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Sulfluramid Volatility Reduction by β-Cyclodextrin

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Sulfluramid is an expensive active principle of insecticidal baits that is lost by volatilization during the pelletization of baits. To increase the thermal stability of sulfluramid, we tested its molecular encapsulation in β-cyclodextrin (β-CD), using molar ratios of 1:1 and 1:2 (sulfluramid:β-CD), using the complex preparation techniques of coprecipitation and kneading. The physical mixture of sulfluramid and β-CD was also tested for comparison. The products of complexation were characterized by differential scanning calorimetry, thermogravimetry, and derivative thermogravimetry, indicating the formation of a sulfluramid/β-CD complex and showing that the release of the complexed sulfluramid occurs in the range of 270−300 °C, a temperature range that is well above the temperature at which sulfluramid sublimates (40 °C). This result warrants a reduced sulfluramid loss in the preparation of insecticidal baits. The preparation of the complex by kneading with molar ratio of 1:2 gave the highest yield of complex, about 64%, in relation to the theoretical maximum.

KEYWORDS: Sulfluramid; β-cyclodextrin; inclusion complex; DSC; TGA

1. INTRODUCTION

Cyclodextrins are cyclic molecules produced from starch that have received lately increased academic and industrial interest because of their ability to form inclusion complexes with a variety of chemical substances. Usually, the encapsulated substances present higher thermal and chemical stability and then have an increased resistance to damaging ambient factors, such as oxygen, light, and heat. Owing to these advantages, cyclodextrins (CDs) are used in various industrial applications, including the production of food, medicines, cosmetics, household products, agrochemicals, textiles, paper, chemical technology, analytical chemistry, and others (*1*−*6*).

There are many publications and patents covering the application of CDs in the formulation of agricultural products, for example, the formulation of fungicides, herbicides, insecticides, and stabilizers (*3*, *4*). The general aim is to obtain products with higher performance and higher added value.

The complexation of fungicides with CDs has conferred them stability, extending the period of effective action, and even has improved the product activity. Herbicides have been included in CDs resulting in formulations with lower toxicity, reduced unpleasant odor, and prolonged active life (*3*, *4*).

Sulfluramid is an active ingredient in insecticides commonly used for the control of cockroaches and ants (**Figure 1**). These insecticides use sulfluramid at a concentration of 3 g/kg, mixed with citric fruit pulps and soybean oil. The mixture of these materials is extruded to form pellets of the insecticide, which are usually called *baits*. As the mixture is extruded, there is considerable loss of sulfluramid, because this substance sublimates easily, starting at about 40 °C. In the conventional established technology for producing these pellets, the industry compensates the loss of sulfluramid by using an excess of 25% of this active ingredient. However, this alternative is costly since the price of sulfluramid is $300 U.S./kg (*7*).

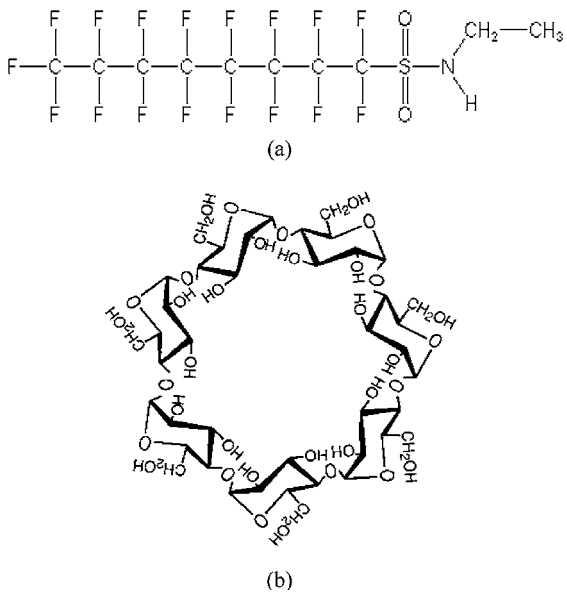

Figure 1. Chemical structure of (**a**) sulfluramid and (**b**) β-cyclodextrin.

In this work, we decided to investigate the molecular encapsulation of sulfluramid in cyclodextrin as an alternative to increase its thermal stability, because this could reduce the loss of sulfluramid at the insecticide extrusion step. This seemed a good idea because the added cost of complexation with CDs

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would be much lower than that of the loss of sulfluramid, since CD prices vary between $6 and $25 U.S./kg, depending on the CD type (*8*).

We present here data on the formation and thermal stability of the sulfluramid/β-CD inclusion complex, using at the preparation stage molar ratios of 1:1 and 1:2 (sulfluramid:β-CD) as physical mixtures and kneaded and coprecipitated products.

2. MATERIALS AND METHODS

2.1. Materials. Technical sulfluramid (MW 527.2 g/gmol), 95% pure, was supplied by Milenia Agro Ciencias S. A. (Brazil), and β-cyclodextrin (MW 1135 g/gmol) was acquired from Sigma Chemical Company Ltd-U.K. Analytical grade solvents and distilled water were used throughout this work.

2.2. Complex Preparation. Sulfluramid is practically insoluble in water, but it is soluble in methanol and in methanol−water mixtures with a high content of methanol. In consequence, to prepare the complex by the coprecipitation technique, relatively large volumes of water and methanol had to be used, to guarantee that sulfluramid would not precipitate after the mixture of their individual solutions of β-CD and sulfluramid.

Another special detail of the protocols we choose for preparing the complexes is that, except for the preparation called real physical mixture, all the solid products obtained by complexation were heated at 150 °C for 1 h, with the hope of volatizing the free sulfluramid.

2.2.1. Coprecipitation Technique. β-CD (0.925 mmol) was dissolved in water (120 mL) at 25 °C, with stirring. To this aqueous solution, sulfluramid (0.925 mmol), dissolved in methanol (30 mL), was added and the mixture was stirred for 24 h. Then, the solution was filtered, and the recovered precipitate was washed with methanol and water. The precipitate product was finally dried at ambient temperature (25 °C) for 24 h and then heated at 150 °C for approximately 1 h.

2.2.2. Kneading Technique. β-cyclodextrin (0.925 mmol) was kneaded with a 1 mL methanol:water solution (80:20), at ambient temperature, until homogenization (approximately 5 min). Then, sulfluramid (0.925 mmol) was added to the paste and kneading followed for a further period of 20 min. The resulting paste was dried at ambient temperature (25 °C) for 24 h and then heated at 150 °C for approximately 1 h. The methanol:water (80:20) solution was chosen because it is able to dissolve some of the sulfluramid present, while with less methanol sulfluramid solubility tends quickly to almost zero.

2.2.3. Physical Mixture Technique. β-cyclodextrin (0.925 mmol) and sulfluramid (0.925 mmol) were manually mixed, for a period of 10 min, and then dried and heated at 150 °C for approximately 1 h.

A real physical mixture was prepared as above but without any drying or heating of the product, which served for comparison with the heated products.

The above-described protocols have used equimolar quantities of sulfluramid and β-cyclodextrin. Another series of experiments was carried out with 1:2 (sulfluramid:β-CD) molar ratio, with the quantities being 0.925 mmol of sulfluramid and 1.850 mmol of β-CD.

2.3. Characterization Methods. *Thermogravimetric Analysis (TGA) and Derivative Thermogravimetry (DTG).* Samples (approximately 6 mg) were analyzed in a Shimadzu thermobalance, model TGA-50, under dynamic nitrogen atmosphere (20 mL/min) and heating rate of 10 °C/min using platinum crucibles. The temperature range was from 20 to 500 °C.

Differential Scanning Calorimetry (DSC). Aluminum capsules containing approximately 6 mg of samples were analyzed in a Shimadzu calorimeter, model DSC-50, under dynamic nitrogen atmosphere (20 mL/min) and heating rate of 10 °C/min, in the temperature range of 20−350 °C.

3. RESULTS AND DISCUSSION

3.1. Differential Scanning Calorimetry (DSC). Figure 2 shows the DSC curves for sulfluramid and β-cyclodextrin. The thermogram of sulfluramid presents two endothermic peaks: the first at 84.10 °C that corresponds to the melting point of sulfluramid and the second at 184.45 °C corresponding to the boiling point of sulfluramid. For β-CD, there are two stronger endothermic peaks at 85.30 °C and 320.57 °C associated with the loss of humidity and thermal degradation of β-CD, respectively. In addition, at 218.32 °C there is a small endothermic peak that occurs without any mass loss, and it is thought to be associated with a reversible molecular transformation of an unknown nature (*9*).

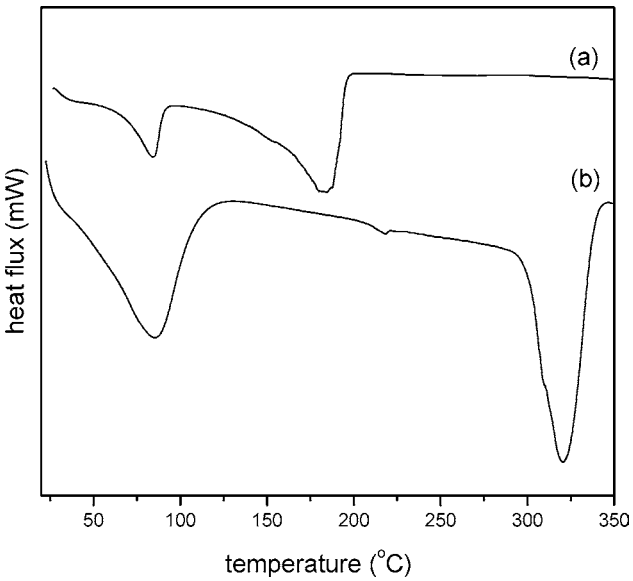

Figure 2. DSC thermogram for (**a**) sulfluramid and (**b**) β-cyclodextrin.

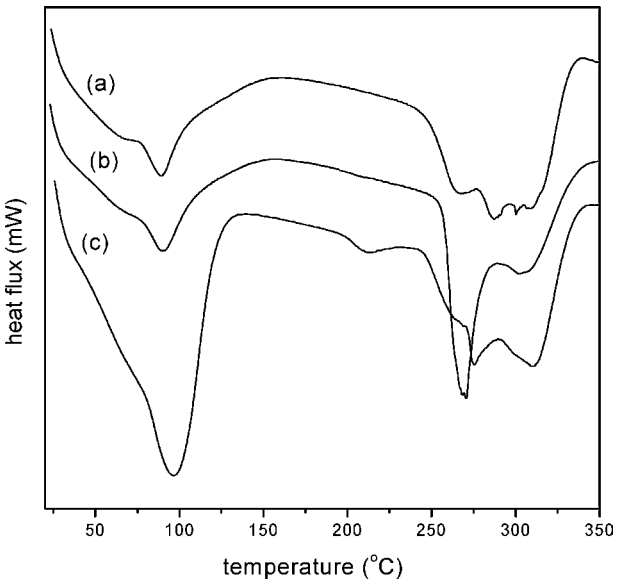

Figure 3. DSC curves for the products obtained from the complex preparation techniques: (**a**) coprecipitation, (**b**) kneading, and (**c**) physical mixture plus heating, at 1:1 (sulfluramid:β-CD) molar ratio at the preparation stage.

The DSC thermograms obtained for the products from the complex preparation techniques, for sulfluramid:β-CD molar ratios 1:1 and 1:2 at the preparation stage are shown in **Figure 3** and **Figure 4**, respectively.

As the sulfluramid melting point is close to the boiling point of water, their endothermic peaks overlap in the temperature range of 80−100 °C, and it is not possible to distinguish the amount of sulfluramid lost in this temperature range. However, comparing the DSC curves for pure sulfluramid (**Figure 2**) and the complexation products (**Figures 3** and **4**) in the temperature

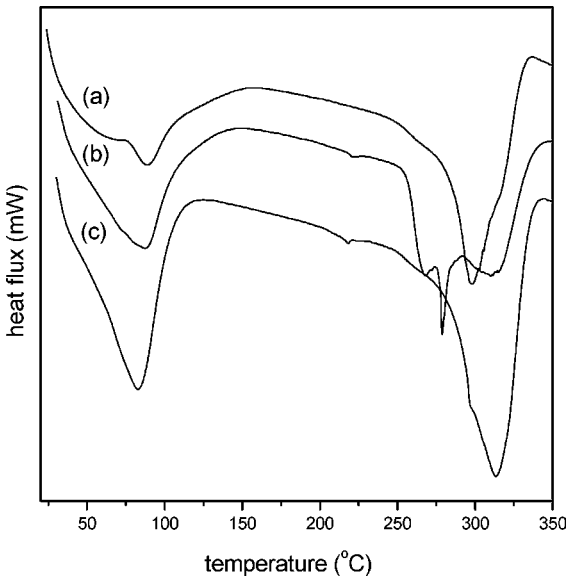

Figure 4. DSC curves for the products obtained from the complex preparation techniques: (**a**) coprecipitation, (**b**) kneading, and (**c**) physical mixture plus heating, at 1:2 (sulfluramid:β-CD) molar ratio at the preparation stage.

range 100−200 °C, in which sulfluramid is expected to volatilize, it can be observed that the endothermic peak has decreased as we pass from the pure sulfluramid to the complexation products. This result is interpreted as a clear indication that the formation of the inclusion complex sulfluramid/β-cyclodextrin has occurred. In addition, it can also be observed that the simple physical mixing of the substances plus heating of the product at 150 °C also produces the complex.

At a higher temperature range in **Figures 3** and **4**, the complexation product thermograms show an endothermic peak that starts at a temperature lower than the degradation of pure β-CD, about 250 °C, and overlaps with the thermal degradation of β-CD (peak at 320.57 °C, according to **Figure 2**). This result indicates that the sulfluramid/β-CD complex starts to absorb heat at an increased rate at about 250 °C, before β-CD is thermally degraded. This absorbed energy will lead to the release of the sulfluramid from the complex, at a temperature that can be better determined with the results of the thermogravimetric analysis given below.

3.2. Thermogravimetric Analysis (TGA) and Derivative Thermogravimetry (DTG). Figure 5 shows the thermogravimetric analysis of sulfluramid and β-cyclodextrin.

For pure β-cyclodextrin, the first stage of weight loss in the thermogravimetric curve occurs in the temperature range of 29−107 °C and corresponds to the dehydration of the β-CD molecule. The weight loss in this stage was 8.6%. The β-CD used in this test was dried beforehand at 150 °C, and the data shows that the amount of water still bound to β-CD was 5.4 mol of water/mol of β-CD. According to published data (*10*), 11 or 12 molecules of water are usually found inside the cavity of the β-CD, but this amount can change, depending on the relative humidity. The second weight loss stage for β-CD occurs in the range of 300−500 °C, with a mass reduction of 79%, and is related to the thermal decomposition of β-CD.

In pure sulfluramid, **Figure 5** shows that there is a single less sharp weight loss stage, starting at about 40 °C and extending up to 181 °C, a temperature at which all sulfluramid sample has been totally volatilized.

Figures 6 and **7** show the thermogravimetric curves for the products obtained with each of the complex preparation techniques and at two molar ratios of sulfluramid:β-CD, 1:1 and 1:2, used in the preparations. Three weight loss stages can be identified in these curves, at progressively higher temperature ranges, which correspond to (i) up to about 100 °C, dehydration, (ii) above 270 °C, loss of the encapsulated sulfluramid, and (iii) above 300 °C, thermal decomposition of β-cyclodextrin.

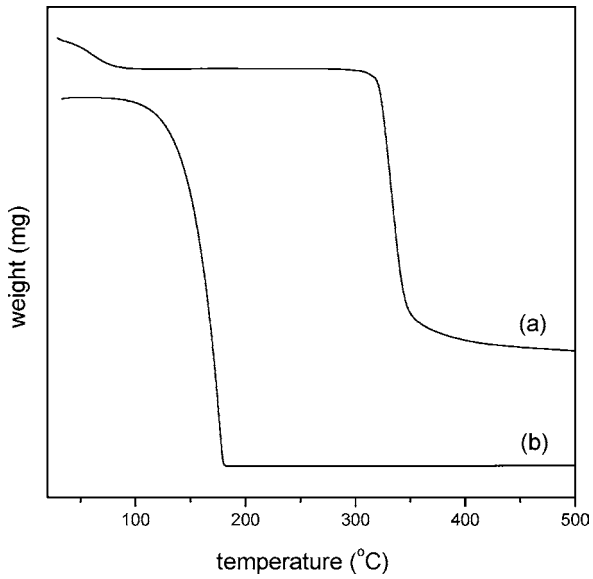

Figure 5. Thermogravimetric curves of the pure substances: (**a**) β-cyclodextrin, (**b**) sulfluramid.

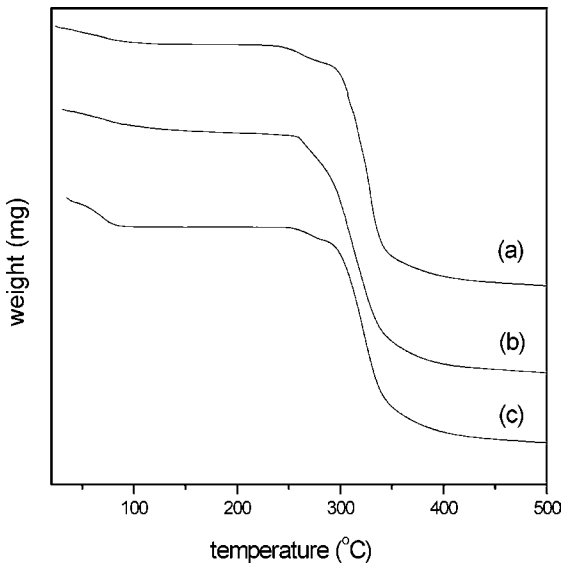

Figure 6. TGA thermograms of products obtained from the complex preparation techniques: (**a**) coprecipitation, (**b**) kneading, and (**c**) physical mixture plus heating, at 1:1 (sulfluramid:β-CD) molar ratio at the preparation stage.

The second stage of the weight loss curves in **Figures 6** and **7**, which is associated with the loss of sulfluramid from the inclusion complex, is a little different for each of the products from the complex preparation techniques but occurs in all cases, before the thermal decomposition of β-CD that, as was established from **Figure 5**, starts at about 300 °C. Applying derivative thermogravimetry to the data of **Figures 6** and **7** (data not shown), a small peak appears around 270 °C.

The real physical mixture (no heating) and the physical mixture, which was heated at 150 °C, are compared in **Figures 8** and **9**. The product of the real mixture first loses more water and free sulfluramid up to 140 °C, and then its weight stabilizes

Table 1. Weight Composition and Other Mass Indices Obtained for the Products of Sulfluramid/β-CD Complexation

complex preparation technique	molar ratio of sulfluramid:β-CD used in the preparation	sulfluramid in the product (%)	β-CD in the product (%)	yield of product (complex + free β-CD) (%)	complex[a] in the product (%)	yield of complex in relation to the theor max (%)
coprecipitation	1:1	8.98	91.02	43.96	28.30	12.44
	1:2	6.92	93.08	53.21	21.85	19.57
kneading	1:1	22.81	77.19	80.44	71.94	57.87
	1:2	15.58	84.42	77.95	49.13	64.44
physical mixture	1:1	9.38	90.62	56.19	29.59	16.62
	1:2	4.92	95.08	66.74	15.49	17.39
real physical mixture	1:1	34.79	65.21	100[b]	14.44	14.44
	1:2	21.06	78.94	100[b]	11.81	19.87

[a] It was assumed that the sulfluramid/β-cyclodextrin complex had a molar ratio of 1:1. [b] Includes water (humidity) and free sulfluramid.

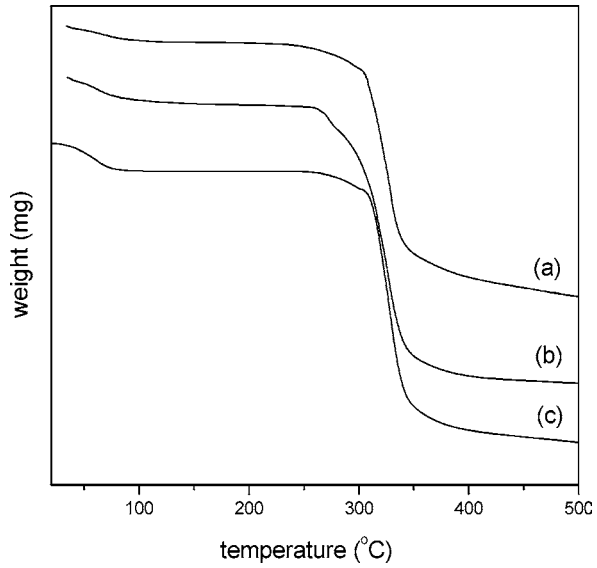

Figure 7. TGA thermograms of products obtained of (**a**) coprecipitation, (**b**) kneading, and (**c**) physical mixture plus heating techniques, at 1:2 (sulfluramid:β-CD) molar ratio at the preparation stage.

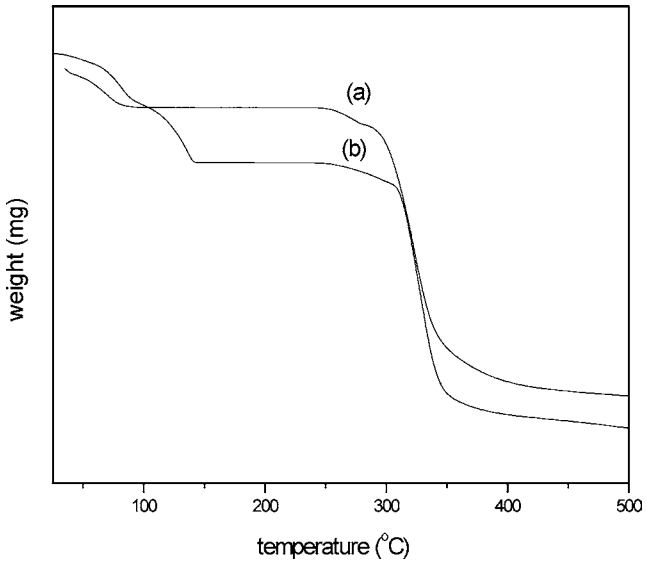

Figure 8. TGA thermograms of (**a**) physical mixture technique plus heating and (**b**) real physical mixture (no heating), at 1:1 (sulfluramid:β-CD) molar ratio at the preparation stage.

up to 250 °C. From 250 to 300 °C, both mixture products loose weight, associated with the release of sulfluramid from the complex. This result demonstrates that the complex is formed

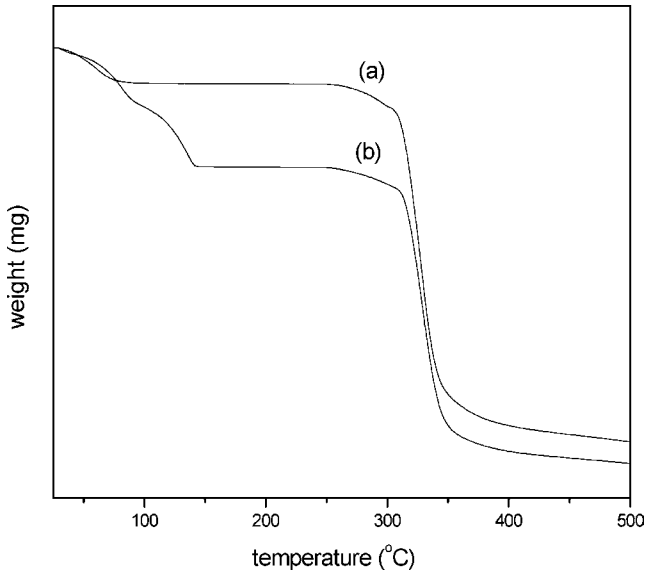

Figure 9. TGA thermograms of (**a**) physical mixture technique plus heating and (**b**) real physical mixture (no heating), at 1:2 (sulfluramid:β-CD) molar ratio at the preparation stage.

in the physical mixture by the application of temperatures above the melting point of sulfluramid (84.10 °C), either during heating at 150 °C or during the thermogravimetric analysis, because the sulfluramid in the molten state gets entrapped.

The mass of the product, dried at 150 °C, obtained from the complex preparation techniques was measured and the product yield is reported in **Table 1**. The product was considered to be formed of free β-CD and the sulfluramid/β-CD complex. The percentage of complex in the product was calculated assuming a 1:1 (sulfluramid:β-CD) molar ratio and the mass of complexed sulfluramid was taken as the TGA mass loss between 250 and 300 °C. The results are shown in **Table 1**. The yield of complex obtained for each preparation technique in relation to the theoretical maximum that could be obtained is also shown in **Table 1**.

Table 1 shows that the coprecipitation technique as used in this work has led to the least valuable results since it gave the lowest yields of product and very low complex yields, probably because of the relatively great amount of liquid and the washing step used in the preparation. As this technique generates residual liquid effluents and gave poor results, it is the least indicated for the industrial preparation of the sulfluramid/β-CD complex to be used in the insecticide.

The real physical mixture (no heating) and the physical mixture, which was heated at 150 °C, have produced the

complex at a relatively low yield, which is nevertheless still comparable to the coprecipitation technique.

The best set of results was obtained with the kneading technique. For kneading with molar ratio of 1:1 (sulfluramid:β-CD), the yield of product was highest 80.44%, the percentage of complex in the product was 71.94%, and the yield of complex obtained in relation to the theoretical maximum was the second best, 57.87%. For kneading with molar ratio of 1:2 (sulfluramid:β-CD), the percentage of complex obtained in relation to the theoretical maximum was the highest, 64.44%. In addition, the kneading technique is relatively simple, it uses a very small amount of solvents, and the product can be quickly and easily dried.

Therefore, the kneading technique for preparing the sulfluramid:β-CD complex has the highest potential for industrial application in the production of the insecticidal baits, because its highest complex yield would reduce to the greatest extent the loss of sulfluramid. The entrapped sulfluramid will be released from the complex only at high temperatures, much higher than encountered in the pelleting of the insecticidal baits. Hence, the reduction of volatility of sulfluramid by complexation with β-CD will lead to a more economical industrial process. However, since the yield of complex in relation to the theoretical maximum has reached only 64.44%, for industrial application the product of kneading should not be dried at 150 °C to avoid the loss of free sulfluramid. Also, because the complex yield increased with an increased ratio of β-CD, higher ratios of sulfluramid:β-CD, greater than 1:2, could be advantageous.

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