

**Charles University in Prague**  
**Faculty of Pharmacy in Hradec Kralove**

Department of Pharmaceutical Technology

**FLOW EQUATION OF GRANULES PREPARED  
FROM SORBITOL**

Diploma Thesis

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## **Statement of originality**

I declare that this diploma thesis is my own, original, personal work. All literature and other resources I used while processing are listed in the reference list and are properly cited.

Date:

Signature:

# Acknowledgments

I would like to express my great appreciation and gratitude to my supervisor Assoc. Prof. PharmDr. Zdenka Sklupalova, Ph.D. for her patient guidance, enthusiastic encouragement and useful critiques throughout this work. I wish to acknowledge the very valuable help of Ing. Hana Hurychová, Mrs. Fendrichová and everyone in the department of pharmaceutical technology for their special assistance that without their passionate participation, my research could not have been successfully conducted. I would also like to extend my thanks to my lovely family and friends for their endless support.

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# 1 Abstract

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Title of Thesis:                          Flow equation of granules prepared from sorbitol

The aim of this thesis is to study the flow and compression behaviour of size fractions of the granules prepared from sorbitol by wet granulation method. The granules were classified according to their size. A bimodal distribution was observed. The polynomial relationship between angle of repose and the particle size was detected as well as between the latter and bulk density measured in a volumeter. The mass flow rate  $Q$  (g/s) through the circular orifice of a conical stainless steel hopper was measured and a mathematical model of Jones – Pilpel power regression was applied to describe the relationship between the mass flow rate and the diameter of the hopper orifice. Using parameters of the generated equation, the average precision of mass flow rate prediction of 4.29 % was detected for the granules regardless of the particle size.

## **2 The aim of study**

In the theoretical part of this thesis, the aim is to refer to main principles of the wet granulation process. Variables affecting flowability and the mathematical procedures used to express the relationship between the flow rate, the bulk density and the hopper diameter (the flow equation) are referred to.

The experimental part would study the flow and compression behaviour of size fractions of the granules prepared from sorbitol by wet granulation method. The standard pharmacopoeial methods are used in testing. The relationship between the particle size and the mass flow rate through the orifice of a stainless steel conical hopper is studied and modelled by the Jones-Pilpel power equation.

### 3 List of abbreviations

Symbol	Unit	Meaning
A	-	Parameter of JP equation
AOR, $\alpha$	°	Angle of repose
b	cm <sup>2</sup>	surface of a circular base
CI	-	Compressibility index
D	cm	Diameter of the hopper orifice
D <sub>0</sub>	cm	Inner diameter of the hopper
d <sub>b</sub>	g/ml	Bulk density
d <sub>p</sub>	g/ml	Pile density
d <sub>t</sub>	g/ml	Tapped density
g	cm/s <sup>2</sup>	Acceleration of gravity
h	Cm	Height of a pile
HR	-	Hausner ratio
M	G	Mass
n	-	Exponent (Parameter of JP equation)
Q	g/s	Flow rate
Q <sub>pred</sub>	g/s	Predicted flow rate
R	cm	Radius of the base
r	-	Coefficient of correlation
RH	%	Relative humidity
SD	-	Standard Deviation
V	ml	Volume
x	Mm	Particle Size
x <sub>50</sub>	Mm	Median particle size
x <sub>90</sub>	Mm	Particle size representing 90% of cumulative undersize distribution
$\Delta$	%	Percentage deviation
$\Sigma$	g %	Sum
d <sub>true</sub>	g/ml	The true density

## **4 Introduction**

Drugs have been produced in many dosage forms, however, the most used and significant ones are tablets. It offers the easiest and most convenient type of administration, plus, they have many advantages including simple, fast and economical production. The main applied way of tablet manufacturing is through the compression of granules made by wet granulation which confirms the importance of granulation in pharmaceutical industry. Even though it usually require expensive equipment and additional drying step, particle size and drug content uniformity and enhanced mechanical characteristics compared to the corresponding powders are among the many advantages of wet granulation (Florence and Siepmann 2009).

## **5 Theoretical section**

### ***5.1 Granulation***

The process of aggregating particles together into bigger clusters where the initial particles are able to be identified is called granulation. By this transformation of powders to granules we minimize dust and the potential for explosion and inhalation. The other advantages of the granulation process include better control, handling and promote the flowability; rise the bulk density; keep considerable part of the surface; reduce particle segregating risk, and improve the compaction properties (Iveson et al. 2001).

#### **5.1.1 Development**

In the past centuries, honey and sugar were used combined with pharmaceutical drugs to produce the required pills, which was before the 19<sup>th</sup> century when tablets pressing techniques arose. From that time, due to increasing need for tablets, perceiving of more materials and the growing of new processes and techniques, granulation usage began to widen in the pharmaceutical industry. Now, granules are mainly used in the production of tablets, plus they can be employed in filling of hard capsules and when the medications' doses are huge to swallow orally, granules can be used in sachets products (Cantor et al, 2008).

#### **5.1.2 Granulation types**

Granulation can be divided mainly into two types: wet and dry granulation. In wet granulation, the powder particles are mixed and sprayed by a fluid binding substance which plays the role in establishing forces between particles to form the granules. The second type is dry granulation where there is no liquid usage. Two rotating cylinders compress the dry powder into a hard mass which is then grinded into granules (Bacher et al, 2008).

To be more accurate and detailed, granulation can be classified according operating process into 8 regimes (Cantor et al, 2008):

- (1) Dry granulation: aggregating the dry powder particles by direct physical compressing,
- (2) Wet high shear granulation: aggregating of particles by addition of liquid binder with high-power-per-unit mass through high shear mixing,
- (3) Wet low shear granulation: aggregating of particles by addition of liquid binder with low-power-per-unit mass through low shear mixing,
- (4) Low shear tumble granulation: aggregating of powder particles by addition of liquid binder with low-power-per-unit mass through rotating of the container tank or/and intensifier bar,
- (5) Extrusion granulation: forcing a mass through a sized orifice while applying linear shear forces,
- (6) Rotating granulation: centrifugal or rotational forces done by rotating wall or/and rotating disk that leads to spheronization, aggregating and/or densification of a mass which can be dry or wetted, in this process, liquid and/or drying can be incorporated too.
- (7) Fluid bed granulation: aggregating of powder particles using atomized granulation liquid on these particles with little or no shear with continuous gas stream.
- (8) Spray dry granulation: atomization of liquid that contains suspended or dissolved solids and producing of dry particles by controlled gas stream.

### **5.1.3 Granules characterization**

Assessing dosage form can be done by characterization program that can be applied, for example, to granules to examine their chemical and physical attributes. Product research and its development are the main terms when this characterization is carried out. (Parikh, 2005)

- Particle Morphology

Optical microscopy or scanning electron microscopy are the main techniques to study particle morphology. To quantify particle shape, various methods are used, Heywood coefficients are the most common. This coefficient is defined as “the ratio of the surface shape coefficient to the volume shape coefficient (Parikh, 2005). Granules shape affect other properties, for example, increasing shape coefficient decreases bulk density and flow rate of the tested particles.

- Particle Size Distribution

Measuring particle size distribution is conducted by sieve analysis, optical microscopy, laser light scattering. Sieve analysis is the most appropriate and convenient technique. Optical microscopy is demanding, but it offers an accurate measurements unlike laser light scattering which is not often used in granules testing due to their wide size distribution.

- Powder X-ray Diffraction

While processing with granules, polymorphic changes may occur to crystal form of the granules, to detect and analyze these transitions, x ray diffraction may be used. This method define and determine the crystalline form of the tested particles.

- Thermal Analysis

In which changes of granular substances is recorded while varying temperature. Many types of thermal analysis exists, however differential scanning calorimetry, differential thermal analysis and thermogravimetric analysis are the most used.

- Near Infra-Red Spectrophotometry

Near infrared spectroscopy is a quick method that can be conducted to measure the moisture content and to identify any changes to material during granulation. It's a fast, nondestructive technique in which absorption is essentially caused by overtones and combination vibrations.

- Electrostatic Charge

When two materials come into contact and then they separate, some electrons move from one to the other forming electric charge so called static charge which may influence the handling of the material, for example, ungranulated acetaminophen

powder has more static charge than the granulated one that leads to worse flow of the powder form (Parikh, 2005)

- Surface Area

One of the most profound properties of granules is their surface area which can affect various different characteristics of the granules. To measure the surface area, gas adsorption is the most used technique, however liquid penetration methods are used for the same purpose.

- Porosity of the granules

Pores sizes and their distribution in granules is measured mostly by mercury intrusion techniques where a pressure is applied to the mercury liquid to fill the pores and its volume is recorded. Higher granular porosity, for instance, increases their tendency to form stronger tablets.

- Granules Strength

Several factors contribute to granular strength: (1) solid bonds between particles, (2) interfacial forces and capillary pressure that exist in liquid surfaces, (3) affinity between particles, (4) bridges' cohesive and adhesive forces, (5) mechanical particle interlocking. To measure granules strength, there are many approaches. One of the most used is by recording the required force to crush the granules.

- Granular Flow and Density

Granules flow behavior is a critical factor that can be influenced by many elements, such as, the equipment used for handling with granules and their physical properties. To estimate flowability more directly, flow through an orifice method can be carried out in which the flow rate during the discharge of a hopper is measured. Angle of repose (AOR) measuring technique assesses inter-particulate friction and cohesion between granules providing us with a profound fundamental evaluation of flowability. In general, the higher it gets, the worse the flowability of the material becomes. Compressibility can be also measured to evaluate the flow behavior. The percentage compressibility (the Carr's index, CI) is commonly used to express flowability according to the European Pharmacopoeia 8.0 (2.9.35). Using a shear cell

in which the resistance to shear is recorded can give us even a better assessment of granular friction and cohesion forces.

- *Moisture Content*

Final dosage form performance can be affected by moisture content of the used granules, this shows the importance of controlling this parameter. Flow behavior, stability, tablet disintegration and compression, crystal behavior and capsule fragility are the main factor that are affected by the moisture content. Moisture analyzer is a very popular used technique determining the water content.

## ***5.2 Wet granulation***

Pharmaceutical tablets are by far the most common dosage form and most of these preparations are formulated from granules prepared by wet granulation which shows the importance of this method of granulation. It's the first choice approach for many formulations apart from its dose. It's popular because of its positive effects on the drug substance including: better compatibility with the used excipients and active ingredients, homogenous distribution of drug, better flow and more controllable drug release. Furthermore, by this method we are able to bring other agents such as stabilizing agents into direct contact with the drug that can play a big role in stabilizing the formulation more. Complexity is one of the disadvantages of this approach, in addition to that, water usage may bring some undesirable effects on the drug affecting its stability. Despite these downsides, it's the most applicable method used nowadays (DFE pharma, manufacturer's information).

### **5.2.1 Types of wet granulation**

Low shear, high shear and fluid bed granulation are the three main types of the wet granulation process.

Low shear granulation is the traditional way where a low speed mixer is used to stir the drug with its excipients which are sprayed by a binder solution. The resulted mass is screened followed by drying of the granules. The dried particles are sieved or

milled and mixed with other excipients. Long drying time, manual handling and open nature of this equipment are its main disadvantages.

High shear granulation uses two high speed mixers: an impeller and a chopper. By this faster method, a very efficacious mixing is done with the low consumption of water. In this type, less manual handling is needed and the high shear mixer is a closed bin. Plus, this regime can be applied to various types of formulations. Overgranulation can be a disadvantage of this intense blending. The mutual downside of the low and high shear granulation is the direct contact of water with the drug and its excipients for a considerable amount of time which may trigger some unwanted changes to these substances.

The disadvantage discussed in shear granulation is minimized in Fluidized bed granulation which consists of fluid bed processor that contains the drug with its excipients and the mix is sprayed by a liquid binding agent with permanent drying by warm air. In this processor, three procedures take place: mixing, granulation and drying. Blending by fluidizing air steam to warm the particles while providing homogeneity too. Granulation is proceeded by applying the binder and finally drying of these formed granules. All of these processes occur in the same equipment which is the main advantage of the fluidized bed granulation. In addition to the downside that using air flow may entrain the fine micronized particles, some specific mixtures of drugs and excipients cannot be fluidized, however, these issues can be solved by a pre-mix preparation (DFE pharma, manufacturer's information).

### **5.2.2 Excipients used in wet granulation**

In wet granulation process, many common excipients can be used. Binders, diluents, disintegrants and lubricants. Stabilizing agents, wetting agents and colorants can be used too. Binders are often hydrophilic polymers applied in the process as solutions to ease granular growth and to improve compressibility such as starches, cellulose derivatives, for example, hydroxypropyl cellulose and povidone. Diluents are used to provide bulk helping manipulation of the granules. Microcrystalline cellulose, lactose and mannitol are the most used diluents in wet granulation. Lubricants, for instance,

magnesium stearate, sodium stearyl fumarate and stearic acid plus talc combination are commonly used to minimize inter-particular friction between the granules enhancing flowability. Croscarmellose sodium, sodium starch glycolate and crospovidone are commonly used disintegrants to ease disintegration of granules releasing the active substance. Other excipients can be used to improve granules' properties depending on the used formulation, for example, stabilizing agents may be used to protect drug from undesirable reactions such as sodium carbonate. (DFE pharma, manufacturer's information).

### 5.2.3 Granulation behavior

- **Particle-liquid interaction**

To describe granulation, group of three procedures should be explained and they are: (Iverson et al.2001)

- 1) **Wetting and nucleation:** when the dry powered particles are exposed to the liquid binder and this contact leads to the nuclei formation of the granules.
- 2) **Consolidation and growth:** where the granules collide with each other or with the power particles or with the hard surface of the instrument, hence the granules become bigger and harder
- 3) **Attrition and breakage:** this happens when the formed granules degrade into smaller particles due to friction, collisions or other forces during production or while handling.

In Figure (1): description of the liquid bridge between 2 solid particles of the same size:

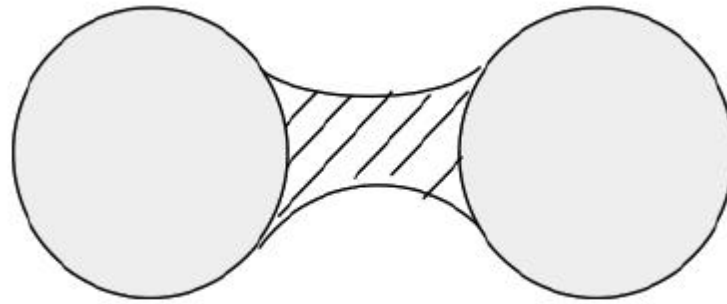
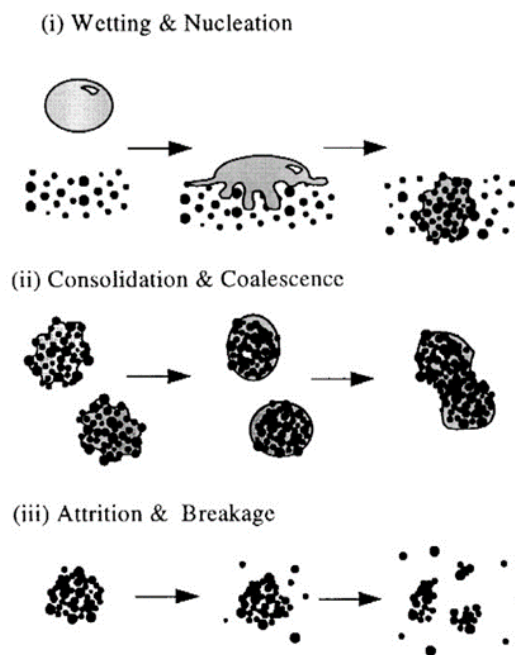


Figure (1): Schematic of the liquid bridge formed between two particles (Cantor et al, 2008)

In the following Figure (2), you can see these processes describing the granulation.



Figure(2): Illustration of the formation of granules during the wet granulation (Iverson et al.2001)

- **Particle-particle interaction**

In particles interaction, there are 5 main types of bond formation mechanisms: (1) Solid bridges: Dissolution by the solvent during granulation followed by drying leads

to solid bonds formation. Heat hardening and chemical processes can create also these bridges. (2) Immobile liquids: this type of bonds is formed by the usage of binders that take up the solvent and attach and adhere to the particles and become hard after drying establishing these bridges. (3) Mobile liquids: these bonds are formed when liquids fill the gaps between the particles creating fluid bridges. (4) Intermolecular and long range forces: these links are generated by van der Waals and electrostatic forces. (5) Mechanical interlocking: pressure during granulation can lead to granular deformation and modification to create shape related links or causes fiber-like particles to twine together forming these bonds. (Cantor et al, 2008)

### ***5.3 Granular flowability***

In many industries flowability is one of the major elements; especially for the pharmaceutical industry where it is a very critical character of powders and granules in manufacturing of solid dosage forms. Different procedures and processes which are carried out on granules such as mixing, transport, compressing and storage depend on particles flowability; furthermore, one of the most important causes to transform powders to granules is to improve its flow. Good flowability doesn't have a specific single definition, however it mainly means that the particles are able to flow spontaneously without any aid.

When the particles flow through funnels or hoppers, there are two types of flow that may occur: mass flow or funnel flow.

In ***mass flow*** which is the more appropriate regime, all particles are moving. The first particles which enters the hopper are the ones which exit first from the end so this regime is called also (first-in-first-out) type.

***Funnel flow*** happens when the middle core of the particles is the first to exit the funnel followed by the particles that remained in the sides which are actually the first part that entered the hopper so this type of flow is called also (first-in-last-out). A (rathole) case occurs when the material that resides on the edges of the hopper doesn't flow at all and remain there. Another special case can happen when an arch

is formed in the lower part of the funnel which leads to blockage of the flow. If this dome is deformed, chaotic flow or (flooding) can happen. For more illustration, figure (3) describe the previous regimes: (Emery 2008).

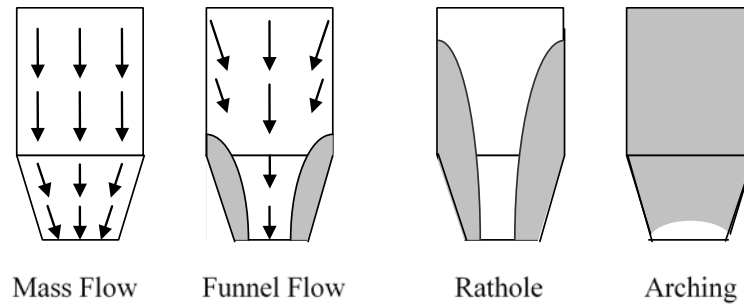


Figure (3): illustration of the flow types and its common issues (Emery 2008)

### 5.3.1 Variables affecting flowability

Many factors affect flowability of powder and granules. Particles size, shape and moisture content are the main influencing variables. Increasing the moisture content increase the liquid bridges between the particles leading to stronger binding forces that decreases the flowability. Smaller particles have generally lower flowability due to their larger surface area allowing more cohesive forces to form (Fitzpatrick et al, 2004). Granular flowability is influenced also by the particles shape because it defines the quantity of friction points between each of the grains which subsequently affect the inter-particle forces. (Emery, 2008).

### 5.3.2 Measuring flowability

As discussed earlier, flowability is a complex value that depends on many variables so there isn't only one specific test to evaluate it and one defined value cannot express it. The reason for this is that flowability is an observation and an outcome of both of the effects of particles properties plus the used equipment. The evidence for this is that one single powder can flow readily in one hopper and in another equipment cannot. Similarly, some particles flow freely and different ones flow poorly using the same single equipment. Therefore, many tests are conducted to

express flowability such as angle of repose (AOR), bulk and tapped densities expressed by Hausner ratio and Carr's index or flow through an orifice. (Prescott, Barnum 2000).

## ***5.4 Describing flowability mathematically***

Discharge of the powder through an orifice by gravity forces is the general test to evaluate flowability. Powder flow rate can be defined as a power law where the mass flow rate is proportional to the orifice diameter raised to the power 5/2 (Brown and Richards 1960; Beverloo et al, 1961)

This law has enough robustness for many particles types apart from density, surface properties, shape and packing fraction when the orifice diameter is more than 6 times of the particle diameter.

Common guidelines and conditions, describing the relationship between particle diameter  $D$  and geometry of the hopper, have been proposed to have a reliable and uniform powder discharge through the orifice and they are:

(1) The inner diameter of the hopper  $D_0$  is more than 2.5 times of the orifice diameter ( $D$ ):

$$D_0 > 2.5 D \quad (1)$$

(2) The difference between the inner diameter of the hopper and the diameter of orifice is more than 30 times of the particle diameter  $x$ :

$$D_0 - D > 30 x \quad (2)$$

To evaluate flow rate of a powder through a hopper, various equations have been introduced. In general, the mass flow rate  $Q$  (g/s) depends on the orifice diameter  $D$  average particle diameter  $x$  and powder true density  $d_{\text{true}}$ . The first main equation was proposed by Brown and Richards (1960):

$$\frac{Q}{(\pi/4) \cdot d_{\text{true}} \cdot g^{1/2} \cdot (D - k \cdot x)^{5/2}} \quad (3)$$

Where acceleration of gravity  $g$  (equals to  $980.6 \text{ cm/s}^2$ ) and  $k$  is the dimensionless shape coefficient. The authors assume that particles centres cannot approach the orifice's edge within a distance  $(k \cdot x/2)$ , therefore,  $(k \cdot x)$  was the term which was

interpreted as the “empty annulus” which resembles this phenomenon (Brown and Richards, 1960)

The more applicable equation is called Beverloo equation (Beverloo et al, 1961), in which the dimensionless discharge coefficient  $C$  represents the quadrature of the circle ( $\pi/4$ ), considering that  $C < (\pi / 4)$ . According this equation, flow rate  $Q$  can be measured by:

$$Q = C \cdot d_b \cdot g^{1/2} (D - k \cdot x)^{5/2} \quad (4)$$

Due to the difficulties measuring the true density in Brown and Richards equation, bulk density is here expressed. ( $C, k$ ) are empirical coefficients which have to be defined in experiment. Value of  $k$  can differ, however, a range of ( $1 < k < 2$ ) is often referred with  $k=1.5$  as a mean value (Beverloo et al, 1961)

Newer equations were developed, suggesting a variable exponent expressed by  $n$  rather than the constant  $5/2$  to offer more manipulation. This modified flow equation was proposed by Jones and Pilpel (Jones, Pilpel. 1966)

$$D = \left[ \left( \frac{4}{\pi} \right) \cdot \frac{Q}{d_b \cdot g^{1/2}} \right]^{1/n} \quad (5)$$

Where  $n$  is the parameter of this equation. Even though, this substitution with  $n$  makes evaluating the flow rate  $Q$  more difficult, it can improve accuracy of the measurement.

## **6 Experimental section**

### ***6.1 Materials***

Sorbitol (Merisorb®200 Pharma) Tereos Syral SAS Nestle, France

Purified water

### ***6.2 Equipment***

Moisture analyzer XM 60 (precision 0.001 g, Precisa, Switzerland)

Extruder (Erweka, Germany)

Optical microscope Olympus BX51 with a digital camera (Olympus, Czech Republic)

Vibratory Sieve Shaker AS 200 basic (Retsch, Germany)

Granulate Tester Type GTB (Erweka, Germany)

Scott volumeter Copley, (Sotax, UK)

Tapped Density Tester (Erweka, Germany)

### ***6.3 Methods***

All methods were done under normal laboratory conditions of temperature  $23\pm 1^\circ\text{C}$  and relative air humidity (RH)  $22\pm 3\%$ .

#### **6.3.1 Wet Granulation**

I prepared granules by the traditional wet granulation method. I used sorbitol powder (MS 200) and water as the binder in an approximate 10/1 ratio of the mix. I homogenized the mixture manually with regular spraying of water trying to obtain good wetting characteristics of each part of the particles. The checking of the quality of wetting was made by using the snow ball method.

Then, I extruded the granulated matter through a sieve having 1 mm mesh size. Afterwards, I let the granules to dry on sheets of paper at room temperature (at normal laboratory conditions).

### **6.3.2 Loss on drying**

I measured the content of water in the granules using Moisture analyzer at temperature 70 °C by taking three samples each time. I weighed approximately 1 g of each sample (with precision of 0.001 g) on the metal bowl and started measurement until the equilibrium has been achieved and I registered the results. The moisture content evaluation results are summarized in Table (2). Data are completed with standard deviation (SD).

### **6.3.3 Analytical Sieving**

According to the European Pharmacopeia 8.0 (2.9.38), I used vibratory sieve shaker to classify the granules by particle-size distribution. I weighed each of the test sieves before the beginning of the process and recorded the results. I put approximately 50 g (precision 0.01 g) of the granules on the top of the coarsest sieve and replaced the cover. The mechanical agitation was started for 10 min with amplitude 30, then I took each test sieve carefully to minimize material loss and I reweighed it to determine the amount of granules on each of them. The sieves were returned to their previous state in the apparatus and the agitation was restarted for 10 min again in the same conditions. I continued the same way until the equilibrium had been achieved when the mass on each test sieve didn't change by more than 5%. After the endpoint was achieved, I put the granules in each sieve in a separated bottle to minimize the loss and uptake of moisture.

I repeated the sieving procedure ten times. From these results, I estimated the total amount of granules in each out of the fractions and I expressed the percentage of mass of the granules on each sieve. The results are summarized in table (3) (Sum is expressed as  $\Sigma$ ) and figure (8) (Undersize cumulative distribution)

### 6.3.4 Microscopy

I used optical microscope with a digital camera to characterise particles of each fraction of the granules according to European Pharmacopeia 8.0 (2.9.37), I took a sample from each bottle, put a small amount of it on a clean slide and tried to disperse the granules by vibrating the slide gently manually. I observed samples at magnification 10 and I took photos by a digital camera with black background and with white background for each fraction. These photos are displayed in Table (1).

### 6.3.5 Angle of repose

To measure the angle of repose (AOR), I used a prototype apparatus which has a base with a protruding outer edge to keep a layer of the granules as a base for the pile - see Figure (4). The horizontality of the hopper and the base was carefully levelled. The hopper which has 0.6 mm aperture was placed to touch the upper surface of the base and then filled with enough amount of granules.

I elevated carefully and slowly the funnel creating a pile of the granules till a symmetrical cone is accomplished which has a radius equal to the radius of the base (r). The height (h) of the tip of the formed cone is measured by a micrometre.

Then the angle of repose can be determined by the following equation according the European Pharmacopeia 8.0 (2.9.36):

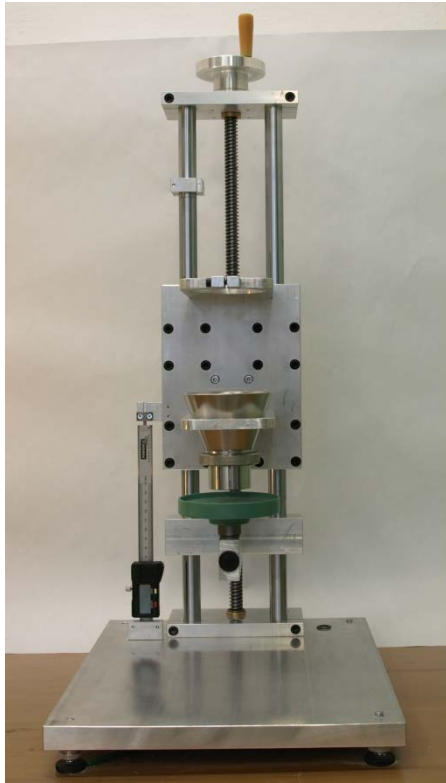
$$\operatorname{tg} \alpha = \frac{h}{r} \quad (6)$$

$\alpha$  ... angle of repose ( $^{\circ}$ )

h ... height of the tip of the formed pile (mm).

r ... radius of the base (mm)

I measured AOR 5 times for each fraction and calculated the angle of repose. The results are displayed in table (4) and table (5).



(a)



(b)

Figure (4). The used prototype apparatus to measure the AOR.

### 6.3.6 Bulk Density

Using a Scott Volumeter (Figure 5), the bulk density of the fractions was measured according to European Pharmacopoeia 8.0 (2.9.34).

I put an excess amount of the particles on the top of the sieve (1 mm). The particles pass through a sieve to the baffle box where they slide and bounce on 4 baffle glasses, then they end in a 25 ml cup placed directly below. With a card, I scraped the excess amount from the top of the cup carefully and perpendicularly to prevent removing or compressing material. The cup was weighed on a balance (precision 0.1 mg) to measure the mass of the material. The bulk density  $d_b$  (g/ml) can be calculated then by the following equation:

$$d_b = M / V \quad (7)$$

$d_b$  ....bulk density of the material (g/ml)

M ....mass of the material (g)

V.....volume of the cup (ml), 25.00 ml

The bulk density was measured 10 times for each fraction and the results are summarized in Table (6).

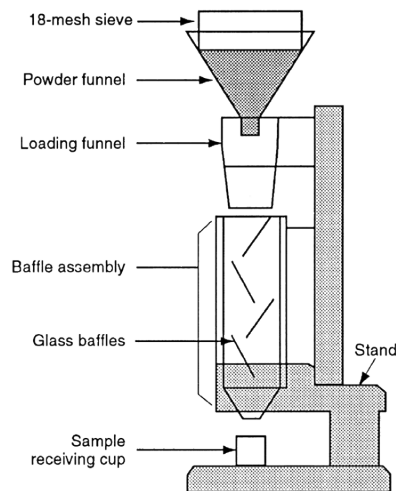


Figure (5): Scott Volumeter (European Pharmacopeia 8.0)

### 6.3.7 Tapped Density

I measured the tapped density using Tapped density tester apparatus (see Figure 6) according to European Pharmacopoeia 8.0 (2.9.34).

I carefully put approximately 50 g of a sample weighed on a balance (with a precision 0.01 g) in a graduated cylinder 100 ml. The bulk volume  $V_0$  (ml) was recorded and the cylinder was fixed to the device by the support. I performed 10, 100, 500, 1250 taps on the same sample and the associated volume is observed and registered each time  $V_{10}$ ,  $V_{100}$ ,  $V_{500}$ ,  $V_{1250}$ . These measurements were carried out 10 times for each fraction. I calculated the tapped density  $d_t$  (g/ml) using the average tapped volume  $V_{1250}$  (ml).

The average of the bulk volume  $V_0$  (ml) and the tapped volume  $V_{1250}$  (ml) were also taken for calculation of Compressibility Index (CI) and Hausner Ratio (HR) by equations:

$$CI = 100 \frac{V_0 - V_{1250}}{V_0} \quad (8)$$

$$HR = \frac{V_0}{V_{1250}} \quad (9)$$

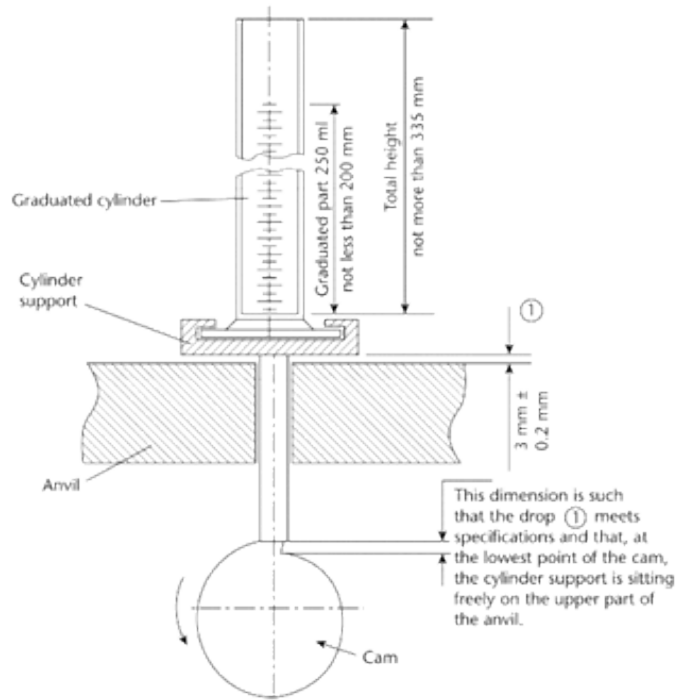


Figure (6): Settling device for measurement of tapped density (European Pharmacopoeia 8.0)

### 6.3.8 Mass Flow Rate

I measured the flow rate using Granulate Tester apparatus according to European Pharmacopoeia 8.0 (2.9.36).

I weighed 50 g of the granules on a balance (with precision 0.01 g) and put it carefully with a spoon into a 200 ml size stainless steel conical hopper. I used the aperture size of 0.6, 0.8, 1.0, 1.13, and 1.5 cm.

After opening of an aperture, the time the granules need to pass through the orifice was measured for every fraction 10 times. I calculated the average mass flow rate  $Q$  (g/s) and standard deviation (SD). The data are shown in Tables (8) and (9).

### 6.3.9 Mathematical model

I used Jones & Pilpel equation (5) to model flow rate data (Jones, Pilpel. 1966). To calculate the parameters A and n, I used the equation in the following form:

$$D = A \left( \frac{4Q}{\pi \cdot d_b \cdot \sqrt{g}} \right)^{\frac{1}{n}} \quad (10)$$

Where D (cm) is diameter of the orifice, Q (g/s) is the flow rate,  $d_b$  (g/ml) is the bulk density and g is the acceleration of gravity (981 cm/s<sup>2</sup>). The phrase in bracket ( $\frac{4Q}{\pi \cdot d_b \cdot \sqrt{g}}$ ) represents the complex independent variable.

To predict  $Q_{\text{pred}}$  (g/s), I used the equation in a form:

$$Q_{\text{pred}} = \left( \frac{D}{A} \right)^n \cdot \frac{\pi}{4} \cdot d_b \cdot \sqrt{g} \quad (11)$$

To express how accurate the used mathematical model is, I calculated percentage of deviation  $\Delta$  (%) between the experimental flow rate Q and that predicted by the generated equation. The results are summarized in Table (10).

## 7 Results

Table (1): Photos of each fraction (black background and white background) taken from a microscope.

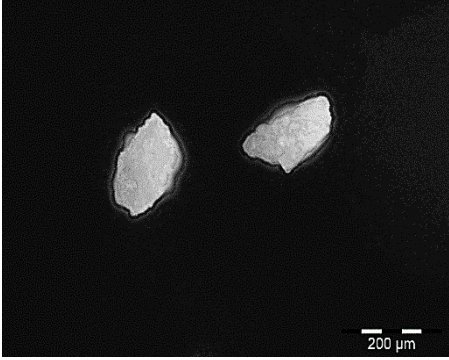
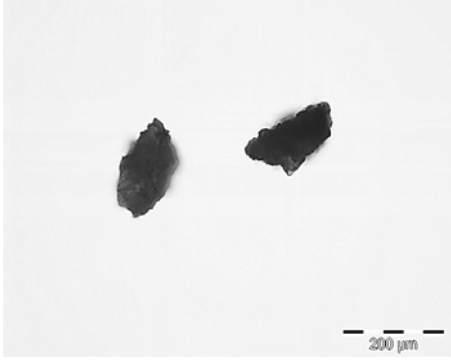
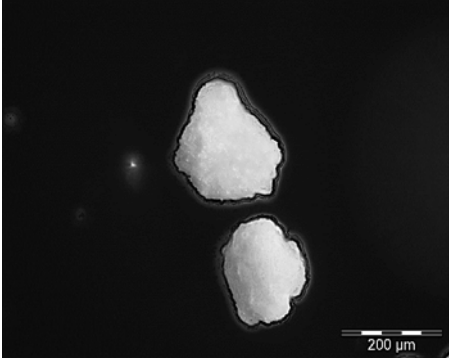
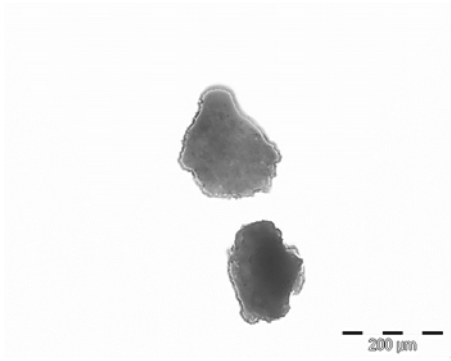
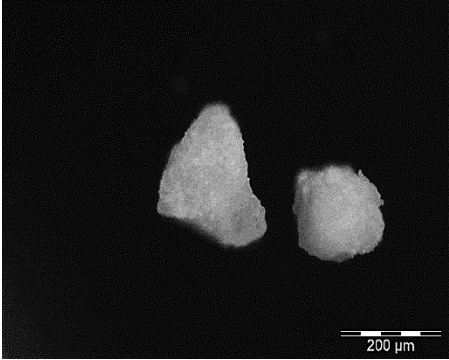
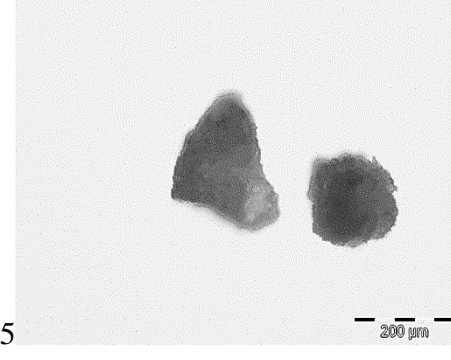
Sieve Size (mm)	Black Background	White Background
0.080		
0.125		
0.200		

Table (1) continued: Photos of each fraction (black background and white background) taken from a microscope

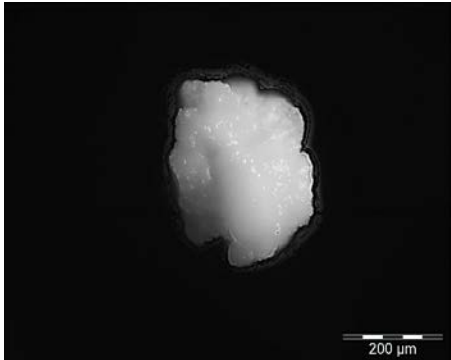
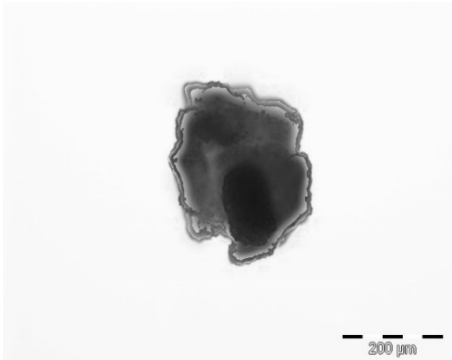

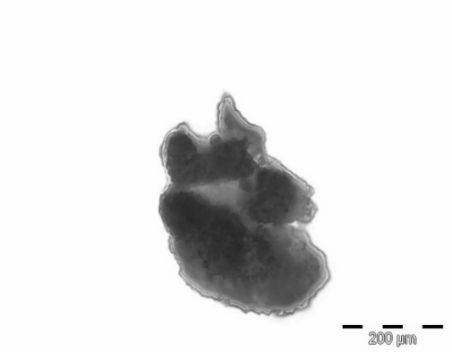
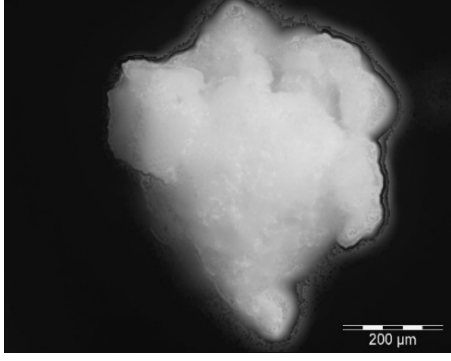
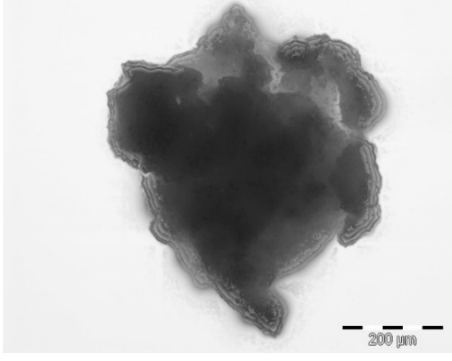
0.300		
0.400		
0.500		

Table (1) continued: Photos of each fraction (black background and white background) taken from a microscope

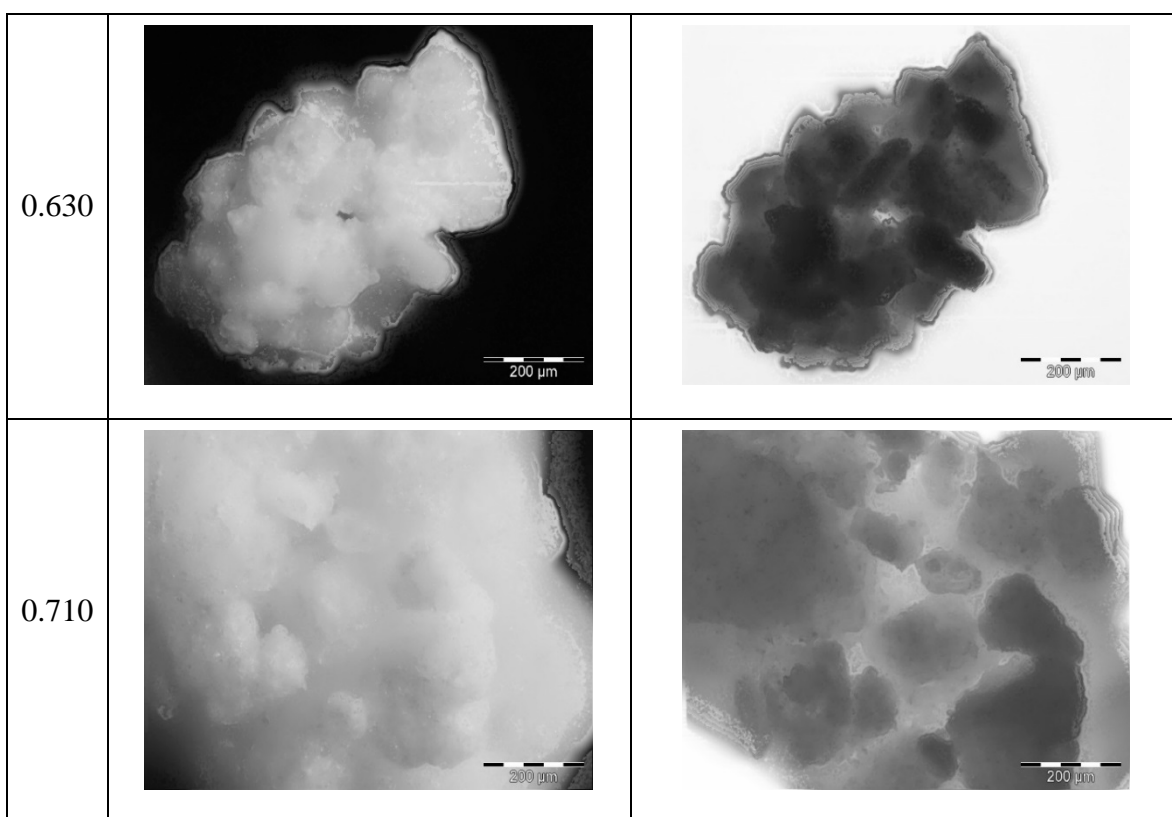


Table (2): The results of loss on drying measurement of granules

	Content of moisture (%)		
	Fresh	after 3 days	after 4 days
	3.80	1.12	0.65
	4.25	0.93	0.88
	3.28	1.01	0.88
average	3.78	1.02	0.80
SD	0.485	0.095	0.133

Table (3): The results of analytical sieving (mass in grams) of granules

	Sieve mesh size (mm)								
	Bottom	0.080	0.125	0.200	0.300	0.400	0.500	0.630	0.710
Mass (g)	0.07	1.04	4.97	12.63	14.40	4.87	3.81	1.90	5.83
	0.12	0.70	4.23	11.67	15.00	5.04	3.98	2.35	6.86
	0.19	0.95	4.87	12.09	14.36	4.68	3.88	2.16	6.83
	0.16	0.78	4.61	13.36	15.26	4.96	3.60	2.07	5.98
	0.18	0.93	4.70	12.26	15.22	4.92	3.74	2.17	6.16
	0.17	0.90	4.76	12.73	14.95	4.92	3.65	1.98	5.96
	0.15	0.84	5.07	12.94	14.97	4.92	3.58	2.03	5.52
	0.18	0.85	4.34	11.97	14.97	5.27	4.01	2.26	6.14
	0.11	1.32	5.81	11.89	14.62	4.90	3.64	2.27	5.51
	0.11	1.14	5.04	11.22	14.0	5.29	3.96	2.42	6.21
$\Sigma$ (g)	1.44	9.45	48.40	122.76	148.45	49.77	37.85	21.61	61.00
$\Sigma$ (%)	0.29	1.89	9.67	24.52	29.65	9.94	7.56	4.32	12.18

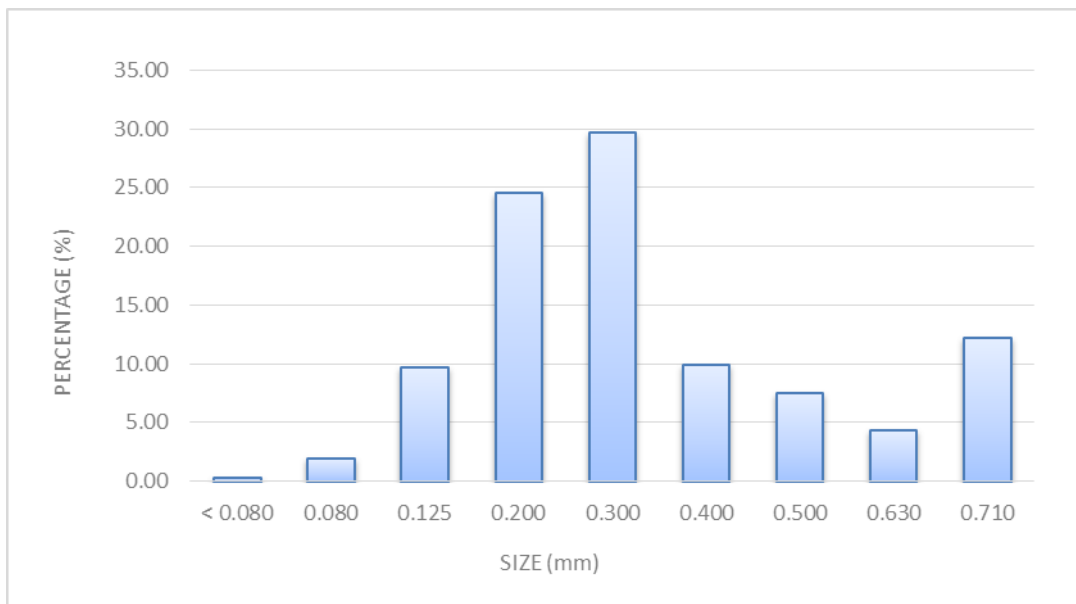


Figure (7): Histogram of sorbitol granules

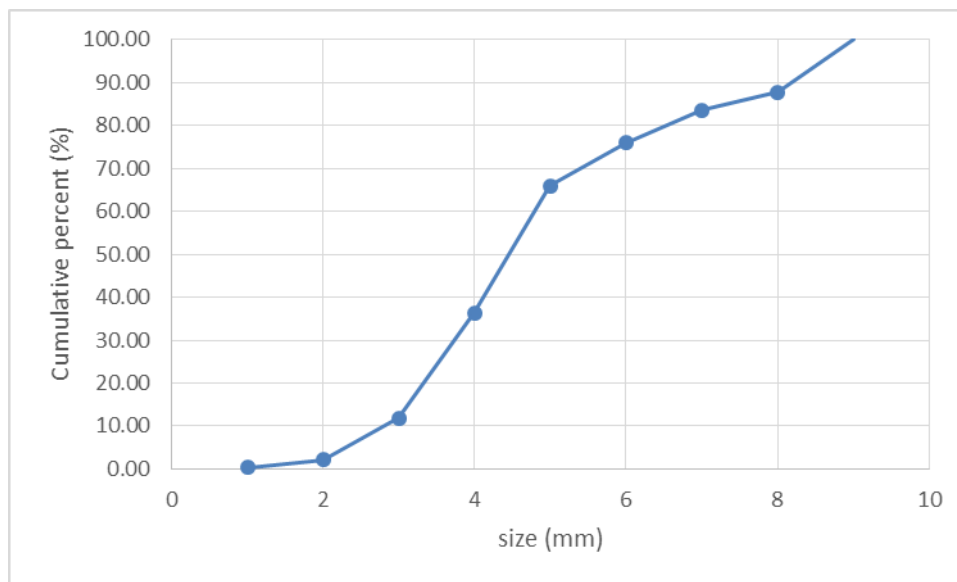





Figure (8) Cumulative curve of sorbitol granules

Table (4): Illustration of angle of repose measurements for each size fraction of sorbitol granules

x (mm)	Picture
0.245	
0.346	
0.447	
0.561	

0.669	
0.843	

Table (5): Results of AOR measurements of sorbitol granules

x (mm)	height of pile (cm)	AOR (°)	mass of pile (g)	d <sub>p</sub> (g/ml)
<b>0.843</b>	3.872	37.80	51.23	0.5054
<b>0.669</b>	3.865	37.70	53.46	0.5283
<b>0.561</b>	3.860	37.67	54.43	0.5386
<b>0.447</b>	3.799	37.23	55.77	0.5607
<b>0.346</b>	3.500	34.99	55.74	0.6083
<b>0.245</b>	3.442	34.54	55.06	0.6110

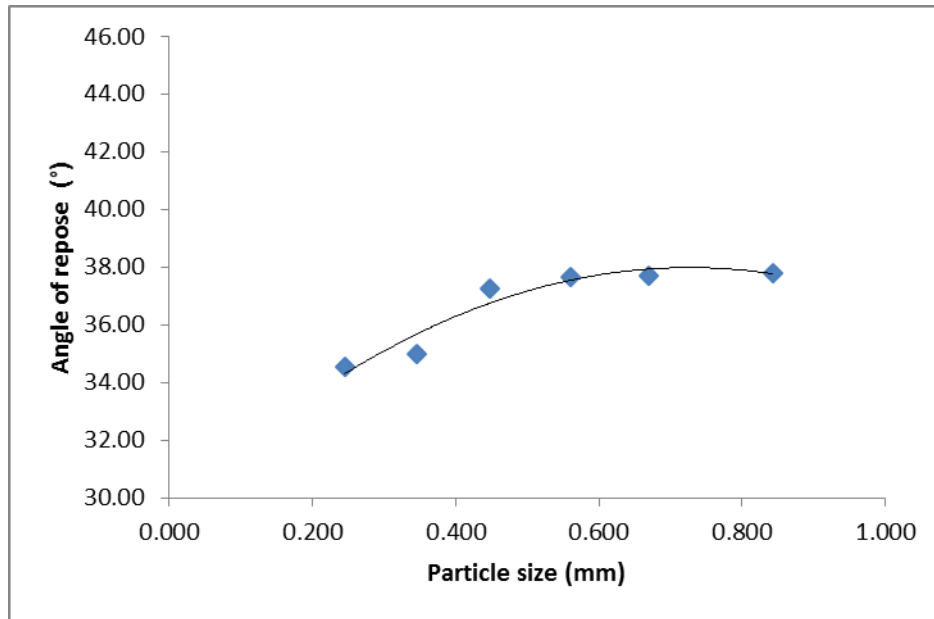


Figure (9): The influence of particle size on angle of repose of sorbitol granules

Table (6): Results of measuring bulk density of each fraction of sorbitol granules (Scott Volumeter)

x (mm)	0.843	0.669	0.561	0.447	0.346	0.245
Mass (g)	13.7237	14.2751	13.6331	13.4714	14.1800	14.7580
	13.4418	13.7978	13.9530	13.5770	14.4427	14.5563
	13.4487	13.7157	13.6550	13.4314	14.4752	14.6648
	13.2859	13.6072	13.5742	13.5700	14.4022	14.6355
	13.2152	13.8861	13.4720	13.5741	14.4328	14.6722
	13.5555	14.0277	13.3592	13.6318	14.2132	14.5982
	13.3115	13.9417	13.3519	13.4350	14.3005	14.4454
	13.5199	13.7824	13.6257	13.4929	14.5284	14.2991
	13.6116	13.8992	13.8619	13.6556	14.5879	14.3904
	13.8134	13.9166	13.7711	13.6282	14.7150	14.4698
Average (g)	13.4927	13.8850	13.6257	13.5467	14.4278	14.5490
d <sub>b</sub> (g/ml)	0.5397	0.5554	0.5450	0.5419	0.5771	0.5820

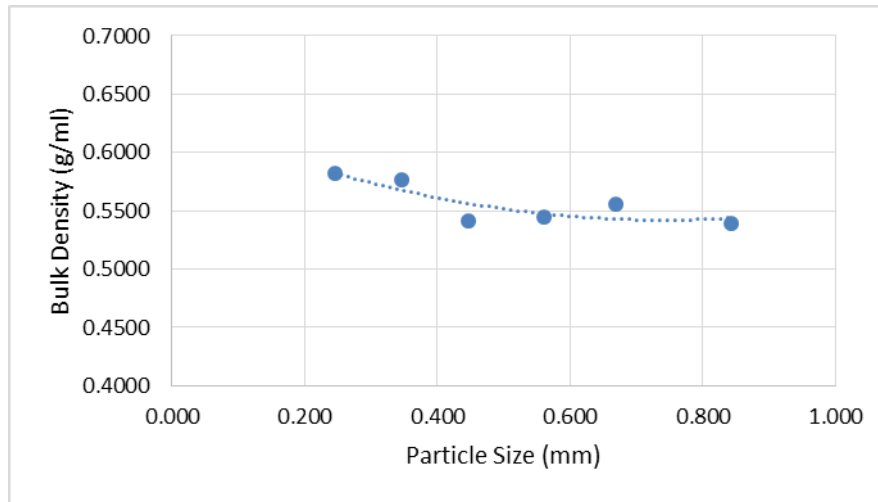


Figure (10): The relationship between the particle size and bulk density of sorbitol granules

Table (7): Results of density in cylinder  $d_c$  (g/ml), tapped density  $d_t$  (g/ml), Compressibility Index (CI) and Hausner Ratio (HR) for sorbitol granules.

<b>x (mm)</b>	<b><math>d_c</math> (g/ml)</b>	<b><math>d_t</math> (g/ml)</b>	<b>CI</b>	<b>HR</b>
0.843	0.5705	0.5952	4.16 %	1.04
0.669	0.5206	0.5828	10.67 %	1.12
0.561	0.5255	0.5875	10.56 %	1.12
0.447	0.5394	0.6064	11.06 %	1.12
0.346	0.5814	0.6460	10.00 %	1.11
0.245	0.5734	0.6702	14.45 %	1.17

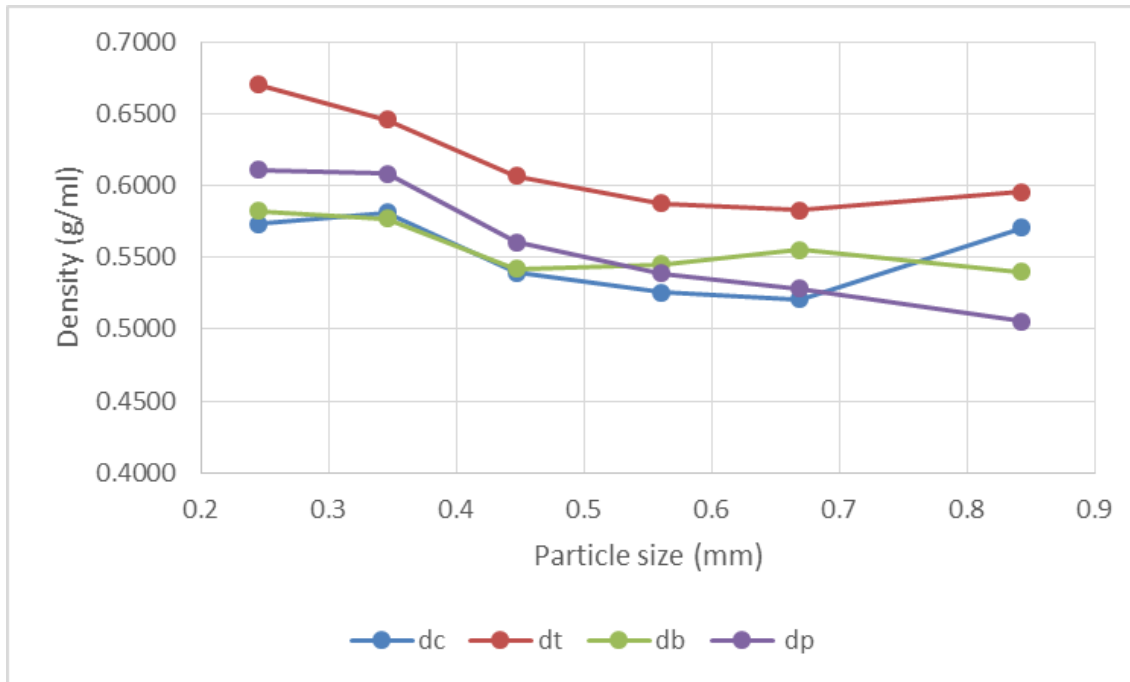


Figure (11): Comparison of bulk density  $d_b$ , tapped density  $d_t$ , density in cylinder  $d_c$  and pile density  $d_p$  for each size fraction of granules

Table (8): Influence of particle size  $x$  (mm) on the mass flow rate  $Q$  (g/s) of sorbitol granules.

<b>x (mm)</b>	<b>D (cm)</b>				
	<b>0.60</b>	<b>0.80</b>	<b>1.00</b>	<b>1.13</b>	<b>1.50</b>
<b>0.245</b>	2.1	5.6	10.5	15.7	45.0
<b>0.346</b>	1.9	5.3	10.1	14.4	43.9
<b>0.447</b>	1.7	4.5	8.6	12.6	37.3
<b>0.561</b>	1.5	4.0	7.8	12.1	33.6
<b>0.669</b>	1.4	3.6	7.4	11.6	33.3
<b>0.843</b>	1.3	3.4	7.1	11.5	32.5

Table (9): Influence of diameter of an orifice  $D$  (cm) on the mass flow rate  $Q$  (g/s) of sorbitol granules.

<b>D (cm)</b>	<b>x (mm)</b>					
	<b>0.843</b>	<b>0.669</b>	<b>0.561</b>	<b>0.447</b>	<b>0.346</b>	<b>0.245</b>
<b>0.60</b>	1.3	1.4	1.5	1.7	1.9	2.1
<b>0.80</b>	3.4	3.6	4.0	4.5	5.3	5.6
<b>1.00</b>	7.1	7.4	7.8	8.6	10.1	10.5
<b>1.13</b>	11.5	11.6	12.1	12.6	14.4	15.7
<b>1.50</b>	32.5	33.3	33.6	37.3	43.9	45.0

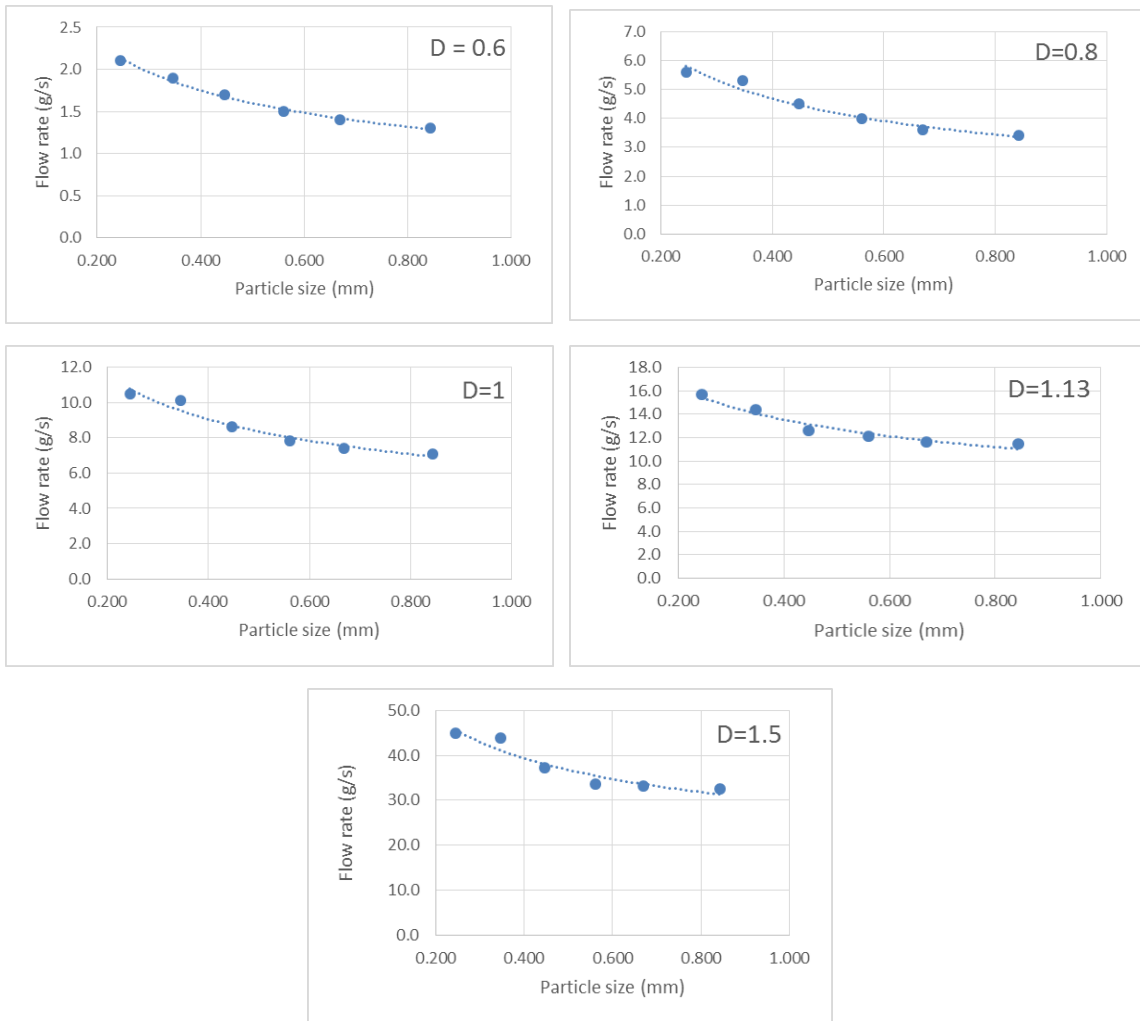


Figure (12).: Influence of particle size  $x$  (mm) on the mass flow rate  $Q$  (g/s) of sorbitol granules through the orifice of a conical hopper

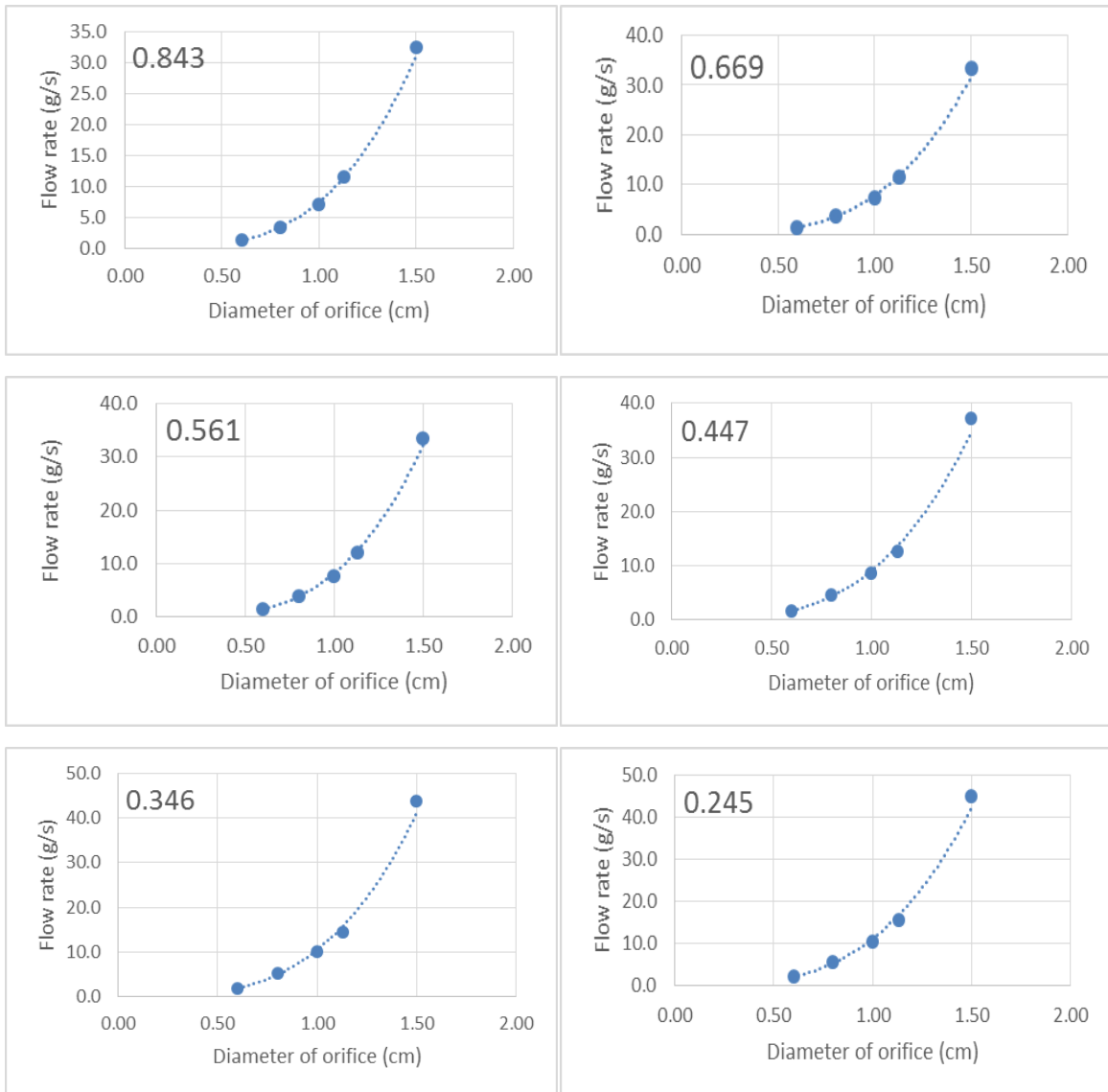


Figure (13): Influence of diameter of the orifice  $D$  (cm) on the mass flow rate  $Q$  (g/s) of size fractions of sorbitol granules

Table (10): Parameters of Jones-Pilpel equation for size fractions of sorbitol granules

<b>x (mm)</b>	<b>d<sub>b</sub> (g/ml)</b>	<b>A</b>	<b>n</b>	<b>R</b>	<b>Δ (%)</b>
<b>0.245</b>	0.5820	1.0787	3.30142	0.9987	4.88
<b>0.346</b>	0.5771	1.0931	3.368137	0.9982	5.57
<b>0.447</b>	0.5419	1.1227	3.325574	0.9985	5.27
<b>0.561</b>	0.5450	1.1553	3.368137	0.9994	3.36
<b>0.669</b>	0.5554	1.1754	3.448276	0.9993	3.63
<b>0.843</b>	0.5397	1.1752	3.512469	0.9994	3.05
<b>Average</b>					<b>4.29</b>

## 8 Discussion

Knowing the properties of granules is a very crucial point in pharmaceutical industry. Granules flowability especially is one of the most important features in different processes like blending, compression of tablets, filling of capsules, transportation and in scale-up operations (Sarraguca et al, 2010).

Using traditional wet granulation method, I prepared granules which were classified according to their size in the range of 0.200 to 1 mm by analytical sieving. Those granules then were characterized with a content of moisture, angle of repose (AOR), bulk density  $d_b$ , tapped density  $d_t$  and also they were being observed by a microscope for each fraction size. The mass flow rate  $Q$  (g/s) through an orifice of a conical stainless steel hopper was measured and the influence of particle size  $x$  (mm) on flow rate was observed, a mathematical model of Jones – Pilpel power regression (Jones, Pilpel. 1966) was applied to study the influence of orifice diameter  $D$  (cm) on the flow rate.

### *8.1 Preparation and characterization of granules*

I prepared granules by the traditional method of wet granulation followed by the manual sieving (extrusion) through a 1 mm sieve. I regularly sprayed water on the surface of sorbitol powder (MS 200) and mixed carefully to achieve optimal plasticity of material for granulation (the snow ball method). The ratio of MS 200 and water was approximately 10:1.

To mix material, I tried to use a large scale granulator (see figure 14-a) and a small homogenizer following with extrusion of wetted material in the extruder apparatus. Unfortunately, both homogenizers did not provide good wettability to the particles; moreover, the extruder apparatus produced granules of needle like shape because of the plasticity and sticky properties of wetted sorbitol mass so it was not appropriate for next use (see figure 14-b).



Figure (14): Granulation using a large-scale production apparatus

Although the manual method requires a lot of time and effort, however, it offers more control of the production process and has better results because I could control more the wetting of the powder which is an essential point in granulating and it produced less waste of material.

I let the granules to dry on sheets of paper at room temperature at normal laboratory conditions. In table (2), the results of loss on drying are shown. It could be visible that the moisture content decreased from 3.78 % immediately after producing to approximately 0.80 % after 4 days of drying at normal conditions and it remained stable during the experimental work.

In order to characterise particles of each fraction of the granules, I used optical microscope with a digital camera. In table (1), the photos illustrate agglomerates of sorbitol for each out of the tested size fraction in a range of 0.200 mm – 1 mm. The main problem while using a microscope is that it's an apparatus to characterise two-dimensional particles and granules are three-dimensional ones so there were some difficulties in taking accurate photos especially in bigger fractions which have larger thickness. Therefore, I used both black background and white background to see distinctly the agglomeration of particles that form irregular, different shapes of granules.

To classify the particle-size distribution of granules, I used vibratory sieve shaker. I followed the recommendations of the European Pharmacopeia 8.0 (2.9.38), using 0.200 – 0.300 – 0.400 – 0.500 – 0.630 – 0.710 mm sieves. Particles larger than 1 mm are considered as waste and they were eliminated after production and also after drying because during drying agglomeration might happen. Similarly, particles less than 0.200 mm are not considered for further tests because they are more like a powder than granules.

I measured the mass of product (g) retained on each out of the sieves 10 times, then, I calculated the sum  $\Sigma$  (g) at every sieve and expressed it in percentage  $\Sigma$  (%). The results are presented in table (3). A histogram in figure (7), shows a bimodal distribution of particles having the first maximum at particle size of the 0.300 mm sieve and the second one at particle size of the 0,710 mm sieve.

Figure (8), shows undersize cumulative distribution. Plotting the relationship in a logarithmic-probability grid paper, I estimated the values of  $x_{50} = 0.270$  mm (median particle size) and  $x_{90} = 0.620$  mm (particle size representing 90% of cumulative undersize distribution) as in the European Pharmacopoeia 8.0 (2.9.35).

For the flowability behaviour testing, each particle size fraction was signed in mean particle size  $x$  (mm) 0.245, 0.346, 0.447, 0.561, 0.669, and 0.843 mm as a geometrical mean of the used range of sieves.

## ***8.2 Testing of flow properties of granules***

### **8.2.1 Angle of Repose**

I measured the angle of repose (AOR) by a prototype apparatus for each fraction using a stainless steel conical hopper with a 0.6 cm aperture. Checking of the horizontality of the hopper and the base is important because false orientation of any of them may lead to false results.

Before the measurements of AOR, I used part of the same granules to fill the base to eliminate the external friction effect on flow behaviour of granules that a different material of a base (plastic) may cause. The filling of the hopper was done by a spoon carefully and slowly to reduce damaging of the granules and to prevent the aeration of the granules. When endpoint (a regular pile) was achieved, I stopped elevating the hopper and I measured height  $h$  (cm) of the pile by a micrometre. In table (4), the piles of individual size fractions of granules are illustrated.

Using the formula (6), I calculated the angle of repose for all out of the size fractions tested. Results are summarized in table (5). From the values of AOR, we can evaluate the flowability of each fraction according to the European Pharmacopeia (see table 11) from good (smaller fractions) to fair (greater fractions).

Table (11): Evaluation of the flowability of size fraction according to AOR value according to European Pharmacopoeia 8.0 (2.9.36).

<b>x (mm)</b>	<b>AOR (°)</b>	<b>Evaluation of the flowability</b>
<b>0.245</b>	34.54	Good
<b>0.346</b>	34.99	Good
<b>0.447</b>	37.23	Fair
<b>0.561</b>	37.67	Fair
<b>0.669</b>	37.70	Fair
<b>0.843</b>	37.80	Fair

Figure (9) shows the relationship between particle size  $x$  (mm) and angle of repose AOR (°). A non-linear relationship was noted which can be defined by the polynomial equation with correlation coefficient equal to  $r = 0.9609$ :

$$y = -15.901x^2 + 23.099x + 29.588 \quad (11)$$

Where  $y$  is angle of repose AOR (°),  $x$  is particle size (mm).

When I finished the measurement of a pile height, I carefully scraped the pile from a base and weighed the its mass  $M$  (g) so that calculating of the density of pile  $d_p$  (g/ml) is possible after calculating a cone volume by the equation:

$$V = \frac{1}{3}h \cdot b \quad (12)$$

V.....volume of the cone (ml)

h.....height of the cone (cm)

b.....surface of a circular base which equals  $b = \pi r^2$  (cm<sup>2</sup>)

The results are summarized in table (5).

### 8.2.2 Bulk density

I used Scott Volumeter according to the European Pharmacopeia 8.0 (2.9.34) to measure the bulk density  $d_b$  (g/ml) of each granule size fraction. The sample is poured from the top through a 1 mm sieve, bouncing on the baffle glasses and it ends in a 25 ml cup. When the particle size  $x$  (mm) decreases, passing through the sieve was getting easier and easier. In contrast, to measure the bulk density  $d_b$  (g/ml) of the biggest fraction 0.843 mm a 2 mm sieve was necessary as the granules didn't pass through the 1 mm sieve.

Using the mass of the granules in the cup and volume of the cup, bulk density  $d_b$  (g/ml) was calculated; in table (6), the average of 10 measurements is used.

The relationship between the particle size  $x$  (mm) and bulk density  $d_b$  (g/ml) (See Figure 10) can be described with the polynomial equation with correlation coefficient  $r = 0.8498$ :

$$y = 0.1639x^2 - 0.2431x + 0.6323 \quad (13)$$

Where  $y$  is bulk density  $d_b$  (g/ml), and  $x$  is particle size (mm).

### 8.2.3 Tapped Density

Using the Tapped density tester apparatus, density in the cylinder  $d_c$  (g/ml) and tapped density  $d_t$  (g/ml) were measured for each fraction size of the granules according to the European Pharmacopeia 8.0 (2.9.34). The sample was carefully

poured through a funnel into the cylinder and  $V_0$  was registered. Then, tapping started and  $V_{10}$ ,  $V_{100}$ ,  $V_{500}$ ,  $V_{1250}$  were recorded also for every step. The bulk volumes  $V_0$  (ml) and the tapped volumes  $V_{1250}$  (ml) were used to calculate density in cylinder  $d_c$  (g/ml, tapped density  $d_t$  (g/ml), Compressibility Index (CI), and Hausner Ratio (HR) by equations mentioned in the experimental methods. Results are summarized in table (7).

CI and HR are important measures to know because they indicate some properties of the granules such as their ability for being compressed (compressibility) which is an important factor in pharmaceutical industry. The following Table evaluates the flowability of each fraction according to the CI and HR values according to the European Pharmacopoeia 8.0 (2.9.35). Excellent and good compressibility properties were noted.

Table (12): Evaluation of flowability for each size fraction according to CI and HR values.

<b>x (mm)</b>	<b>CI</b>	<b>HR</b>	<b>Evaluation</b>
<b>0.843</b>	4.16 %	1.04	Excellent
<b>0.669</b>	10.67 %	1.12	Good
<b>0.561</b>	10.56 %	1.12	Good
<b>0.447</b>	11.06 %	1.12	Good
<b>0.346</b>	10.00 %	1.11	Good
<b>0.245</b>	14.45 %	1.17	Good

### 8.2.4 Comparison of densities

Manipulation with a particulate material influences its aeration when layered into a bed. The amount of air in the inter-particulate space affects the density of material. To study density of granules under different experimental conditions, three types of bulk density were investigated for each of the size fractions: the volumetric bulk

density  $d_b$ , the density in a cylinder  $d_c$ , and the density of a pile  $d_p$ . In figure (11), they are compared with the tapped density  $d_t$ .

By forming the pile slowly step by step, the aeration between granules is minimized. The orifice size 0.6 cm was uniformly used for all out of tested size fractions. If any flow blockage occurred slight knocking on the hopper wall was necessary and from the mass of the pile, density  $d_b$  was estimated. When particles bounce off the baffle glasses in Scott volumeter, in opposite, height aeration occurs. The lower values of the bulk density  $d_b$  could be expected. The density measured in a cylinder  $d_c$  includes voids between particles. The amount of space depends on the manner of a bed formation. Moreover, determining of the volume of material in the graduated cylinder is not very precise because the upper surface of the sample is difficult to level horizontally. No significant difference between the three studied kinds of the bulk density ( $d_b$ ,  $d_c$ ,  $d_p$ ) were observed for granules of sorbitol.

The highest values of the tapped density were observed as a result of tapping which is associated with decrease in inter-particle space.

Generally, the granule density decreases when particle size increases. This is fully true for density of a pile estimated for all size fractions as well as for the density in a cylinder and the tapped density up to size fraction 0.669 mm. In the case of the largest size fraction 0.843 mm, the differences between bulk densities probably resulted from the different manipulation needed. For example, a 2 mm sieve was necessary to use for filling a volumeter as well as a longer paper funnel for filling a cylinder.

### **8.2.5 Flow Rate**

I measured the time for the flow of 50 g of each out of the size fractions through a conical hopper using different aperture sizes  $D$  of 0.60, 0.80, 1.00, 1.13, and 1.50 cm. The mass flow rate  $Q$  (g/s) was calculated. The results are summarized in tables (8) and (9) showing the influence of particle size  $x$  (mm) and orifice diameter  $D$  (cm).

However, while using the 0.6 cm aperture with bigger fractions (especially 0.843 mm), sometimes the flow might not start immediately and spontaneously thus a gentle knock was applied to the hopper. In opposite, small fractions (especially 0.245 mm) also were facing some issues regarding their possessing of electrostatic charge leading to the adhesion to the inner wall of a hopper. This problem was effectively minimized by cleaning the hopper before each measurement with a special anti-static cloth.

The relationship between particle size  $x$  (mm) and the mass flow rate  $Q$  (g/s) through a constant hopper orifice diameter  $D$  (cm) is a power function represented clearly in figure (12). This relationship can be represented by the following general formula:

$$Q = a \cdot x^n \quad (14)$$

Where  $a$  is the equation parameter,  $n$  is exponent, and  $x$  is the mean particle size (mm). The actual coefficients of determination  $r^2$  were within the range of 0.9112 and 0.9906.

In the granule size range we used, the flow rate increased if the granule size decreased. This complies with the results of Danish & Parrott (1971) who concluded that particle size reducing results in improved flow till a range of 0.2-0.3 mm approximately where further diameter reduction leads to flow decline due to increased cohesion forces between the particles. Similar conclusions were earlier observed for size fractions of free-flowable powder excipients (Zatloukal & Sklupalova 2012)

The influence of the aperture sizes  $D$  (0.60 - 1.50) cm on the flow rate  $Q$  (g/s) for every fraction size  $x$  (mm) is shown in figure (13). The relationship can be described by a power equation; when aperture size increases, the flow rate is improved.

### ***8.3 Mathematical model***

To study the relationship between the diameter of an orifice  $D$  (cm) and the mass flow rate  $Q$  (g/s), I applied the Jones & Pilpel mathematical model represented by the equation (5).

This model, generally, represents a power law with the complex independent variable

$\left( \frac{4Q}{\pi \cdot d_b \cdot \sqrt{g}} \right)$  and parameters A (unitless) and n (reciprocal value of exponent). The

D, Q, and  $d_b$  are as mentioned above.

In table (10), the parameters of Jones&Pilpel equation are summarized according to the granule size fraction. Data are completed with the correlation coefficient (r) in a range of 0.9982-0.9994.

For every fraction size, I could see the level of accuracy of the applied mathematical model, it's expressed as the value  $\Delta$  (%) which is the deviation in percentage between the experimental flow rate Q (g/s) and the predicted flow rate  $Q_{pred}$  (g/s). The values of  $\Delta$  (%) ranged from 3% to approximately 5% depending on the size of the granule fraction. Regardless of the granule size, the total average deviation is 4.29 %.

## 9 Conclusions

- 1- The manual manipulation in the traditional method of wet granulation offered more control in wetting the sorbitol powder which led to minimization of material waste and better results than the automatic procedure.
- 2- Content of moisture in the tested granules were approximately 0.7% after 4 days of drying at normal conditions and it remained stable during the experimental work.
- 3- A bimodal distribution was noted for the granules of sorbitol using analytical sieving method with a maximum at the particle size of 0.300 mm and 0.710 mm sieve.
- 4- From the cumulative curve, median particle size  $x_{50} = 0.270$  mm and  $x_{90} = 0.620$  mm as a size representing 90% of cumulative undersize distribution were estimated.
- 5- The flowability of granule size fractions from good (smaller fractions) to fair (greater fractions) was observed according to values of angle of repose (AOR). Based on the Compressibility Index and Hausner Ratio values, compressibility of the granule size fractions was generally excellent and good.
- 6- The polynomial relationship between the particle size and bulk density  $d_b$  as well as between particle size and AOR were detected.
- 7- No significant difference between the three studied kinds of the bulk density ( $d_b$ ,  $d_c$ ,  $d_p$ ) were observed for granules of sorbitol. The tapped density ( $d_t$ ) was significantly higher than all of them. Density generally decreases when particle size increases.
- 8- In a range of particle size tested, the mass flow rate increases when the particle size decreases or when the aperture size increases in a power function relationship.
- 9- The actual parameters of the used mathematical model of Jones & Pilpel allowed the mass flow rate prediction with the average precision of 4.29 % for sorbitol granules regardless of the particle size.

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