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NEW APPROACH TO AQUEOUS GRANULATION OF HIGHLY HYDROSOLUBLE DRUGS.

J.L. Fábregas*, and J. Cucala

Research Institute

Laboratorios Almirall, S.A.

Barcelona (08024), SPAIN

ABSTRACT

The critical effect of binding solvents in aqueous wet granulation,on the physical stability of tablets was investigated. The implications of the shelfcementation process in aqueous granulation of Piracetam are discussed.

INTRODUCTION

The tablet is the most widely used dosage form in the medicine of today. Tablets may be produced either by dry or wet granulation methods, although the latter is the most used for all types of pharmaceutical powder mixtures, and for this reason has been extensively studied[1-7]. However, no information has been published on the influence of the granulation solution on the long term physical stability of the tablets.

In the present work, the granulation of Piracetam (2-Oxo-1-pyrrolidineacetamide), with several aqueous binder solutions was investigated. This compound was selected as a model of highly hydrosoluble drug, with a high oral unit dose (800 mg). The quality of the resulting granulates, and the galenical stability of the tablets produced from them, were studied. It appears that the kneading solvent is more important than the binder itself in influencing the physico-chemical stability of the tablets.

EXPERIMENTAL

Materials

Piracetam (UCB, Belgium) Polyvinyl pirrolidone, mean molecular weight 40,000 (GAFC, USA), 96% Ethyl-alcohol and Magnesium stearate (both from E. Merck, W. Germany) were used.

Aparatus

An ultrarapid mixer (Lodige M5, W. Germany) operating at constant velocity (300 rpm), was used in all experiments. The granulates were compressed in a single punch tablet press (Korsch EK-O, W. Germany), using circular (11.0 mm) biconcave punches.
Airjet sieve (Alpine 200), friabilator (Roche), volumeter (Engelmann A-G), durometer (Heberlein), and disintegration tester (Erweka ZT-2), were used as control instruments. Porosity data were determined by a mercury intrusion porosimeter (Carlo Erba, model 225). The surface tension of binding solutions were measured with a Traube stalagmometer.

Tablet preparation

Excluding experiment A (dry mix procedure), crystalline Piracetam (mean particle size 250 μ) was directly kneaded into an ultrara-

TABLE I

BINDING DISSOLUTIONS

Granulate	Binder	Surface tension for binding dissolutions (dyne . cm^{-1})
A	Without binder (dry mix)	
B	Ethanolic polyvinyl pirrolidone (3% w/v)	26.45
C	Distilled water	74.10
D	Aqueous polyvinyl pirrolidone (3% w/v)	85.90
E	Aqueous Piracetam (5% w/v)	87.04
F	Aqueous Piracetam (10% w/v)	90.59
G	Aqueous Piracetam (15% w/v)	87.83

pid blender, using different binding solutions (Table I) in a ratio to solid bulk of 0.15 ml/g. Binder spray time (2 min.), and kneading time (3 min.) were the same in all experiments. The resultant granules were dried for 4 hours at 60ºC, screened through a 0.8 mm sieve, and mixed with magnesium stearate (0.5%). The granulates were tableted in a single punch press, at an uniform weight (830 mg) and height (6.6 mm).

Test Methods

Granule properties investigated include very fine powder content (as % sieved through a 125 µm screen), apparent density, true density, Hausner's number, and friability (as increase of very fine

powder content from the fraction coarser than 125 µm assayed during 30 minutes in the friabilator).

The tablets were checked for their hardness, disintegration time, friability, and surface porosity. The tablets were stored in open bottles at 80% relative humidity at 25ºC and variations in hardness, and moisture absorption were studied. Tablets were also placed in an special PVC rack, simulating a conventional blister pack but without plastic nor aluminium alveolus cover, to allow individual observations of tablet volume variations under high humidity conditions (80% R.H.) for a period of 45 days.

RESULTS AND DISCUSSION

The physical characteristics of granulates prepared with different binder solutions are shown in Table II. The high friability observed when pure water was used as kneading liquid (granulate C) is noteworthy.

The starting galenical data for the tablets are listed in Table III. Interbatches differences were negligible, with the exception of high friability and low hardness of sample A, that invalidates the direct compression method. On the contrary the highest hardness with low friability and disintegration time was achieved with binder procedure D. Furthermore, the very low porosity and small pore radius range of table D is evident from the data plotted in Fig. 1, when compared with the high porosity of sample C and the largest mean pore radius of sample A.

The eficacy of binding strategies, in the physical stability of the tablets was verified in a study of the hardness variation as function of moisture absorption. In this way, tablet samples contained in open bottles were maintained at 25ºC and 80% relative humidity, and hardness variations and weight increases were measured at 45 and 30 days, respectively.

TABLE II

PHYSICAL CHARACTERISTICS OF THE GRANULATES

Granulate	Very fine powder, %	Apparent density g . mL^{-1}	True density g . mL^{-1}	Hausner's number	Friability %
A	6.6	0.735	0.833	1.133	4.55
B	9.6	0.632	0.740	1.170	4.32
C	4.9	0.645	0.735	1.139	10.40
D	10.0	0.591	0.714	1.208	4.20
E	4.4	0.625	0.746	1.194	3.55
F	9.5	0.632	0.719	1.138	3.80
G	7.8	0.625	0.735	1.176	4.80

The mean results for fluctuant hardness (expressed as a percentage of the initial value) of ten individual tablets of each batch with time, stored at 80% R.H., are plotted in Fig. 2. General behaviour includes a first step when hardness increases, corresponding to initial water absorption, especially for tablets with lower residual humidity at zero time. Secondly, the hardness decreases due to the effect of the excessive amount of water absorbed. Only sample D shows a nearly constant value within the usual range accepted (±20%) for non-critical tablet hardness variations.

Weight increase was investigated in formulations A to E under 80% relative humidity, in the rack described above. The results are plotted in Fig. 3. The observations were interrupted when significant alterations of tablet surface were evident (first detected in sample B), but clearly formulation D was again the most stable

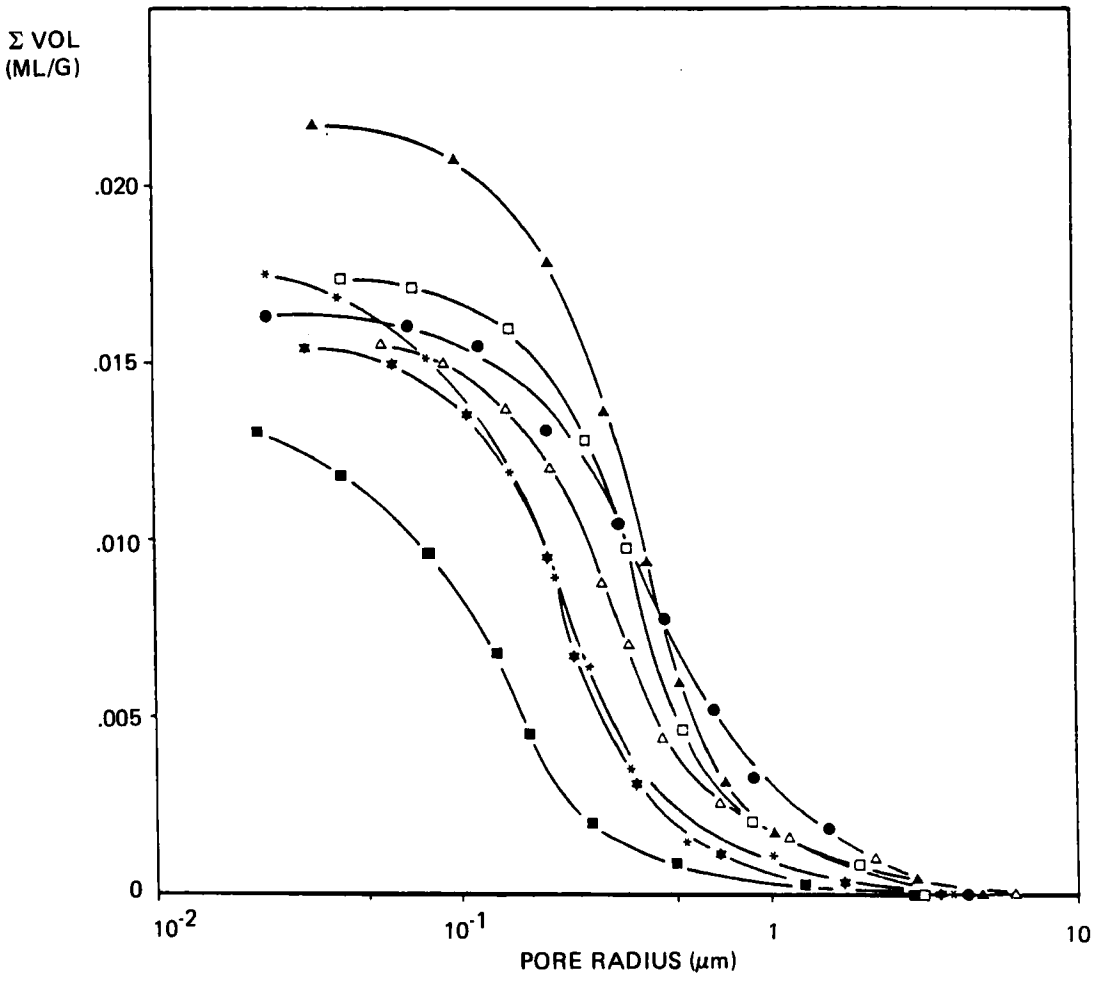

FIGURE 1

Porous structure data for different Piracetam tablets. Key : A (●), B (✱), C (▲), D (■), E (★), F (△), G (□).

tablet. There was a slight increase of disintegration time at the end of the study (Table III).

The irregular interformulation behaviour in presence of moisture was not attributable to the partial formation, during the kneading procedure, of different Piracetam polimorphs[8-9], because in-

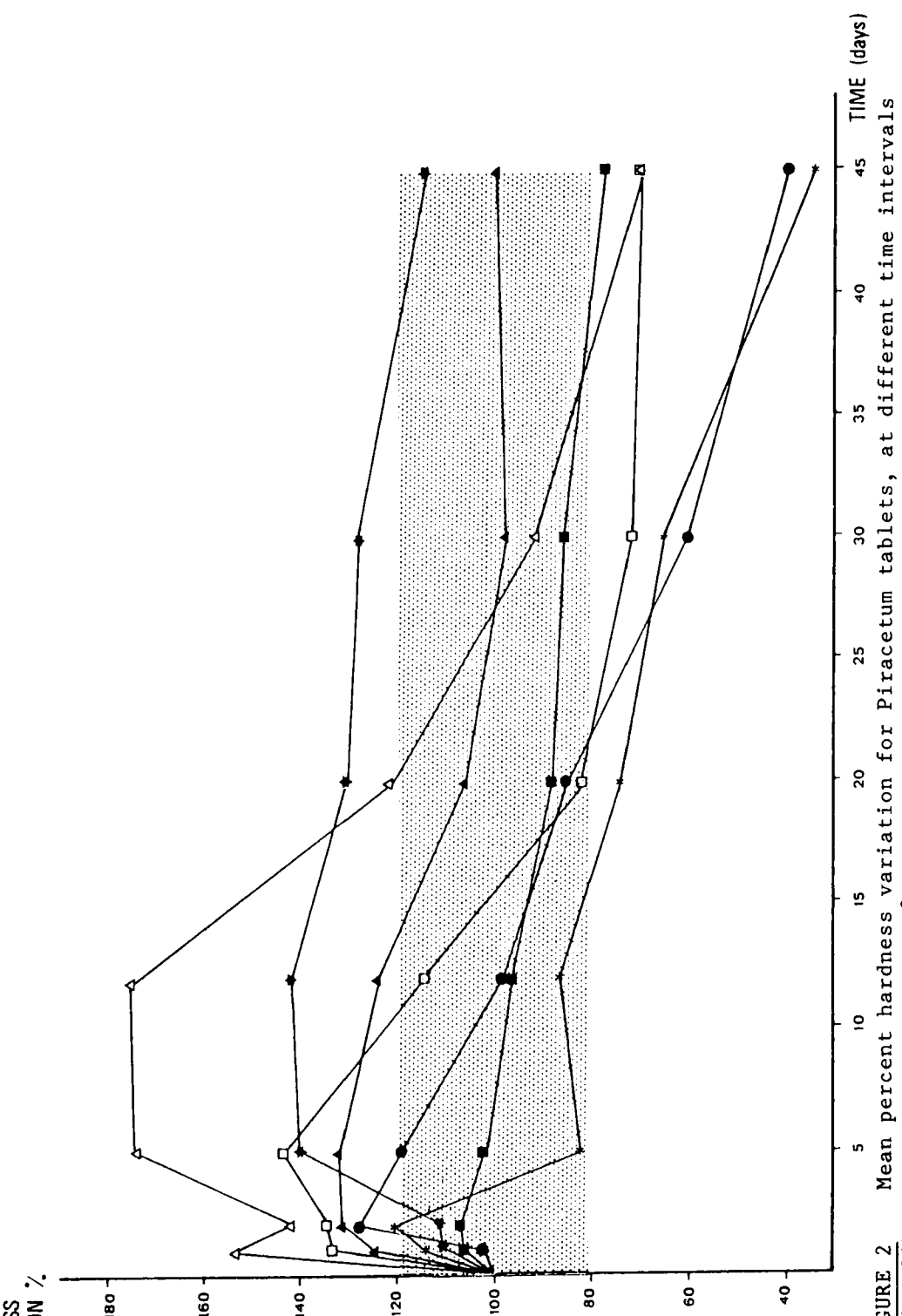

FIGURE 2 Mean percent hardness variation for Piracetum tablets, at different time intervals under 80% relative humidity at 25°C. Same key as Fig. 1.

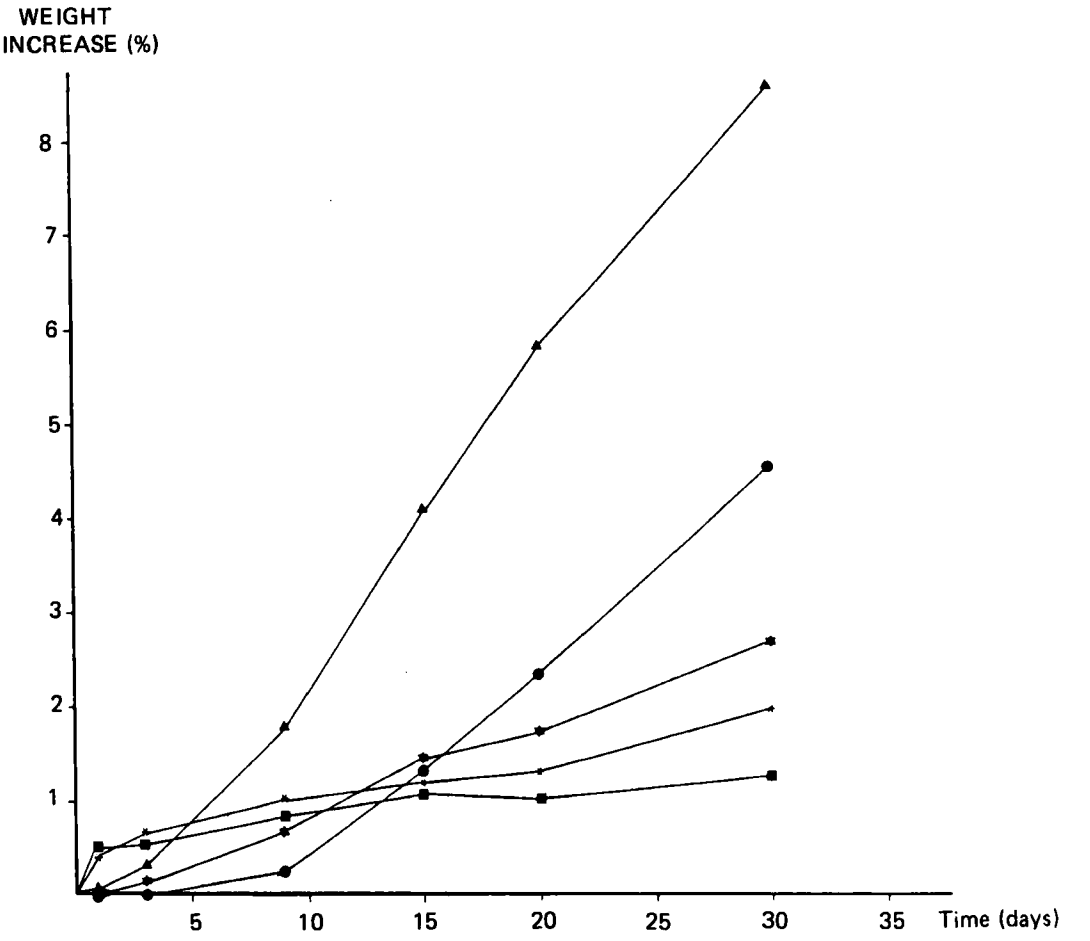

FIGURE 3

Kinetics of moisture uptake (as weight increase) for Piracetam tablets, under 80% relative humidity at 25ºC. Same key as Fig. 1.

frared spectra and differential scanning calorimetry curves were identical in all cases.

The results presented in this report clearly show that a kneading liquid must be individually selected. On the basis of the study, the following three tablet criteria were stablished to assist in kneading liquid selection: Minimum porosity, water absorption, and loss of hardness.

TABLE III

POROUS STRUCTURE DATA AND RELATED CHARACTERICS OF PIRACETAM TABLETS

Batch	Total Pore Volume mL . g^{-1}	Mean Pore Radius µm	(1) Hardness Kp.	Friability %	Residual Humidity %	Disintegration time(2), min.	Disintegration time(3), min.
A	0.01650	0.440	4.8	0.88	0.02	3.42	5.75
B	0.01735	0.210	11.0	0.39	0.31	3.33	3.83
C	0.02179	0.360	8.3	0.37	0.16	3.33	5.92
D	0.01302	0.130	18.7	0.19	0.28	3.37	4.67
E	0.01546	0.220	11.4	0.29	0.01	3.22	4.83
F	0.01554	0.320	8.7	0.32	0.02	3.25	4.58
G	0.01742	0.370	8.2	0.36	0.01	3.32	4.83

(1) Mean of twenty determinations.

(2) Measurements agree with the USP XX method.

(3) Determined on samples maintained for 45 days at 80% relative humidity conditions.

During the kneading step with water or aqueous solutions, a minor but varying amount of Piracetam is dissolved depending on the disposable water in the binding solution. During the drying process, this Piracetam is precipitated at molecular level, occupying void spaces in the aglomerated material, giving rise to a secondary - binder effect when a true binder (polyvinylpirrolidone, PVP) is present. Formulation D yields tablets with the minimum water absorption due its low porosity caused by cementation with precipitated Piracetam.

This cementation is not possible if the Piracetam is insoluble in the kneading liquid. In formulation B, only macroscopic granule aggregation,due to PVP, occurs. The low surface tension of the alcoholic kneading dissolution allows a good penetration into bed powder, but the absence of molecular deposition of Piracetam leaves open small channels that are responsible for the water inclusion when tablets are exposed to high humidity conditions. As a consequence, the tablet easily swells and hardness decreases.

Under similar conditions, the initial water absorbed by tablets of formulation D slowly dissolves the molecular deposed Piracetam, without disintegrating the tablet, being the large Piracetam granules still aglomerated by the PVP effect.

The loss of hardness of the tablets (G > F > E > D, Fig. 2) is related to the quantity of Piracetam dissolved. A very important - amount of Piracetam deposed at molecular level (formulations E to G) implies an excessive channels network filled with microcrystalline Piracetam, leading to easy crumbling of the tablets. Aqueous binding solutions containing exclusively Piracetam give tablets with more stable characteristics than those prepared using pure water as binder (formulation C), but not as stable as those prepared from aqueous binding solutions of a true binder (PVP) supported by a moderate quantity of Piracetam at molecular size.

Ethanolic solutions of PVP does not reach an stable binder effect in Piracetam granulates.

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