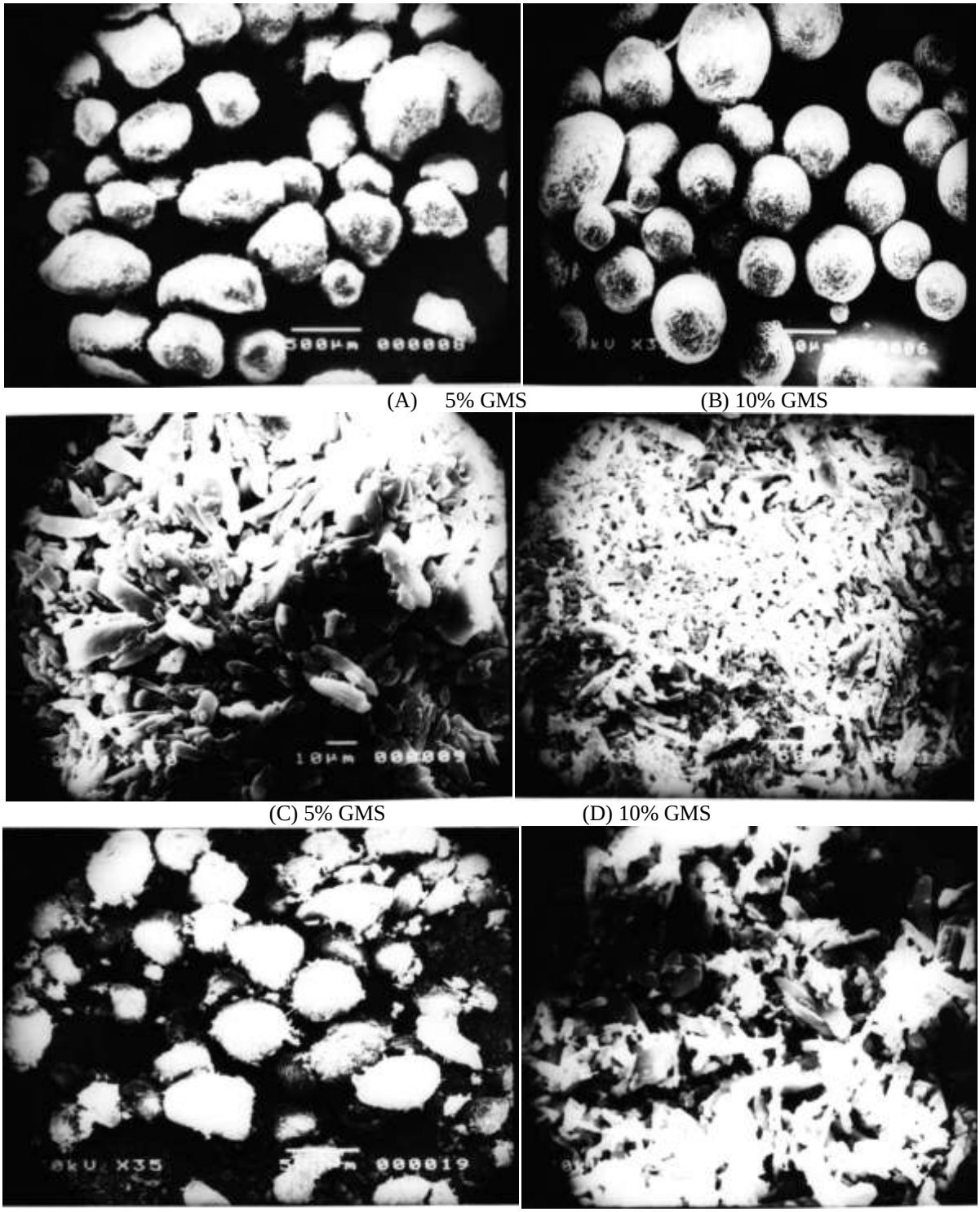


Figure 4: Modes of melt agglomeration: (a) Distribution and (b) Immersion

The granulating agents used added as a solid binder which is melted after mixing with the drug powder . The temperature of the mixture is started to increase using water path while stirring at 80℃. GMS is melted at 56-58℃ while SA at 69℃ [17]. Accordingly it can be expected that GMS will be rapidly liquid and also remain longer than SA in liquid stat. That gives GMS the chance to produce nucleation by both immersion and distribution mechanism. Not only that but also the coalescence of the produced nuclei will be optimal because lower melting point of GMS which means the nuclei have residual surface liquid to promote a successful fusion. In addition the roll of the emulsifying property of GMS should be also considered in the nucleation and coalescence steps and also on changing the surface characters of the formed nuclei. The surface liquid on the nuclei imparts plasticity to the nuclei and is essential for enabling the deformation of nuclei surface for coalescence as well as promoting the rounding of granulation which can be noticed from electron scanning photograph (Figure 5). Figure (5A) shows irregular paracetamol granules prepared on using 5% GMS which became spherical when prepared by using 10% GMS (figure 5B) [18]. The effect of GMS on the coalesces of the drug crystal can be noticed from figure (5C) which is the same figure (5A) with higher magnification. From the figure it can be noticed the coalesces of the aggregated drug crystals but it can be also distinguish the drug crystals which indicate the change on its surface. The coalescences of the drug crystals will be better noticed from figure (5D) which is like figure (5B) with higher magnification. From the figure it can be noticed that the coalescence is denser and the drug crystal cannot really so easy to distinguish. These finding will support the explanation stated before. At the same time and due to the higher melting point of SA and its solid distribution in the drug powder, it can be expected the nuclei formation would be occurred by immersion mechanism. That is may be as a result of; when SA particle soften or melted it will be rounded with drug particles which is shielded the SA particle from further heating. This led to control the coalesces of the formed nuclei, formation of powder with small mean particle size and the formed particles will have irregular surface in case using higher concentration of SA. In addition SA has not surface activity like GMS. This explanation is also supported with finding stated before about the frequency distribution curve of the products prepared on using SA. Also figure (5E) shows the irregular particles formed on using 20% SA as a granulating agent. In addition figure (5F) which is the same figure (5E) with higher magnification shows loose aggregated drug particles prepared on using 20% SA.



(A) 5% GMS (B) 10% GMS

(C) 5% GMS (D) 10% GMS

(E)20% SA (F)20% SA higher magnification

Figure (5): Electron scanning microscope (ESM) for different products:

Process quality control parameters (Angle of repose, Loose bulk density (LBD), Tapped bulk density (TBD), Carr ̀s index and Haunsr ̀ratio) were evaluated for the flow properties and the compressibility of each granules prepared by either using SA or GMS as granulating agents. Bulk density is very important in different steps from transport of the raw material passing the manufacture process till to commercial product. It accounts not only for the volume of the solid portion of the particles (true density), and the voids within each particle (internal porosity), but also for the voids between the particles [19]. From table (3) it can be noticed that the bulk density of the products was increased with increasing the concentration of SA which has a linear relationship till 15% with r^2 equal to 0.98 but the value of r^2 will be 0,707 on using the value of the bulk density at 20% SA. In case of using GMS, The bulk density was increased with increasing the concentration of GMS till 15% GMS used without any linear correlation and then markedly decreased on using 20% GMS (Table 5).

Table (3): In process quality control parameters of granules prepared by SA:

	0 % SA	5% SA	10% SA	15% SA	20% SA
Bulk density (g/cm^3)	0,320	0,321	0,323	0,325	0,342
bulk volume (cm^3/g)	3,125	3,115	3,096	3,077	2,924
Taped density (g/cm^3)	0,431	0,445	0,454	0,464	0,496
Carrs index	25,754	27,865	28,855	30,000	31,048
Hausner ratio	1,316	1,386	1,406	1,428	1,450
Angle of repose	50,123	52,346	52,474	54,808	55,555

Table (4): kinetics data of the correlations between the physical properties and SA concentrations.

	r^2	k	intercept
Bulk density	0.9797	0.034	0.3197
Tapped density	0.9274	0.298	0.4282
Carrs index	0.975	25.446	26.16
Hausner ratio	0.9124	0.62	1.3352
Angle of repose	0.9466	26.652	50.396

Table (5) : In process quality control parameters of granules prepared by GMS:

	0 % GMS	5% GMS	10% GMS	15%GMS	20%GMS
Bulk density	0,320	0,334	0,496	0,547	0,397
Balk volume	3,125	2,994	2,016	1,828	2,519
Taped density	0,421	0,451	0,584	0,594	0,457
Carrs index	25,754	25,942	15,068	7,912	13,129
Hausner ratio	1,316	1,350	1,177	1,086	1,151
Angle of repose	50,123	50,392	37,117	37,493	33,690

It was reported that, the bulk density increases when the powder particle size distribution has been changed such that smaller particles filter into the interstices created by the orientation of the large particles [19]. This explanation is also in agreement with what observed from the bimodal particle size distribution curve which stated before. The interesting finding is that, in case of using SA, the regression intercept of bulk density has the exact value of the balk density of the pure drug which is preheated and measured under the same condition (table 4). This finding will support the regular change of the bulk density till 15% SA. At 20 % SA the value of bulk density will be higher than before but in case of using GMS it is markedly lowered. That is may be due the change in the particle size which is reflected on the products frequency distribution stated before. Another measure often used is bulk volume, which is the reciprocal of balk density was also calculated (table 3, 5) and the results show that the balk volume decrease as concentration of SA and GMS increased [19].

The tapped density which is measured after mechanical tapping of the cylinder containing the powder till no volume change observed. This led to an increase from the initial bulk density to final bulk density (also known as tapped density, equilibrium or consolidated density) when it has attained its most stable i.e. unchanged arrangement [20]. From table (3) it can be noticed that at all SA concentrations used the value of tapped density is higher than that bulk density. Also there is a linear correlation between SA concentrations used and the tapped density indicating the value of tapped density depends on the concentration of SA (table 4). In case of using GMS (Table 5), it can be observed that the tapped density is higher than that bulk density without any correlation to the concentration of GMS used.

Hausner ratio values were also calculated to predict both interparticle friction and the flow properties of the products [20]. From table (3) it can be noticed that the flow of pure preheated drug is passable (may hang up) while that for the products prepared on using SA are poor (must agitate/vibrate) [21]. There is also correlation between Hausner ratio values and the concentrations of SA used (table 4). The value of r^2 will equal 0.999 with rate constant 0.428 and intercept of 1.364 if the value of preheated drug excluded from the correlation. The same results can be also noticed in case of studying the compressibility percent and angle of repose. These results indicated that the increasing in the Hausner values, compressibility percent and angle of repose are related to the concentration of SA used.

In case of using GMS the flow of the products changed from passable in case of pure drug and on using 5% GMS to fair (aid not needed) on using 10% GMS to excellent on using 15%GMS and then to good on using 20% GMS. These results indicated that the flow property of the product prepared on using GMS increased with increasing GMS concentration. That is may be due to spherecity of the granules as stated form ESM before. The flow property of the product prepared on using 20% would be noticed lower than that on using 15% GMS which could be due increase the surface hydrophobicity of the granules during coalescence step as a result of increasing the concentration of GMS. The same results can be also noticed in case of studying the compressibility percent and angle of repose. These results indicated that the increasing in the Hausner values, compressibility percent and angle of repose are related to the concentration of GMS used. Hausner ratio values showed that powders with low interparticle friction, such as coarse spheres, had ratios of approximately 1.2 whereas more cohesive, less free-flowing powders such as flakes have Hausner ratios greater than 1.6 [20].

From table (3) it can be noticed that Hausner ratio values, in case of SA, are between 1.386 and 1.450 indicating that the products have mixture of different particle sizes and shapes which is reflected on the bimodal distribution curve stated before. In case of GMS the values are lowered to be 1.086 indicating the spherecity of the products which also noticed by ESM (table 5).

CONCLUSION:

From the above it can be concluded that it can add the waxy granulating binder in the powder form at low concentration to produce granules with normal stirring process and elevation of the temperature. Such technique in this way will reduce the preparation steps and produce drug granules for tableting at low binder concentration to avoid the retarding effect. Also to qualify the prepared granules, particle size distribution curve can be used as a tool for the granulation process.

REFERENCES:

1. Wells J, Langridge J, Dicalcium phosphate dihydrate-microcrystalline cellulose systems in direct compression tabellting. *Int.J. Pharm. Technol. Prod. Mfr*, **2012**; 2: 1-8.
2. Mollan M, Celik M, Tabletting of maltodextrins and acetaminophin mixtures, *Drug Dev. Ind. Pharm*,**1994**; 20: 3131-3149.
3. Lin M, Duncan-Hewitt W, Deformation kinetics of actaminphen crystals. *Int. J. Pharm*, **1994**; 106: 187-200.
4. Malamataris S, Hatjichristos TH, Rees J. Apperent compressive elastic modulus and strength isotropy compacts formed from binnary powder mixes. *Int. J. Pharm*, **1996**; 141: 101-108.
5. Parmentier W., Warum deckeln tabletten? . *Harm. Ind*, **1980**; 42: 752-756.
6. Barlow C, Harrison W. *Britich Patent,* **1975**; 1: 390,032.
7. Vogel U, US Patent, **1984**; 4,469,453.
8. Schaefer T, Holm P, Kristensen H. *Drug develop. and ind. pharmacy*,**1990**; 16(8): 1249-1277.
9. Kinget R, Kemal R, *Acta pharma. Technol*, **1985**; 31-57.
10. Flanders P, Pryer G, Jordan D. *Drug dev. Ind. Pharm*, **1987**; 13: 1001.
11. Rubinstein M. and Musikabhumma P. *Drug. Dev. Pharma*, **1980**; 6(5): 451-473.
12. Martindale "the extra pharmacopoeia" twenty-ninth, the Pharmaceutical press, **1989**, london.
13. Behera B, Sao S, Dhal S, Baric B and Gupta K. Characterization of Glipizide-Loaded Polymethacrylate Microspheres Prepared By an Emulsion Solvent Evaporation Method. *Trop.J.Pharm.Res*, 2008; 7(1): 879-885.
14. Bryan J. Ennis, Theory of Granulation: An Engineering Perspective Granulation, Chapter 2 Handbook of Pharmaceutical Technology, Third Edition, Read more http://informahealthcare.com/doi/abs/10.3109/9781616310035.002.
15. Sree B, Siva N, Swetha M, Gupta M, Devanna N and Madiha S. *Der Pharmacia Lettre*, **2013**; 5(1): 107-115.
16. Schafer T, Mathiesen C. Melt pelletization in a high shear mixer. IX. Effect of binder particle size**.** *Int. J Pharm*, **1996**; 139: 139-148.
17. Merck index, 11th edition, **1989**; 705.
18. Ravidra K, Ajaykumar, Kakasaheb M, Anant P. Ibuprofen-gylcryl monstearate beads using melt solidification, *International Journal of Pharmacy and Pharmaceutical Sciences*, **2010**,2(4): 100-104
19. Liebermann A, Lachman L, Schwarz. Pharmaceutical dosage forms, tablets, 2nd ed volume 3, Marcel Dekker, **1990**; 165-167.
20. Aulton M. Pharmaceutics the science of dosage form design, Churchill livingstone, **1996**; 612.
21. Singh I, Kumer P. Preformulation studies for direct compression suitability of cefuroxime axetil and paracetamol: A graphical representation using SeDeM diagram. Acta Poloniae–*Drug research*, **2012**; 69(1): 8793.