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RHEOLOGICAL STUDY OF LACTOSE COATED WITH ACRYLIC RESINS

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ABSTRACT

We present a rheological study of different powders obtained by the coating of lactose with different kinds and percentages of Eudragit (R) type acrylic resins. This test is completed with a correlation study according to the properties that define powders.

INTRODUCTION

Every active substance requires an adecuate external disposition so as to reach the best bioavailability characteristics, to insure its stability and to help in its administration. There are necessary previous studies -preformulation studies (1)- over the active substance (2, 3) and the excipients (4, 5) before the

elaboration of the formulation. These last substances, the excipients, no longer maintain the initial concept of "inactive support" (6) because of the decisive influence they have both over biopharmaceutical aspects (7-10) and technological factors of the industrial production of the pharmaceuticals (5, 11-12). This is the cause of the great interest shown by Pharmaceutical Industry in the obtention of new excipients, according to works of Claude (5), Gissinger and Stamm (13).

Lactose is a powder commonly used as an excipient for solid pharmaceutical forms for oral administration (3, 14), not only because of its chemical inertia but also because of its economy. Nevertheless, its unfavourable technological properties, defined by its rheology (15-17), implies problems when we use high speed automatized production chains (18-19). This is the reason for which authors such as Delacourte-Thibaut et al. (20), Bossert et al. (17), Schildcrout (21) and Stamm (11) produce certain transformations over lactose so as to improve its technological properties.

This is also the objective of the present paper: to obtain, through the coating of lactose particles with different kinds and percentages of Eudragit (R), powders with rheological properties improved in comparison with the initial product.

MATERIAL AND METHODS

Coating

Core material: lactose.

Suspension medium: Alcohol 96 and purified water.

Coating material: Acrylic resins type Eudragit (R): E 12.5, L 12.5, S 12.5, E 30D and L 30D (22).

The coated powders with different core to wall ratios, were prepared using the phase separation technique, induced by the evaporation of the solvent present in the system (23). We have made suspensions of lactose in alcohol, when we use Eudragit (R) E 12.5, L 12.5 and S 12.5, and in water for the Eudragit (R) E 30D and L 30D, both in a 2:1 proportion. These suspensions were stirred in a magnetoagitator for five minutes at a constant temperature of 40 °C. Then we added the required volumes of each Eudragit (R) so as to obtain the desired proportion of coating: 2%, 4% and 6%. The larger part of the solvent was removed by decreasing the pressure of the system using a water pump. The drying of the powders is finished in a stove at 55 °C during 12 hours for the organic solutions and 48 hours for the aqueous suspensions. The products obtained were softly triturated in a mortar until the total of the particles that compose powders were smaller than 200 μ.

Rheological tests

1. Flow rate (g/s). 35 g of the powder in study was added to a funnel with the following dimensions: internal diameter at top 14.5 cm and internal diameter of efflux tube 1.2 cm. The time period for the material to flow through this funnel was determined with a chronometer.

2. Angle of repose (degrees). These measurements were performed through a "free flowing method", using 10 g of the powder in study, and a funnel with an internal superior diameter of 9.7 cm, and inferior of 0.8 cm, terminating 4 cm above an horizontal surface. The angle was calculated by a simple geometry from the base and height of the conical heap formed.

3. Bulk density (g_o/cm^3) (ρ_o). Measurements were carried out in this way: 25 g of the powder were poured into a 50 mL glass measuring cylinder, which was then tapped three times against a wooden surface, measuring the volume occupied.

4. Tapped density (g_a/cm^3) (ρ_a). The same cylinder with the powder was then tapped 500 times until the volume becomes constant. The bulk and tapped density were calculated from these initial and final volumes.

5. Haussner Index (IH) and Percentage of Compressibility (%C). Used as dimensionless numbers, these parameters were calculated according to the relation between tapped and untapped densities. The equations used were:

$$IH = \frac{\rho_a}{\rho_o} \qquad \%C = \frac{\rho_a - \rho_o}{\rho_a} \times 100$$

Statistical treatments

The results obtained through these rheological tests were studied by statistical treatments with original programs made in our Department. We used a Hewlett Packard computer model HP 87.

RESULTS AND DISCUSSION

Individualized study of each parameter.

We have made all tests over two different samples from the same coated product separately obtained so as to determinate the reproductibility of the technique used by us. From each test, we have obtained 20 effectives, of which 10 were randomly for their statistical treatment.

Tables 1 and 2 show mean values ($\bar{x}$), standard deviations (SD) and variation coefficients (CV) for each parameter studied for each powder.

TABLE 1

Mean values ($\bar{x}$), standard deviations (SD) and variation coefficients (CV) for each parameter tested.

Powder	Flow rate			Angle of repose			Bulk density		
	$\bar{x}$	SD	CV	$\bar{x}$	SD	CV	$\bar{x}$	SD	CV
Lactose	19.57	0.98	5.00	41.04	0.65	1.57	0.64	0.015	2.25
E 2%	21.23	0.68	3.19	44.63	0.92	2.05	0.67	0.004	0.62
E 4%	24.33	0.86	3.54	34.71	1.15	3.30	0.66	0.003	0.44
E 6%	27.37	0.95	3.46	35.36	0.67	2.65	0.68	0.004	0.51
L 2%	25.77	0.99	3.85	43.83	0.57	1.30	0.63	0.003	0.53
L 4%	26.79	1.53	5.70	46.11	0.84	1.81	0.68	0.003	0.43
L 6%	27.44	1.14	4.15	46.38	1.58	3.39	0.60	0.001	0.15
S 2%	20.52	1.06	5.18	46.27	0.32	0.69	0.65	0.004	0.57
S 4%	21.91	0.92	4.18	47.41	0.93	1.97	0.65	0.006	0.86
S 6%	25.96	1.01	3.90	40.18	1.13	2.82	0.63	0.004	0.60
E30D 2%	19.50	0.65	3.31	44.18	0.43	0.97	0.67	0.007	1.06
E30D 4%	19.63	0.60	3.08	46.23	0.20	0.43	0.66	0.005	0.70
E30D 6%	20.86	0.74	3.54	43.20	0.60	1.39	0.69	0.007	1.04
L30D 2%	14.58	0.49	3.33	48.44	0.42	0.86	0.58	0.003	0.48
L30D 4%	15.96	0.37	2.32	47.04	0.13	0.28	0.61	0.007	1.15
L30D 6%	19.66	1.09	5.56	44.63	0.53	1.18	0.67	0.007	1.11

TABLE 2

Mean values ($\bar{x}$), standard deviations (SD) and variation coefficients (CV) for each parameter tested.

Powder	Tapped density			Haussner Index			Percentage of compressibility		
	$\bar{x}$	SD	CV	$\bar{x}$	SD	CV	$\bar{x}$	SD	CV
Lactose	0.94	0.004	0.44	1.46	0.04	2.91	31.48	1.71	5.44
E 2%	0.95	0.010	1.07	1.41	0.03	1.79	29.11	1.11	3.81
E 4%	0.92	0.008	0.90	1.39	0.01	0.94	28.08	0.60	2.13
E 6%	0.88	0.013	1.51	1.29	0.01	0.93	22.36	0.86	3.83
L 2%	0.83	0.006	0.68	1.31	0.01	0.75	23.17	0.65	2.74
L 4%	0.90	0.009	1.08	1.33	0.02	1.49	24.33	1.04	4.29
L 6%	0.87	0.002	0.21	1.44	0.01	0.49	30.56	0.33	1.08
S 2%	0.97	0.021	2.20	1.51	0.01	0.17	33.83	0.35	1.02
S 4%	0.95	0.012	1.27	1.44	0.02	2.03	31.28	1.35	4.32
S 6%	0.88	0.014	1.61	1.37	0.02	1.55	26.67	1.16	4.33
E30D 2%	0.93	0.004	0.42	1.38	0.01	1.11	27.87	0.78	2.78
E30D 4%	0.93	0.007	0.76	1.40	0.01	0.60	28.81	0.40	1.39
E30D 6%	0.89	0.001	0.15	1.30	0.02	1.23	23.64	0.85	3.61
L30D 2%	0.93	0.007	0.79	1.60	0.01	0.88	37.43	0.61	1.63
L30D 4%	0.93	0.007	0.73	1.54	0.02	1.25	34.71	0.79	2.28
L30D 6%	0.93	0.004	0.40	1.39	0.02	1.29	28.06	0.76	2.72

Table 3 represents the results obtained after the application of ANOVA . Even though there was a clear difference between lactose and each group of coating, we used this analysis so as to statistically show such.

It can be seen that, with the unique exception corresponding to the comparison of tapped density between lactose and the group of coating with Eudragit (R) L 30D, there was statistical significance in all the cases. For this reason, we have completed the study using Scheffé's test. The results are shown in tables 4 and 5.

In tables 1 and 2 we can observe the variation of each parameter tested after the coating of lactose. There can be appreciated an important improvement in flow rate: 19.57 g/s for the initial powder and 27.44 g/s after its covering with a 6% of Eudragit (R) L 30D. This means an increase of 7 units. There is a difference in its behaviour, according to the use of the Eudragit (R) in organic solutions or in aqueous suspensions. Therefore, the use of Eudragit (R) E, L and S for the coating permits the obtention of powders with flow rate values superior to those at the initial lactose, although there was no significative statistical difference with 2% Eudragit (R) S. On the

TABLE 3

Results obtained after the application of ANOVA over each test.

Eudragit (R)		Flow rate	Angle of repose	Bulk density	Tapped density	Haussner Index	Percentage of compressibility
E	F	155.742	945.242	45.021	112.256	68.997	114.216
	α	0.005	0.005	0.005	0.005	0.005	0.005
L	F	93.630	63.078	186.693	599.685	93.646	145.193
	α	0.005	0.005	0.005	0.005	0.005	0.005
S	F	80.207	199.400	12.835	82.631	39.801	57.631
	α	0.005	0.005	0.005	0.005	0.005	0.005
E30D	F	7.336	185.761	37.894	173.058	67.261	95.881
	α	0.005	0.005	0.005	0.005	0.005	0.005
L30D	F	104.838	475.063	160.391	0.287	126.791	145.492
	α	0.005	0.005	0.005	N.S.	0.005	0.005

TABLE 4

Results obtained after the application of Scheffé's test.

Powder	Flow rate		Angle of repose		Bulk density	
	F	∝	F	∝	F	∝
Lactose-E2%	5.990	0.005	28.498	0.005	24.378	0.005
Lactose-E4%	49.413	0.005	88.473	0.005	9.309	0.005
Lactose-E6%	132.665	0.005	542.900	0.005	40.090	0.005
E2%-E4%	20.994	0.005	217.395	0.005	3.559	0.05
E2%-E6%	82.274	0.005	820.168	0.005	1.944	N.S.
E4%-E6%	20.147	0.005	193.050	0.005	10.763	0.005
Lactose-L2%	45.888	0.005	13.170	0.005	5.842	0.005
Lactose-L4%	62.342	0.005	43.913	0.005	40.090	0.005
Lactose-L6%	73.946	0.005	48.825	0.005	49.896	0.005
L2%-L4%	1.258	N.S.	8.822	0.005	76.537	0.005
L2%-L6%	3.331	0.05	11.096	0.005	21.591	0.005
L4%-L6%	0.495	N.S.	0.130	N.S.	179.432	0.005
Lactose-S2%	1.496	N.S.	68.389	0.005	3.383	0.05
Lactose-S4%	9.190	0.005	101.611	0.005	1.390	N.S.
Lactose-S6%	68.781	0.005	1.854	N.S.	2.231	N.S.
S2%-S4%	3.270	0.05	3.278	0.05	0.436	N.S.
S2%-S6%	49.989	0.005	92.759	0.005	11.108	0.005
S4%-S6%	27.689	0.005	130.911	0.005	7.143	0.005
Lactose-E30D2%	0.016	N.S.	65.649	0.005	12.122	0.005
Lactose-E30D4%	0.007	N.S.	179.396	0.005	9.027	0.005
Lactose-E30D6%	4.798	0.01	31.229	0.005	37.604	0.005
E30D2%-E30D4%	0.046	N.S.	27.999	0.005	0.227	N.S.
E30D2%-E30D6%	5.374	0.005	6.321	0.005	7.025	0.005
E30D4%-E30D6%	4.430	0.01	60.926	0.005	9.782	0.005
Lactose-L30D2%	65.916	0.005	413.241	0.005	70.908	0.005
Lactose-L30D4%	34.401	0.005	272.727	0.005	16.830	0.005
Lactose-L30D6%	0.019	N.S.	97.638	0.005	12.593	0.005
L30D2%-L30D4%	5.079	0.005	14.778	0.005	18.647	0.005
L30D2%-L30D6%	68.203	0.005	109.144	0.005	143.265	0.005
L30D4%-L30D6%	36.059	0.005	43.600	0.005	58.540	0.005

other hand, when we use Eudragit (R) E 30D and L 30D, the values were near those obtained from the excipient without coating. There was no difference with 2% and 4% of Eudragit (R) E 30D nor with 6% Eudragit (R) L 30D, while with 2% and 4% of Eudragit (R) L30D, the powders

TABLE 5

Results obtained after the application of Scheffé's test.

Powder	Tapped density		Haussner Index		Percentage of compressibility	
	F	∝	F	∝	F	∝
Lactose-E2%	4.218	0.05	4.410	0.01	7.123	0.005
Lactose-E4%	6.115	0.005	9.328	0.005	14.715	0.005
Lactose-E6%	63.341	0.005	64.032	0.005	105.720	0.005
E2%-E4%	20.490	0.005	0.910	N.S.	1.362	N.S.
E2%-E6%	100.252	0.005	34.832	0.005	57.961	0.005
E4%-E6%	30.096	0.005	24.480	0.005	41.551	0.005
Lactose-L2%	544.259	0.005	61.252	0.005	88.361	0.005
Lactose-L4%	55.173	0.005	43.189	0.005	74.864	0.005
Lactose-L6%	220.057	0.005	0.785	N.S.	1.251	N.S.
L2%-L4%	252.859	0.005	1.574	N.S.	0.559	N.S.
L2%-L6%	73.166	0.005	48.166	0.005	68.588	0.005
L4%-L6%	54.856	0.005	32.326	0.005	56.764	0.005
Lactose-S2%	11.691	0.005	6.242	0.005	5.894	0.005
Lactose-S4%	0.880	N.S.	0.745	N.S.	0.053	N.S.
Lactose-S6%	29.009	0.005	14.027	0.005	24.778	0.005
S2%-S4%	6.155	0.005	11.300	0.005	6.939	0.005
S2%-S6%	77.531	0.005	38.982	0.005	54.843	0.005
S4%-S6%	39.996	0.005	8.306	0.005	22.765	0.005
Lactose-E30D2%	2.662	N.S.	14.048	0.005	19.683	0.005
Lactose-E30D4%	1.001	N.S.	8.928	0.005	10.768	0.005
Lactose-E30D6%	133.036	0.005	65.742	0.005	92.721	0.005
E30D2%-E30D4%	0.399	N.S.	0.578	N.S.	1.334	N.S.
E30D2%-E30D6%	98.059	0.005	19.009	0.005	26.963	0.005
E30D4%-E30D6%	110.959	0.005	26.216	0.005	40.294	0.005
Lactose-L30D2%	0.079	N.S.	53.051	0.005	52.227	0.005
Lactose-L30D4%	0.195	N.S.	15.566	0.005	15.414	0.005
Lactose-L30D6%	0.232	N.S.	10.645	0.005	17.323	0.005
L30D2%-L30D4%	0.026	N.S.	11.144	0.005	10.995	0.005
L30D2%-L30D6%	0.040	N.S.	111.223	0.005	129.708	0.005
L30D4%-L30D6%	0.002	N.S.	51.954	0.005	65.418	0.005

obtained show even smaller flow rate values, having statistical significance.

The same circumstance can be appreciated in the other parameters, though not so apparent as in the case of the flow rate. There it appears a progressive augmentation in the values of this last property as we increase the percentage of every Eudragit (R) used for the coating, being almost linear in the cases of Eudragit (R) E and L.

This general augmentation is due to the obtention of particles with a more regular superficial structure than the initial ones (24). That means a considerable diminution in the interparticular friction and an augmentation in the flow characteristics of the powders (25-26). Besides this, the coating permits an increase in the particular diameter (24) and a greater fluidity (18, 27-28).

From the values presented on tables 1,2,4,5, it can be appreciated that the effectiveness of the coating with the Eudragit (R) in organic solvents is already manifested at 2% and progressively up to 6%. The greatest amelioration corresponds to Eudragit (R) E, followed by Eudragit (R) L and S. The use of Eudragit

(R) in aqueous dispersions was not equally useful in the percentages tested.

The values corresponding to the angle of repose are not so clear since percentages superior to 6% -in Eudragit (R) E from 4% on-, are required so as to yield a positive influence of the coverment over this parameter. This circumstance did not appear in the flow rate, but it is normal since the flow representativity of both tests are different, being the flow rate more important in comparison with the angle of repose (25, 29). This circumstance induces authors such as Minet et al. (16), Delacourte-Thibaut et al. (30), Michoel et al. (31) or Jones (19), to refuse this parameter (angle of repose) in their rheological studies over different powders.

In similar studies about starch, we could observe a statistical correlation between parameters. This circumstance could be due to the great positive modification that appeared in covered powders in relation to the initial starch (23).

In the Pharmaceutical Industry, a big difference between bulk and tapped density means a greater irregularity in the fabrication of solid forms for oral administration, because of an important irregularity in

the surface of the powder particles (18, 20). In this way, every change made over a powdered excipient must involve an approach between these two densities.

The values corresponding to these two parameters are shown in tables 1 and 2.

The similitude between the data of the two densities implies Haussner Index values near the unity and lower values of Percentage of Compressibility, compared to initial lactose. The most important and sequential difference appears in the group coated with Eudragit (R) E. With a 6% of this Eudragit (R), the percentage of compressibility decreased in almost nine units. This coated powder has the highest significative statistical difference in its comparison with the initial lactose.

The change obtained in the rheology of these powders has allowed their use as excipient for direct compression so as to manufacturate tablets in which we have included acetaminophen -powder of very unfavourable rheology- in a high dosification. The inclusion of these powders has not only exerted a positive influence in the technological elaboration of the pharmaceutical form -allowing the obtention of tablets of acetaminophen by direct compression-, but

TABLE 6

Multiple linear regression parameters
(1) Estimated constant term; (2) Standard error of estimated;
(3) Regression coefficient; (4) Standard error

		Correlation coefficient	(1)	(2)	(3)	(4)	F	Prob.
Flow rate	Angle of repose	-.492					4.466	0.053
	Bulk density	0.261					1.025	0.329
	Tapped density	-.686	87.530	2.984	-71.783	20.339	12.456	0.003
	Haussner Index	-.704	67.879	2.913	-32.562	81.777	13.762	0.002
	Percentage of compressibility	-.711	40.858	2.881	-0.656	0.173	14.376	0.002
Angle of repose	Bulk density	-.392					2.542	0.133
	Tapped density	0.336					1.783	0.203
	Haussner Index	0.517	-6.358	5.149	35.059	15.514	5.106	0.040
	Percentage of compressibility	0.542	21.998	5.057	0.732	0.304	5.810	0.030
Bulk density	Tapped density	0.142					0.288	0.600
	Haussner Index	-.689	0.989	0.022	-0.241	0.068	12.667	0.003
	Percentage of compressibility	-.651	0.780	0.023	-0.005	0.001	10.301	0.006
Tapped density	Haussner Index	0.607	0.535	0.031	0.268	0.094	8.148	0.013
	Percentage of compressibility	0.654	0.748	0.030	0.006	0.002	10.450	0.006
Haussner Index	Percentage of compressibility	0.992	0.841	0.011	0.020	6E-04	888.437	0.000

has also changed their biopharmaceutical characteristics.

CORRELATION BETWEEN THE TECHNOLOGICAL PARAMETERS TESTED

Once we have determined the difference in the behaviour between the initial lactose and each powder obtained after the coating with each one of the five types of Eudragit (R) used at the three percentages, this study was completed with a correlation test according to the rheological properties that define the powders so as to determine the existence of statistical significance in these correlations. The correlation study was done comparing the powders all together.

Table 6 expresses the multiple linear regression parameters found between the assays tested.

CONCLUSIONS

We have found that powders obtained after the coating of lactose with acrylic polymers type Eudragit (R) by means of phase separation technique induced by the evaporation of solvents, have been improved in their rheological properties. This amelioration is greater with the use of Eudragit (R) E 12.5, L 12.5 and S 12.5 than with Eudragit (R) E 30D and L 30D, which shows the

greater advantages of using resins in organic solutions than in aqueous suspensions. There is also a progressive improvement shown with an increase in the percentage of the Eudragit (R) used in this study, from 2% to 6%. In this way, we create the possibility of using these powders as excipients for direct compression.

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