WET GRANULATION: PHYSICO – CHEMICAL EVALUATION AND STATISTICAL ASSESMENT

Preparation of the Granulatum simplex

The Granulatum simplex was prepared as describe in Formulae magistrales et reagentia (12).

Lactose (60 g) and starch (Maydis amylum, 140 g) were homogenized and wetted with previously prepared gelatinous solution (1,6 g of gelatin in 38,4 g of distilled water). Wetted granulation was pressed through the sieve No. 2 (mesh size 2 mm), using Erweka apparatus, FSG, FRG. The obtained granulation was then dried to the constant weight at 60ºC.

Different determined densities of granulation (g/cm³):

bulk density	**0,502**
tapped density	**0,714**

Real density (using He picnometer) 1,54 ± 0,01 g/cm³

Table 1: Real densities of the granulation determined by nonsolvent method.

Solvent	Determined density
aceton	1,580 g/cm³
chloroform	1,565 g/cm³
cyclohexane	1,520 g/cm³
average density:	1,555 ± 0,031 g/cm³

Molecule diameters for the nonsolvents used and He (m • 10^{-10}):

He	1,08
chloroform	3
aceton	4
cyclohexane	5

Total porosity: $E_t = 1 - \rho_b/\rho$ is 67,4%.

ρ_b – bulk density, ρ – true density

Table 2: Parameters of granulation porosity at different pressure values.

Pressure (PSI)	Pore diameter (μm)	Cumulative intrinsic volume (cm^3/g)		Cumulative pore surface area (m^2/g)	Differential intrinsic volume (dV/dD) ($cm^3/g \cdot \mu m$)
0,7	251,1997	0,0020		0,0000	0,0002
7,5	24,1827	0,0216		0,0015	0,0004
15,1	11,9547	0,0471		0,0085	0,0066
25,6	7,0561	0,2414	max	0,0969	0,0573
54,7	3,3069	0,2591	Δ vol.	0,1120	0,0063
142,6	1,2680	0,2748		0,1361	0,0020
338,6	0,5342	0,2866		0,1950	0,0267
825,6	0,2191	0,2866		0,1950	0,0000
8880,6	0,0204	0,2885		0,5320	0,3336
23395,6	0,0077	0,2905		1,4252	0,9266
30163,5	0,0060	0,2905		1,4252	0,0000
14115,6	0,0128	0,2905		1,4252	0,0000
8403,6	0,0215	0,2905		1,4252	0,0000
850,6	0,2102	0,2905		1,4252	0,0000
156,6	1,1551	0,2905		1,4252	0,0000

max P

pressure (PSI, pounds per square inch) – pressure of mercury necessary for intrusion, 1 PSI = 6895 Pa)

pore diameter – diameter of pores which are filled under defined pressure

cumulative intrinsic volume – cumulative pore volume in cm^3 per g of the sample

cumulative pore surface area – cumulative pore surface in m^2 per g of the sample

differential intrinsic volume – increment intrinsic volume divided by pore diameter

Figure 1: Cumulative pore volume per gram % vs. pore diameter (micrometers).
Maximum intrusion = = 0,2905 cm^3/g

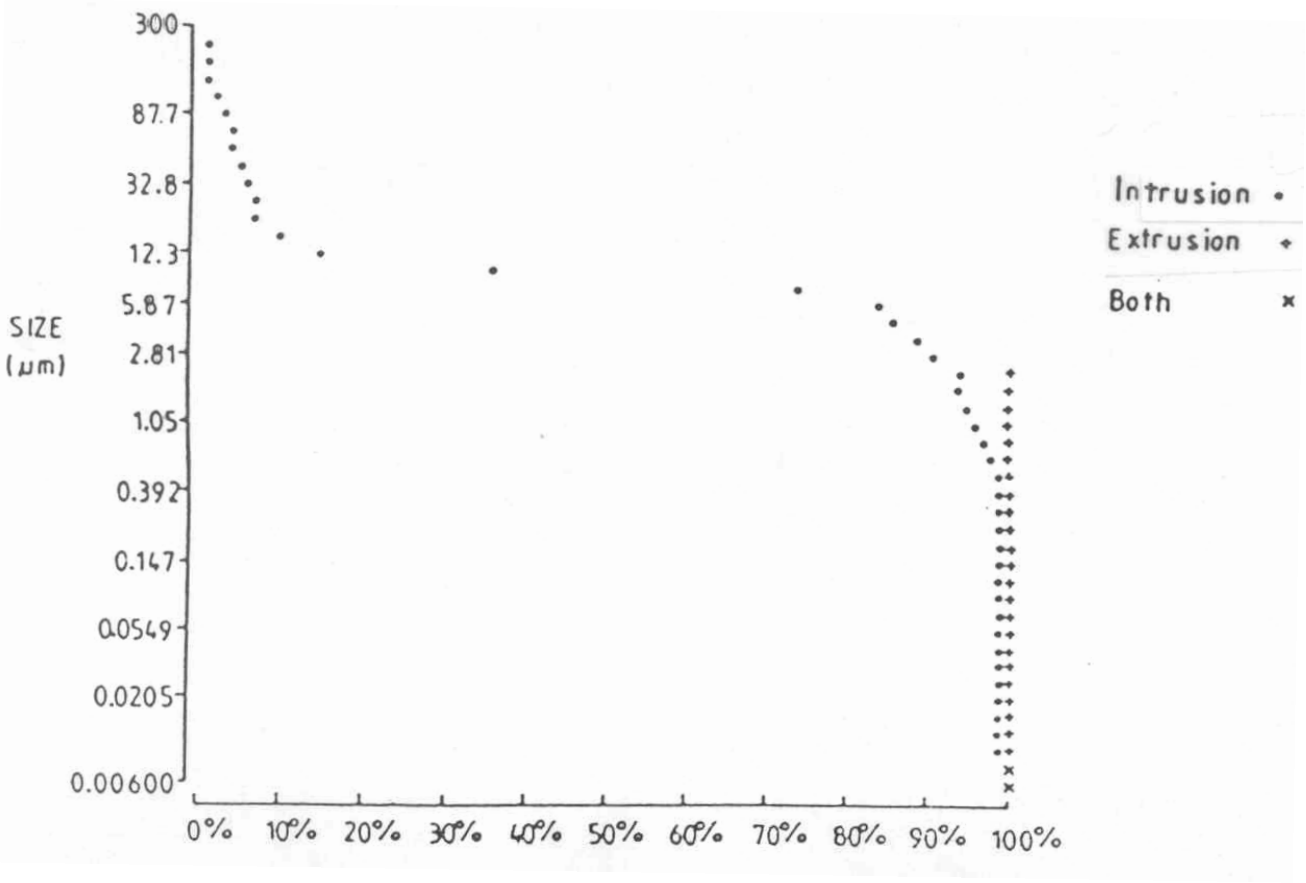
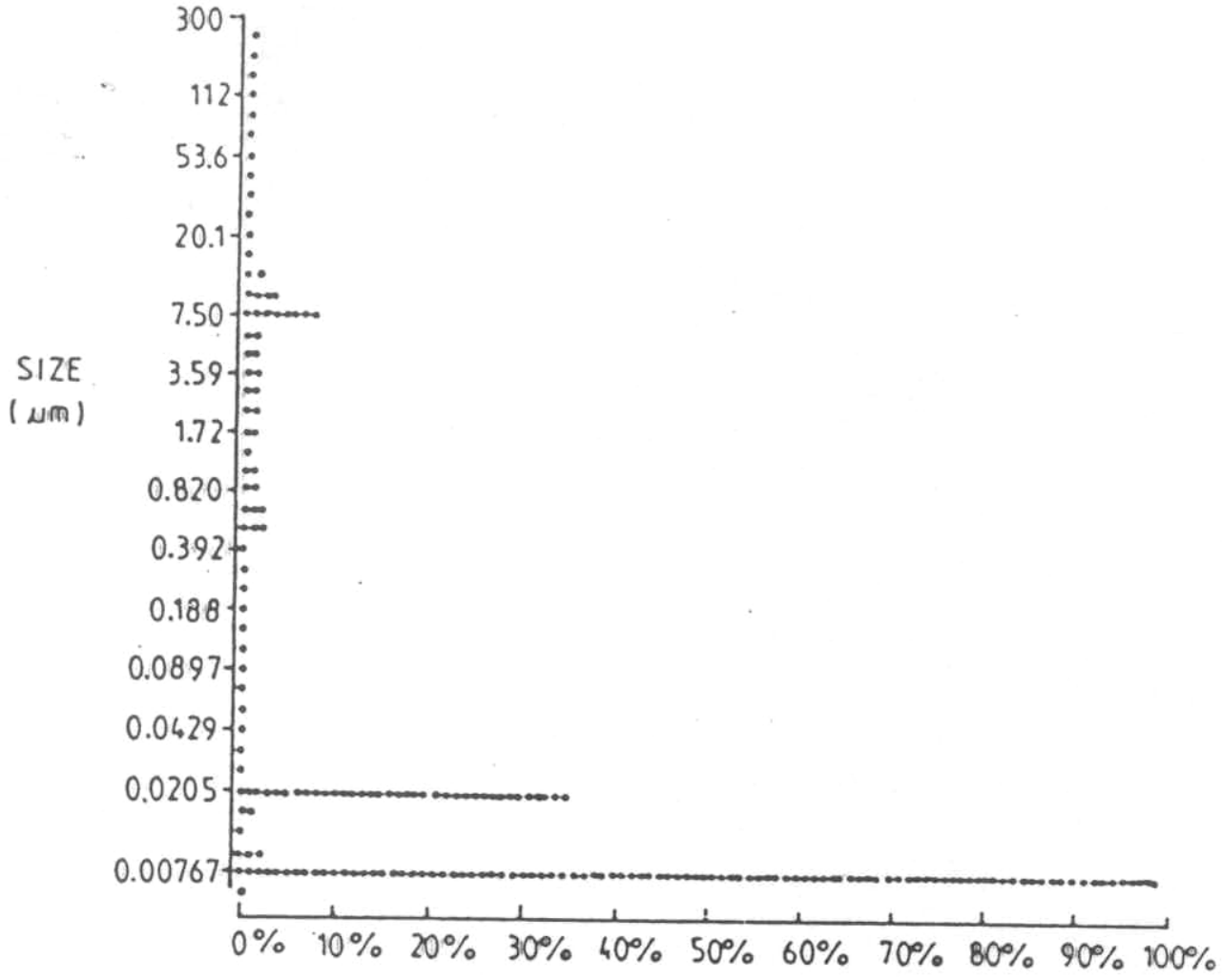


Figure 2: Differential volume per gram % vs. Pore diameter (micrometers). Maximum differential volume = 0,9266 $cm^3/g \bullet \mu m$.



Average diameter of the granulation before and after the friability test with corresponding X^2 exp. values:

	log d	X^2 exp.		
before:	2,53	3,5		
after:	2,43	5,9	$X^2tab = 13,277$	$\alpha = 0,01$

Sieve analysis

The sieve with following mesh sizes were chosen: 80, 125, 200, 315, 500, 800 μm to perform subsequently chi – square test for log – normal distribution of particles:

$$X^2 = \Sigma ((O - E)^2 \cdot E^{-1})$$

where O is observed weight of individual fraction and E is expected weight of the sample fraction, calculated from accomodated normal distribution.

Table 3: The masses shaken and corresponding chi – square values.

Granulation mass (g)	10	30	50	100	200
X^2exp	3,1	8,9	29,1	54,8	110,1

Table 4: The values for independent and dependent variables

Independent variables (granulation properties) | **Dependent variables (tablet properties)**

granular size fractions	granular diameter (µm)	repose angle (º)	flow rate (g/s)	crushing strength (N)	average mass (mg)	liberation constant (min^{-1})	friability (mass loss in %)
1	0–80	41,4	0	72,7	446	0,34	1,80
2	80–125	33,0	33,0	69,7	479	0,32	1,46
3	125–200	33,3	32,3	89,6	474	0,36	1,09
4	200–315	30,8	36,1	87,9	432	0,27	1,23
5	315–500	26,6	36,1	99,6	438	0,11	0,87
6	500–800	24,2	34,9	113,5	518	0,23	0,78
7	800<	22,5	34,9	108,2	467	0,19	0,86

Bulk densities for different granule size fractions:

granule size fractions	1	2	3	4	5	6	7
bulk density (g/cm^3)	0,548	0,555	0,562	0,650	0,643	0,655	0,554

Dissoltion rate constant (k) is calculated from:

$$\ln(c_\infty - c_t) = kt$$

c_∞ – the concentration when all the drug is dissolved

c_t – the concentration of the drug at time t

Simple regression procedure was performed using four different models:

a) linear: $y = a + bx$

b) exponential: $y = e^{a+bx}$

c) reciprocal: $1/y = a + bx$

d) multiplicative: $y = a \cdot x^b$

The values for granulation parameters represented the independent variable x and the values for tablet parameters are taken for dependent variable y. In Table 4 all the values for both variables are presented.

Correlation coefficients for each pair of tested parameters are presented in Table 5.

Table 5: Correlation coefficients for different pairs of tested parameters.

Independent variables	regression model	Dependent variables			
		crushing strength	average mass	liberation constant	friability
granule diameter	L	0,857	0,204	0,654	0,776
	E	0,841	0,198	0,545	0,803
	R	0,822	0,192	0,416	0,817
	M	0,921	0,099	0,640	0,939
repose angle	L	0,892	0,153	0,753	0,939
	E	0,885	0,138	0,670	0,939
	R	0,872	0,123	0,562	0,928
	M	0,897	0,165	0,672	0,932
flow rate	L	0,534	0,025	0,454	0,786
	E	0,546	0,039	0,413	0,719
	R	0,554	0,052	0,360	0,650
	M	–	–	–	–

Legend: L-linear model, E-exponential model, R-reciprocal model, M-multiplicative model