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A Novel Physical Model and Mathematical Equation for Pre-process Wet granulation Endpoint Prediction

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ABSTRACT

In this study we propose a mathematical formula to estimate the amount of granulating liquid needed in the wet granulation process, which saves time, money and minimizing errors during formulation. The end point of wet granulation can be defined as the uncritical granulating liquid amount that is needed to produce the intended granular size distribution. Most frequently, this end point is determined during the process of wet granulation and, until today, there are no pre-process methods for its determination. Our equation is a modification of Washburn equation, where he described the flow of liquids in powders stacked in a column. The modification of the equation depended on the wetting characterization of the powder bed and sucking saturation level. Moreover, in order to validate the equation, lactose monohydrate, corn starch and mixtures of different percentages of starch and lactose were granulated using the amount of PVP solution calculated for each case. Drop on powder test was used to measure the level of saturation of pores of the powder bed by the PVP solution. The amount of liquid used was according to the calculated porosity, or according to the amount calculated by the modified Washburn equation. The resulting granules proved to have good flow properties. The normality of the granular size distributions curves was confirmed by linear normal probability Q-Q plots, as was shown by the values of R^2. The narrowness of the distribution was characterized by the mean, median, standard deviation and span for starch, lactose, and their mixtures. A narrow size distribution was obtained, indicating that the calculated volume of the granulating liquid succeeded in reaching the optimum end point. The three end points used resulted in similar granular properties, indicating the potential advantage of using the amount calculated by the modified Washburn equation. Our results indicate also the ability of this equation to take into account the effect of physicochemical properties of the inactive materials used in tableting on the amount of granulating liquid. In conclusion, this new physical model can be proposed to estimate the amount of granulating liquid depending on: the wetting characterization of the powder bed and sucking saturation level. List of abbreviations used throughout the text:**I**: is the height of penetrating liquid in the cylinder, **r**: Pore effective radius, γ: the liquid surface tension, **t**: is the time needed by the liquid to reach the front of the powder bed, **μ**: The liquid viscosity, **cosθ**: is the cosine of the contact angle between solid and liquid, **ε**: porosity, **Vb**: powder bulk volume , **Vfp**: the liquid amount calculated with considering porosity determined by liquid displacement method, **Vfe**: the experimental value of porosity that represents the value of liquid interring the column in the classical Washburn method ,**Vfw**: the value calculated by equation **15**.

Keywords: Wet granulation, Endpoint , Washburn Model , Saturation , PVP, Lactose , Starch.

INTRODUCTION

Wet granulation is a common process in the pharmaceutical field (1). Granulation is performed to produce suitable feed material for tableting and other processes. Among many benefits, the target of granulation is to improve powder flow, decrease dust, get better handling, homogeneous distribution and good compaction. These aims can be achieved by wet granulation process by producing granules with narrow and normal granular size distribution (2).The wet granulation process was considered in the past as a work of art (3,4), and it was the expertise of the formulator that controls the feature of the processes; most importantly the amount of granulating liquid that must be added, and consequently the end point of the granulation process. The end point can be classically defined as "the uncritical liquid amount that is needed to produce the intended granular size distribution"(5).

However, the increase understanding of both formulation and process parameters in the past three decades shuttled this principle from art to science(4). The accurate and precise determination of wet granulation endpoint achieves two major advantages; i,e. batch optimization and reproducibility (6).

The amount of liquid required for granulation depends on a large number of factors including: feed material properties (particle size, particle shape, solubility of the powder in the liquid and the ability of the powder to absorb the liquid.), liquid characteristics (viscosity, surface tension and interfacial tension) and parameters related to the equipment(5).

Attempts to identify the end point of the wet granulation process included direct and indirect *in process* methods. Indirect methods depend on monitoring the electrical and mechanical parameters of the process including power consumption (7), enhancing liquid distribution by considering spray flux number (8,9) , controlling liquid feeding rate (10), shear stress (11,12,13), dynamic heat and mass transfer (14) and vibration acoustic emission (15,16,17,18). An integrated method was the use of torque measurements, that reflects the rheological changes within the powder bed along liquid addition progress (19, 20, 21, 22, 23). On the other hand, direct methods depend on the change in the properties of the powder mixture, including the dimensionless stocks growth number that control the extent and type of growth and attrition (25,26,27),the spray flux number that controls the nucleation process (28,29), and the drop on powder test and the effect of spreading energy (30,31,32,33, 34,35). Other newer methods attempted the use of a combination of thermal effusivity and powder rheology in end point predictions (55, 56). Still, these methods are only preliminary and do not provide an exact end point.

The aim of the present study was to offer a physical method and an empirical formula for end point determination of the wet granulation process, considering the basic influential formulation parameters affecting the process, and to set forward a general method which helps formulators to predict the suitable amount of granulating liquid yielding the best granular characteristics. This approach will decrease the dependence on ordinary in-process control methods.

The approach is based on focusing on the "wetting" nature of the process. Ennis et al, proposed that the formation of granules depends on the meniscus volume built by liquid bridges between granules, which is directly affected by the pendular cohesive forces (24, 36, 37). Rheological changes keep occurring within the powder bed that transform the bed from one rheological phase to another, as a result of increasing cohesive forces between particles due to formation of liquid bridges, till reaching the capillary state where the cohesiveness of the particles begin to decrease as a result of increased thickness of the liquid bridge according to Newitt and Conway-Jones (1958) (39).

In this study, we will treat the granular bed as a static one, for the sake of experimentation. This resembles a law shear mixer. Process parameters are mostly useful in the engineering of scale-up and enhance uniformity of granules only, but not necessarily for formulation design issues like end point determination. (52)

Theoretical work

The empirical formula proposed in this study was developed by tracking the major principal formulation determinants for wet granulation and taking in consideration the present models in the literature that provide mathematical formulae describing wetting operations. The derivation of the formula depends on the assumptions that the degree of wetting of a powder bed by a liquid depends on three important parameters:

1. The porosity of the powder, which reflects the void volume that should be saturated with the right quantity of liquid binder to get the best granular characteristics which is also referred to as the saturation level (39).
2. Viscosity of the granulating fluid and primary particle size (42).
3. Contact angle between the granulating liquid and the powder; which affects the distribution of binder and nucleation (24, 29, 31, 33).

The starting point was the utilization and modification of the Washburn model that deals with the flow of liquids in porous materials (43). In 1921 the German scientist. Edward W. Washburn assumed that when liquid flows in a porous material it flows in an assembly of very small cylindrical capillaries and the height of a liquid penetrating a column of a porous material in a certain time would be given by the equation (43).

$$I^2 = \frac{r\gamma\cos\theta t}{2\mu} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (1)$$

In which:

I: is the height of penetrating liquid in the cylinder containing powder bed.

r: Pore effective radius, a parameter characterizing the structure of the powder bed.

γ: is the liquid surface tension

t: is the time needed by the liquid to reach the front of the powder bed in the cylinder.

μ: The liquid viscosity.

cosθ: is the cosine of the contact angle between solid and liquid.

The application of Washburn equation to a powder will give information about the effective radius, r (which is the actual radius of the pores that permits the flow of liquid). It also defines the contact angle between the liquid and the powder, which expresses the value of the surface tension between the two phases.

A simple presentation of the Washburn method is shown in the picture below (figure 1), which depicts a plastic test tube fitted with a closure and used as a column packed with the powder. The lower end of the test tube is cut and plugged with glass wool to allow upward liquid flow while keeping the packed powder in the tube.

Modification of Washburn method

The original Washburn method was not suitable for all types of liquids, especially viscous ones. Diggins et al (44) made a modification of this method, in which they introduced a way to enable the flow of viscous liquids through the powder bed. In their method, the liquid is not placed directly below the powder, instead, it is placed in a neighboring reservoir connected by a rubber tube to the column containing the powder (figure 2). The elevation of the reservoir will form additional force that would exert a pushing force on the liquid to flow through the column. As a result, the cosθ calculated in this case will exceed unity, and is replaced by a composite factor, k, referred to as the wetting coefficient in some references (45).

$$I^2 = \frac{r\gamma kt}{2\mu} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (\mathbf{2})$$

Derivatization of the equation.

In a powder bed wetted by a liquid, the saturation level is expressed as,

$$S = \frac{Vf}{Vp} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (\mathbf{3})$$

S: saturation level

Vf: fluid absorbed volume

Vp: pores volume

The porosity of the powder bed is expressed as,

$$\varepsilon = \frac{Vp}{Vb} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (\mathbf{4})$$

ε: porosity

Vb: powder bulk volume

- by rearrangement of (3) and (4) we gain the following equality:

$$Vp = \frac{Vf}{S} = \varepsilon\, Vb \dots\dots\dots\dots\dots\dots\dots\dots\dots (\mathbf{5})$$

By rearrangement of equation (5).

We gain either

$$Vf = SVp \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (\mathbf{6})$$

Or

$$Vf = S\,\varepsilon\, Vb \dots\dots\dots\dots\dots\dots\dots\dots\dots (\mathbf{7})$$

According to equations (7) we can conclude that the saturation level by the granulating liquid that wet any type of powder as a function of its porosity.

Since the powder will occupy a cylindrical shape (the shape of the pipette as in figure 1) then the volume of the powder is:

$$Vb = \pi d^2 I \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (8)$$

By rearrangement of (8):

$$I = \frac{Vb}{\pi d^2} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (9)$$

By substitution of (9) in the square root of the equation (2):

$$\frac{Vb}{\pi d^2} = \sqrt{\frac{r\gamma Kt}{2\mu}} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (10)$$

Then the bulk volume of the cylindrical powder, Vb:

$$Vb = \pi d^2 \sqrt{\frac{r\gamma Kt}{2\mu}} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (11)$$

The true volume of the bed is assigned as (Vt) then:

$$Vb = Vt + Vp \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (12)$$

Then

$$Vb - Vt = Vp \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (13)$$

By substituting (11) in (13):

$$\pi d^2 \sqrt{\frac{r\gamma Kt}{2\mu}} - Vt = Vp \dots\dots\dots\dots\dots\dots\dots\dots\dots (14)$$

According to equation (14) the effective pore volume (Vp) depends on the effective radius calculated.

Integrating equation (3) and equation (14) gives the mathematical formula:

$$Vfw = S\left(\pi d^2 \sqrt{\frac{r\gamma Kt}{2\mu}} - Vt\right) \dots\dots\dots\dots\dots\dots (15)$$

Equation (15) predicts the granulating liquid required for wet granulation end point "Vfw", in terms of effective radius and effective porosity, the surface tension, the viscosity of the liquid, and the time required for the granulating liquid to wet the powder bed.

The practical objectives of the study were:

1. Application of the Washburn Model to calculate effective radius, r, of lactose, starch and mixtures of both.
2. Application of drop on powder test to estimate sucking saturation level of studied mixtures.
3. Application of modified Washburn method to calculate composite factor wetting coefficient (K) of above mixtures.

Granulation of starch, lactose and mixtures of both was carried out to evaluate the end point proposed by our model and evaluation of granular properties (flow and particle size analysis).

MATERIALS AND METHODS

MATERIALS

Lactose monohydrate (D(0.5)=31µm, Moisture content ≈*0.5%(W/W)*), corn starch (D(0.5) = 13µm, Moisture content ≈ *11% (W/W)* and Polyvinylpyrrolidone K30, were kindly supplied by Berziet-Palesine Pharmaceuticals co.(Palestine) nHexane (dynamic viscosity=*0.00294 Poise* and surface tension =18.4dynes/cm) was purchased from Sun-Farm (Palestine). All other materials were of analytical grade, otherwise mentioned.

METHODS

Wetting Experiments

The ordinary Washburn method (figure 1) was used to determine the effective radius r in equation 1 for mixtures mentioned in Table 1 **(**This value will be used in equation 1 to calculate cosθ, and equation 15 to calculate Vfw).

Hexane was chosen as a liquid that exhibits a contact angle of zero, so the cosθ will equal to 1. The viscosity of hexane was measured by Ostwald-Type Viscometer and the surface tension was measured by the capillary rise method.

Table (1): The composition of the binary starch and lactose mixtures.

Material	Lactose ratio	Starch ratio
Mix1	0.9	0.1
Mix2	0.8	0.2
Mix3	0.7	0.3
Mix4	0.6	0.4
Mix5	0.2	0.8
Mix6	0.1	0.9

The setting of the experiment was as follows: A 15 ml poly ethylene test tube fitted with a closure was used as a column for powder packing (figure 1). The lower end of the test tube was cut off and plugged with a glass wool plug to allow upward liquid flow while keeping the packed powder in the tube. The volume of the bed was 5ml and its height was 2.5 cm(I=2.5 cm). The time of the flow of the n-hexane (considered to have a contact angle =zero) (46) was measured in order to calculate r using equation 1.

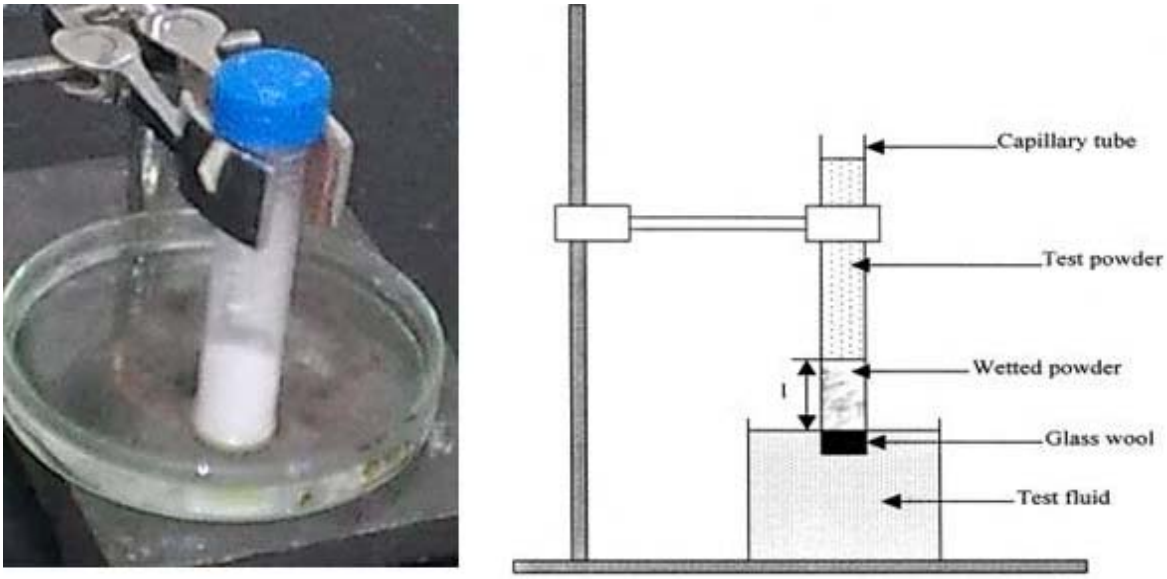

Figure (1): The setting of Washburn experiment (Classical).

The Washburn experiments were performed in triplicate. The modified Washburn method was used to determine the time needed for a 10% W/V PVP aqueous solution to flow through a powder column consisting of the mixtures mentioned in Table 3and 5.

The powder was packed in 10 ml plastic pipette, connected with a latex pipe to a reservoir. The reservoir was slightly elevated to enhance the flow of PVP solution. The height of the powder bed; I in equation 1, was 10.5 cm. The measured time "t" was used in equation 1 to measure cosθ, using the values of viscosity and surface tension of PVP, and the radius found by the ordinary Washburn method for the different powder mixtures.

The K is a composite factor replaces the cosθ resulted due to difference in setting between modified method and ordinary method (Table 3).

Drop on powder test

This test is used to measure the level of saturation of pores of the powder bed by the PVP solution (10% (W/W)); a drop (0.07 ml), was allowed to completely penetrate a powder bed. The resulting wet disc was separated from the bed by tweezers and weighed. The drop on powder test was repeated 30 times for each mixture, and values are shown in Table 4. The saturation level within the disc calculated using the following rearrangement of equation (7).

$$S = \frac{\text{drop volume}}{\varepsilon\, Vb} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (16)$$

The porosity of the bed ε was determined by liquid displacement method, as described elsewhere (47). The liquids used for porosity determination were as follow: water for starch and acetone for lactose and its blends with starch. The porosity determination experiments were repeated three times. The viscosity of the PVP solution was measured by Ostwald-Type Viscometer, and the surface tension was measured was by the capillary rise method. The data obtained so far was used in equation 15 to calculate Vfw.

Granulation

Granulation of the starch, lactose and their binary mixtures mentioned in Table 1 was performed, using PVP 10% as the granulating liquid. In the granulation process we used three different amounts of granulating

liquid, designated as: a) Vfp, which refers to the liquid amount calculated with considering porosity determined by liquid displacement method, b)Vfe, is the experimental value of porosity that represents the value of liquid interring the column in the classical Washburn method and, c)Vfw, which the value calculated by equation 15.

Wet granulation was operated for lactose alone or starch alone or their mixtures mentioned in Table 1 using low shear mixers, Dito-Soma F23200 (100RPM) and Universal Kitchen mixer (100RPM). The intended volume of the binder solution was intermittently added every 2 minutes time intervals. Then the wet masses of lactose, starch, and of mixtures also were screened through sieve number 16, and sieve number 18 respectively. All screened wet masses were dried by tray oven at50-57 ^{o}C for sufficient time until loss on drying becomes 3.5-4.5%. Then the dried granules were passed through sieve number 12. The results are expressed as a mean of three measurements. Granules evaluation: All granules were evaluated for flow properties and granular size distribution.

Compressibility index (Carr's Index) CI

Carr's index was calculated by using the following equation:

$$CI = \text{TD - BD X 100 /TD} \qquad (17)$$

Sieve analysis

Particle size analysis was performed on a sieve analyzer (UK standard BS 410:1969), comprising consequent sieves with the following sizes: (63µm, 75µm, 90µm, 160µm, 200µm, 250µm, 500µm, 710µm, 1000µm, 1600µm, 2000µm). The samples sizes were 50g and the agitation time was 10 minutes.

The frequency granular size retained on each sieve calculated using the following expression:

$$f = w_i / \sum w_i$$

Where, f is the relative frequency and w_i the net particles weight retained on each sieve.

The frequency data was used to calculate the mean particle size (M) for each batch according to the following expression:

$$M = \sum \left(\frac{S_i + S_{i+1}}{2} \right) w_i$$

Where S_i is the sieve size and $S_{i+1}$is the next sieve size, which is the net particles weight retained on each sieve.

Calculation of the Span

The span for each particle size distribution for each batch was calculated using the expression:

$$span = \frac{(D(0.9) - D(0.1))}{D(0.5)}$$

Where, *D(0.9)* is the diameter where 90% of the particles lay below it,

D (0.1) is the diameter where 10% of the particles lay below it and D(0.5) is the diameter where 50% of the particles lay below it. The span was calculated to confirm the narrowness of the particle size distribution.

RESULTS

Table 2 shows the findings of effective radius for the mixtures mentioned in Table 1, calculated from the time of penetration of n-Hexane through a column of powder (according to equation 2).

It is shown that the effective radius of lactose is larger than that of starch. For the binary mixtures, values of the effective radius decrease as the percentage of starch in the mixture increases.

The results for the modified Washburn experiments with PVP are shown in Table 3, which clarifies the time needed for PVP 10% solution to penetrate the column of the relevant mixture, and the calculated value of the wetting coefficient K. It is shown that the time needed by PVP solution to penetrate lactose column was less than that for starch (61.67 seconds for lactose and 198.67 seconds for starch). The time also increased as the percentage of starch in the mixtures increases.

Table (2): The values of the time of penetration, and the effective radius obtained in the Washburn experiments for n-Hexane. n=3

Mixture	t(sec.)[b]	SD[b]	r[b]	SD
Lactose	21.66	1.53	9.25E-05	6.68E-06
Mix1	23.66	0.58	8.44E-05	2.09E-06
Mix2	25.50	0.87	7.84E-05	2.72E-06
Mix3	29.66	0.58	6.73E-05	1.33E-06
Mix4	35.00	1.00	5.71E-05	1.63E-06
Mix5	54.66	0.58	3.65E-05	3.88E-07
Mix6	71.00	1.00	2.81E-05	3.96E-07
Starch	56.00	1.00	3.57E-05	6.37E-07

[b]Where t is the n-Hexane Penetration time, SD is the standard deviation and r is the pore effective radius.

Table (3): The values of PVP K30 penetration time and the wetting coefficient obtained by the modified Washburn experiments (n=3).

Mixture	t[b](sec.)	SD[b]	k[b]	SD
Lactose	61.67	1.53	23.26	2.02
Mix1	77.00	2.65	20.41	1.00
Mix2	82.33	3.5	20.56	1.10
Mix3	84.83	0.76	23.22	0.26
Mix4	104.33	3.06	22.28	1.04
Mix5	146.33	1.15	24.81	0.07
Mix6	180.67	4.51	26.10	0.60
Starch	198.67	4.73	18.72	0.30

[b]Where t is the PVP K30 Penetration time, SD is the standard deviation and K is wetting coefficient

The results for the drop on powder test and saturation factor S are shown in Table 4, where it demonstrates the weight of the wet disc obtained after a drop of PVP was administered over each mixture.

As it is seen, the saturation level increases as the percentage of starch increases and conversely, the weight of the obtained disc decreases.

The amounts of granulating liquid determined as Vfw, Vfe and Vfp for the different powder mixtures are shown in Table 5. It is seen that they can be ordered as Vfw<Vfe<Vfp.

Table (4): The weight of the wet masses obtained by the drop on powder test and the values of sucking saturation level, S, calculated by Eq[5].

Material	wet mass (g)	SD	S	STD
Lactose	0.381	0.004	0.192	0.002
Mix 1	0.347	0.010	0.218	0.007
Mix 2	0.291	0.006	0.257	0.006
Mix 3	0.297	0.014	0.252	0.016
Mix 4	0.264	0.008	0.284	0.008
Mix 5	0.225	0.005	0.322	0.009
Mix 6	0.206	0.008	0.337	0.018
Starch	0.198	0.010	0.409	0.034

Table (5): The values of Vfw, Vfe and Vfp for the different powder mixtures.

Mixtures	Vfw[a] (ml/g)	Vfe[a] (ml/g)	Vfp[a] (ml/g)
Lactose	0.173	0.192	0.224
Mix1	0.197	0.215	0.258
Mix2	0.240	0.267	0.303
Mix3	0.242	0.265	0.309
Mix4	0.271	0.296	0.359
Mix5	0.367	0.413	0.444
Mix6	0.393	0.437	0.512
Starch	0.432	0.507	0.560

[a] Where Vfw is the endpoint calculated by Equation [15], Vfe is the endpoint calculated considering Experimental value of PVP K30 that penetrates the powder column and Vfp is the endpoint calculated considering the full pore volume of powder column.

Table 6 shows the results for the Carr's index, which evaluates the flow of the granules. The values indicate that all granules produced are of excellent flow since the values of compressibility index were below 15.

Table (6): The Carr's Index for Vfw, Vfe and Vfp for the produced granules. (n=3).

Mixtures	End-point	Vfw (ml/g)	Vfe (ml/g)	Vfp (ml/g)
Lactose	Carr's Index	3.33	3.67	NA
Mix1		5.83	5.17	3.89
Mix2		3.15	7.37	8.90
Mix3		7.34	4.26	2.04
Mix4		3.33	5.30	NA
Mix5		6.82	6.78	NA
Mix6		4.36	9.39	5.37
Starch		6.83	5.11	4.61

The granular size distributions for the granulated mixtures were evaluated in terms of narrowness and normality of the distribution.

The narrowness of the distribution is a function of central tendency of the size distribution data and is characterized by the mean, median, the standard deviation and the span as shown in Table 7 for starch and lactose and in Table 8 for their mixtures.

A narrow size distribution was obtained as verified by the span values, for starch, lactose and their mixtures.

It is noteworthy, that the properties of the granules were similar despite the fact that starch and lactose were granulated in a different setting (larger batch size and a larger mixer).

The aim of using different settings was to verify that the theory of end-point determination is applicable no matter what the mixing system was.

The mean and median for lactose granules produced were close to each other by one standard deviation. The values of the span for the lactose granules were the smallest upon all granules. It is shown that 89.26% of the data lie within ±1 STD of the mean. The mean size for lactose was larger than starch granules (Table7).

As seen in Table 8, as the amount of starch increases in the mixtures the size mostly decreases with an increase in the span. In case of starch, the distance between the mean and the median was less than one standard deviation.

Table (7): The mean, median, (SD), D0.1, D0.9 and span of granular size (Mm) for granules produced by the end points Vfw, Vfe and Vfp for starch and lactose (granulated by by Ditto- soma F23200 mixer lab-scale low shear mixer) .(n=3).

Material	Starch			Lactose		
Endpoint	Vfw	Vfe	Vfp	Vfw	Vfe	Vfp
Mean	716.42	846.98	893.83	1203.46	1213.77	NA
Median	925.63	1075.51	1150.45	1512.64	1520.97	NA
SD	376.81	378.44	386.91	301.8	299.64	NA
D0.1[a]	380	405	376	107.9	184.5	NA
D0.9[a]	1641	1675	1204	1758	1533	NA
Span	1.36	1.18	0.72	0.45	0.89	NA

[a] Where D0.1 is the diameter where 10% of the particles lay below it and D0.9 is the diameter where 90% of the particles lay below it.

Table (8): The mean, median, standard diviation (SD), D0.1, D0.9 and span of granular size (Mm) for granules produced by the endpoints Vfw, Vfe and Vfp for the binary mixtures (granulated by universal low shear kitchen mixer). (n=3).

Material	Mix1			Mix2			Mix3		
End-point	Vfw	Vfe	Vfp	Vfw	Vfe	Vfp	Vfw	Vfe	Vfp
Mean	621.60	587.30	729.08	571.89	699.94	648.16	484.02	530.40	679.14
Median	838.04	763.27	983.92	725.80	933.96	863.19	571.76	642.54	904.81
SD	285.33	285.57	263.90	283.35	294.50	302.96	284.32	277.21	300.05
D0.1	205.39	180.41	392.74	172.09	301.15	197.07	138.79	159.39	222.05
D0.9	1221.22	1204.57	1258.69	1196.24	1267.02	1250.36	1137.95	1162.93	1262.86
Span	1.21	1.34	0.88	1.41	1.03	1.22	1.75	1.56	1.15
Material	**Mix4**			**Mix5**			**Mix6**		
End-point	Vfw	Vfe	Vfp	Vfw	Vfe	Vfp	Vfw	Vfe	Vfp
Mean	508.21	540.62	NA	452.25	587.30	NA	477.68	456.07	613.70
Median	600.90	655.03		534.29	763.26		567.60	534.29	759.10
SD	279.55	279.46		265.30	283.51		271.68	250.05	251.38
D0.1	155.44	167.92		142.94	180.41		142.94	176.52	376.09
D0.9	1154.61	1171.26		1083.83	1204.57		1117.42	1071.34	1204.5
Span	1.66	1.53		1.76	1.34		1.72	1.68	1.09

The size distribution of the log data was further subjected to the normality statistical test (Shapiro-Wilki) and the results are shown in Table 9. It is shown that all mixtures, except for lactose, showed good normality (P values larger than 0.05). Around 85% of lactose granules were distributed around one size category and this may be due to the compacted particles of lactose (which can be proved by the small value of effective radius of lactose) and the absence of tortious structure of the lactose bed compared to starch.

The normality of Starch and mixtures distributions was also confirmed by linear normal probability Q-Q plots and the resulting R^2 is shown in Table 10. It is noted that the values of R^2 were the lowest for lactose granules and highest for starch –rich granules.

Table (9): Normality evaluation of granular size distributions. Shown are the percentages of data that lie within 1 SD of the mean and the P value of log transformed data using Shapero-Wilki test.

Materials	% of data Lies within 1STD of the mean			P value of Log transformed data		
	Vfw	Vfe	Vfp	Vfw	Vfe	Vfp
Lactose	89.26	89.62		0.035	0.013	
Mix1	81.99	80.55	86.86	0.712	0.301	0.177
Mix2	79.83	82.52	80.28	0.230	0.285	0.691
Mix3	49.85	51.41	83.84	0.614	0.538	0.349
Mix4	51.99	52.99		0.541	0.144	
Mix5	56.31	80.55		0.303	0.301	
Mix6	56.86	63.04	92.47	0.347	0.100	0.565
Starch	50.17	47.55	70.68	0.719	0.737	0.642

*Where P Value is probability of obtaining the null hypothesis (Normality).

Table (10): The R^2 of the fit line of the observed log transformed data of granular size distribution on the Q-Q normal probability plot for the different end points.

Material	Vfw	Vfe	Vfp
Lactose	0.791	0.818	NA
Mix1	0.791	0.942	0.893
Mix2	0.933	0.924	0.966
Mix3	0.953	0.969	0.936
Mix4	0.97	0.923	NA
Mix5	0.931	0.942	NA
Mix6	0.952	0.89	0.961
Starch	0.966	0.979	0.972

*Where R^2 is regression coefficient.

DISCUSSION

The method and theory proposed in this research depends on the assumption that the amount of granulating liquid per amount of particles to be granulated is constant (43), regardless of the batch size, so as to produce ideal granules. The amount of granulating liquid is also linearly dependent on batch size (53) and so the liquid amount is scale up independent (54). The liquid amount depends on feed material properties (particle size distribution, solubility in the binder liquid and the ability to absorb the binder liquid) and the binder liquid characteristics (viscosity and surface tension) (44). Therefore, we demonstrated the theory on mixtures of lactose and starch, as the most widely used inactive ingredients working at a laboratory scale, and using a low shear mixer and then would suggest that the result can be further examined on other powder mixtures.

These experiments elucidate some of the properties of polymers used in the granulation during tableting, that affect the amount of granulating liquid added. As was shown in Table 2, the time needed for n-Hexane to penetrate the column increases as the percentage of starch in the mixture increases. These results can be explained by the fact that starch resembles a branched long polymer and the time needed for n-hexane to advance inside the pores of starch and transverse the powder column is presumably more than the time needed to wet the lactose powder column which is a dimer that includes less level of tortuosity. It is interesting to notice that the time calculated seems to be an additive property of starch and lactose, as it can be approximately calculated as a mean average of the two components in the mixture based on the time required for each substance alone. Based on this finding, it can be postulated that one can predict the time and so the effective radius, from the percentages of the materials in the mixture. The overall tortuosity of the mixtures, governed by the relative amounts of starch and lactose, seems to govern the proceeding of the liquid in the column bed. This could also suggest that the liquid amount is patch size independent and is an intrinsic property of the material itself.

It is noted that the time for the penetration of all mixtures was more for PVP as compared to n-hexane (as seen in Tables 2 and 3). This could be explained by the higher density and viscosity of PVP and also by the formation of hydrogen bonds between the PVP and the powder mixtures, thus retarding the upward flow of PVP. The higher molecular weight of starch and higher tortuosity and so the more availability of hydrogen bond are believed to cause the formation of more binding forces with PVP solution. This is in agreement with the findings of Kaspar den Driest et al (48). Also the small value of effective radius of starch (Table 2) could be a considered as a cause also. It is also worth to note that the time recorded of each mixtures in this test is an additive property that depends on the weight fraction of starch and lactose, and this could also support that the test is batch size independent.

The reason for adopting the expression "K" instead of $\cos\theta$, is the fact that the values recovered were more than unity, which lead us to rehearse this phrase in the original equation as in equation 1. The assumption that we can make is that this result originated from difference in the setting between our experiment and the original Washburn experiment. In our setting, the reservoir of the PVP was elevated to some extent and so exerted a static head pressure on the column, which was not the case in the original Washburn setting. This is thought to add additional impact on the volume of binder solution en-

tering the column and so, the value represented by cosθ is amplified. This issue was addressed by other scholars in fields of petrology and geology (47).

The drop-on-powder test was used to measure the saturation factor S. This type of study gives an idea about the dynamics of wetting, in which wetting of a powder bed by a liquid is directly affected by the effective porosity (30), which agrees with the assumption of Ennis et al (25). It is stated that the formation of granules depends on the meniscus volume built by liquid bridges between granules, which is directly affected by the pendular cohesive forces (24, 36, 37) as mentioned in the introduction. In case of starch this volume is larger due to small r that fill the same pore volume when compared to lactose. Once again we see that it is an additive property of the mixtures. The obtained value of S is introduced in the equations as it resembles the actual level of liquid needed to fill the pores between the powder particles and compose the binding liquid bridges, in other words, it is a manifestation of the effective porosity. The assumption is that the amount of binder required to achieve optimum granular size, with a normal and narrow size distribution, is related to the effective porosity as reflected by the degree of saturation (see equation7).

The normality of Starch and mixtures distributions was confirmed by linear normal probability Q-Q plots, and we found that the three end points used (Vfw, Vfe and Vfp) resulted in correlation coefficient close to unity. Their results were also close to each other.

CONCLUSION

In conclusion, we reveal that this method, which is an integration of the Washburn method and the drop on powder test, is suitable for helping in end point determination and succeeded in producing granular size distributions that is characterized by narrowness and normality. The method introduced herein suggests that the endpoint is an intrinsic property for materials and an additive property for mixtures. This conclusion is in full agreement with findings elsewhere, postulating that the amount of granulating liquid per amount of particles to be granulated is constant and scale up independent (43). However, these experiments are only preliminary, since only two types of inactive substances were used (starch and lactose). Further experiments are ongoing in this direction using other inactive materials and also introducing active pharmaceutical ingredients in the granule mixtures to elucidate the validity of this principle as a general tool in wet granulation. Improvements of the method are underway also to make it automated, with less personal errors and less time consumption.

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CONFLICT OF INTERESTS

The authors report no conflicts of interest in this manuscript

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