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# EFFECT OF BINDER AND ITS CONCENTRATION ON THE PHYSICAL CHARACTERISTICS OF SULFADIAZINE GRANULES AND TABLETS PREPARED BY WET AND FLUIDIZED-BED GRANULATION METHODS

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*Sulfadiazine was granulated by the fluidized-bed (Uni-Glatt), as well as by the conventional massing and screening (Wet granulation) methods. The effects of binder concentration and its type on the mechanical properties of granules and their corresponding tablets, as well as on disintegration time and drug content were studied. It was found that the fluidized bed method was an efficient with all tested binders to produce superior granules. However, disintegration time of the corresponding tablets was found to be increased markedly and was greatly affected by the type and the concentration of the binder. Some suggestions to overcome this problem are stated.*

Not only, the binder used in the granulation process that affects the physico-chemical properties of the granules and the quality of their corresponding tablets, but also the method of granulation may greatly affect these properties. Wet granulation which is considered the most applicable technique, involves several steps, requires different equipment and is time consuming.[1] Among the problems associated with the wet methods, is the presence of the liquid component within the

granules. This may cause crystal bridge formation; lowering the activity of micronized drugs[2]; and act as a vehicle for chemical reaction through hydrolysis and microbial growth. Decomposition of thermolabile substances during the subsequent drying process, is one of the major drawbacks of wet granulation method. In the last few years, new techniques have been developed to reduce processing time, and to improve tabletting properties of the granules. Of these, granulation in fluidized bed had received great attention as it allows to carry out the whole granulation process in a single equipment. Moreover, the hardness, rate of production of granules, size range and sphericity are affected by a number of operating variables Of these are depth of the bed, the size and size distribution of the particles and of the droplets, and the rate of evaporation of the solvent. All the operating variables are easily adjustable and controlled to produce granules with desirable physical characteristics.

The object of this investigation was to study the suitability of fluidized-bed method for granulation. The characteristics of the granulate obtained in this way were compared with those of granulates prepared by the conventional was massing method. The influence of binder type and its concentration on the physical characteristics of sulfadiazine granules and tablets prepared by both methods, was the second purpose of this study.

## EXPERIMENTAL

### 1. Materials and Apparatus

Sulfadiazine (ACF, Holland) USP grade, gelatin powder(150 bloom) Brit. Roure Bertrand B Dupont, PVP (K90) supplied by kahera Chemical Co., Egypt, Acacia BP (=963).

Niglatt " Wurster " system, CH-4133, Binzen-Haltingen, West-Germany Tablet Press, Erweka-Apparatebau, G.M. B.H., E.K.O., West-Germany. Air comparison Pycnometer, Model 930, Bechman Instruments Ltd. Erweka Tablet Hardness Tester, Erweka-Apparatebau, West-Garmany. USP Disintegration Apparatus, Erweka-Apparatebau, G.M.B.H., West-Germany. Roche Friabilator, Erweka-Apparatebau, G.M.B.H., West-Geramy . Dry Granulator, Erweka, type T.G. West-Germany Test Sieve Shaker , Erweka, West-Germany. Unicam Sp 600 UV Spectrophotometer.

2. Wet Granulation method.

Different batches of sulfadiazine granules using three binder solutions, gelatin, acacia and PVP were prepared. Each binder was used in three concentrations 5, 10 and 15% w/w. 80 ml of the binder solution was found to be sufficient to wet 200g. of sulfadiazine. The doughty mass produced was granulated through sieve no. 8 (B.P), dried at 60° and then passed through dry granulator.

3. Fluidized-bed method.

200g. sulfadiazine was introduced into the conical container, and fluidized from below by a stream of air. After a mixing time of about 5 minutes, whereby the exhaust filter was shaken from time to time, the spraying of the binder solution was started after adjusting the atomized compressed air at 29 psi. The discharge volume of the spray liquid pump was adjusted to be 15 RPM and the temperature of the bed being maintained at about 60°. The volume of the binder solution needed to produce the desirable granules was 200 ml. When the granules were formed and the granulating fluid was

finished, spray was turned off and the product dried by continuing to fluidize at the same elevated temperature.

4. Characterization of granules

Granules size analysis

Using Erweka test sieve shaker, 100g. granules were subjected to shaking for a period of 10 min. The average granules diameter $DP_{av}$ of each prepared batch of granules was calculated by[4]

$$DP_{av} = \frac{\Sigma(W.\ Dp)}{100}$$

Where W is the % of weight of granules retained between two sieves of mean aperture Dp.

Granules density ($\rho$)

This was calculated using the method adopted by Stanley-Wood and Shubair[5]

Tapped density

The tapped density of each granulation was measured according to the method used by Khan and Rhodes[6]. This was calculated in g $ml^{-1}$ and Values recorded are averages of 6 checks.

Bulk density

Using 20g. of each granules, bulk density was determined by the adopted method of Stanley-Wood and Shubair[5]. The bulk density was calculated as g $ml^{-1}$, and the values recorded are the average of six determinations.

Percent compressibility

This was calculated from the difference between the tapped (T) and bulk densities (B) using the formula of

$$\frac{T - B}{T} \times 100$$

as being used by Baichwal and Seshadrinathan[7].

Hausner ratio[8]

This is the ratio between tapped and bulk densities and was calculated from these values.

Friability

The method used by Stanley-Wood and Shubair[5] was adopted to calculate the friability percent for each granulate. Average of three determination was recorded.

Flowability

Flow rate was determined by the funnel method[9].

Geometric surface area

The equation of Stanely-Wood and Shubair[5] was adopted to determine the geometric surface area

$$Sw\ (m^2 g^{-1}) = \frac{\alpha sv.t \quad Sv\ (m^{-1})}{\rho\ (Kg\ m^{-3})}$$

5. Compression into Tablets

Granules prepared by the two granulation methods, were compressed in form of tablets. Granules were mixed with 10% potato starch and 5% talc powder. At constant weight and pressure, the tablets were compressed using Erweka Tablet Press.

6. Evaluation of Tablets

The tablets prepared from all granule batches were evaluated for weight variations (U.S.P.), thickness (micrometer), hardness, disintegration time (U.S.P.) friability, and drug

content.

## RESULTS AND DISCUSSION

A. Granule characteristics

1- Particle size and surface area.

With the same type and concentration of binder solutions, the average granule size obtained by wet granulation was higher than that of fluidized-bed granulate, with the exception of granules produced with PVP(Fig. 1A & B and Table 1). This increasing in size in case of gelatin and acacia may be attributable to the increase in penetration and wetting of the particles by the mucilage. The higher viscosity of the liquid between the particles might help in producing a larger particles by holding the smaller ones together. The small proportions of mucilage covering the particles would be synergestic for this action. This is in agreement with the findings of Davis and Gloor[10] in case of dicalcium phosphate particles, whose sizes increased as a result of penetration, covering or wetting by the mucilages. Carstensen et al.[11] have stated that, starch mucilage up to 10% w/w may alternatively cause an increase in the number of bond formations until an equilibrium granular state is acheived. On the other hand, PVP shows a reduction in particle size as the concentration increased (Fig. 1C). This could be due to the more viscous mucilage, producing pasty masses, which were not easily screened. The granules were not firm resulting in the production of a large amount of fines. In the granule size distributions of the various granulated samples, the percentage of fines (less than 75 um) were 0.81, 2.2 and 3.7

for 5, 10 and 15% w/w respectively. This is in agreement with Stanley Wood and Shubair[5], where the authors found that, with higher concentration of starch mucilage, the percentage of fines increased.

For the granulate obtained by fluidised-bed method, the particle size was less than that obtained in case of wet granulation (Fig. 1 A,B and C). As the result of temperature ($60^{o}$) during the spraying of binder solution over the granular bed inside the Glatt apparatus, water which constitutes the higher ratio of binder solution evaporated, leaving a thin film surrounding the individual particles. This will affect the cohesion of mucilage molecules to each other in such that the powder particles are not strongly bonded to each other by a mucilage bridge. This is as expected with low binder concentration. Moreover, the large particles formed could be broken up during the drying stage due to bombardment of the particles with the container wall. The particles size was greatly increased as the binder concentration increased. This is due to the delay in the water vaporization during the granulation stage as a rresult of higher viscosity of binder solution. It could be expected that, the small particles would be highly bonded to each other by the mucilage bridge producing larger ones.

The results obtained with particle size could also be accessed from the change of geometric surface area at different mucilage concentrations (Table 1 and Fig. 1A, B&C). It can be shown that, there is a slight reduction in surface area for granules prepared with gelatin and acacia (Fig. 1 A & B). This observation was in contrast with what was obtained in case of PVP (Fig. 1C). In case of fluidized-bed granulation, a higher reduction in surface area

of granules was obtained with 10% w/w binder solution (Fig. 1 A, B &C). It is worthwhile to mention that Stanly-Wood and Shubair[5] found that, with 10% w/w starch mucilage a 40% reduction in surface area from that of the initial dicalcium phosphate powder was produced.

2. Friability and density

Comparing the surface area with the friability percent in Figure 1, it is obvious that the strength of granules increased with decrease in surface area. This was explained by other workers[5], as a result of increase in bond formation. The same workers concluded that, there is a correlation between bond formation, granule strength and available surface area. The correlation between the particle density and friability percent is quite clear in Fig. 1 A, B & C. The reduction in the amount of granule less (lower friability percent) as a result of increased binder content seemed to be more significant for the fluidized bed granulate. This may be due to the development of more and stronger interparticle solid bridges of binder . From figure 1C, it can be seen that the higher viscosity of PVP (15%w/w) gave rise to granules with lower friability percent.

3- Other characteristics

The increase in binder concentration yielded larger granules (previously explained) with lower bulk density (Table 1). This latter effect probably results from the larger volume of intraparticulate voids associated with the larger granule size Bulk tapped density for wet granulated sulfadiazine shows higher values, and this is obviously related to the granules enlargement produced as a results of increased binder content Granules of fluided-bed granulation method, shown a lower bulk density resulted from small granule size. This indicates that

the capillary forces are likely to be far less effective in the consolidation of sulfadiazine powder[12].

In general, granulate obtained by wet method was less flowing , more hard, dense and cohesive than that obtained by fluidized-bed method. The good flowability may be due to the expected smooth outer wall of the granules due to the presence of the binder film around the particle, which would reduce the friction between the particles. Rough surfaces of wet granulate as a result of mass screening is responsible for poor flowability.

The relation between Hausner ratio and flow rate found by Baichwal and Seshadrinathan[7] was not clear in this investigation.

B. Tablets Characteristics

In order to study the influence of the nature of granules on their tablets, the granules obtained by two methods were compressed into tablets. It was noted that, all binder used were more effective in producing tablets as their concentration increased. Produced tablets were satisfied the USP requirments for weight uniformity (CV ranged from 0.85 to 3.12). It was interesting to note that, the coefficient of variation for mean weight (Table 2) was lower for tablets prepared from fluidized-bed granules because of their better flowability (Table 1). The uniformity of thickness resulting with each was parallel to that of weight(Table 2). Tablets prepared from wet method exhibits good mechanical properties towards hardness and friability, however tablets prepared from fluidized-bed granulate show a higher friability percent. This may be due to the lower moisture content for the granules prepared by this method as a result of high temperature used

throughout the granulation and drying stages. This could be overcome by exposing the granules to humidity conditions before compression, assuming that the drug content is stable against moisture. The longer disintegration time of tablets prepared from fluidized-bed granulate is probably caused by the inhibition of swelling and dissolution of the binder coat around the particles. Incorpcration of suitable disintegrants or surfactants might enhance the disintegration time.

The higher degree of homogenity in the mixing of powders throughout the fluidized-bed granulation, produced tablets with very slightly higher drug content as shown in Table 2. This is important in case of potent drugs.

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Table (1) Physical Properties of Sulfadiazine Granules.

| Granulating fluid | | Average granule size mm | | Bulk density kg $m^{-3}$ x $10^3$ | | Tap density kg $m^{-3}$ x $10^3$ | | Hausner ratio | | Compressibility % | | Granule density Kg $m^{-3}$ x $10^3$ | | Geome. surface area* $m^2 Kg^{-1}$ | | Flowability g/Sec. | | Friability % | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Binder type | Conc. %W/W** | I | II | I | II | I | II | I | II | I | II | I | II | I | II | I | II | I | II |
| Gelatin | 5 | 0.968 | 0.574 | 0.476 | 0.294 | 0.500 | 0.333 | 1.05 | 1.13 | 4.8 | 11.7 | 1.26 | 1.22 | 5.62 | 10.11 | 6.40 | 6.58 | 7.31 | 7.00 |
| | 10 | 0.984 | 0.880 | 0.435 | 0.286 | 0.476 | 0.317 | 1.09 | 1.11 | 8.6 | 9.8 | 1.21 | 1.19 | 5.73 | 5.46 | 5.88 | 6.36 | 4.50 | 2.30 |
| | 15 | 1.013 | 1.039 | 0.417 | 0.227 | 0.455 | 0.233 | 1.09 | 1.03 | 8.4 | 2.6 | 1.19 | 1.16 | 5.56 | 5.22 | 5.20 | 5.40 | 4.08 | 1.31 |
| Acacia | 5 | 0.901 | 0.605 | 0.417 | 0.417 | 0.455 | 0.455 | 1.09 | 1.09 | 8.4 | 8.4 | 1.39 | 1.30 | 5.66 | 5.76 | 6.12 | 6.90 | 5.24 | 6.40 |
| | 10 | 0.973 | 0.688 | 0.417 | 0.370 | 0.434 | 0.400 | 1.04 | 1.08 | 3.9 | 7.5 | 1.36 | 1.28 | 5.31 | 7.75 | 6.18 | 6.40 | 5.07 | 4.65 |
| | 15 | 0.991 | 0.823 | 0.385 | 0.344 | 0.400 | 0.385 | 1.04 | 1.12 | 3.8 | 10.6 | 1.34 | 1.24 | 5.16 | 6.40 | 5.90 | 6.12 | 4.50 | 4.00 |
| PVP | 5 | 0.962 | 0.247 | 0.435 | 0.417 | 0.455 | 0.455 | 1.05 | 1.09 | 4.4 | 8.4 | 1.17 | 1.14 | 6.01 | 25.30 | 6.39 | 6.60 | 5.00 | 5.16 |
| | 10 | 0.935 | 0.340 | 0.407 | 0.256 | 0.417 | 0.263 | 1.02 | 1.03 | 2.4 | 2.7 | 1.14 | 1.11 | 6.03 | 18.19 | 6.42 | 6.99 | 4.51 | 4.00 |
| | 15 | 0.888 | 0.441 | 0.388 | 0.208 | 0.400 | 0.244 | 1.03 | 1.17 | 3.0 | 14.8 | 1.12 | 1.09 | 7.97 | 16.77 | 6.10 | 7.10 | 3.63 | 1.93 |

*Size distribution.

**Binder concentration was calculated as weight percent from the weight of sulfadiazine used in each batch.

I-Granules prepared by wet granulation.

II-Granules prepared by fluidized-bed method.

*Effect of binder and its concentration on the physical characteristics of sulfadiazine granules and tablets prepared by wet and fluidized-bed granulation methods*

Table (2) Physical Properties and Drug Content of Sulfadiazine Tablets.

| Granulating fluid | | Weight* mg | | | | Thickness* mm | | Hardness* Kg | | Friability** | | Disintegration*** time min. | | Drug content % | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Binder type | Conc. %w/w++ | Mean I | Mean II | CV I | CV II | I | II | I | II | I | II | I | II | Mean I | Mean II |
| Gelatin | 5 | 252.3 | 252.6 | 3.12 | 1.27 | 4.64 | 4.82 | 3.08 | 3.21 | 0.36 | 0.63 | 2.83 | 3.41 | 100.00 | 100.97 |
| | 10 | 246.9 | 258.8 | 2.32 | 0.83 | 4.6: | 4.84 | 3.97 | 4.60 | 0.33 | 0.41 | 4.97 | 6.25 | 99.79 | 100.20 |
| | 15 | 251.7 | 255.5 | 1.48 | 1.64 | 4.64 | 4.90 | 4.70 | 4.64 | 0.23 | 0.41 | 12.93 | 14.70 | 99.08 | 100.02 |
| Acacia | 5 | 250.6 | 257.0 | 1.56 | 0.73 | 4.55 | 4.48 | 3.57 | 4.02 | 0.55 | 0.65 | 3.73 | 4.68 | 99.91 | 100.12 |
| | 10 | 249.8 | 252.9 | 1.81 | 0.90 | 4.50 | 4.61 | 4.00 | 4.40 | 0.55 | 0.62 | 5.33 | 7.00 | 98.99 | 100.09 |
| | 15 | 248.9 | 263.1 | 1.91 | 1.06 | 4.06 | 4.66 | 4.98 | 5.46 | 0.48 | 0.46 | 13.95 | 12.62 | 99.81 | 100.14 |
| PVP | 5 | 249.1 | 249.6 | 1.51 | 2.07 | 4.63 | 4.48 | 3.38 | 2.61 | 0.46 | 0.53 | 1.93 | 2.44 | 100.01 | 100.20 |
| | 10 | 253.6 | 256.2 | 1.39 | 3.05 | 4.75 | 4.82 | 4.27 | 4.24 | 0.27 | 0.52 | 2.92 | 4.55 | 99.20 | 99.99 |
| | 15 | 248.2 | 258.0 | 0.88 | 0.85 | 4.70 | 4.78 | 4.78 | 4.79 | 0.21 | 0.48 | 7.37 | 8.29 | 99.95 | 100.34 |

++ I, II — As in table (1)

*Average of 20 determinations. **Average of 3 readings. ***Average of 12 readings.

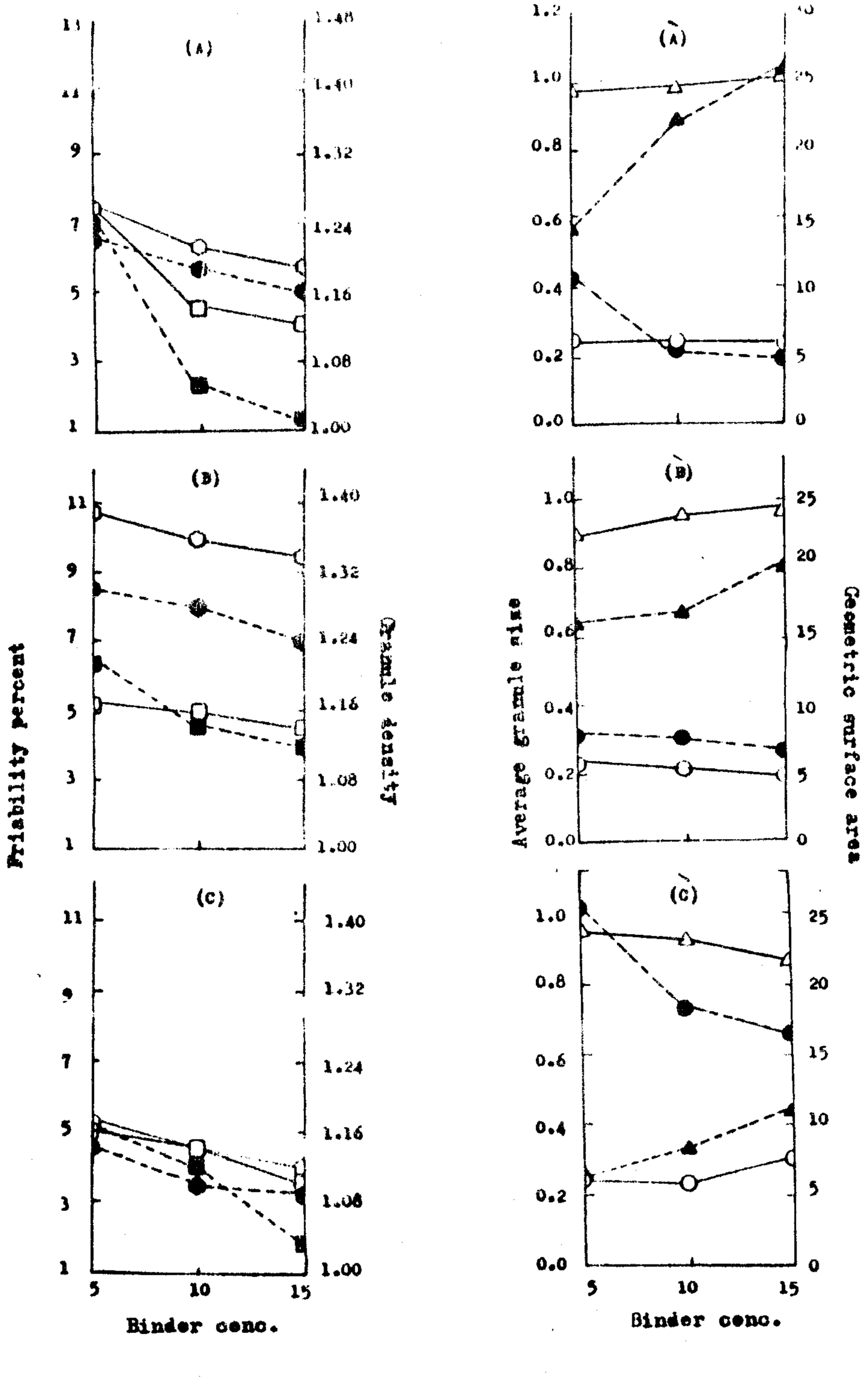


Fig.1 Effect of binder concentration on the physical properties of granules. (A) Gelatin, (B) Acacia, (C) PVP. (——) Wet granulation, (- - -) Fluidised-bed granulation. Friability %□■ Granule density○ ● Average granule size△ ▲ Geometric surface area○ ●

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# دراسة تأثير نوع وتركيز الروابط المختلفة على الخواص الميكانيكية للحبيبات المحضرة بطريقتى التحبيب الرطب والرش باستخدام جهاز جلات - كذا الاقراص المحضرة منها .

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قد تم تحضير حبيبات السلفاديازين بطريقتى التحبيب الرطب والرش فى درجة حرارة ٦٠ بأستخدام جهاز جلات. وقد تمت دراسة تاثير نوع وتركيز الروابط المختلفة مثل الجلاتين - الصمغ العربى - وعديد فينيل البيروليدون على الخواص الميكانيكية للحبيبات وكذلك الاقراص المصنوعة منها .

ولقد تمت دراسة زمن التفتت وتركيز العقار بالاقراص بوجه خاص . ولقد أتضح من الدراسة ان الحبيبات المحضرة بطريقة الرش باستخدام جهاز جلات لها صفات ميكانيكية أفضل ولكن يعيبها أن الاقراص المحضرة منها لها زمن تفتت أطول.

ولقد أقترحت عدة حلول للتغلب على طول مدة التفتت وبذلك يمكن الحصول على أقراص جيدة الصفات الميكانيكية كذلك زمن التفتت وتركيز العقار من الحبيبات المحضرة بطريقة الرش.

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