In vitro evaluation of formulation factors: the granule size and type of binder upon physiochemical characterisation of paracetamol capsules

1-Assistant Lecturer / Malathe Abdul latif Alshawi* MSc Pharmaceutics / Industrial Pharmacy
malathe_alshawi@yahoo.com
2-Lecturer / Mohammed Sabar Al-Lami* PhD Pharmaceutics (mohsabbar@gmail.com)
* Department of Pharmaceutics / College of Pharmacy / University of Basrah.
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Abstract:

Paracetamol is antipyretic and analgesic agent. It has been used for long time in different types of dosage forms. Capsule is one of the common dosage forms that characterized by ease of production and faster release in comparison to tablet. The release of active pharmaceutical ingredient (API) from capsules is dictated by formulation factors of binder and particle size of the granules. Those factors were investigated here to find out the appropriate binder and the optimum granule size. In addition, characterization of the flow properties, friability of the granules, the actual content, the release profile, kinetic of release were investigated

It was found that the optimum granule size in term of flow property is 25-mesh size. There was no significant difference in release profile among all the examined binders (starch, acacia, and PEG4000). However, using of PEG4000 as binder gives granules with reasonable hardness that can with stand subsequent process (i.e., capsule filling). These facts make PEG4000 as binder to be more preferable.

التقييم المختبري لعوامل الصياغة التركيبية:حجم الحبيبات ونوع المادة الرابطة على الخواص الفيزيوكيميائية لكبسولات البراسيتامول

الكلمات المفتاحية: الكبسول, البراسيتامول, المادة الرابطة, حجم الجسيمات, تدفق الحبيبات, حركية الاطلاق.

الملخص:

يعتبرالكبسول من اشكال الجرعات الدوائية الرائجة. البراسيتامول هو علاج خافض للحرارة ومسكن للآلام .تم استخدامه لفترة طويلة في اشكال جرع دوائية مختلفة . مع ذلك يتميز الكبسول بسهولة الانتاج وسرعة في الاطلاق الدوائي بالمقارنة مع الاقراص. الاطلاق الدوائي للمادة الفعالة من غلاف الكبسول يكون تحت تاثير الصياغة التركيبية من المادة الرابطة وحجم الجسيمات. تم التحقق من هذه العوامل لمعرفة المادة الرابطة المناسبة والحجم الامثل للحبيبات.بالاضافة لذلك تم توصيف خاصية تدفق الحبيبات و المحتوى الفعلي و صورة وحركية الاطلاق للمادة الفعالة وتفتت الحبيبات.

وقد وجد ان حجم الحبيبات الامثل هو حجم ٢٥شبكة. هذا الحجم قد أظهر افضل خاصية تدفق. مع ذلك، لايوجد فرق في الاطلاق الدوائي بين جميع المواد الرابطة من الناحية الاحصائية) (النشأ ، السنط ، بولي اثيلين كلايكول ٤٠٠٠) . بينما استخدام بولي اثيلين كلايكول ٤٠٠٠ كمادة رابطة يعطي حبيبات ذات صلادة معقولة والتي يمكنها المقاومة في الخطوات اللاحقة مثل ملئ الكبسول. هذه الحقائق تجعل استخدام بولي اثيلين كلايكول ٤٠٠٠ كرابط تبدو مفضلة.

Introduction:

Capsule is a single unit dosage form and the most convenient for oral administration. Capsule is one of the most popular oral dosage form available on the market[(1)]. It is

characterized by fast production rate, fewer processing steps and faster drug release in comparison to conventional tablets as the compression step is eliminated in capsule manufacturing[2].

Capsule provides affordable dosage form with cheap production cost and less production steps. It can be used to mask the unpleasant taste of many medicines; e.g., paracetamol, chloramphenicol [1, 3]. Paracetamol has analgesic and antipyretic activity. It has been used effectively in market in different formulations for long time, which ranges from conventional tablets to modified release formulations. However, continuous optimization of these formulation parameters is still being investigated and far from ending[4].

Granule size is very important parameter to be studied. It has a particular importance on the flow properties of powder during mixing and capsule filling steps to make sure a uniform filling of capsules [1, 5]. Therefore, in this work the optimum granule size was investigated. Another factor, of a great influence on capsules properties, is the type of binders (6). Binder (granulating agent) is an adhesive material, which links the particles together to form larger particles or granules. It greatly affects the disintegration time and release profile of the capsule [7, 8]. The type of granulating agent and size of granules were evaluated via assessing the flow properties, fragility of granules and release profile.

In this study, the flow properties and release kinetics of different granule sizes (15, 25 and 40-mesh size) were compared to the pure powder. Then the release profiles of different formulations containing different binder were evaluated to select the optimum granule size and type of binder.

Materials and method:

Paracetamol was a gift form Al Faihaa Drug Industry; Iraq. Starch (Al Hanoof for medical & lab Supplies; India), Acacia (Scharlau chemie, Barcelona, Spain), and PEG 4000 (Lab. Fine chemical, Mumbai; India) were used as binder. Methanol (Schar. Lab. S.L., Spain) and HCl (vadhani Mumbai, India) were used in this work.

Preparation of paracetamol granules:

200g of paracetamol was granulated with 20% of different binders (starch, acacia, PEG 4000) by addition of binder drop by drop until dough like consistency was accomplished and examined by squeeze hand test. The wet mass was passed through 8-mesh size and dried at 60° C for 1hr using a hot air oven. After complete drying of granules, the granule bed was passed through (8-mesh size) sieve again and the resultant granules were separated into different mesh size using frequent manual sieving through 15, 25, 40-mesh size [9]. The formulations are listed in Table 1.

Table 1: List of formulations and their codes

Formula code	Binder	Granule size (mesh size)
F1	Nil	Pure powder

F2	Starch	15
F3	Starch	25
F4	Starch	40
F5	Acacia	25
F6	PEG4000	25

Powder flow measurement:

Angle of repose

The funnel-Petri dish powder flow tester (Copley; UK) was used to measure angle of repose. 50g of different granule sizes was loaded into the funnel, and permitted to flow. The height and the radius of the formed cone was recorded and the angle of repose (α) was estimated from equation 1[10]

$$\tan \alpha = h/r \quad \text{.....Equation 1}$$

Bulk density, Tapped density and Carr's index, Hausner ratio

Bulk density and tapped density were measured to estimate Hausner ratio and car's index to select the optimum granule size for formulation.

Bulk density

The bulk density was measured according to USPXXX. An excess of granules was allowed to flow through (Bulk density tester (Copley; UK) to fill the receiving cup. The excess was removed from the cup. The mass of powder was measured and the bulk density was estimated from equation 2 [10].

$$P_B = m/v \quad \text{.....Equation 2}$$

Tapped density

Tapped density tester (Copley; UK) was used to measure the tapped density according to USPXXX. The graduated cylinder was filled with 50g of the examined sample and the volume was recorded after 500 taps to calculate the tapped density according to equation 3 (10)

$$P_t = m/v_{tapped} \quad \text{.....Equation 3}$$

Carr's index and Hausner ration:

Carr's index and Hausner ratio are referring to the compressibility and flow properties of powders. They have become the simple, fast, and popular methods of predicting powder flow characteristics[11].

Compressibility index = (Tapped density − Bulk density/tapped density) x 100……Equation 4

Hausner ratio = Tapped density / Bulk density…… Equation 5

Standard curve of paracetamol

100mg of paracetamol was dissolved in 100mL of 99.5% methanol or 0.1N HCl. Then a 1mL volume was withdrawn from each solution and diluted with original media up to 100mL, and then further dilutions were performed to make (8, 6, 4 and 2µg/mL) standard solutions. The absorbance was recorded at 248nm in methanol and 242.5nm in 0.1N HCl using Cecil spectrophotometer CE7200 (Cecil Instruments Ltd., Cambridge, UK). Each measurement was performed in 3 replicates [(12)].

Measurement of actual content

A 100mg of each formulation (acacia, starch and PEG4000 containing granules) was dissolved in 100mL of methanol, and then 1mL was further diluted up to 100mL of methanol to measure the actual content. Absorbance was recorded at 248nm using spectrophotometer[(13)].

In vitro release study of paracetamol from capsules:

An equivalent weight of 250 mg of active paracetamol of final formulation was loaded manually into each capsule. The dissolution performed according to USP using basket dissolution (Apparatus I) machine (Caleva 10+ST; Germany). The dissolution media was 900mL of 0.1N HCl, the temperature was maintained at 37±0.5° C, and the stirring rate was 100rpm.

A five millilitres sample was withdrawn from dissolution jar at selected time intervals (5, 10, 15, 30, 45 and 60). At the same time, an equal volume of fresh dissolution media was injected, after filtration and dilution of each sample up to 100 times in dissolution medium. The absorbance was recorded by spectrophotometer at 242.5nm[(11, 14)].

Friability of Granules:

A sufficient amount of granules of each formulation was manually sieved through 60-mesh size sieve to remove any dust material. 10g of granules (M1) retained in sieve was place in the glass jar (Fraibmat SA-400 Copley; UK). The machine was allowed to agitate at 200 and 400 oscillations/minute for 240 seconds. The weight (M2) was recorded after removal of any dust via sieving again in a 60-mesh size sieve. The friability was estimated via the following equation[(15)]:

$$\% \text{ of weight loss} = \frac{M1 - M2}{M1} * 100 \quad \text{.....Equation 5}$$

Results and discussion

Flow properties

The flow property of each granule size was evaluated via measurement of angle of repose, Carr's index, and Hausner Ratio. The results are listed in Table 2 and Table 3

Table 2: Angle of repose value and its interpretation according to BP for each formulation

Formulation	Angle of repose*	Powder Flow
F1	51.11 (±6.5)	Poor
F2	42.95(±3)	Passable
F3	35.71 (±2.96)	Good
F4	50.79 (±4.56)	Poor

*** (n=3) (mean±SD)**

Table 3: Carr's index and Hausener Ratio values and their interpretations according to USPXXX.

Formulation	Carr's index (%)	Hausner ratio	Flow character
F1	28.88	1.40	Poor
F2	6.01	1.06	Excellent
F3	8.36	1.09	Excellent
F4	40.33	1.67	Very poor

The flow properties were measured for each granule size to determine the best size to be selected for formulation of capsule. Capsule dosage form requires the powder to be freely flow to make sure the filling of each capsule is complete during the filling stage[(1)]. Table 2 and Table 3 list the measured flow properties for each size according to USPXXX. The powder flow of F1 and F4 were found to be poorly flow as shown in table 2 and 3. The powder flow properties of F2 were passable (not enough to be selected as the best size for formulation). However, it was found that the best particle size to be chosen for formulation of capsule is 25-mesh size. It has the best flow properties. It could be result of minimum inter particulate frictional forces between particles. Whereas, for mesh size lower than 25, the surface area is higher; and hence, more inter particulate frictional forces might be expected[(16, 17)].

In comparison to the particle size bigger than 25-mesh size, the particle size might be too big and might block the orifice and the mass of granules is too big which might need a higher triggering force to move. This is also confirmed by the results of Cars index, Hausner ratio and angle of repose.

Standard calibration curve of paracetamol

Figures 1 and 2 showed the calibration curves of paracetamol in 0.1N HCl and methanol. Straight lines were obtained by plotting the absorbancies versus concentrations with correlation coefficients of 0.9949 and 0.9995 respectively. This indicates that the calibration curves of the drug obey Beer's law within the concentrations used.

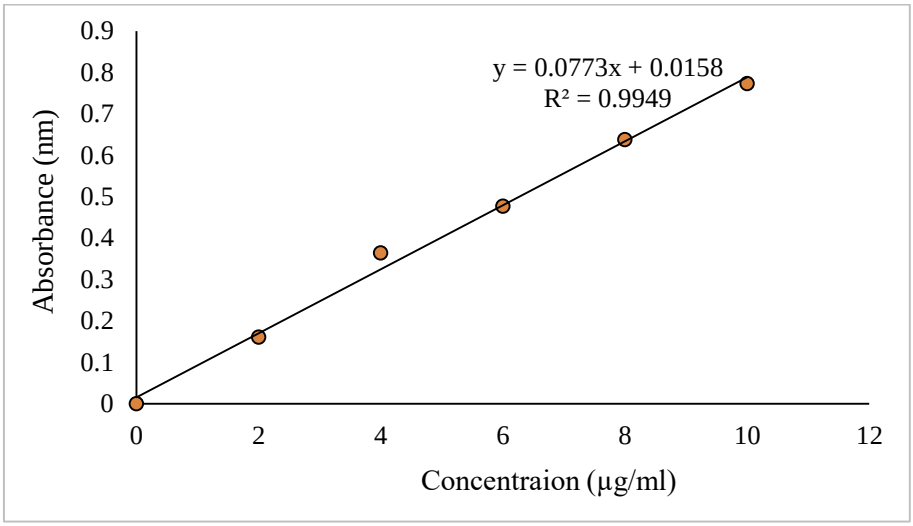

Figure 1: Calibration curve of paracetamol in 0.1N HCl at λ_{max} = 242.5nm

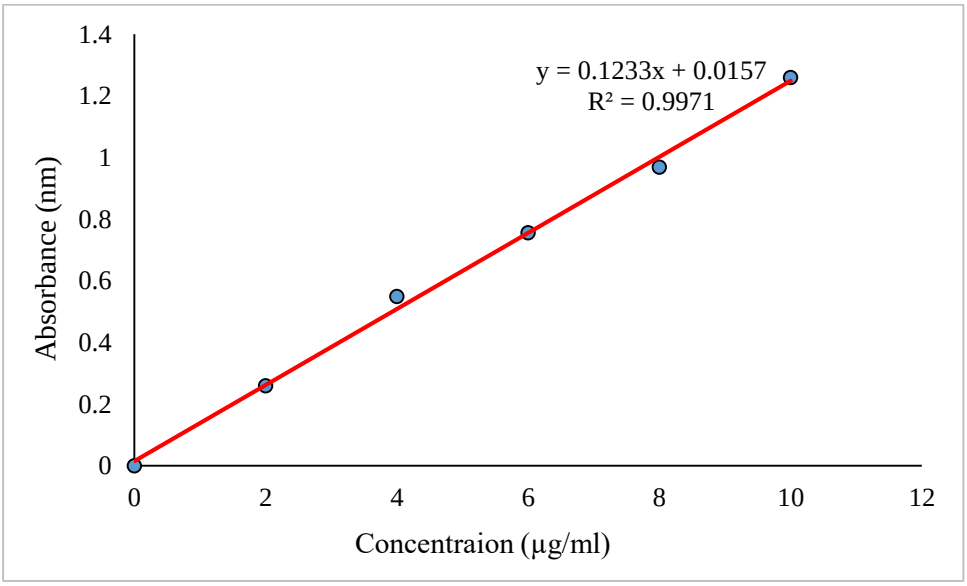

Figure 2: Calibration curve of paracetamol in methanol at (λmax) = 248nm.

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Actual content

It was measured in order to determine the actual amount of paracetamol in 100mg of granules, to state the exact amount of granules to be filled in each capsule, so that each capsule will contain 250mg of paracetamol.

Table 4: Actual content of different formulations made as 25-mesh size granules

Formulation	Actual content % *
F1	95(±1.6)
F2	96 (±2.3)
F3	95 (± 2)
F5	94.6 (±1.8)
F6	96.5 (±4)

*** (n=3) (mean±SD)**

Release study of capsules containing paracetamol granules

The release percentage of paracetamol from capsules in correlation with time was studied. In Figure 3, F1 showed a rapid release of paracetamol. It releases more than 85% of its content within 5 minutes. In comparison to other granule size formulations (F2, F3, and F4) showed a lower release percentage within the same time interval (less than 75%). It is clearly attributed to the fact that the larger granule size exhibits a lower release rate. However, the flow properties of pure paracetamol powder are very poor, which make it not advisable to formulate the capsules as pure powder without granulation. F2, F3 and F4 are having almost the same releasing profile. However, the flow properties of F2 and F4 are not satisfactory to be chosen in formulation. Thus, formulation of paracetamol with granule size of 25-mesh size is found to be the most satisfactory assurance of release and flow properties.

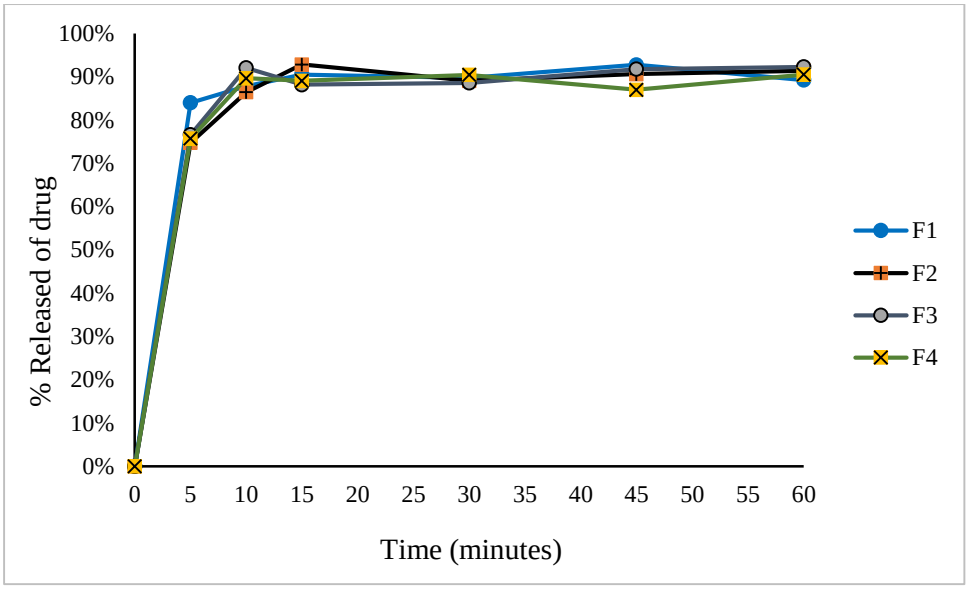

Figure 3: Release profile of paracetamol granules in 0.1N HCl dissolution media formulated at different size (F1= pure paracetamol powder, F2=15-mesh, F3=25-mesh size, F4=40-mesh size).

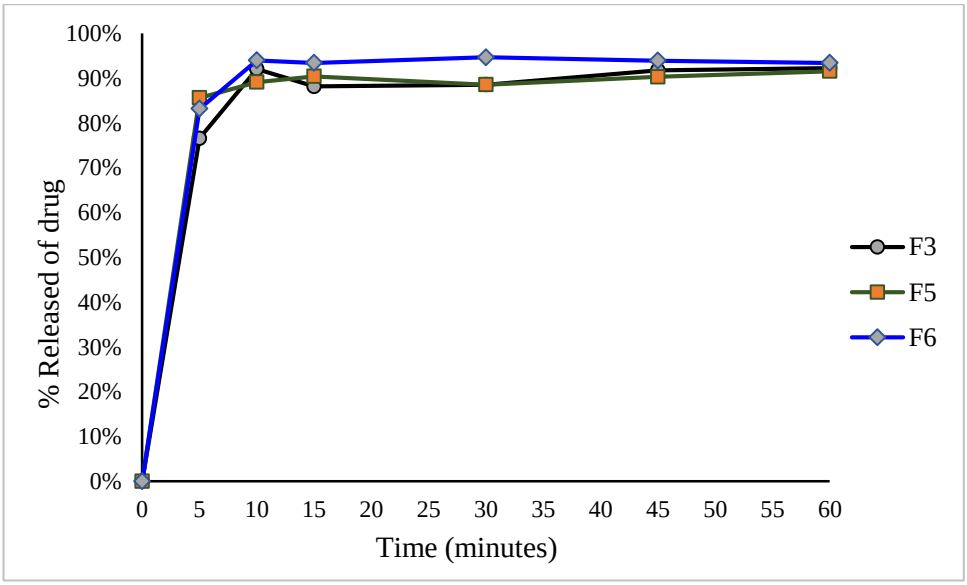

Figure 4: Release profile of 25-mesh size paracetamol granules in 0.1N HCl dissolution media formulated with different binders (F3= starch , F5=acacia, F6=PEG4000)

The formula F3 (Figure 4) showed the lowest release profile in comparison to F5 and F6. That indicates using of a PEG4000 or acacia, as binder is more favourable over starch as they released more than 85% of their content within 5 minutes. It could be attributed to the higher solubilizing activity of PEG4000 and acacia, as well as low water solubility of starch at 37° C[18].

Friability of granules

The results obtained from friability test of granules that prepared by different granulating agent are shown in Table 5.

Table 5: The friability test of granules made with different binders having the same particle size.

Formulations	Weight loss % *	
	Oscillation rate (200/ min)	Oscillation rate (400/min)
F3 (starch)	0.4(±0.07)	4 (±0.17)
F5 (acacia)	3.6(±0.16)	4(±0.12)
F6 (PEG4000)	0.2(±0.01)	0.63(±0.1)

*** (n=3) (mean±SD)**

The formula F6 has exhibited a best hardness, the weight loss % after 400-oscillation rate for 240seconds was the minimum for a granules made with PEG4000 as a binder. Although F6 has greater hardness, the release profile still fast in all terms. Thus, it could be concluded that using PEG4000 as a binder might be advocated.

Conclusion

These formulations parameters are far from ending. In this work, the type of binder and size of granules were evaluated via assessing the flow properties and release profile. 25-mesh size has demonstrated a lower release profile, however, the best granule size was found to be 25-mesh size as it has the best flow properties in comparison to other granule size.

Among the three selected examined binders, starch has shown the lowest release profile properties. Thus, it is recommended to fabricate paracetamol granules by using either PEG4000 or Acacia with granule size of 25-mesh size.

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