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THE EFFECT OF THE BINDING AGENTS ON THE FRIABILITY AND COMPRESSIBILITY OF GRANULES I.[x] Using of the equal amounts of the binding agents which have different molecular weight

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ABSTRACT

The friability of granule is one of the most important parameters which effects the properties of compressed tablet and several factors play an important role. In this study the effects of the molecular weights and types of the binding agents on friability and compressibility of granules were investigated. Possesing various molecular weigths of Polyvinylpyrrolidone and Methylcellulose were used for the preparation of granules and their physico-pharmaceutic properties were evaluated.

INTRODUCTION

A unit of granule is formed, by the agglomeration of the elements of its components through bonds of a certain strength.

The mechanical strength of a granule prepared by the wet granulation method depends on the surface tension of the binding liquid used and the capillary forces between this binding liquid and the solid particles. These forces are responsible for the initial agglomeration of the wet powder(1).

The frictional and abrassive forces acting on dried granules during the manufacturing process modify the physico-pharmaceutic properties of granules. Thus, the determination of granule friability is an important validation parameter for the manufacturing of tablets with uniform properties(2,3).

The friability of granules depends on the following parameters:

a- The type and the concentration of the binding agent used in the granulation process(4).
b- The temperature and the duration of the drying process (taking into consideration the moisture content and the flowrate of the circulating air)(5).
c- The load on the trays, if the drying is carried out in trays and air is circulated horizontally over them(6).
d- The working principle and the geometrical shape of the apparatus employed in the granulation process(7).
e- The length of time in which binding solution is added to the granulation mass(8).

In order to determine the friability of granule, the friability test is performed and the friability index(FI) is determined therefrom(9). For this purpose, the mass-median particle size of tested granules is diveded by the mass-median particle size of the initial granules. This ratio is required to be as close to unity as possible. The lower the value of the(FI) from unity, the more friable is the granule(10).

The purpose of this study was to investigate the effect on the FI values and compressibility of granules of the type and the molecular weight of the polymers used as the binding agent in the wet granulation process. Polyvinylpyrrolidone and Methylcellulose with varying molecular weights were chosen as binders. The effect of uncontrolled variation in size and distribution of the particle on the flow rate, the bulk properties, the consalidation and the compressibility of the granules was also investigated.

EXPERIMENTAL

Materials:

Corn Starch(Pharm. Quality), Lactose(DMV), Elcema P 050(Degussa), Polyvinylpyrrolidone(Kollidon, K-25, K-30, K-90, BASF AG), Methycellulose(Tylose, MH-50, MH-300, MH-1000, Hoechst AG).
A single lot of each material was used for all experiments.

Wet Granulation Process

The wet granulation formulation used was as follows.

Lactose.....665.52 g
Corn Starch.....286.86 g
Elcema P 050.....47.62 g
Binder Solution (6 % w/v).....310 g

Lactose, Corn Starch and Elcema P 050 were mixed in a cubic mixer (Erweka, 15/UG) for 30 minutes at 35 rpm. The wet granulation was effected in a planet mixer (Erweka,PRS) by adding equal portions of the binder solution at equal time intervals in a 30 minutes long process, which was the passed through an oscilatting granulator(Erweka,FGS) with a 18 mesh screen. The granules were dried at 50±2°C for 2.5 hours in a drying oven with a circulating fan. The residual moisture content of the dried granules were determined by an IR apparatus at 80°C for one hour, and was found to be 3.2-3.4 %. The dried granules were passed again through the same screen.

Determination of Average Particle Size

The average particle size and size distribution of the granules were measured by sieve analysis. Fifty grams of granules were placed on a nest of 6 sieves(0.841, 0.707, 0.595, 0.500,0.354, 0.210 mm). The sieves were placed on a sieve shaker(Retsch,vibration amplitude:2 mm) and vibrated for 20 minutes. The fraction remaining of each sieve was weighed. The cumulative percentage oversize was plotted against sieve size on log-probability graph paper. The average particle size of the granules were determined from the graph.

Determination of Granular Friability

The granular friability was determined using the friability test with Roche Friabilator suggested by Rubinstein et.al.(9) and Baykara et.al.(11). Fifty grams of granules were placed in a Roche Friabilator together with 10 rubber balls of diameter 15 mm. The apparatus was rotated for 10 minutes at 25 rpm. The tested granules were called friabled(FR) and the untested granules i.e. initial granules, unfriabled(UFR). Thus 12 different granules of each type were obtained which were coded as follows(Table 1).

The FI values were calculated the ratio of the mean particle size of friabled granules to mean particle size of unfriabled granules.

Determination of the Flow Rate of Granule

The flow rates of the (FR) and (UFR) granules were determined with the Flow Rate(Erweka) apparatus using 60 grams of granules at each time.

Determination of Consalidation Properties of Granules

The consalidation of 10 ml of each granule was realised in a 10 cm^3 graduated cylinder. The granules were poured into the graduated cylinder by using a funnel, in order to avoid percolation and the weight of the 10 ml was determined, the bulk density(BD)

Table I
Codes of Granules

Polyvinylpryrrolidone (Kollidon)	Methyl Cellulose (Tylose)
K-25(UFR)	T-50(UFR)
K-25(FR)	T-50(FR)
K-30(UFR)	T-300(UFR)
K-30(FR)	T-300(FR)
K-90(UFR)	T-1000(UFR)
K-90(FR)	T-1000(FR)

being calculated therefrom. The graduated cylinder was tapped from a height of 10 mm and the resulting reduction in volume was measured after repeating this procedure 5,10,20,50,75,100,120,200,300, 400,500,600, and 700 times. The natural logharitmus of the tapping values,thus obtained,were plotted against the ln ln value of the relative density change(TD^x - BD/TD) (12). The properties of the regression lines calculated with a computer programme(Basic 80) were investigated(13).

Determination of the Compressibility of Granules

The compression properties of (FR) and (UFR) granules were investigated using Heckel and Kawakita(14,15) equations. For this purpose a 10 mm diameter flat face punch and a hydrolic press were used. Equal volumes of granules(1481.57mm^3) were pressed at 767, 1150.5, 1534, 1917.5, 2301, 3068 $kgf.cm^{-2}$. Pressure which maintained at the required value for 30 seconds. The volume of the tablet,V_p, formed at each pressure level was calculated. Results were calculated with a computer programme written by using Heckel and Kawakita equations(13).

RESULTS AND DISCUSSION

The mean particle size of the (FR) and (UFR) granules were calculated from the log-probability graphs plotted according to the results of the sieving analysis and (FI) values were determined for each granule therefrom(Table II).

The flow rates of (FR) granules had in the main changed as a result of friability test and all the flow properties were improved(Table III). The difference obtained between the granule pairs of the same origin i.e. K(FR) and K(UFR) was significant($p<0.01$). The decrease in the flow duration of the (FR) granules was the result of the rolling action of the fine particles produced by breaking down of larger granules during the friability test, thus giving an apparent improvement in the flow properties(17). However it was observed that the variation coefficient of (FR) granules were higher than those of the (UFR) granules. This showed that the regu-

x: TD:Tapped Density

TABLE II

The (FI) values of granules

Type of granule	(FI)
K-25	0.762
K-30	0.808
K-90	0.941
T-50	0.819
T-300	0.840
T-1000	0.854

TABLE III

The flow rates and Hausner Factors of granules which prepared with Kollidon and Tylose

Type of Granule	Flow Rate(g/sec) $(\bar{X} \pm S_x \cdot t_{0.05})$	V.C.[x]	H.I.
K-25(UFR)	0.88 ± 0.0083	1.33	1.19
K-25(FR)	0.68 ± 0.025	5.14	1.19
K-30(UFR)	1.047± 0.0109	1.46	1.25
K-30(FR)	0.70 ± 0.024	4.84	1.23
K-90(UFR)	1.16 ± 0.018	2.16	1.20
K-90(FR)	0.84 ± 0.015	2.50	1.15
T-50(UFR)	1.00 ± 0.014	1.92	1.25
T-50(FR)	0.74 ± 0.014	2.58	1.14
T-300(UFR)	0.95± 0.017	2.36	1.14
T-300(FR)	0.72± 0.019	3.72	1.10
T-1000(UFR)	0.95± 0.011	1.60	1.15
T-1000(FR)	0.70± 0.017	3.46	1.09

x: Variation coefficient
$\bar{X}$: n/10

larity of flow properties of granule mass was changed and particle size distribution range increased. In another word the weigh variation of compressed tablet was increased. This negative result was significant for the granules prepared by the Kollidon, because (FI) values of the Kollidon granules were less than the Tylose granules The similar result was also observed for the Hausner Factor values of (FR) granules. The narrow pressure tolerance limits of such granules might lead to complications at the compression step(18).

The consolidations of powder mass are a function of the interparticular holes, sizes and size distributions of the particles. For this purpose, B.Neumann has evaluated the linear relationship of the tapping number versus relative volume change, but at the compression step , the relative density change, i.e. densification has occured. For that reason the correlation coefficient of

TABLE IV

The consalidation relationship characters of the (FR) and (UFR) granules prepared by using Kollidon and Tylose

Type of granule	r^2	Slope	Intercept	S.D.Reg.
K-25(UFR)	0.9750	6.387×10^{-2}	-1.0337	0.0163
K-25(FR)	0.9058	7.622×10^{-2}	-1.0757	0.0372
K-30(UFR)	0.9811	7.998×10^{-2}	-1.0265	0.0177
K-30(FR)	0.9083	7.965×10^{-2}	-0.9286	0.0390
K-90(UFR)	0.9674	9.775×10^{-2}	-1.1690	0.0293
K-90(FR)	0.9689	10.169×10^{-2}	-1.2517	0.0255
T-50(UFR)	0.9745	8.191×10^{-2}	-0.9304	0.0195
T-50(FR)	0.9669	9.902×10^{-2}	-1.2310	0.0239
T-300(UFR)	0.9684	10.359×10^{-2}	-1.3984	0.0298
T-300(FR)	0.9050	7.989×10^{-2}	-1.3220	0.0382
T-1000(UFR)	0.9449	13.150×10^{-2}	-1.4990	0.0507
T-1000(FR)	0.9032	9.450×10^{-2}	-1.3560	0.0411

ln ln relative density change versus tapping number relationship has more increased. The determination coefficient of UFR granules were higher than those of the FR granules for the consalidation test. This occured due to the change of homogenity in particle size distribution as a result of friabilty test(Table IV). This change is opposed to the powder densification and interparticular holes filling rules by increasing of tapping number for granules and powders.Therefore the determination coefficients of regression lines of FR granules was less than those of UFR granules. Tapping number versus relative density change relationship was changed as a result of irregular and/or uncontrolled particle breakdown. The intercept values also inreased. The increase was directly proportional to the increase of the slope of the regression line of FR granules. For that reason,during the compression step,the upper punch falls down from the required position,so energy consumption incresed(19).

The determination coefficients of regression lines of UFR granules obtained by the Heckel equation were higher than those of FR granules(Table V). The yield pressure(P_y) values of FR granules which obtained from the reciprocal values of the slope of regression plots were increased(20). These results indicated that the compressibility of FR granules were changed negatively. This variation shows that the difference between elastic and plastic deformation pressure of system was reduced(21). The pressure increase may lead to capping easily in such a granule mass(22). Consumed energy to compress the tablets was also increased.

The line obtained by Kawakita equation was the best fitting line. The (a) value,the initial porosity, reduced as a friability test. Because of this,the intragranular voids were filled by the fine particles which were formed as a result of abrassion of granule units. The (b) value was a parameter releated with the elastic coefficient of granule mass and was reduced all the granule types except T-1000(UFR) and T-1000(FR). The increase of P_y values prove these results(23).

The results of this study showed that the mechanical strength

TABLE V

The Heckel and Kawakita parameters of granules prepared by using Tylose and Kollidon

Type of Granule	r^2 (Heckel)	P_y ($Kgf.cm^{-2}$)	r^2 (Kawakita)	$ax10^{-1}$	$bx10^{-3}$
K-25(UFR)	0.9348	$0.030x10^2$	0.9999	7.233	6.382
K-25(FR)	0.9697	$1.176x10^3$	0.9993	6.279	5.375
K-30(UFR)	0.9865	$1.041x10^2$	0.9999	7.086	6.454
K-30(FR)	0.9801	$6.577x10^2$	0.9997	6.658	4.737
K-90(UFR)	0.9769	$1.116x10^3$	0.9998	7.563	5.748
K-90(FR)	0.9638	$9.610x10^2$	0.9994	6.988	5.179
T-50(UFR)	0.9242	$4.504x10^2$	0.9994	6.955	4.694
T-50(FR)	0.8899	$6.224x10^2$	0.9998	6.459	5.182
T-300(UFR)	0.9464	$5.894x10^2$	0.9984	6.936	4.640
T-300(FR)	0.9458	$1.171x10^3$	0.9994	6.519	4.178
T-1000(UFR)	0.9678	$1.333x10^3$	0.9994	7.022	3.961
T-1000(FR)	0.9791	$1.653x10^3$	0.9991	6.446	4.166

of granules was changed by using equal amount of the same type of binding agent which has different molecular weight. This uncontrolled variation effects the other properties of the granule mass(mechanical,consolidation and compressibility). In this study it was observed that the increase in the molecular weight of the binding agent of Kollidon granules increased the mechanical strength of the granule. The FI values were changed in the following order; K-25<K-30<K-90 (Table I). The similiar sequence was observed for the Tylose granules,i.e. T-50<T-300<T-1000. But the difference of (FI) value of Tylose granules were less than the Kollidon granules. All properties of the granule changed with the difference of the (FI) values. It was concluded that the difference of the molecular weight of binding agent was an important parameter effecting the mechanical strength of granules.

FOOT NOTES

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REFERENCES

1- C.G. Barlow, Chem.Eng.(London), 220, 196(1968)

2- H.Sucker, "Praxis der Validierung", Wissenschaftliche Velagsgesellschaft mbH., Stuttgard, 1983, p.23.

3- T.Baykara, Lecture Notes, Frei-Universitaet Berlin, 1986.

4- N.G. Stanley-Wood and M.S. Shubair, J.Pharm.Pharmac., 31, 429(1979)

5- T.K. Sherwood, Ind.Eng.Chem., 21, 976 (1929).

6- W.Jost, "Diffusion", Academic Press, New York, 1960, p.46

7- D.E. Fonner, G.S.Banker and J.Swarbrick, J.Pharm.Sci., 55, 181 (1966).

8- A.A. Chalmers and P.H.Elworthy, J.Pharm.Pharmacol., 28, 239 (1976).

9- H.Rubinstein and P.Musikabhumma, Pharm.Acta Helv., 53, 125 (1978).

10- H.Sucker, Pharm.Ind., 44, 312 (1981).

11- F.Acartürk and T.Baykara, S.T.P. Pharma, 2, 522 (1986).

12- T.Baykara and M.M.Süleyman, Consalidation Kinetics of Pharmaceutical Powders (unpublished data)

13- M.M.Süleyman and T.Baykara, presented at the 3rd Int.Pharm.Technol. Symposium, Ankara, Septemper 9-11, 1986.

14- R.W. Heckel, Trans.AIME, 221, 1001 (1961).

15- K.H. Lüdde and K.Kawakita, Die Pharmazie, 21, 393 (1966).

16- Z.T. Chowhan and Y.P. Chow, Drug Devel.Ind. Pharm., 6, 1(1980)

17- T.M.Jones, J.Soc.Cosmet.Chem., 21, 483 (1970).

18- P.H. List, "Arzneiformenlehre", Wissenschaftliche Verlagsgesellschaft, mbH, Stuttgard, 1985, p.45,97

19- B.S. Neumann, "Flow Properties of Powders", H.S. Bean, A.H.Beckett and J.E.Carless, (Eds.), "Advances in Pharmaceutical Sciences", Academic Press, London, 1967, Vol.2, p.199-206.

20- E.L. Parrot, "Compression", H.A.Lieberman and L.Lachman, (Eds.),

"Pharmaceutical Dosage Forms", Marcel Dekker, Inc.New York,Vol 2, 1981, p.154.

21- A.Michoel, K.Peeters, P.Rambaut and R.Kinget, Pharm.Ind.,48, 961 (1986).

22- W.Jetzer and H.Leuenberger, Pharm.Acta Helv., 59, 2 (1984).

23- K.Kawakita and K.H. LÜdde, Powder Technol.,4, 61 (1970/1).