Drug Development and Industrial Pharmacy, 25(10), 1073–1081 (1999)

RESEARCH PAPER

Improved Dissolution Behavior of Fenbufen by Spherical Crystallization

P. Di Martino,[1] C. Barthélémy,[2,*] F. Piva,[2] E. Joiris,[2] G. F. Palmieri,[1] and S. Martelli[1]

[1] *University of Camerino, Dip. Scienze Chimiche, Via S. Agostino, 1–62032 Camerino, Italy*
[2] *University of Lille II, 3 rue du Pr. Laguesse, B.P. 83, 59006 Lille Cedex, France*

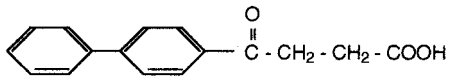
ABSTRACT

Fenbufen is an analgesic, antipyretic and anti-inflammatory drug that is characterized by poor water solubility, a defect increased by very low wettability. Poor water solubility, particularly at low pH, could decrease absorption in the upper part of the gastrointestinal tract, which would be inconvenient for good bioavailability. Different spherical crystallization processes have been considered as methods to improve fenbufen dissolution behavior. A two-solvent system, in the presence of a bridging liquid, is the only method capable of producing spherical fenbufen crystals. In a first step, fenbufen solubility was considered in different solvents. The drug crystals formed were typically needle shaped. This characteristic was considered as a favorable parameter to obtain spherical crystals. After the selection of the best fenbufen solvent, several ratios of solvent (S)–nonsolvent (NS) (tetrahydrofuran [THF]–demineralized water) were studied. The addition of a bridging liquid (isopropyl acetate) improved spherical crystallization. The results from this method were reproducible batch to batch. The spherical crystals obtained showed a clear improvement in dissolution capacity, probably due to better wettability. Dissolution studies were then carried out on these spherical crystals stored for 1 month at different relative humidities (RHs). The dissolution profiles remained unchanged.

* To whom correspondence should be addressed.

INTRODUCTION

Fenbufen is a nonsteroidal, anti-inflammatory, analgesic, and antipyretic agent. It is an acidic compound. According to the pH-partition theory of Shanker (1), the absorption of this drug should begin as soon as it is dissolved in the stomach.



The very poor solubility of fenbufen at low pH (<3 mg/L in HCl 0.1 N at 20°C) is a limiting factor for good absorption in the upper part of the gastrointestinal tract. This is the reason why it would be useful to improve the fenbufen dissolution rate to obtain rapid analgesic and antipyretic effects.

In addition, powders with good flow properties are of great advantage in technological processes. This led us to consider the preparation of spherical crystals of fenbufen.

Spherical crystallization has been described as a very effective technique in improving the dissolution behavior of some drugs that are characterized by low water solubility and a slow dissolution profile. It has also been applied to improve the flowability and the compression ability of some powders (2).

Several spherical crystallization methods have already been described. One method consists of a three-solvent system, which has been used for several important drugs (3–5). Liquid A is a solvent for the drug. Two other liquids, which have to be nonmiscible with each other, are submitted to continuous stirring at room temperature. One of these liquids (B) is a nonsolvent (NS) for the drug; the other one (C), which cannot dissolve the drug, nevertheless is capable of wetting its crystals. The drug solution in liquid A is added to the emulsion of the two liquids B and C under continuous stirring. The drug precipitates, and crystals gather together in the droplets of liquid C, in which crystal agglomerates densify and grow spherically.

Other systems are spherical agglomeration and the quasi emulsion solvent diffusion technique (6–8).

We carried out all these techniques to check all possibilities for obtaining spherical crystals of fenbufen.

MATERIALS AND METHODS

Fenbufen BP was kindly supplied by Secifarma (Italy). Isopropyl acetate came from Aldrich Chemical (France) and tetrahydrofuran (THF) from Carlo Erba (Milan, Italy).

Passive Diffusion Study

The diffusion study was carried out on a Resomat II Dibbern's apparatus (Desaga, Heidelberg, Germany). Artificial lipidic polypropylene membranes were obtained from a Celgard® 3501 weft (Célanèse, Charlotte, NC) with a thickness of 25 μm and a pore size of 0.04 μm. A method and lipidic mixture formulation for membrane impregnation have been initiated and validated in our laboratory (9).

The impregnation of 50 membranes was obtained after overnight immersion in a mixture of Miglyol® 812 (Hüls, France)/tributylphosphate/chloroform (100/100/50) at 30°C; then, they were dried between two filters and stored at room temperature. These artificial membranes have liposolvent properties similar to those of biological membranes.

The Resomat device was thermostated at 37°C. The donor compartment contained 50 ml of artificial digestive medium (gastric artificial USP liquid in which NaOH is added progressively to simulate pH changes in the digestive tract), and the receptor compartment had 200 ml of isotonic phosphate buffer pH 7.35 (4.46 g of $NaH_2PO_4 \cdot 2H_2O$, 36.18 g of $Na_2HPO_4 \cdot 12\ H_2O$, plus distilled water in a quantity sufficient to make 1 L). Monosodium phosphate and disodium phosphate were Rectapur grade from Prolabo (Paris, France). The artificial membrane, which separates donor and receptor compartments, was fixed under the upper donor compartment with a glass ring and an elastic band. Two magnetic stirrers guaranteed the homogeneity of each compartment.

The aim of the passive diffusion study was to simulate a digestive pH cycle (30 min each at pH 1.2, 5, 6, 6.5, 7, 7.5) in the donor compartment with fenbufen powder (50 mg) to verify the optimal absorption pH of this drug.

The amount of drug that permeated through the artificial membrane was calculated from the drug concentration in the receptor phase by continuous monitoring with an ultraviolet (UV) spectrophotometer (UV 1205, Shimadzu, Kyoto, Japan).

Solubility of Fenbufen in Tetrahydrofuran

Fenbufen solubility in THF was measured at different temperatures, from 20°C to the THF boiling point (66°C).

Preparation of Spherical Particles

Fenbufen (5.7 g) was dissolved in 30 ml of THF heated to its boiling temperature (66°C). The solution was poured quickly into 100 ml of water maintained at

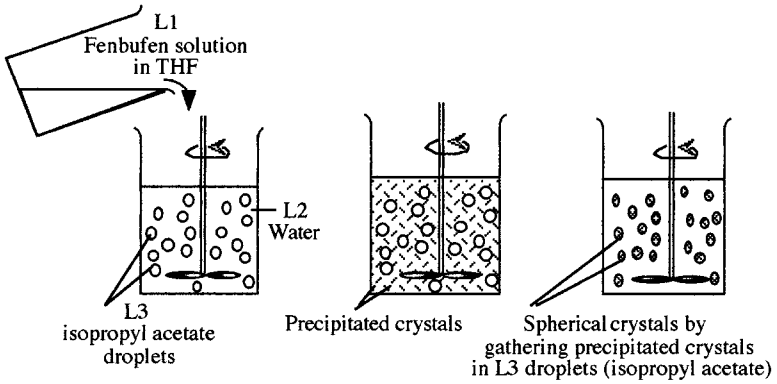


Figure 1. Schematic description of the spherical crystallization of fenbufen.

room temperature under continuous stirring at 500 rpm with a paddle device. A weak tendency toward particle agglomeration could be observed. After 10 min, 9 ml of isopropyl acetate, as a bridging liquid, was added. After this addition, the suspension began to clarify and the particles began to agglomerate with each other. After 30 min stirring, spherical crystals were formed (Fig. 1). The spherical crystals were separated from the liquid by filtration. The recovered crystals were dried in an oven at 50°C for 12 hr.

Particle Study

Particle Shape of Fenbufen Crystals

Particle shapes of fenbufen raw material and fenbufen spherical crystals were observed using an electron scanning microscope (Cambridge S 360, England). The samples were prepared by disposing the crystals on a Temp-fix® resin and covering them with a gold layer of 200 Å thickness using a metallizator (Balzers MED 010, Liechtenstein).

Particle Size of Fenbufen Crystals

The particle size of spherical crystals was determined by measuring the Ferret mean diameter under an optical microscope (Wild Leitz M20).

Flow Properties

Flowability was evaluated according to the European Pharmacopeia on 10 g of fenbufen.

X-ray Diffraction Study

An X-ray diffraction study was carried out to exclude any polymorphic transition during fenbufen crystallization. A Philips PW 1730 was used as an X-ray generator for CuK_α radiation ($\lambda = 1.54178$ Å). The experimental X-ray powder patterns were recorded on a PH 8203 (Philips, The Netherlands). The goniometer was a PH 1373, and the channel control was a PH 1390 (Philips). The data were collected in the continuous scan mode using a step size of 0.01° 2θ. The scanned 2 range was 2θ to 35°.

Dissolution Study

If the agglomeration tendency of the powder is taken into account, the basket and the paddle devices should be avoided. Therefore, the dissolution rates of fenbufen raw materials and spherical crystals were determined using a continuous flow cell method (10). The flow was 50 ml/min. The dissolution medium, according to the monograph of fenbufen tablets in the British Pharmacopoeia, is a pH 7.5 phosphate buffer; 4 ml of dissolution medium were withdrawn every 15 min over 90 min. The amount of dissolved drug was determined using a UV spectrophotometric method (UV 1205, Shimadzu, Japan) at 283 nm. The results are the mean of six experiments.

Powder Bed Hydrophilicity

To explain the differences observed in dissolution rates, a wettability test was carried out using a very simple device (11). Fenbufen (0.5 g; as raw material and then as spherical crystals) was placed on a sintered glass disk forming the bottom of a glass tube. The whole device was brought into contact with water and adjusted at 1 mm under the surface of the water. Some methylene blue crystals were put on the surface of the drug. The time taken for the capillary rising of water to the surface was noted. This time is visualized by the dissolution of the

methylene blue crystals, which color the powder surface intensively. The shortest rising time would correspond to the most hydrophilic substance, leading to good wettability.

Stability Study

Fenbufen spherical crystals were stored for 1 month at different relative humidities (RHs) (22%, 55%, 85% RH). A dissolution study was carried out again after this storage time.

RESULTS AND DISCUSSION

Passive Diffusion Study

Using the Resomat device of Dibbern (12,13) fitted with an artificial lipidic membrane, the absorption rate of fenbufen through the membrane is obviously very low at pH 1.2, corresponding to the stomach zone. At pH 5, the absorption rate increases, then it is highest between pH 6 and 7.5, corresponding to the intestinal zone (Fig. 2).

Spherical Crystal Obtention

The method described using three liquids is the only spherical agglomeration technique that allows spherical crystal formation.

Choice of the Liquid Media

This study started with the choice of the best solvent for fenbufen. This drug exhibits good solubility in several solvents (acetone, methanol, ethanol, ethyl acetate, 2-propanol, etc.) and, more particularly, in THF (Fig. 3). It is compulsory to select a solvent in which fenbufen exhibits the best solubility; in fact, a very concentrated solution of drug could increase the densification of the material during the crystallization process. As a matter of fact, using all the other solvents considered in which fenbufen is less soluble, an appropriate densification was never reached, and spherical crystals were never formed. The recrystallization of fenbufen from THF by cooling a quasi-saturated solution shows that very fine needles are the standard habit. This observation is very important for successful results (4).

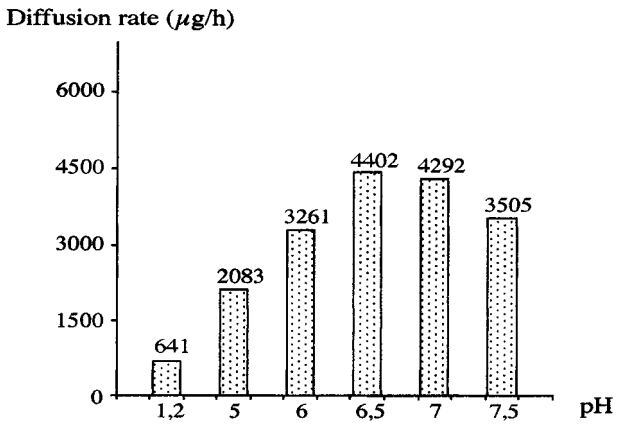


Figure 2. Diffusion rate of fenbufen across artificial lipidic membrane at different pH.

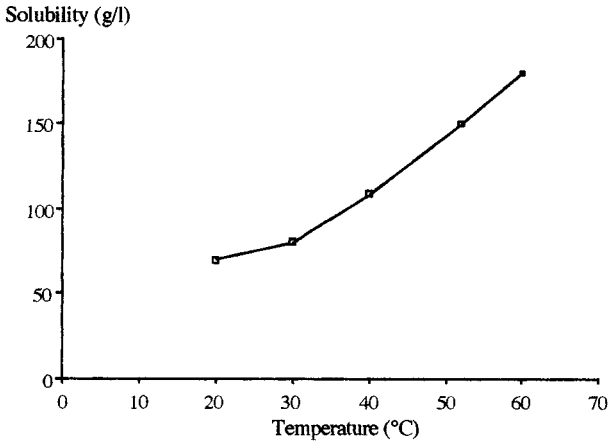


Figure 3. Solubility of fenbufen in tetrahydrofuran (THF) versus temperature.

The addition of the bridging liquid (isopropyl acetate) promotes the transfer of the drug to a third emulsified phase in which crystal agglomerates densify and grow spherically.

To optimize fenbufen spherical crystallization by the THF/water/isopropyl acetate system, several parameters were considered. Among these are the difference in temperature between that of the THF-fenbufen solution (T_1) and that of water (T_2), the ratio between the amount of THF solution and the nonsolvent (water), the speed of stirring, and the stirring duration.

Temperatures of the Different Liquid Phases

To optimize fenbufen spherical crystal formation, special attention has to be given to the difference between the solution temperature T_1 and the nonsolvent temperature T_2 ($\Delta T = T_1 - T_2$). The nonsolvent temperature was kept unchanged (room temperature), whereas the solution

temperature was modified, and various differences ΔT were tested.

Selection of the Best Liquid Proportions

At first, it must be noted that THF is miscible in any proportion with water and isopropyl acetate. On the other hand, isopropyl acetate is miscible with 23 parts of water. Consequently, if a ternary diagram is envisaged, water and isopropyl acetate are like an emulsion in a large area of this diagram. We have demonstrated that a very concentrated fenbufen solution in THF must be used to obtain sufficient consolidation of spherical agglomerates. This is the reason why we chose to use a quasi-saturated solution at 66°C, the boiling point of THF (i.e., 19% w/v).

To find the best percentage of the three liquids, a ternary diagram was built. The chosen model was an experimental design according to Scheffe (third degree incomplete model). According to this model, seven experiments were still to be carried out (Fig. 4a).

If the parallels to the three sides of the triangle are drawn through the middle of the sides, four new triangles are traced on which seven points are determined in the same way as for the first triangle. As some points are common to both triangles, 19 points can be identified (Fig. 4b).

The points on the vertex correspond to a pure liquid; those on the sides correspond to a mixture of only two liquids. Since the presence of three liquids is compulsory, these points must be excluded. Seven points remain for the experiments: A, B, C, D, E, F, and G (Fig. 4c). The observations are reported in Table 1.

For a thorough study, triangle IJZ was more closely investigated after division into four triangles in the same way as previously described. The new points were A′, B′, C′, D′, E′, F′, and G′ (Fig. 4d). In fact, D′ is the previous point C. The resulting observations are compiled in Table 2.

Last, the investigation of some points in the E′, G′, H′ zone (L, M, N, O, P, Q) enabled us to find the best proportions for spherical crystal obtention (Fig. 4d). These last observations are reported in Table 3. The optimal ratio for spherical crystal obtention is found on the O zone; these THF/water/isopropyl acetate proportions were then finally chosen.

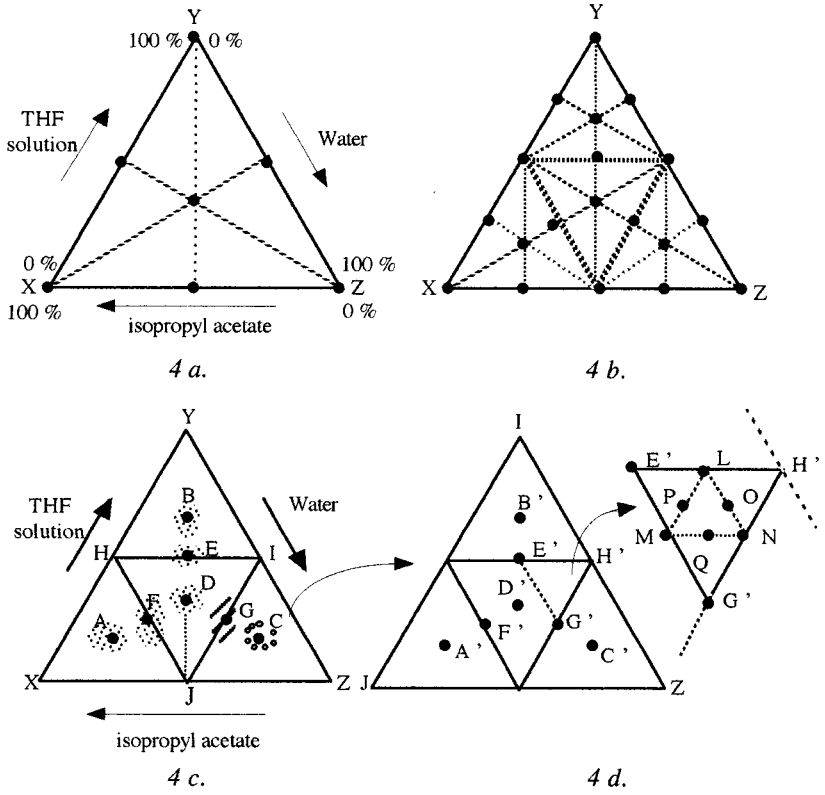


Figure 4. Scheffe tenary diagrams of fenbufen-THF solution/water/isopropyl acetate.

Table 1

Results of the Experiments Corresponding to the Seven Points of Scheffe Ternary Diagram in Figure 4c

	THF (%)	Corresponding Weight of Fenbufen (g)	Water (%)	Isopropyl Acetate (%)	Comments
A	20	3.80	10	70	Very dense suspension
B	70	13.30	10	20	Very dense suspension
C	20	3.80	10	20	Round agglomerates in a one-phase medium
D	33	6.27	33	33	Very dense suspension
E	50	9.50	25	25	Very dense suspension
F	25	4.75	25	50	Very dense suspension
G	25	4.75	50	25	Two limpid phases

Table 2

Results of the Experiments Corresponding to the Seven Points of Scheffe Ternary Diagram in Figure 4d

	THF (%)	Corresponding Weight of Fenbufen (g)	Water (%)	Isopropyl Acetate (%)	Comments
A′	8	1.52	58	34	Two phases, round agglomerates at the interface
B′	34	6.46	58	8	Same as A′
C′	8	1.52	84	8	Same as A′
D′	16	3.04	68	16	Round agglomerates in a one-phase medium
E′	25	4.75	62.5	12.5	Same as D′
F′	12.5	2.38	62.5	25	Flocs in a one-phase medium
G′	12.5	2.38	75	12.5	Same as D′

Table 3

Results of the Experiments Corresponding to the Six Points of Scheffe Ternary Diagram in Figure 4d

	THF (%)	Corresponding Weight of Fenbufen (g)	Water (%)	Isopropyl Acetate (%)	Comments
L	25	4.75	68.75	6.25	Round agglomerates + crystals in suspension
M	18.75	3.56	68.75	12.25	Round agglomerates in one-phase medium
N	18.75	3.56	75	6.25	Flocs
O	**21.875**	**4.16**	**71.875**	**6.25**	**Spherical crystals**
P	21.875	4.16	68.75	9.375	Same as M
Q	18.75	3.56	71.875	9.375	Same as M

Stirring Rate

Different stirring rates were tested because they influence the characteristics of spherical crystals. An optimum was found at 500 rpm. An increase in stirring speed makes spherical crystallization worse because a higher speed induces crystal agglomerate destruction. A lower stirring rate reduces the possibility of obtaining spherical crystals.

Particle Study

Morphological Aspect

Figure 5 shows the typical shape of fenbufen crystals recrystallized from THF without water by cooling a quasi-saturated solution. The electron scanning microscope (ESM) photograph of a spherical crystal in Fig. 6 displays its characteristic aspect. Greater magnification makes it possible to observe the crystal surface, which is made up of very little needle-shaped crystals (Fig. 7).

Flow Properties

The flow properties are considerably improved with spherical crystals (7 sec), whereas no flow is observed with powdered raw material.

Powder X-ray Diffraction

After recrystallization, no polymorphic phenomenon is detected using X-ray diffraction (Fig. 8). Actually, the diffraction angles are similar as far as both X-ray diffraction patterns are concerned. Only a decrease in reflection intensities can be pointed out for the spherical crystal sample; crystallinity could be inferior.

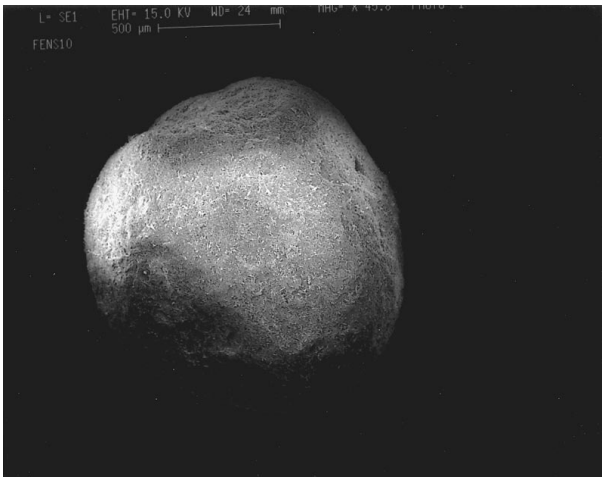


Figure 6. ESM photograph of a spherical crystal of fenbufen.

Dissolution Study

As can be seen in Table 4 and Fig. 9, the dissolution profiles of fenbufen exhibit better dissolution behavior for spherical crystals than for powder raw material. The standard deviations are also much lower for spherical crystals. The reason for this faster dissolution could be linked to the better wettability of the spherical crystals.

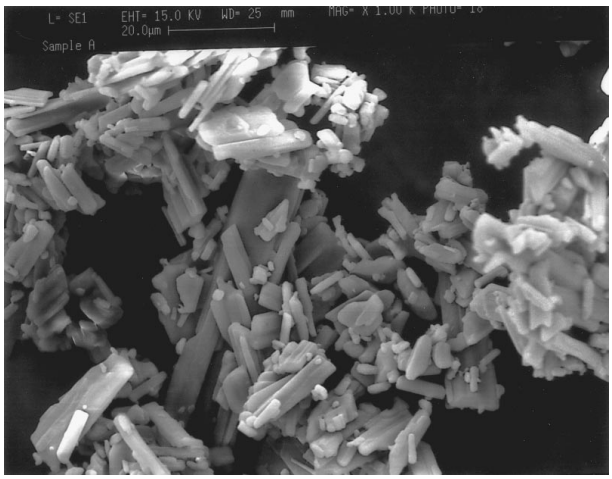


Figure 5. ESM photograph of fenbufen recrystallized from THF.

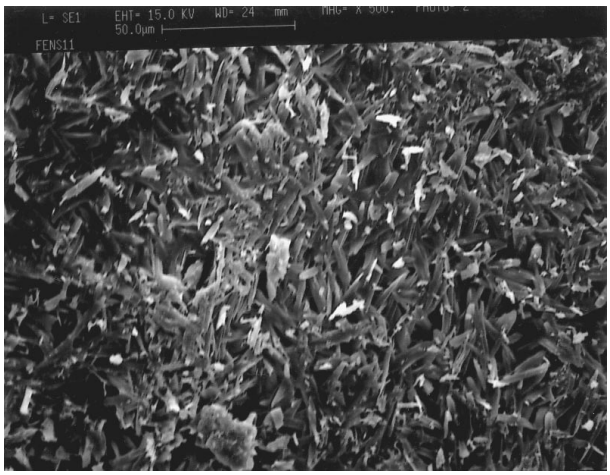


Figure 7. ESM photograph of fenbufen spherical crystal surface at high magnification.

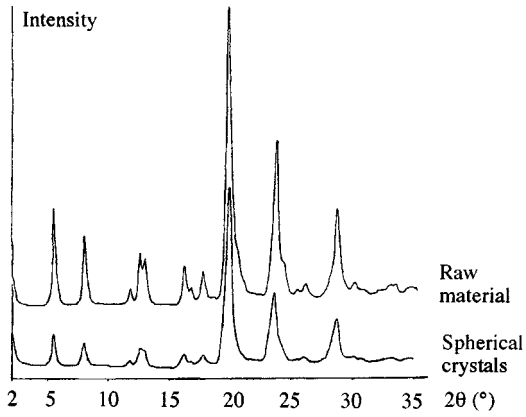


Figure 8. Comparative X-ray diffraction patterns of fenbufen raw material and fenbufen spherical crystals.

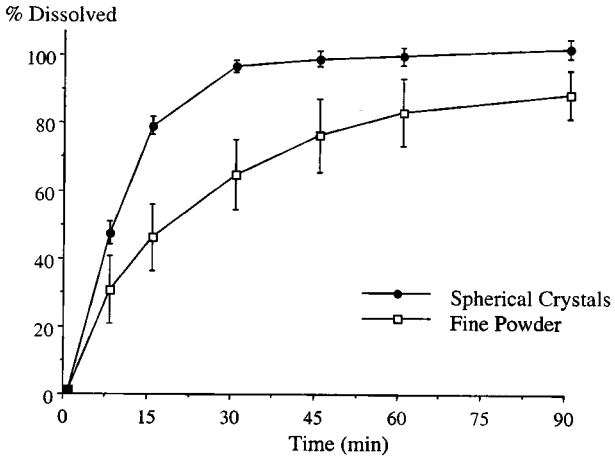


Figure 9. Dissolution profiles (at pH 7.5) of fenbufen spherical crystals compared with powdered raw material.

Powder Bed Hydrophilicity

The shortest rising time corresponding to the most hydrophilic substance is clearly observed with spherical crystals (45 min for spherical crystals, whereas nothing rises after 48 hr for powdered raw material), leading to very good wettability.

Stability Study

After 1 month of storage at different relative humidities, no difference was noted for all the samples considered. The dissolution profiles are very similar to those previously observed at zero time.

CONCLUSION

Spherical crystals of fenbufen were obtained by a process derived from the Kawashima technique in a three-liquid medium. These spherical crystals greatly enhance the flow properties and dissolution rate of fenbufen by improving the wettability of particles.

ACKNOWLEDGMENTS

We thank Mrs. Tavernier for her kind help with the English translation. We gratefully acknowledge the fi-

Table 4

Dissolution Rate of Fenbufen Spherical Crystals Compared to Powder Raw Material (Continuous Flow Cell Method)

	Powder			Spherical Crystals		
Time (min)	% Dissolved	± SD	VC%	% Dissolved	± SD	VC%
7.5	29.44	9.92	33.7	46.23	3.37	7.3
15.0	44.84	9.64	21.5	77.70	2.68	3.5
30.0	63.42	10.27	16.2	95.28	1.92	2.0
45.0	74.95	10.91	14.6	97.49	2.26	2.3
60.0	81.91	9.92	12.1	98.41	2.60	2.6
90.0	87.21	7.02	8.0	100.60	2.79	2.8

SD = standard deviation; VC% = variation coefficient.

nancial support of the Italian NURST, Fondi 40%—Progetto Nazionale Technologie Farmaceutiche.

REFERENCES

1. L. S. Shanker, D. J. Tocco, B. B. Brodie, and C. A. M. Hogben, J. Pharmacol. Exp. Ther., 123, 81–88 (1958).
2. Y. Kawashima, F. Cui, H. Takeuchi, T. Niva, and K. Kiuchi, Pharm. Res., 12(7), 1040–1044 (1995).
3. F. Guillaume, A. M. Guyot-Hermann, and J. C. Guyot, Il Farmaco, 48(4), 473–485 (1993).
4. Y. Kawashima, M. Okumura, and H. Takenaka, Science, 216, 1127–1128 (1982).
5. Y. Kawashima, A. Shigeru, and H. Takenaka, Chem. Pharm. Bull., 30(5), 1900–1902 (1982).
6. A. Sano, T. Kuriki, Y. Kawashima, H. Takeuchi, T. Hino, and T. Niwa, Chem. Pharm. Bull., 40(11), 3030–3035 (1992).
7. A. Ettabia, E. Joiris, A. M. Guyot-Hermann, and J. C. Guyot, Die Pharm. Ind., 59(1), 625–631 (1997).
8. Y. Kawashima, Proc. 5th Int. Conf. Pharm. Technol. Paris, 3, 228–234 (May 1989).
9. C. Barthélémy, C. Lefèbvre, and A. M. Guyot-Hermann, Il Farmaco, Ed. Prat., 41(11), 363–376 (1986).
10. C. Merle, C. Mangin, and A. M. Guyot-Hermann, Bull. Soc. Pharm. Lille, 2(3), 87–94 (1977).
11. C. Lefèbvre, C. Barthélémy, A. M. Guyot-Hermann, and J. C. Guyot, Drug Dev. Ind. Pharm., 14(15–17), 2443–2465 (1988).
12. H. W. Dibbern and G. H. Scholz, Drug Res., 19, 1140–1145 (1969).
13. A. M. Guyot-Hermann, C. Bonnet, H. Robert, and P. Balâtre, J. Pharm. Belg., 29(4), 297–318 (1974).