A GRANULE MODEL FOR EVALUATING ADHESION OF PHARMACEUTICAL BINDERS

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ABSTRACT

Granule capability is defined in terms of the strength of individual granule and friability of granulation batch to withstand breaking, abrasion and compactibility. Binder(s) are added to perform the above properties .The common methods to asses their capability are to test crushing strength of the granules directly and to make statistical analysis and /or testing the friability of bulk granulation.

In this work four substrate models including polymethylmetacrylate beads(PMMA),glass powder, acetaminophen, and para-aminobebzoic acid were chosen. The binder models were corn starch, gelatin, methylcellulose (MC) and hydroxypropylmethylcellulose (HPMC).

After massing the substrates with the binder solutions, discs were produced by the mean of the mold technique. The discs were dried and conditioned and then tested for tensile strength while the failed areas were scanned by SEM. Various granulations were made and the results of friability and crush strength were compared with the discs strength .The bond areas in the SEM showed the trend with the binder concentration .A comparison of the standard deviation shows that discs have much lower level of the strength than granules. The resulting discs showed a higher performance which is related to the stems for the discs shape .In conclusion, this method is a simple and is applicable to differentiate efficacy of binder under studies.

Key words :Binder; Granulation; Granule strength; Granule Model; Granule Friability; Adhesion .

INTRODUCTION

Granulation is a process usually carried out for formation of aggregates (1) that have pseudo spherical shape, better flow properties and enhancement of compressibility (2).

The capability of binder(s) are related to their appropriate interparticulate bonds (3,4). The granulation properties are evaluated in an indirect manner by the measurement of the adhesiveness between sheets or film adhesion (5, 6). The capability of adhesive results in the strength of particulate system, that is the strength of the granules bed (7,8) and ultimately tensile strength of tablets(9,10,11).However, glass ballotoni has been used as a substrate model either in the form of hydrophilic or hydrophobic to compare different binders(8).

Due to the presence of some formulation materials other than binders in tablets making, the strength of tablet could not be related easily to binder capability alone. Therefore adhesion of binder has been evaluated on the basis of granule bed strength, friability testing, or the strength of individual granule (8,9).

Crush strength testing of individual granule has been usually carried out (12) by the use of large number of granules and statistical analyses has been applied to determine significant differences (13,14).

Leucaena leucocephala seed gum have been evaluated as tablet binder using compressibility ,micromeritics, and mechanical properties of granules with acetaminophen which is badly compressible(15).It has been shown(16) that the lack of shape performance results in high discrepancies which are difficult to interpret.

The proposed method in this work, is based on making a large well defined granules *i.e.* discs of known substrate and binder which have same performance of granules by massing technique but have well known cylinder shape for calculation of strength directly and accurately The accuracy would be anticipated by statistical analysis and comparison.

MATERIALS AND METHODS

Materials

Polymethylmetacrylate (PMMA) beads, were from BDH, England; Acetaminophen and 2-aminobenzoic acid were received from Daru

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pakhsh, Pharmaceutical Company, Iran; and glass bulbs were from, Afrooz Company Iran, as substrates.

The binders were , corn starch from yasoog company ,Iran, Methylcellulose (MC), from Darupakhsh Pharmaceutical company; Gelatin Byco C, and Hydroxypropyl methylcellulose (HPMC E15),were from Colorcon, England.

Methods

Substrates processing:

The bulbs were hand-grinded using mortar and pestle and passed through 75µ sieve. Other substrates were only sieved through 75µ sieves. The beads were fractionated and 125-250µ size were collected and used.

Discs making:

Binder solution were made by dispersing accurate amount of the starch in one–third of the desired cold water and sufficient water then added to make the volume. Methylcellulose and gelatin solution were made by adding them directly to the boiled distilled water. Massing was achieved by hands using beaker and sptula. Seven ml of binders with specified concentration (W/W) was used and 0.8 gram of the mass was transferred to a stainless steel mold with 1.2 cm diameter. Five kilograms weight was then put on the punch for three seconds to assure constant loading for packing. The discs were then removed and dried in oven at 60 ^{o}C for 3 hrs and equilibrated at room temperature for 10 minutes before testing.

Tensile testing:

Ten discs were tested for each experiment using tensile testing R.D.P. Howden Ltd. Leamingston Spa, England. Tensile strength of the discs were calculated using the equation $\delta = 2F/DH$, where δ, F,D and H are tensile strength (MPa), Force (Newton), diameter and thickness (m) of the discs respectively.

Granulation:

The reported method (8) was followed except that hand making was used for massing and screening and the use of 710 µ sieves.

Resistance to crushing: This was determined using Shear Apparatus (E.L.E. Ltd Hemel Hempstead, U.K.) modified in such a way to measure mall loads in compression (10) with cross head of 1 Cm per minute .The thickness of the bar was 2mm calibrated before testing by different weights .

Granule friability:

Five grams of the granules of the 500-710 µ size fraction were placed in friabilator, Erweka, Offenbach, F.R.G., and tumbled for 5 minutes at 25 rpm. The percentage of loss, after sieving by 710 µ sieve size was recorded. These granules were stored at 12% RH to maximize differences between binding agents.

Scanning Electron Microscope (SEM):

The failed discs of PMMA bead were gold coated and scanned with Cambridge electron microscope and photographed.

Failed bonded area measurement:

Transparency copies of SEM photographs were prepared and reflected on checkered paper using shading technique .The shaded areas were cut, weighed and turned to area (cm^2).

Statistical analyses:

Student t-test was applied for significant difference on the level of p= 5 %**.**

RESULTS AND DISCUSSION

Table 1 shows results of tensile strength of all model binder /substrate systems. As the results indicate, there are low standard deviations for the strength of the discs compared to granules which could imply performance and accuracy of the method .Also the trend of different binders for substrates supports the above conclusion. A comparison of these results with those of granulation show that the latter have higher standard deviation that are implying discrepancies of the bond texture and only statistical calculations could interpret them.

Figure 1 shows distribution of the binder (HPMC E15) throughout the well defined shape particle of PMMA beads as well as the shape of the adhesive bonds present. As the results indicate (table 2), increasing the amount and concentration of the binder did not alter the distribution which usually happened during drying process, rather the binder film just shrink, and the area of the bond increased causing higher bond strength (table 1) Increasing the amount of binder does not necessarily indicate better distribution throughout the bed. While in all cases, both granulation and discs models, it was expected that the all of the polar binders would migrate toward the surface of the both models,a comparison of results did not confirmed this idea..

A comparison of different binders showed effects of the surface energies of both binders and substrates (17) *i.e.* gelatin and starch having more polar energetic binder had higher strengths on glass having higher polarity, than on lower energy acetaminophen, and 2-aminobenzoic acid and intermediate energy PMMA(18).

Table 1.The strengths of different binder / substrate systems

Binder-substrate	Granule strength(gm)	Standard deviation(%)	Friability(%)	Discs strength (Mpa)	Standard deviation (%)
Glass					
Gelatin	43(12)	27.9	23	4.82 (0.55)	11.4
HPMC	36(10)	27.7	26	3.78 (0.31)	8.2
MC	33(9)	27.2	31	3.15 (0.25)	8.0
Corn starch	28(7)	25.0	4	2.95 (0.28)	9.5
Acetaminophen					
Gelatin	30(8)	26.6	12	4.15 (0.52)	12
HPMC	38(9)	23.7	11	6.22 (0.62)	10
MC	44(7)	16.0	8	8.98 (0.69)	7.0
Corn starch	22(6)	27.3	31	1.48 (0.28)	9.0
Paraaminobenzoic acid					
Gelatin	22(6)	27.2	20	2.40 (0.27)	10.5
HPMC	35(8)	22.8	12	7.22 (0.56)	7.7
MC	46(8)	17.4	6	8.87 (0.61)	6.8
Corn starch	23(7)	30.4	21	2.80 (0.26)	9.0
PMMA					
Gelatin	--	--	--	1.02 (0.06)	5.9
HPMC	--	--	--	0.75 (0.07)	9.3
MC	--	--	--	0.68 (0.08)	11.7
Corn starch	--	--	--	0.55 (0.07)	12.7

Table 2.Binder concentration and related bond area from figure (1).Inbrackets standard deviation.

Concentration(% W/W)	Discs strength(Mpa)	Bond number	Bond area(cm^2)
5	0.75(0.07)	24	11.68
6	0.82(0.06)	23	13.53
7	0.88(0.08)	25	16.71
8	1.02(0.06)	23	21.66
9	1.21(0.06)	27	23.35
10	1.45(0.07)	22	26.33

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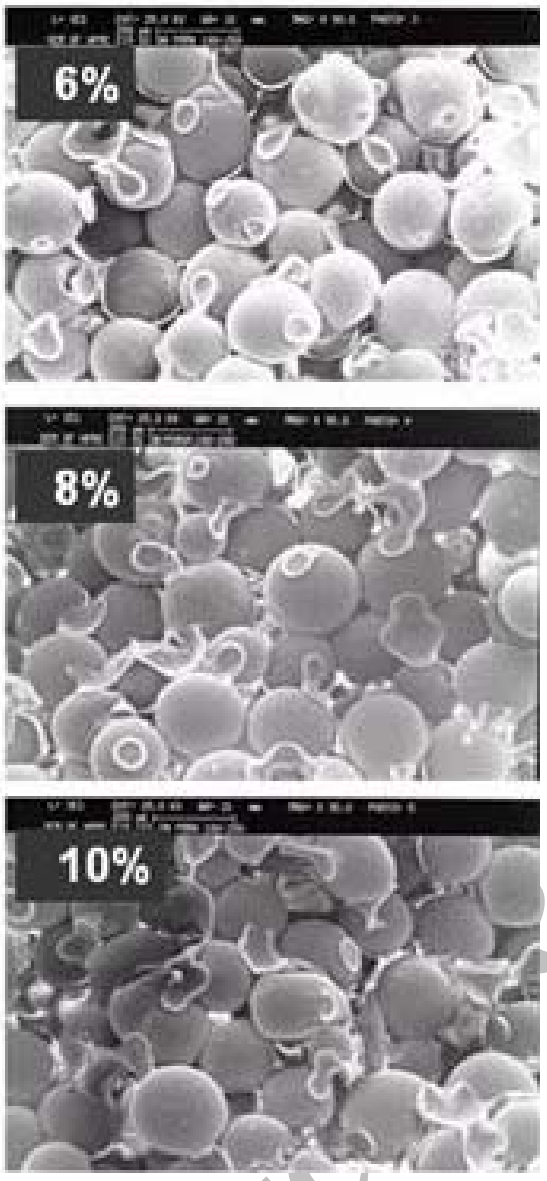

Figure 1. SEM photograph of the failed area of mold discs using different concentrations of HPMC (6%,8% and10%) descending respectively) with PMMA beads.

In the all mentioned cases the bond strength in the three states *i .e* individual granule, granule bed and the discs, were consistent except that standard deviation was much lower for the discs This finding might be attributed to the well defined and bigger shape of discs where the granulation had wider distribution of sizes and shape.

On the other hand, the individual granule could not be defined very well due to the aggregates formation during granulation process .Also the small load necessary for granule to fail may cause lower accuracy in a way that only statistical calculation could interpret results.

Other methods like tablet hardness -crushing and friability testing for the binder evaluation may not be applicable binder evaluation. This might be due to different deformation nature of the binder and/or substrate during high loading of compactions.

As indicated, this work has been done on different substrates with wide ranges of surface energies irrespective of their particle sizes that have often potential effects in granulation efficiency.

CONCLUSION

From the results it might be concluded that this method is a very suitable and simple for evaluation and comparison of binder efficiency. Also this method may be used potentially for multiple phases granulation. On the other hand it could be concluded that irrespective of their amounts, binders distribution is homogenous completely if it is wetted well.

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