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DESIGN AND FORMULATION OF TABLETS OF A NEW ANTINEOPLASTIC DRUG: AMONAFIDE.

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The design and formulation of tablets of amonafide, a new antineoplastic drug, is carried out.
In the preformulation step, those characteristics of the drug with a special importance for the successful development of the formulation phase are determined. Due to the results of the preformulation step, it was necessary to replace amonafide by the correspondent dichlorhydrate salt. The high porosity, low compressibility and bad flow properties of amonafide 2HCl advise to reject the direct compression as a tablet manufacture method. Through a wet granulation or simply through an agglomeration of the drug with alcohol, the characteristics of the material to be compressed improve significantly.

As results of the formulation studies, two formulations of tablets obtained by wet granulation and a third formulation obtained by direct compression of the agglomerates are selected. They meet all the requirements imposed to this pharmaceutical form for oral administration.

MATERIALS

- Drug substances: amonafide (CAS 69408-81-7) and amonafide dichlorohydrate, supplied by Laboratorios Knoll S.A.(1).
- Excipients: mycrocrystalline cellulose (Avicel PH101®), dicalcium phosphate dihydrate (Emcompress®), povidone K30 (Kollidon 30®), magnesium stearate Eur. Ph. grade (2).
- Experimental hydraulic press with detectors that register the force and displacement parameters during the whole compression process.

- 11 stainless steel vibratory sieves with a screen mesh of 700, 600, 500, 400, 300, 250, 200, 150, 100, 75 and 50 μ.
- Karl Fisher Titrater (Metrohm).
- Pharmaceutical tablet compression single-stoke machine with a set flat-faced bevel edged punch cup of 11 mm of diameter.
- Tray/truck drying even (J.Bonals).
- Hardness tester (Erweka).
- Friabilator (Erweka).
- USP disintegrator test device.
- USP dissolution test apparatus (Sotax AT7), method 1.
- Spectrophotometer (DU Beckman).

METHODS

Characterization of the Active Substance

The true density (d_t) is determined at 20°C through the method of displacement in liquid, using ethyl ether saturated with active substance. The bulk density is determined by the method described by Van Ooteghem (3).

From the values of true density and of bulk density before (d'_b) and after (d_b) subjecting the material to shaking the porosity (ϵ) and the compaction grade (C) are calculated by use of the equations 1 and 2.

$$\epsilon = \left(1 - \frac{d_b}{d_t}\right) 100 \qquad (1)$$

$$C = \frac{d_b - d'_b}{d_b} 100 \qquad (2)$$

Particle size analysis of the material are carried out by sieving with a mechanical shaker. 5 sieves with a screen mesh between 250 and 50 μ are used.

The flowability is evaluated by the determination of the static angle of repose through the technique of fixed-funnel with closing system.

With the purpose of determining the compressibility of the material, this is subjected to different pressures using a hydraulic press. From the data of the material resistance according to the displacement of the upper punch, the corresponding diagram is built up.

Elaboration of Tablets

The hygroscopic behaviour of amonafide 2HCl (4) makes it necessary to work under controlled relative humidity environments lower than 48%.

Tablets are prepared with 200 mg of amonafide (251 mg of 2HCl amonafide) by two different methods (figure 1):

a)- Wet granulation: the composition (in weight%) of the obtained tablets is shown in table 1. A 7.5% povidone solution in 25% ethanol is used as liquid binder. This is incorporated into the drug-avicel mixture in the case of the tablets I. The wet mass is passed through a 700 μ screen. The resultant granulation is dried up for four hours at 45°C and it is characterized by the corresponding tests.

The lubricant, magnesium stearate, is added in a concentration of 3% and of 0.8% (W/W), obtaining the mixtures typified as I(A) and I(B). From the I(A) mixture, two batches of tablets are obtained: I(A)1 and I(A)2 on applying a medium and a low pressure respectively in the compression step.

The mixture typified as I(B) is compressed by applying three pressures (high, medium and low). So, three batches of tablets are obtained: I(B)1, I(B)1 and I(B)3.

In the case of tablets II, the disintegrant (Avicel) is incorporated by external addition, due to the high solubility of the active substance (5).

b)- With the initial purpose of obtaining a raw material with a less dangerous manipulation, it is agglomerated wetting with alcohol and, later, it is passed through a 300 μ screen. When this granulation is dry, it is mixed with direct compression excipients and it is compressed obtaining the batch III of tablets, which composition (in weight%) is shown in table 1, too.

The applied pressure during the compression step is expressed through the compression ratio (C.R.), that is the quotient between the height of the compressed mass and the height of load in the die.

Characterization of Granulations

The bulk density, the compaction, the size particle distribution, the flowability, the friability (6), the moisture by Karl Fisher method (7), the drug content uniformity by spectrophotometry test (8) and the dissolution kinetic (9) are determined. The amount of sample used in these last two tests corresponds with the dosage. The work conditions in the study of the dissolution kinetics are 37°C and 100 r.p.m., and HCl 0.1N is used as liquid of attack. From the dissolved amount of analyte versus time curves, the t_{70} parameter or dissolution time of the 70% of the dosage is calculated as representative parameter of the dissolution process.

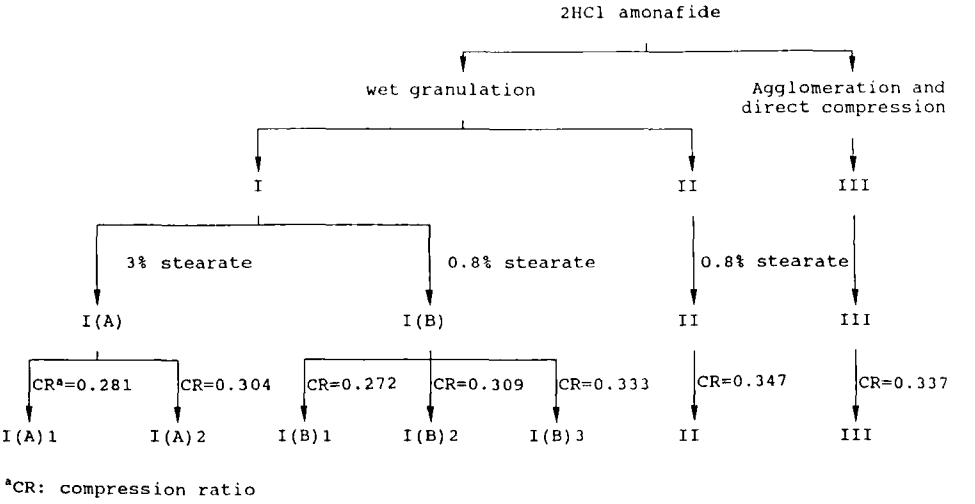

FIGURE 1
Development of the formulation phase.

TABLE 1

	Tablets			
Constituent	I(A)	I(B)	II	III
2HCl amonafide	61.10	62.02	60.02	69.44
Emcompress®	---	---	30.01	24.80
Avicel PH101®	30.55	31.24	4.96	4.96
PVP K30	5.34	5.46	4.20	---
Mg stearate	3.00	0.80	0.80	0.80
Theoretical weight (mg)	411.6	402.4	419.0	362.2

Composition (in weight%) of the Elaborated Tablets.

Characterization of Tablets

The size, the hardness, the friability (10), the disintegration time (11), the drug content uniformity and the dissolution kinetic are determined.

RESULTS AND DISCUSSION

The values of the parameters considered in the raw material characterization are collected in table 2. The low bulk density of amonafide, due to, partly, its sheet-shaped presentation, causes problems of handling, even in basic operations as transporting or weighing. So, it is not considered as a suitable raw material for its industrial transformation into a pharmaceutical form and it is replaced by the dichlorhydrate one. Amonafide 2HCl is presented as a powdered material, with a low bulk density and accordingly a high porosity. The 90.93% by weight is constituted by particles smaller than 100μ and the 41.33% smaller than 50μ (figure 2). With an angle of repose value (α) higher than 45°, the material is classified as cohesive. The obtained resistance/displacement diagram (figure 3) is indicative of the low compressibility of the material.

These characteristics of amonafide 2HCl, together with the high established drug dose (251 mg) force to reject the direct compression as a method of tablet manufacture.

Through the granulation process a significative improvement of these parameters with regard to the raw material is achieved (table 3). It is shown up the high mechanical resistance of the granulations I, II and III, with a weight loss after shaking for 10 min lower than 5%, yet allow the rapid dissolution of the drug. The values of angle of repose, between 30 and 40°, show the balance between flowability and cohesion of the material, which is necessary for the right development of the compression process (figure 4). The incorporation of a 0.8% (W/W) of lubricant involves, in all cases, a slight improvement in the flowability,but this improvement is not bigger when the percentage of lubricant is a 3% (W/W) (mixture I(A)).

All types of tablets elaborated from these granulations present a good content uniformity, with a coefficient of variation lower than 3% (table 4).
The I(A)1 tablets, with a 3% (W/W) of lubricant, shows a high mechanical resistance, but the disintegration time, higher than 20 min, is considered excessive. In view of the high hydrosolubility of the drug, this disintegration time does not involve problems for the drug release, but the obtained values of t_{70} are considerably higher than the values obtained from the corresponding granulation.

TABLE 2

Property	Mean (Coefficient of variation)	
	Amonafide	2HCl Amonafide
Bulk density (g/ml)	0.0817	0.3552 (1.61%)
True density (g/ml)	---	1.6923 (3.16%)
Porosity (%)	---	78.90
Compaction (%)	---	15.16
Angle of repose (°)	---	48.80 (1.45%)

Characterization of Amonafide as Raw Material.

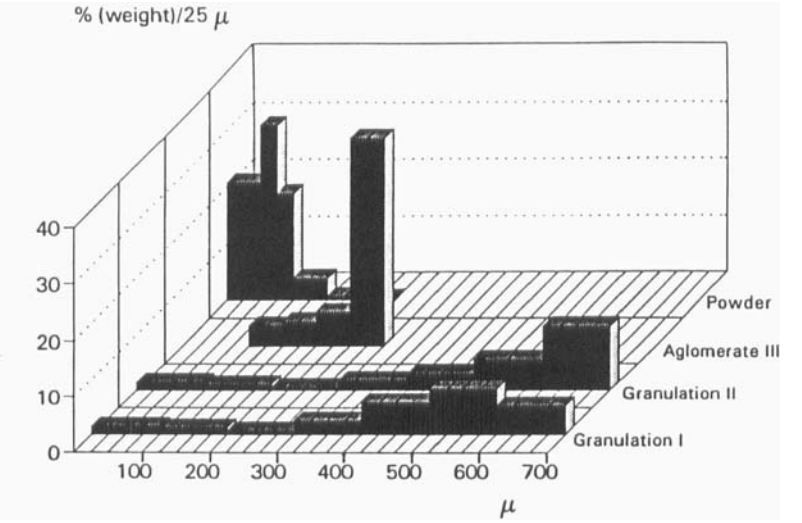

FIGURE 2
Particle size distribution.

With a decrease in the compaction pressure used to make tablets (I(A)2 tablets), the disintegration time is decreased, but the mechanical resistance of the tablets drastically decreases too, in such a way that a percentage weight loss higher than the limit (0.8%) is obtained in the friability test for 100 revolutions.

The three types of I(B) tablets contain a 0.8% (W/W) of lubricant. In this tablets, the inverse relation between the applied compaction pressure and the mechanical resistance of the tablets is made evident. In the extreme case of I(B)1 tablets, their break happens

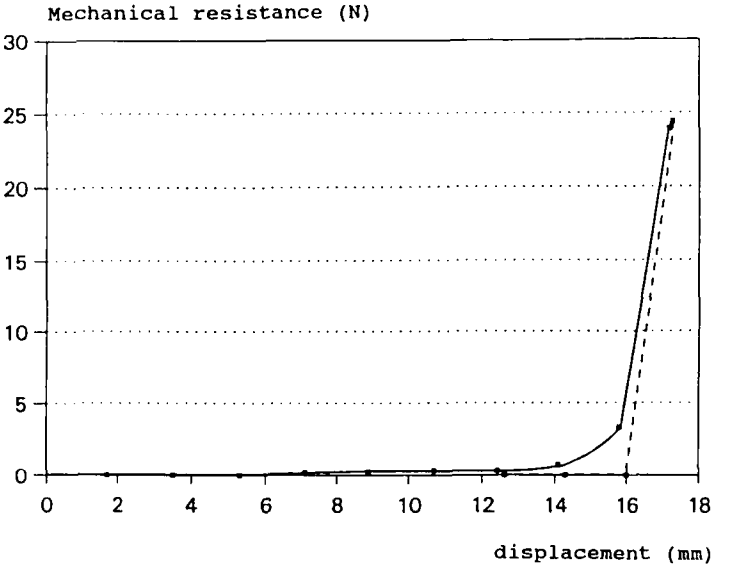

FIGURE 3
Mechanical resistance/displacement diagram.

applying a force higher than 15 Kg and the percentage weight loss in the friability test for 500 revolutions is lower than 0.11%. On the other hand, the average hardness of the mean hardness of the I(B)3 tablets is about 5 Kg and the percentage weight loss in the friability test is slightly bigger.

Small differences between the disintegration time values of the three types of tablets exists, being this value for the I(B)1 tablets slightly higher than 15 min.

Great differences with regard to the drug dissolution kinetics does not exist in the three types of tablets (figure 5$_a$), with a t_{70} value lower than 9 min inclusively in the case of I(B)1 tablets.

In view of these results, it is considered that the addition of a 3% of magnesium stearate to the granulation does not bring any improvement as opposed to the addition of a 0.8%. On the contrary, tablets with lower mechanical resistance are obtained because of the decrease of the cohesion forces between the granules. This lower mechanical resistance, together with the highly hydrophilic character of the drug make negative effects be scarcely shown over the disintegration and the

TABLE 3

	Granulations		
Property	I	II	III
Bulk density(C.V)[a]	0.3587g/ml(1.19%)	0.5814g/ml(0%)	0.4356g/ml(0.4%)
Compaction	7.80%	7.80%	5.10%
$d_{v/s}$ (s_g)	471.49μ(1.98μ)	513.86μ(2.21μ)	250.19μ(1.29μ)
Friability[b]	4.59%	3.68%	2.24%(2.61%)
Moisture (C.V)	2.37%(3.83%)	2.70%(10.53%)	3.72%
Average content(C.V)	198.75g(1.60%)	198.80g(1.16%)	201.85g(1.70%)
Dissolution: t_{70}	< 2min.	2.06min(5.47%)	< 1min.

Characterization of the Granulations. [a]C.V: coefficient of variation. [b]Loss of weight after 10 min of waving.

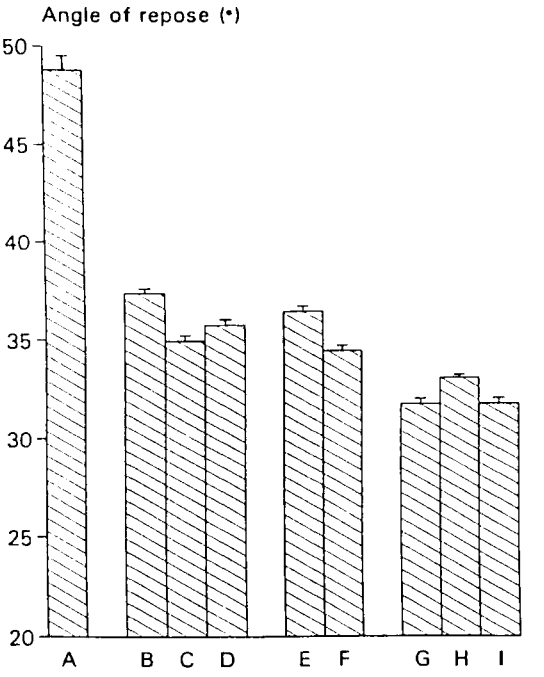

FIGURE 4

Flowability of 2HCl amonafide as powder (A), granulation I (B) with 3% (C) and 0.8% (D) of magnesium stearate, granulation II (E) with 0.8% of magnesium stearate (F), agglomerated 2HCl amonafide (G), mixture with excipients of direct compression (H) and with 0.8% of magnesium stearate (I).

dissolution. The three types of I(B) tablets are considered valid from technological and biopharmaceutical viewpoints. Nevertheless, due to economic considerations, the I(B)2 and I(B)3 batches are selected because of their high mechanical resistance applying a smaller compression pressure.

The type II tablets present a hardness higher than the I(B)3 tablets, even though the applied compression pressure is slightly lower. This fact can be owing to the binding properties of avicel which favours the particle-particle bonding during the compression process when it is added to the dry granulation. In the same way, the incorporation of emcompress to granulation II can be the reason of the slight increase in the friability values observed. This increase is more clear in the type III

TABLE 4

	Tablets						
	I(A)1	I(A)2	I(B)1	I(B)2	I(B)3	II	III
Content uniformity[a]:							
x(%)	98.97		99.09			98.98	100.92
C.V(%)	1.42		2.23			1.79	1.71
Range(%)	101-96		103-97			102-96	104-99
Dimensions:							
Diameter(cm)	1.107	1.110	1.104	1.101	1.102	1.105	1.105
Thickness(cm)	0.396	0.490	0.355	0.388	0.415	0.353	0.279
Hardness(Kg)	10.30	2.25	>15	9.75	5.25	8.75	8.35
Friability(%):							
4 min.	0.27	0.83	0.06	0.12	0.14	0.16	0.24
20 min.	0.38	1.60	0.10	0.25	0.33	0.35	0.58
Disintegration (min)	20.75	9.85	16.67	12.22	7.83	8.87	6.23
Dissolution: t_{70}(min)	10.12	6.32	8.66	6.68	5.97	2.56	2.40

Characterization of the Tablets. [a] expressed as percentage of the theoretical value of drug sustance.

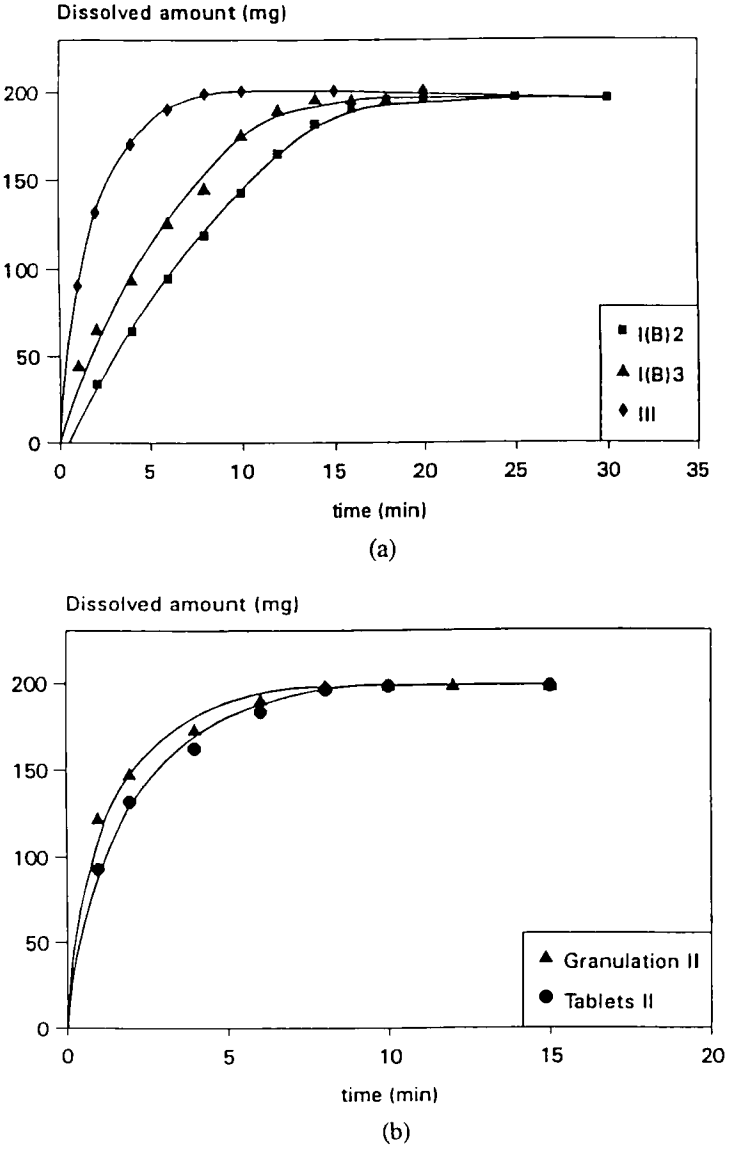

FIGURE 5
Dissolution kinetics of amonafide formulated in tablets I and III (A) and II (B).

tablets, in which the emcompress is incorporated as direct compression excipient. It is proper to show up, too, with regard to the type II tablets, the low t_{70} value (2.56 min) in such a way that the differences between the dissolution kinetics of the drug formulated in these tablets and in the tablet granulation do not almost exist (figure 5_b). This rapid drug release is shown too in the case of type III tablets.

Because of all these considerations, the series II and III tablets are considered valid from biopharmaceutical and technological viewpoints.

CONCLUSIONS

The bad flow properties and the low compressibility of amonafide 2HCl, together with the high established dose, advise to reject the direct compression as tablet manufacture method for this antineoplastic agent.

Through a wet granulation process, the characteristics of the material for compression improve significantly.

Two formulations of tablets of amonafide obtained by wet granulation are selected. They meet all the requirements for this pharmaceutical form and therefore are valid for the oral administration of the antineoplastic drug.

Besides, a third formulation is proposed. It is obtained by agglomeration of the drug with alcohol, mixing the agglomerates with direct compression excipients and, later, compression. This technique, in addition to its speed and its comfort, presents the advantage of a rapid drug release from the tablets.

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