DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(12), 1911-1931 (1989)

EFFECT OF DRUG AGGLOMERATES UPON THE KINETICS OF MIXING OF LOW DOSAGE COHESIVE POWDER MIXTURES.

LOUIS H. CARTILIER AND ANDRÉ J. MOËS
LABORATOIRE DE PHARMACIE GALENIQUE ET BIOPHARMACIE - CP 207
INSTITUT DE PHARMACIE
UNIVERSITE LIBRE DE BRUXELLES
CAMPUS DE LA PLAINE, 1050 - BRUXELLES, BELGIQUE

INTRODUCTION

THE MOST IMPORTANT FUNCTION OF THE SOLID - SOLID MIXING OPERATIONS IS TO ENSURE THE CONTENT UNIFORMITY, ESPECIALLY IN THE PRODUCTION OF LOW DRUG CONTENT DOSAGE FORMS.

TWO MAJOR PROBLEMS ENCOUNTERED IN POWDER MIXING ARE SEGREGATION (1) AND THE INABILITY OF MIXERS TO BREAK DOWN AGGLOMERATES (2).

MICRONIZED POWDER PARTICLES POSSESS INTRINSIC COHESIONAL PROPERTIES AND ADHERE TO LARGE PARTICLES OF A SECOND CONSTITUENT; THIS SYSTEM, WHICH IS CALLED AN ORDERED

MIXTURE IS NOT PRONE TO SEGREGATION (UNLESS THE PARTICLE - PARTICLE BONDS CAN BE BROKEN EASILY).
THUS, SEGREGATION IS NOT THE MAJOR PROBLEM FOR MICRONIZED POWDERS (3).

NEVERTHELESS, THE HIGH TENDENCY OF MICRONIZED POWDERS TO AGGLOMERATE PRODUCES GENERALLY POORLY HOMOGENIZED MIXES, ESPECIALLY WHEN LOW DRUG CONTENTS ARE CONCERNED; THIS IS DUE, MOST OF THE TIME TO REMAINING OF DRUG AGGLOMERATES.
INDEED, LOW - POWER MIXERS ARE NOT ABLE TO SEPARATE COHESIVE POWDERS TO THEIR ELEMENTARY PARTICLES, SO THAT AGGLOMERATES STILL EXIST AND DO NOT PERMIT THE RELATIVE MOVEMENT BETWEEN PARTICLES TO OCCUR (4), WHICH IS THE NECESSARY INITIAL CONDITION PRIOR TO A MIXING PROCESS (5).

THE INFLUENCE OF THE PHYSICAL STATE OF THE ACTIVE CONSTITUENT UPON THE KINETICS OF MIXING OF LOW DOSAGE POWDER MIXTURES WAS INVESTIGATED.

MATERIALS AND METHODS

IRON (II) GLUCONATE (DIHYDRATE) (MERK,DARMSTADT,R.F.A.) WAS USED AS THE POWDER ACTIVE CONSTITUENT AND THREE TYPES OF ALPHA - LACTOSE MONOHYDRATE (200 MESH, 100 MESH AND 80 MESH) (D.M.V.,THE NETHERLANDS) WERE USED AS THE EXCIPIENT.

EXPERIMENTS WERE CARRIED OUT USING IRON GLUCONATE IN ITS ORIGINAL GRANULOMETRIC STATE, AND AS MICRONIZED OR AS

MICRONIZED PARTICLES SIEVED TO BREAK DOWN AGGLOMERATES, AND FINALLY AS AGGLOMERATES OF MICRONIZED PARTICLES.

THE IRON GLUCONATE WAS MICRONIZED BY A JETT MILL APPARATUS (TROST JETT MILL DIVISION, HELMETTA, NEW JERSEY, U.S.A.), AND THEN STORED FOR A FEW MONTHS BEFORE ANY EXPERIMENT WAS CARRIED OUT.

THE PARTICLE SIZE CHARACTERIZATION OF IRON GLUCONATE WAS PERFORMED BY SCANNING ELECTRON MICROSCOPY AND SIEVING ANALYSIS (25 GR. OF PRODUCT WERE SIEVED DURING 1 HOUR IN A RHEWUM TYPE A2 SIEVING APPARATUS).

PARTICLE SIZE CHARACTERIZATION OF EXCIPIENTS WAS ACHIEVED BY SIEVING ANALYSIS (50 GR. OF LACTOSE WERE SIEVED DURING 10 MINUTES IN A RHEWUM TYPE A2 SIEVING APPARATUS).

RHEOLOGICAL PROPERTIES OF EXCIPIENTS WERE DETERMINED USING STAMP VOLUMETER (J.E.L. STAV 2003, ENGELSMANN, LUDWIGHAVEN, GERMANY) AND RESPOSE ANGLE METHODS.

THE VARIATION OF THE HAUSNER RATIO LOGARITHM VERSUS THE IMPACTS NUMBER, AND THE FINAL VALUE OF HAUSNER RATIO WERE DETERMINED ($R_H = V_0 / V_{500}$);EXPERIMENTS WERE REALIZED IN TRIPLICATE FOR EACH LACTOSE.

THE DRAINED ANGLE OF RESPOSE (FIXED BASE AND CYLINDER METHOD) WAS DETERMINED AND THE REPORTED VALUE IS THE MEAN OF THREE MEASUREMENTS.

A 1 % W / W DRUG CONCENTRATION WAS CHOSEN IN ALL EXPERIMENTS.

MIXING WAS CARRIED OUT IN A TURBULA MIXER T 2C TYPE, ROTATING AT 42 R.P.M., AND THE LOAD WAS CHOSEN TO CORRESPOND APPROXIMATIVELY TO A 50 % LOADING VOLUME (6).

AN END - SAMPLING THIEF PROBE (7) WAS USED TO REMOVE TEN SAMPLES FROM DIFFERENT PLACES OF THE POWDER MIXTURE AT EACH SAMPLING TIME WHEN LACTOSE 200 MESH WAS USED AS EXCIPIENT.

WHEN FREE - FLOWING POWDERS (LACTOSE 100 MESH AND 80 MESH) WERE INVOLVED IN THE MIXING PROCESS, A SIDE - SAMPLING THIEF PROBE (8) WAS USED.

SAMPLING TIMES WERE GENERALLY CHOSEN ACCORDING TO A GEOMETRIC PROGRESSION AND THE SAMPLE SIZE WAS AROUND 250 MG.

THE IRON GLUCONATE CONTENT OF THE SAMPLES WAS DETERMINED AS FOLLOWS : 250 MG OF POWDER WAS INTRODUCED IN A 100 ML VOLUMETRIC FLASK, AND 1 ML OF 65 % V / V HNO_3 CONC. WAS ADDED ; FINALLY, DEIONIZED WATER WAS ADDED TO COMPLETE TO 100 ML.
THIS SOLUTION WAS ASSAYED BY ATOMIC ABSORPTION SPECTROSCOPY (PERKIN ELMER 372) AT 248,3 NM (SLIT = 0,2 NM);AN AIR - ACETYLENE FLAME WAS USED.

AT EACH SAMPLING TIME, TEN SAMPLES WERE ANALYSED AND THE AVERAGE MEAN CONTENT OF IRON GLUCONATE $\bar{X}_{10}$, AND THE STANDARD DEVIATION S_{10} WERE CACULED.

MIXTURE HOMOGENEITY WAS APPRECIATED BY USING A MIXING INDEX THAT TAKES INTO ACCOUNT $\bar{X}_{10}$, S_{10} , THE NUMBER OF SAMPLES, AND THE U.S.P. XIX CONTENT UNIFORMITY LIMITS (9).

THE QUALITY OF A PRODUCT WHICH IS REPRESENTED IN THIS CASE BY THE CONTENT UNIFORMITY MAY BE SPECIFIED BY AN INTERVAL OF VARIATION. THIS INTERVAL IS BOUNDED BY "TOLERANCE LIMITS".

A SAMPLE OF SIZE N PROVIDES AN AVERAGE MEAN CONTENT $\bar{X}_N$ AND AN ESTIMATION OF THE STANDARD DEVIATION S_N , SO IT IS POSSIBLE TO BUILD AN INTERVAL : $\bar{X}_N \pm K \cdot S_N$ (EQ.1); IN THIS INTERVAL, A CERTAIN PERCENTAGE OF THE POPULATION ($100\,\beta_P$)% IS REPRESENTED WITH A ($100\,\beta_T$) % CONFIDENCE PROBABILITY (β_P IS THE TOLERANCE PROBABILITY AND β_T THE CONFIDENCE PROBABILITY).

THE CONSTANT K IS CALCULED SO THAT IN A LARGE NUMBER OF SAMPLES OF THE SAME SIZE (N = 10 ASSAYS) TAKEN FROM THE SAME STABLE POPULATION, THERE IS A GIVEN PROPORTION β_T OF INTERVALS ($\bar{X}_N \pm K \cdot S_N$) THAT CONTAINS ($100\,\beta_P$)% OF THE ELEMENTS OF THE VARIABLE X DISTRIBUTION (EQ.2) :

$$\text{PROB}\left(\text{PROB}\left(\bar{X}_N - K \cdot S_N < X < \bar{X}_N + K \cdot S_N\right) \geq \beta_P\right) \geq \beta_T$$

K VALUES ARE GIVEN IN BOWKER'S TABLES (10); THEY ARE CALCULED FOR A NORMAL DISTRIBUTION OF THE VARIABLE X.

THESE TABLES HAVE THREE ENTRIES : N, β_P AND β_T (AND TWO LEVELS OF PROBABILITY : β_P , THE TOLERANCE PROBABILITY , AND β_T, THE CONFIDENCE PROBABILITY).

ACCORDING TO THE U.S.P.XIX CONTENT UNIFORMITY SAMPLING PLAN FOR TABLETS, THE TOLERANCE INTERVAL LIMITS ($\bar{X}_N \pm K \cdot S_N$) ARE EQUAL TO ± 15 % OF THE THEORETICAL CONTENT (μ. = 100 %). THE VALUES OF β_T AND β_P WERE FIXED AT THE 0,90 AND 0,95 LEVELS RESPECTIVELY SO THAT, IN NINETY PERCENT OF THE CASES, WHEN REMOVING TEN SAMPLES, THERE IS AT LEAST 95 % OF THE ELEMENTS WHOSE PERCENTAGE LAYS BETWEEN 85 AND 115 % OF THE THEORETICAL CONTENT.

IN BOWKER'S TABLES, K = 3,018 FOR N = 10, β_P = 0,95 AND β_T = 0,90.

STARTING FROM EQUATION (1) AND FROM THE PREVIOUSLY DETERMINED VALUE OF K, THE STANDARD DEVIATION MAXIMUM VALUE FOR A SAMPLE SIZE N = 10, σ_T WAS CALCULED.

σ_T IS FUNCTION OF THE PROBABILITY LEVELS β_T AND β_P , AND ALSO FUNCTION OF THE ABSOLUTE VALUE OF THE DIFFERENCE D = $|\bar{X}_N - \mu.|$ = $|\bar{X}_N - 100|$

$$\text{SO THAT} \qquad \sigma_T = \frac{15 - |\bar{X}_{10} - 100|}{3,018} \qquad \text{EQ.3}$$

KNOWING S_{10} AND σ_T, IT IS NOW POSSIBLE TO CALCULATE A MIXING INDEX M, EQUAL TO S_{10} / σ_T.

THE REQUIRED HOMOGENEITY DEGREE IS OBTAINED WHEN M IS LOWER THAN 1.

TABLE I. GRANULOMETRIC AND RHEOLOGICAL PROPERTIES OF LACTOSES

	GRANULOMETRIC CHARACTERISTICS		ANGLE OF RESPOSE		HAUSNER RATIO	
LACTOSE	D_g μm	σ_g μm	α	CV %	R_H	CV %
200 MESH	63.4	1.6	59.5	4.3	1.48	2.2
100 MESH	132.9	1.5	46.8	1.6	1.17	0.4
80 MESH	198.3	1.5	38.8	1.9	1.17	0.5

IT IS ALSO IMPORTANT TO KNOW THAT THE MIXING INDEX HAS AN INFINITE VALUE WHEN $| \bar{X}_{10} - 100 | \geq 15$ AND THAT WE MUST OBTAIN A STANDARD DEVIATION LOWER THAN 5 % TO SATISFY TO HOMOGENEITY REQUIREMENTS ($M \leq 1$) WHEN $\bar{X}_{10} = 100$ %.

RESULTS AND DISCUSSION

GRANULOMETRIC AND RHEOLOGICAL DATA OF THE THREE LACTOSES ARE SHOWN IN TABLE I (FIGURE 1 A,B AND C).

FROM THE RESULTS OBTAINED WITH THE MIXTURES CONTAINING IRON GLUCONATE IN ITS ORIGINAL GRANULOMETRIC STATE, IT MIGHT BE CONCLUDED THAT IT IS IMPOSSIBLE TO ACHIEVE A SATISFACTORY HOMOGENEITY (TABLE II); THIS IS DUE TO A SEGREGATION OF THE

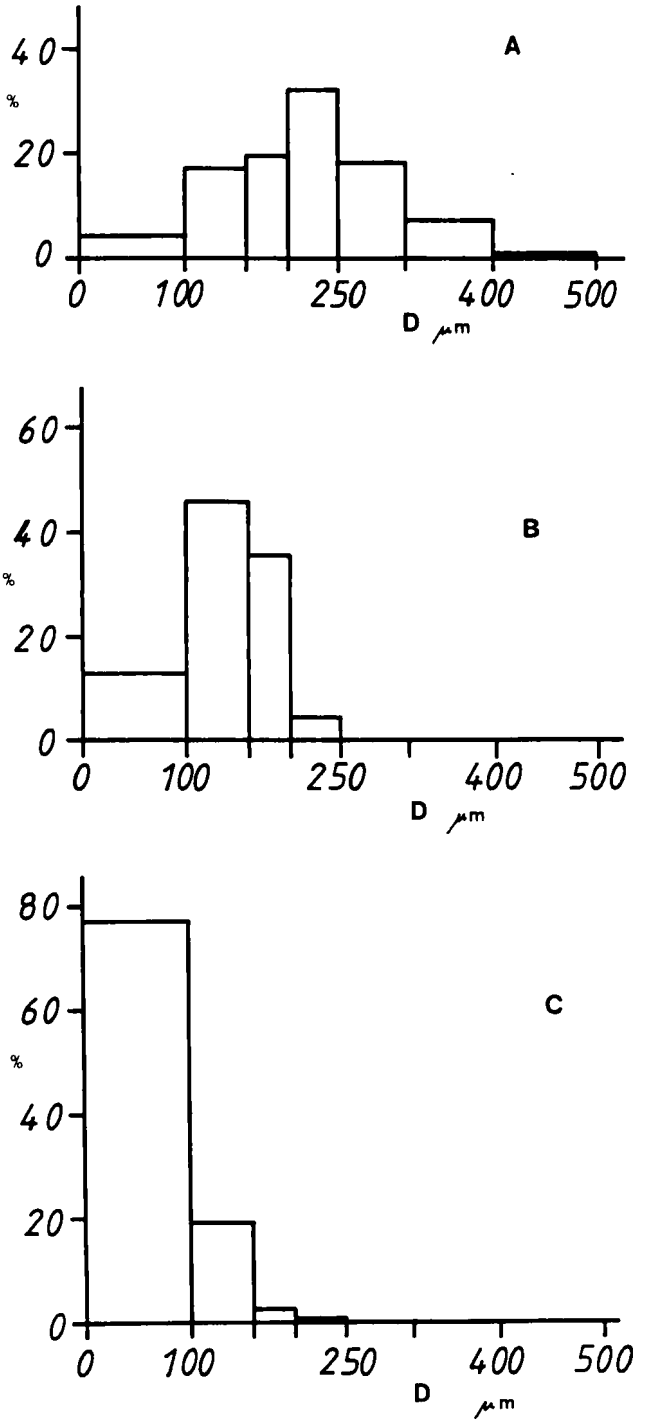

FIGURE 1

A - Sieving analysis of lactose 80 Mesh

B - Sieving analysis of lactose 100 Mesh

C - Sieving analysis of lactose 200 Mesh

TABLE II. KINETICS OF MIXING OF MIXES CONTAINING UNMILLED IRON GLUCONATE

MIXING TIME (MIN)	MIXING INDEX	
	LACTOSE 100 MESH	LACTOSE 80 MESH
1	8,8	/
2	∞	2,1
4	5,0	1,6
8	3,6	2,1
16	29,1	1,1
32	4,3	2,7
64	4,9	2,0
128	/	2,5

ACTIVE CONSTITUENT PARTICLES (FIGURE 2), CAUSED BY A LACK OF INTERACTION AND A DIFFERENCE OF SIZE BETWEEN THE DRUG AND THE EXCIPIENT PARTICLES (TABLE I) (FIGURES 1 AND 3).

FOR MIXTURES CONTAINING MICRONIZED IRON GLUCONATE (FIGURE 4), A GOOD RELATIONSHIP WAS OBTAINED BETWEEN THE MIXING PROPERTIES (FIGURE 5) AND THE FLOWING AND GRANULO - METRIC PROPERTIES OF THE EXCIPIENT (FIGURE 6) (TABLE I).

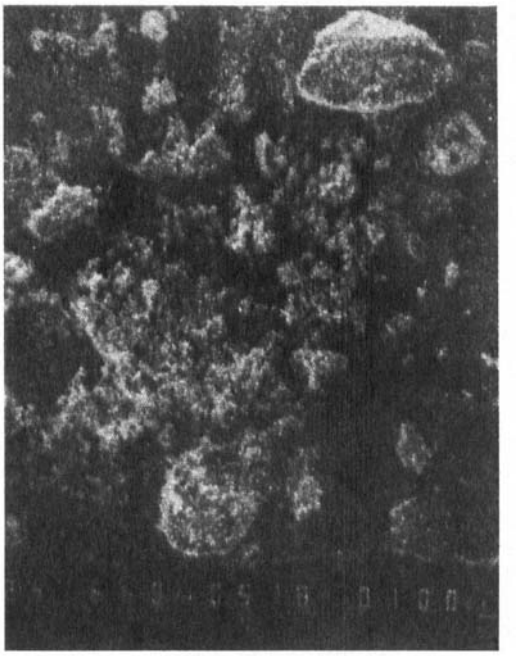

FIGURE 2

Scanning Electron Microscopy of unmilled Iron Gluconate particles

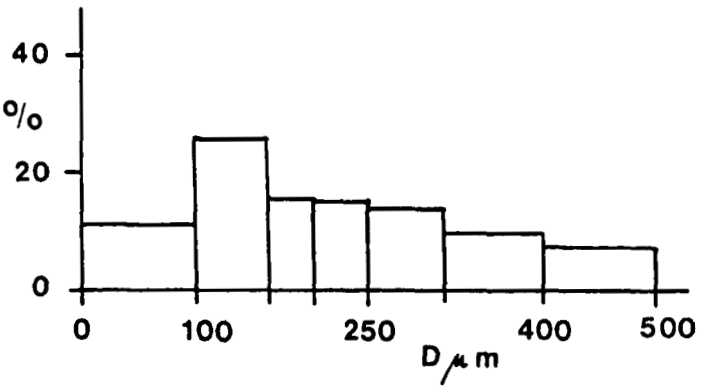

FIGURE 3

Sieving analysis of unmilled Iron Gluconate particles

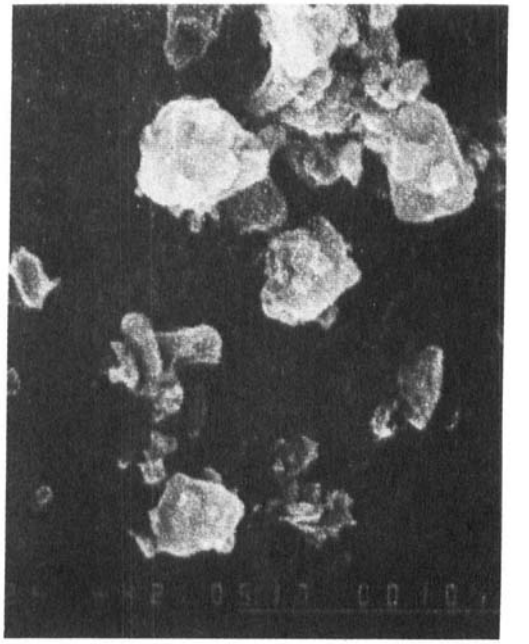

FIGURE 4

Scanning Electron Microscopy of micronized Iron Gluconate particles

IN FACT, INCREASING THE SIZE OF THE EXCIPIENT PARTICLES FACILITATES THE BREAKDOWN OF DRUG AGGLOMERATES BY A KIND OF BALL - MILL EFFECT; SO, THE SEPARATION IN DRUG ELEMENTARY PARTICLES LEADS TO THE ACHIEVEMENT OF AN ORDERED MIXTURE.

FURTHERMORE, THIS PRODUCES AN ENHANCEMENT OF THE RELATIVE MOVEMENT OF PARTICLES, SO THAT THE DIFFUSION AND THE DISTRIBUTION OF THE DRUG INTO THE BULK OF THE EXCIPIENT ARE FACILITATED.

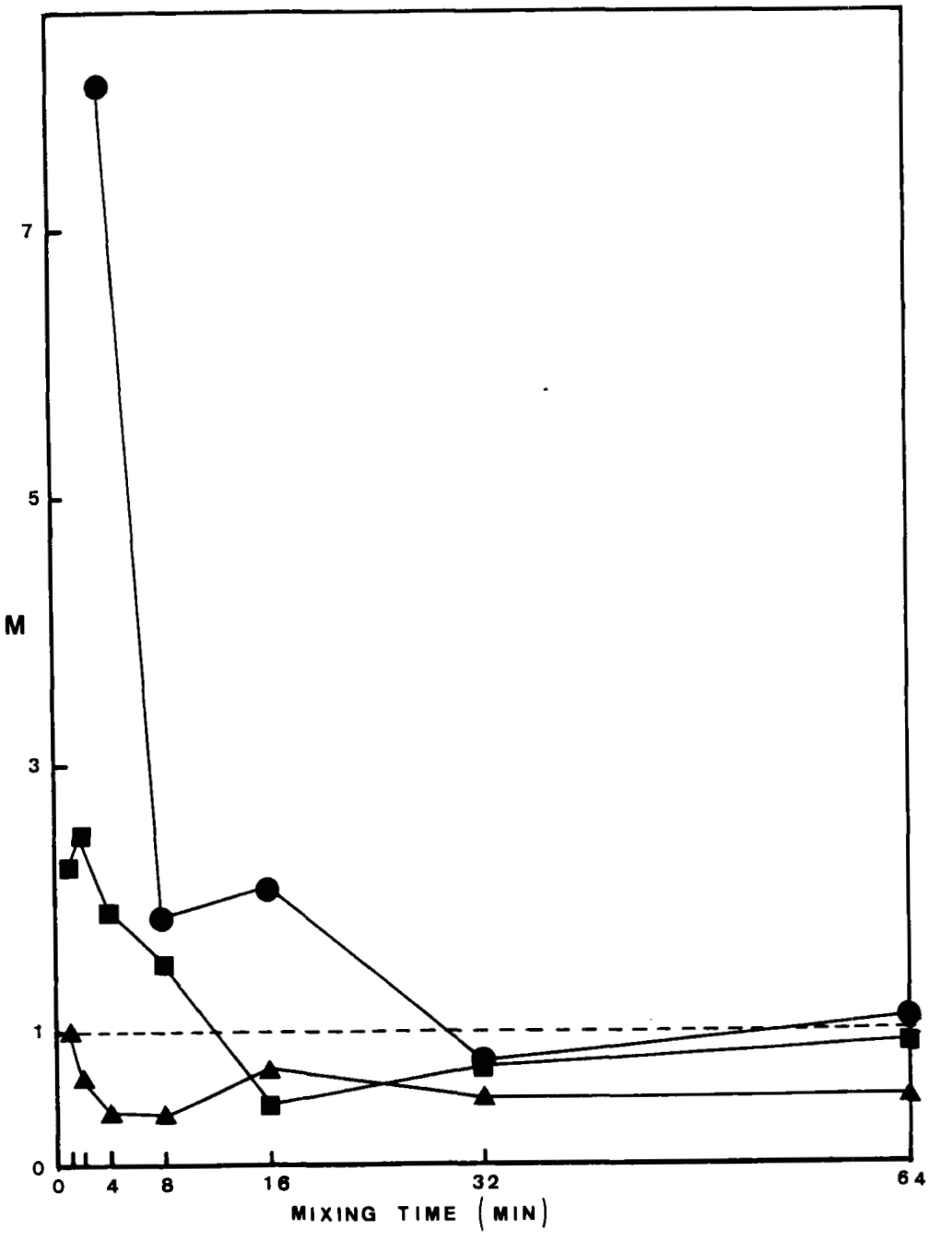

FIGURE 5

Kinetics of mixing of mixes containing micronized drug particles (lactose 80 Mesh : ▲; lactose 100 Mesh : ■; lactose 200 Mesh : ●)

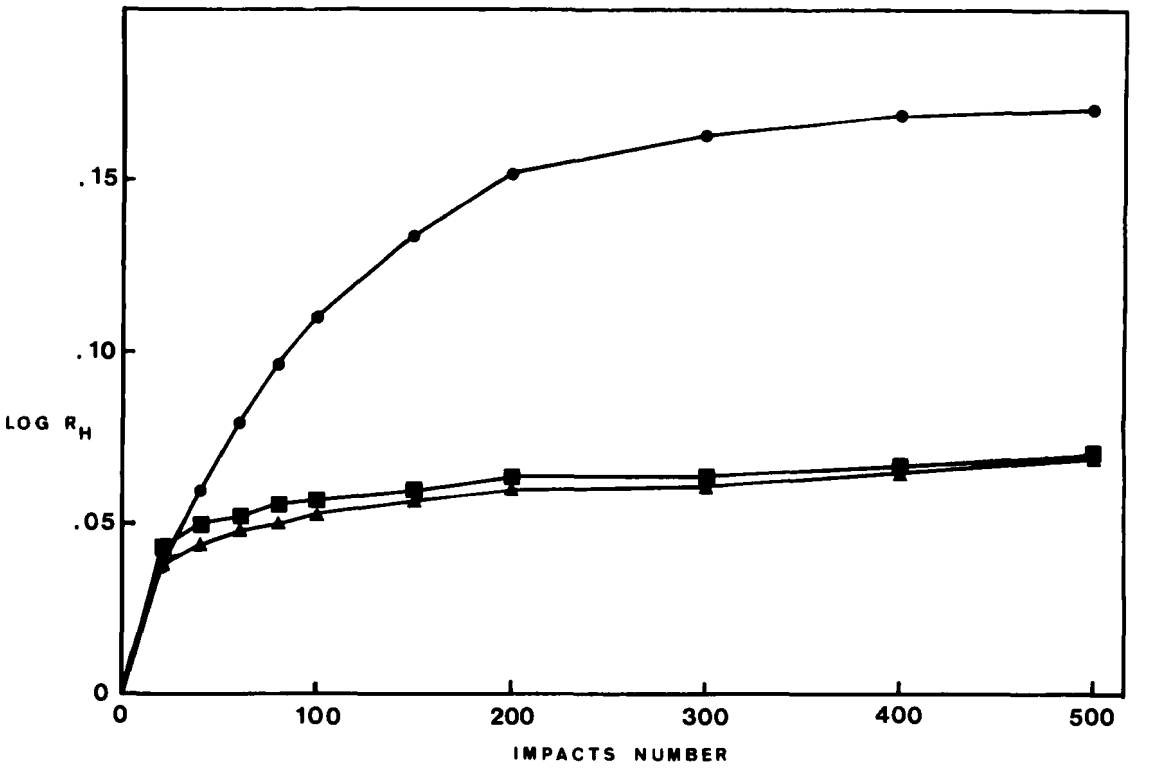

FIGURE 6

Rheological properties of excipients

(lactose 80 Mesh : ▲; lactose 100 Mesh : ■; lactose 200 Mesh : ●)

MIXTURES CONTAINING MICRONIZED AND SIEVED (PRIOR TO MIXING) IRON GLUCONATE PROVED GOOD HOMOGENEITY CHARACTERISTICS (TABLE III).

THE KINETICS OF MIXING SHOWED THAT FOR THESE MIXTURES, HOMOGENEITY OCCURED VERY QUICKLY (FIGURES 7, 8 AND 9), IN FACT MUCH FASTER THAN FOR MIXTURES CONTAINING NON - SIEVED

TABLE III. KINETICS OF MIXING CONTAINING MICRONIZED(M) OR MICRONIZED AND SIEVED(M/S) DRUG PARTICLES

Mixing time (min)	Mixing index					
	Lactose 80 Mesh		Lactose 100 Mesh		Lactose 200 Mesh	
	M	M/S	M	M/S	M	M/S
1	1,00	0,97	2,23	0,58	12,68	0,53
2	0,64	0,66	2,46	0,79	∞	3,42
4	0,40	0,55	1,91	0,35	8,05	0,83
8	0,38	0,34	1,53	0,36	1,86	1,06
16	0,72	0,43	0,46	0,60	2,08	0,61
32	0,50	0,51	0,75	0,54	0,78	0,48
64	0,51	0,56	0,91	,0,59	1,09	0,36

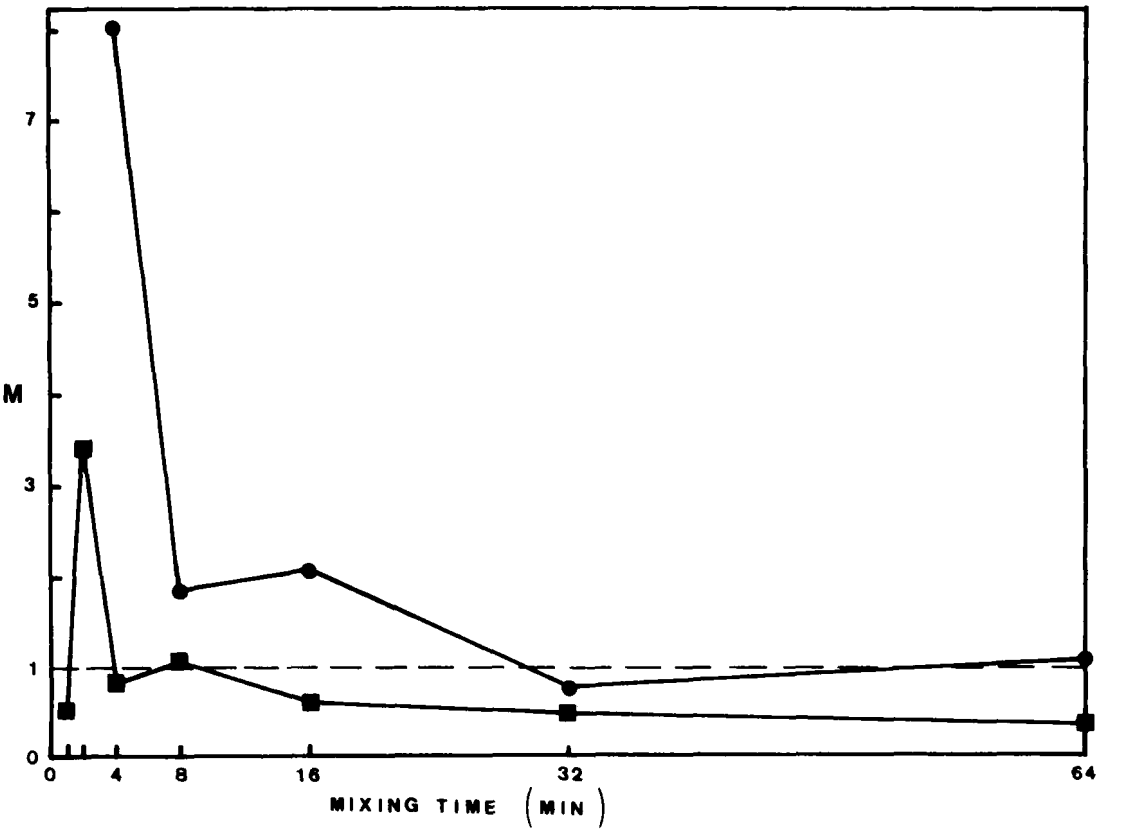

FIGURE 7

Kinetics of mixing - lactose 200 Mesh and micronized (●) or micronized and sieved (■) drug particles

IRON GLUCONATE AND LACTOSE 100 MESH OR 200 MESH: NO IMPROVEMENT OF THE KINETICS OF MIXING WAS NOTICED IN THE CASE OF LACTOSE 80 MESH (FIGURE 9).

THE INFLUENCE OF THE PRELEMINARY DESAGGLOMERATION OF DRUG PARTICLES IS INVERSELY PROPORTIONAL TO THE SIZE AND RHEOLOGICAL PROPERTIES OF THE EXCIPIENT PARTICLES.

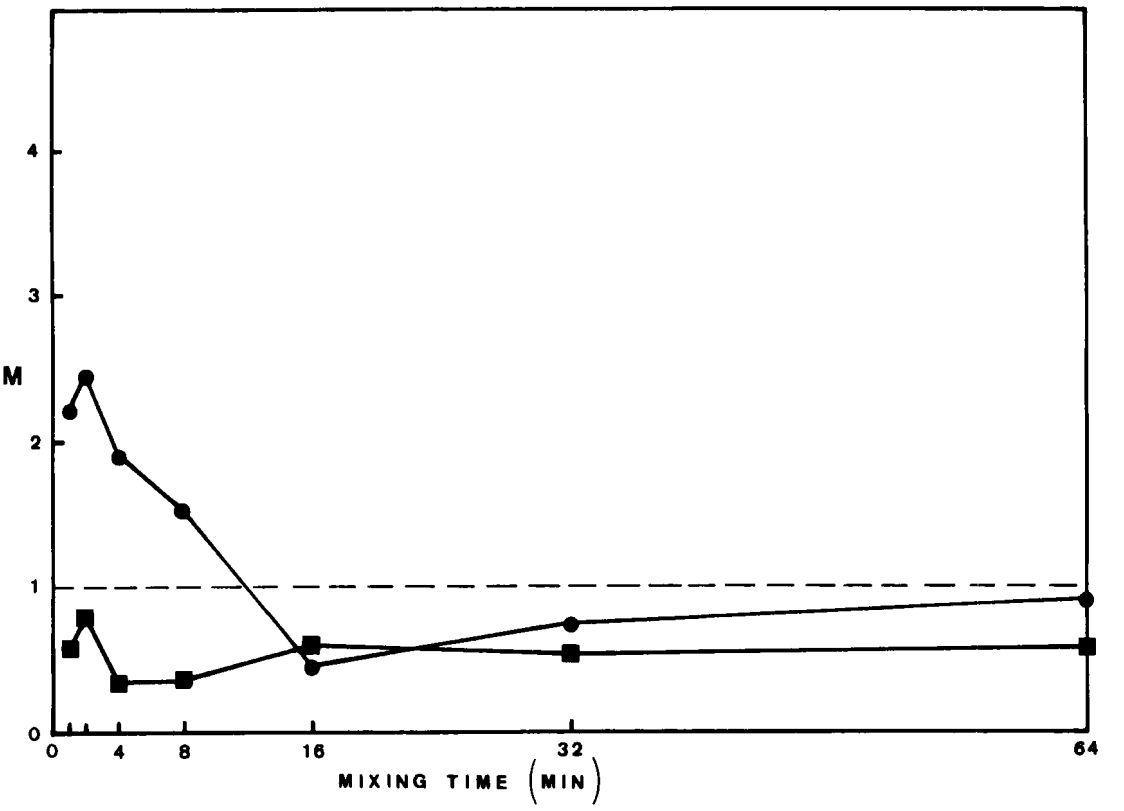

FIGURE 8

Kinetics of mixing - lactose 100 Mesh and micronized (●) or micronized and sieved (■) drug particles

THUS, IT MIGHT BE CONCLUDED THAT THE RATE LIMITING STEP OF THE KINETICS OF MIXING OF LOW DOSAGE COHESIVE POWDER MIXTURES IS THE BREAKDOWN OF DRUG AGGLOMERATES.

MIXTURES CONTAINING ONLY IRON GLUCONATE AGGLOMERATES REACHED A SATISFACTORY HOMOGENEITY AFTER A VERY LONG TIME (TABLE IV).

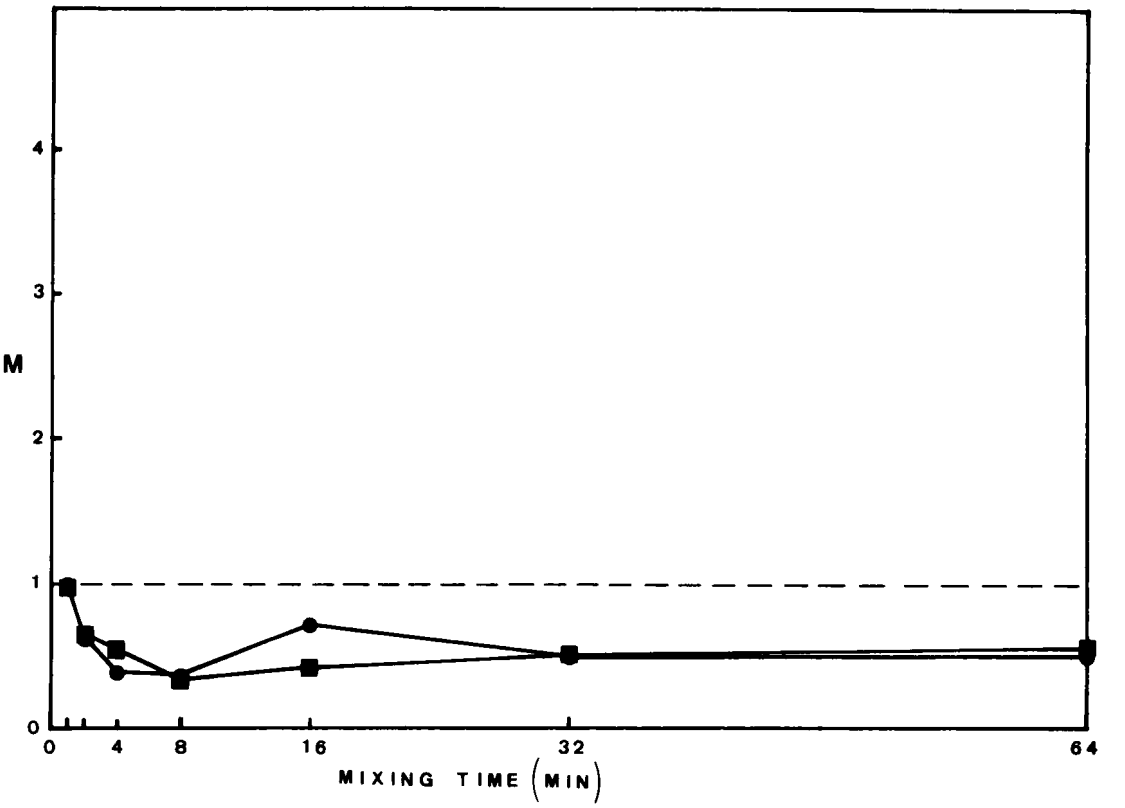

FIGURE 9

Kinetics of mixing - lactose 80 Mesh and micronized (●) or micronized and sieved (■) drug particles

IT MIGHT BE CONCLUDED THAT DURING THE DIFFUSIONAL MOVEMENT OF DRUG AGGLOMERATES IN THE BULK MASS OF POWDER, THERE EXISTS A KIND OF EROSION OF THE DRUG AGGLOMERATES, LEADING TO THE FORMATION OF ORDERED UNITS.

THIS MIGHT BE EXPLAINED BY AN ADHESIONAL PROCESS: THANKS TO VAN DER WAALS AND ELECTROSTATIC FORCES, SINGLE

TABLE IV. KINETICS OF MIXING OF MIXES CONTAINING AGGLOMERATES OF MICRONIZED DRUG PARTICLES AND LACTOSE 80 MESH

MIXING TIME (MIN)	MIXING INDEX: DRUG AGGLOMERATE SIZE 250 μM < X < 1000 μM	MIXING INDEX: DRUG AGGLOMERATE SIZE 1000 μM < X < 2500 μM
1	/	∞
4	/	∞
16	5,52	∞
32	1,52	6,61
64	0,98	0,68
96	0,66	0,58
128	0,88	2,26

PARTICLES OF DRUG ARE LEAVING THE AGGLOMERATES TO ADHERE TO EXCIPIENT PARTICLES.

FURTHERMORE, IT CAN BE SEEN FROM TABLE IV THAT A BETTER KINETICS OF MIXING IS OBTAINED WHEN SMALLER DRUG AGGLOMERATES ARE INVOLVED IN THE MIXING PROCESS; THIS CAN BE EXPLAINED BY THE FACT THAT SMALLER DRUG AGGLOMERATES HAVE A LARGER CONTACT SURFACE WITH EXCIPIENT PARTICLES.

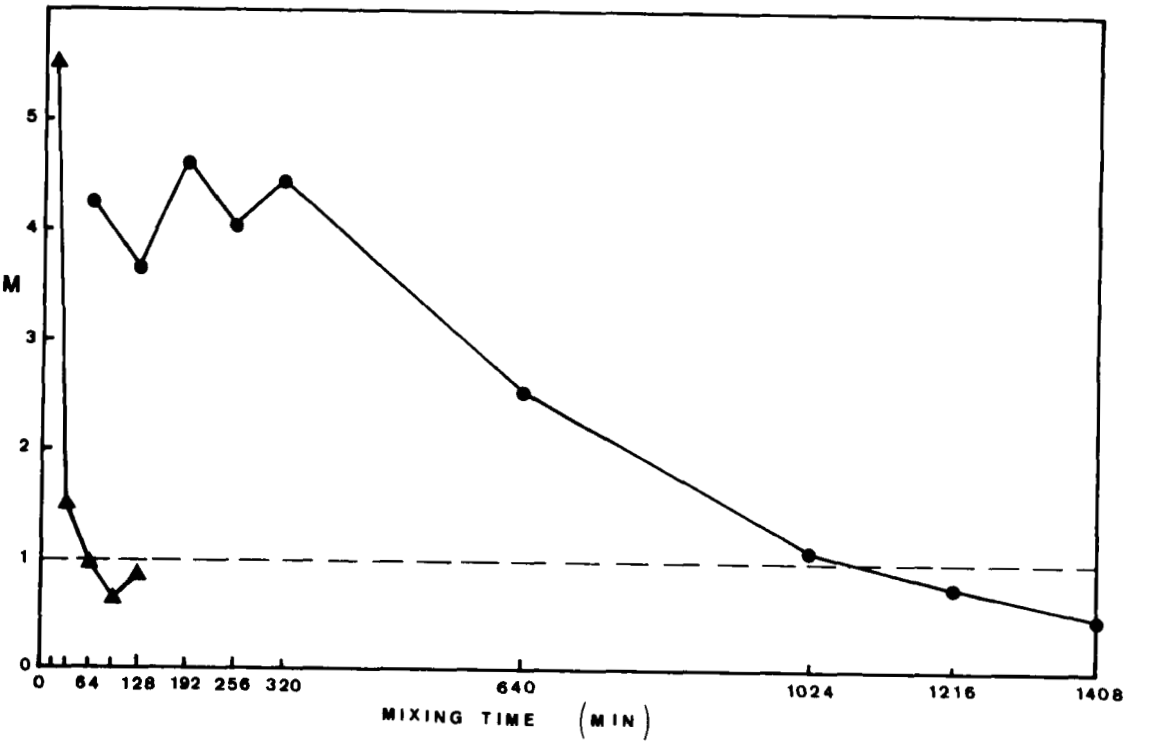

FIGURE 10

Kinetics of mixing - drug agglomerates (0,25 mm < d < 1,0 mm) and lactose 200 Mesh (●) or 80 Mesh (▲)

FINALLY, IT CAN BE CONCLUDED FROM FIGURE 10 THAT THE INFLUENCE OF THE SIZE AND RHEOLOGICAL PROPERTIES OF THE EXCIPIENT UPON THE KINETICS OF MIXING IS MUCH STRONGER WHEN ONLY DRUG AGGLOMERATES ARE INVOLVED IN A MIXING PROCESS .

CONCLUSION

THE INFLUENCE OF THE PHYSICAL STATE OF THE ACTIVE CONSTITUENT UPON THE KINETICS OF MIXING OF LOW DOSAGE COHESIVE POWDER MIXTURES WAS STUDIED.

BOTH KINETICS OF MIXING AND HOMOGENEITY OF MIXES WERE IMPROVED BY MICRONIZING DRUG PARTICLES.

A RELATIONSHIP WAS OBTAINED BETWEEN THE MIXING PROPERTIES AND THE FLOWING AND GRANULOMETRIC PROPERTIES OF THE EXCIPIENT.

THE RATE LIMITING STEP OF THE KINETICS OF MIXING OF LOW DOSAGE COHESIVE POWDER MIXTURES IS THE BREAKDOWN OF DRUG AGGLOMERATES.

FURTHERMORE, THERE EXISTS A KIND OF EROSION OF THESE AGGLOMERATES DURING THEIR DIFFUSIONNAL MOVEMENT; THANKS TO AN ADHESIONAL PROCESS, SINGLE PARTICLES OF DRUG ARE LEAVING THE AGGLOMERATES TO FORM ORDERED UNITS.

ACKNOWLEDGMENTS

WE WISH TO THANK PROF. J. JEDWAB (LABORATOIRE DE GEOCHIMIE, FACULTE DES SCIENCES, U.L.B.) FOR HIS KINDFULL ASSISTANCE IN SCANNING ELECTRON MICROSCOPY.

REFERENCES

(1) WILLIAMS, J., C. AND KHAN, M., I.,
CHEM. ENGNG. (LOND.), JANUARY, 19, (1973)

(2) EGGERMANN, H.,
PHARM. IND., 41, 285, (1979)

(3) HERSEY, J., A.,
INT. J. PHAR. TECH. AND PROD. MFR., 1, 6, (1979)

(4) CARSTENSEN, J., T.,
"SOLID PHARMACEUTICS : MECHANICAL PROPERTIES AND RATE PHENOMENA, ACADEMIC PRESS, N. Y., 1980, P 114

(5) TRAIN, D.,
J. AMER. PHARM. ASS. (SCI. ED.), 49, 265, (1960)

(6) SINAY, Y. AND TAWASHI, R.,
PHARM. ACTA HELV., 47, 265, (1972)

(7) SCHOFIELD, C.,
POWDER TECHNOL., 15, 169, (1976)

(8) KIGER, J., L.,
PRODUITS ET PROBLEMES PHARMACEUTIQUES, 10, 741, (1974)

(9) DELATTRE, L.,
LABO - PHARMA - PROBL. ET TECHN., N° 259, 969, (1976)

(10) DOCUMENTA GEIGY - TABLES SCIENTIFIQUES,
7 IEME ED., CIBA - GEIGY S.A., BÂLE, 1978, P 45