

TECHNOLOGICAL QUALITY DETERMINATION OF PHARMACEUTICAL DISINTEGRANT BY DSC COOLING AND DSC PHOTOVISUAL

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A number of disintegrants are available on the market. They improve tablets' disintegration. The objective of this work is the comparison of the technological quality parameters of disintegrants using different analytical techniques. Three batches of disintegrants and their binary mixtures (water:disintegrants) were investigated. Cooling experiments were used from –30 up to 200°C. The data obtained showed calorimetric differences between the samples. In the binary mixtures water showed different crystallization behaviour from the one found in the literature. According to the results DSC technique helped the quality control of different disintegrants.

Keywords: crystallization water, disintegrants, DSC cooling, DSC photovisual and particles size

Introduction

A number of disintegrants, known as superdisintegrants are available on the market. These disintegrants markedly improve tablets disintegration, but their efficiency depends on the physico-chemical characteristics of the tablet formulation [1].

Croscarmellose sodium is a cross linked polymer of carboxymethyl cellulose sodium. Crosslinking makes it an insoluble, hydrophilic, highly absorptive material, resulting in excellent swelling properties and its unique fibrous nature gives an excellent water wicking capabilities. Croscarmellose sodium provides superior drug dissolution and disintegration characteristics, thus improving bioavailability of formulations [2].

Sodium starch glycolate is a substituted derivative of potato starch. Typically, commercial products are also cross-linked. Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling [3].

Thermal analysis is extensively used analytical technique to study the sample properties as a function of temperature. Macêdo *et al.* showed applications of different thermal analysis techniques in pharmaceutical technology [4–8] and in parameters evaluation of drug behaviour in biological fluid submitted to freeze-thaw studies [9].

The objective of this work is the comparison of the technological quality parameters of croscarmellose sodium (CRC) and sodium starch glycolate (GAS) disintegrants using Karl-Fischer (water content), optical microscopy (particles size), infrared spectroscopy (identification of functional groups), DSC cooling/heating and DSC photovisual (absorption of water, crystallization peak and decomposition) techniques.

Experimental

Material and methods

The samples were constituted using three batches of disintegrants: CRC and GAS named: CRC02 (batch=831) and GAS02 (batch=3003), donated by Pharmaceutical Technology Laboratory, from Federal University of Paraíba (UFPB); and CRC01 (batch=8206), CRC03 (batch=8972), GAS01 (batch=19080) and GAS03 (batch=89090), donated by Industrial Pharmaceutical Laboratory of State of Paraíba (LIFESA).

Karl-Fischer titration

Water content was determined using Karl-Fischer titration, model Titroline KF from Schott. To calibrate the Karl-Fischer apparatus HYDRANAL Water Standard 1.0 equipment was used. At about 100 mg of sample was dissolved in methanol

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(analytical) and then was placed to a PYREX[®] glass flask. Free water present in sample was titrated during 15 min, with Karl-Fischer reagent from Quimex, without pyridine, in a flow of 100 $\mu\text{L min}^{-1}$.

Optical microscopy

Three batches of CRC and GAS disintegrants were analyzed in which at about 500 particles were counted using optical microscopy. During the test different particle forms were observed.

According to their sizes (μm) the particles were classified in different groups by statistical treatment.

Infrared spectroscopy

Absorption spectra in the infrared region were recorded in a PerkinElmer model FTIR-1750 spectrometer using KBr pellets (0.5 mg of sample/100 mg of KBr).

DSC cooling

Binary mixtures were prepared mixed using CRC and GAS disintegrants and deionized water.

100 mg of samples were weighted in watch glasses in a Shimadzu model AEL-40SM balance. The samples were placed in a spot plate for test and deionized water with 2, 4, 6, 8, 12, 16, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65 and 70% (*m/v*) ratios were added. After mixing with a spatula 2-4 mg samples were weighted in aluminum pans which were then hermetically closed and analyzed by DSC cooling.

Calorimetric curves of CRC and GAS disintegrants and their binary mixtures were recorded in a Shimadzu model DSC-60 calorimeter coupled to a model EK₉₀/SH Peltier system. 5°C min^{-1} cooling rate down to -30°C was used. Then, the samples were heated at 5°C min^{-1} heating rate up to 200°C in 50 mL min^{-1} nitrogen flow to keep dry the apparatus.

DSC photovisual

DSC curves were recorded by using a Shimadzu model DSC-50 calorimeter coupled to photovisual system, in the 25–500°C temperature range under nitrogen with constant flow of 50 mL min^{-1} .

Results and discussion

Karl-Fischer titration

Determination of water content, using Karl-Fischer titration method is not sufficient to predict the half-life of the product. Water content present in pharmaceutical samples gives a good indication on the degrada-

tion process that may occur during storage of the products [10].

CRC and GAS disintegrant samples were subjected to Karl-Fischer titration in order to determine the water content of the samples. Mean and standard deviation of CRC samples were: sample CRC01 5.55%, sample CRC02 7.20% and sample CRC03 6.83%. Mean and standard deviation of samples with GAS were: sample GAS01 6.85%, sample GAS02 4.72% and sample GAS03 4.28%.

According to [2, 3] all disintegrants samples fulfil the pharmacopoeian requirements.

Particle size

Particle frequency analysis of disintegrant batches by mean diameter showed that 95.4% of the CRC01 particles has 89.7 μm , 97.0% of the CRC02 particles has 74.7 μm and 92.6% of CRC03 has 49.8 μm of diameter, respectively. 92.6% of GAS01 particles has 16.4 μm , 97.2% of GAS02 has 20.4 μm and 83.4% of the GAS03 particles has 20.1 μm of diameter, respectively (Fig. 1).

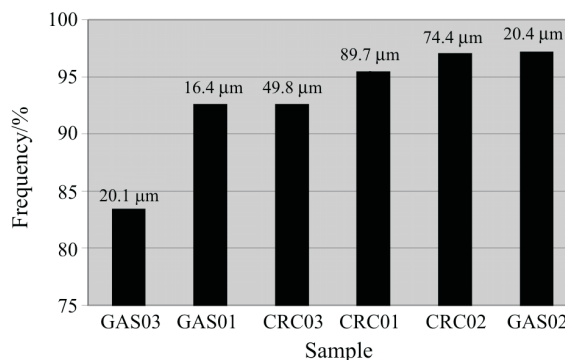


Fig. 1 Particle size frequency for medium diameter of disintegrant samples

According to [2, 3] the particles size distribution of disintegrants like croscarmellose sodium is comprehended in 44.5–73.7 μm . A hundred percent of sodium starch glycolate particles should have less than 106 μm in size. The average particle size distribution is 35–55 μm for Explotab[®].

So, the obtained data are not in agreement with the literature, except for CRC03 batch.

Infrared spectroscopy

The absorption bands in the IR spectra were representative for the croscarmellose sodium and sodium starch glycolate disintegrants.

Thermal analysis

DSC cooling

Figures 2A and B show the DSC cooling curves of croscarmellose sodium and sodium starch glycolate, respectively.

In Fig. 2A1 the croscarmellose sodium samples are without water. They contain only residual water. There are no signals for melting of ice or crystallization of water. The endothermic peaks are characteristic for the evaporation of adsorbed water. Endothermic processes occurred in different temperature intervals for the croscarmellose sodium samples: 81°C for CRC01, 170°C for CRC02 and 141°C for CRC03, respectively.

Figure 2A2 shows that the first crystallization peak of croscarmellose sodium samples can be observed in the presence of 40, 40 and 30% of water for CRC01, CRC02 and CRC03 samples. This process took place at -25.5°C for CRC01, at -22.8°C for CRC02 and at -26.6°C for CRC03, respectively. Endothermic peaks for samples CRCM01, CRC02 and CRC03 appeared at 142, 80 and 103°C, respectively.

In Fig. 2A3 it can be observed that croscarmellose sodium samples contain at about 70% of additional water, exhibiting crystallization/melting peak. Crystallization peak temperatures of water were -26.9°C for CRC01, -27.4 and -24.7°C for sample CRC03. In case of CRC02 no crystallization peak was observed. For CRC03 a double crystallization peak is representative. The temperatures of the endotherms of CRC01, CRC02 and CRC03 samples are 58, 142 and 89°C, respectively.

According to Fig. 2B1 the sodium starch glycolate samples are without water. They contain only residual water. They do not present crystallization and melting peaks of water and ice. The endothermic peaks are characteristics for the evaporation of absorbed water. The peak temperatures of the observed endotherms are of the sodium starch glycolate samples are 72°C (GAS01), 140°C (GAS02) and 63°C (GAS03).

Figure 2B2 shows that the first crystallization peak in sodium starch glycolate samples was observed in the presence of 40, 40 and 65% water for GAS01, GAS02 and GAS03 samples, respectively. This process occurred at -26.7°C (GAS01), -26.4°C (GAS02) and -27.1°C (GAS03). Endothermic peak

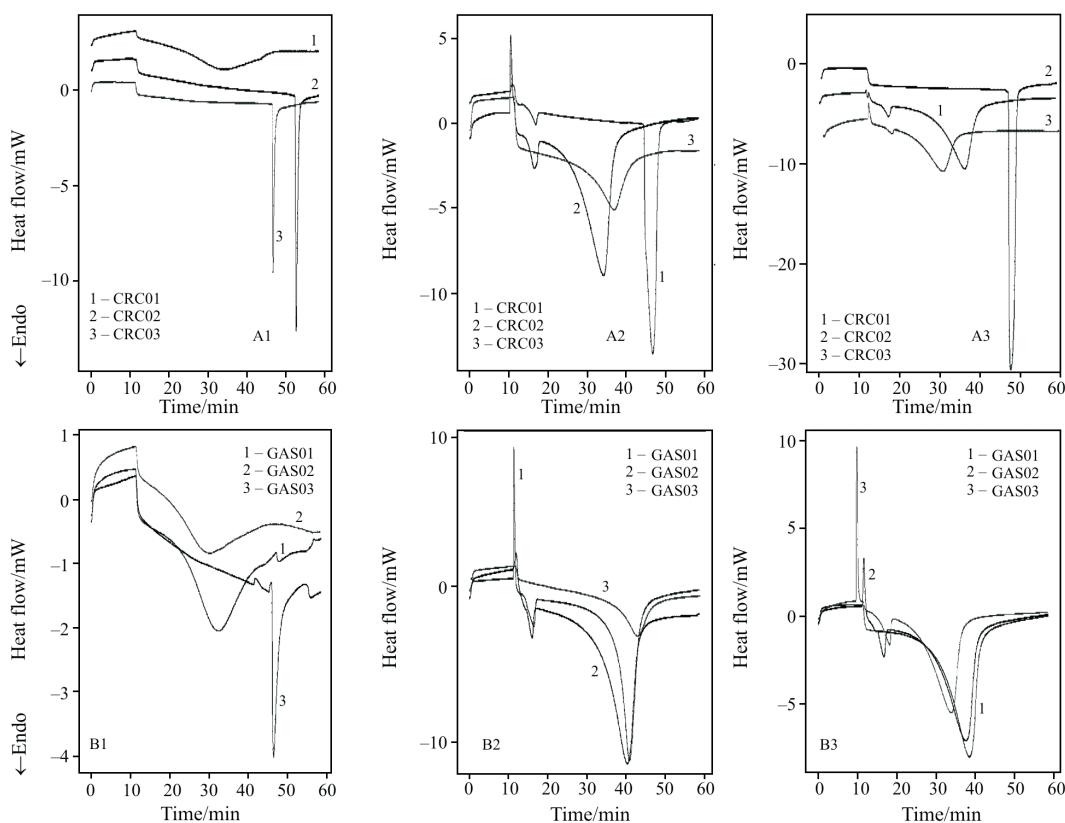


Fig. 2 DSC cooling curves: A1 – croscarmellose sodium samples without water, A2 – croscarmellose sodium samples with 40% (CRC01 and CRC02) and 30% (CRC03) of water and A3 – croscarmellose sodium samples with 70% of water; B1 – sodium starch glycolate samples without water, B2 – sodium starch glycolate samples with 40% (GAS01 and GAS02) and 65% of water (GAS03) and A3 – sodium starch glycolate samples with 70% of water

appeared for GAS01, GAS02 and GAS03 samples at 112, 109 and 67°C, respectively.

In Fig. 2B3 it was observed that sodium starch glycolate samples containing at about 70% of additional water presented crystallization/melting peak. Crystallization temperatures peaks for water were -27.1°C for GAS02 and -19.1°C for GAS03 samples, respectively. Sample GAS01 did not show crystallization peak. The endotherm peak temperatures of GAS01, GAS02 and GAS03 samples were 101.3, 96.9 and 79.4°C .

DSC data revealed that almost in all ratios (m/v) the water crystallization peak could be observed indicating the presence of free water, which is probably due to the excess of water in the mixtures. This parameter was used to compare the differences among the batches. Consequently the different disintegrants do not have a uniform composition.

In agreement with the curves showed for binary mixtures it can be observed that there is not a linear repetition in the peak shape. This lack of repetition can be associated to the lack of uniformity in the samples. Those results indicate the differences among the batches originated from different manufacturers. This difference can result variation in particles size, which leads to different thermal behaviour.

DSC photovisual

Figure 3 presents pictures CRC01, CRC02 and CRC03 croscarmellosodium samples without water. They showed various phase transition processes with complete decomposition at 260°C (A), 270°C (B) and 270°C (C). The first phase transition corresponds to the mass loss and colour changes of samples from 210 (samples A and B) and 200°C (sample C).

Figure 4 presents the pictures of GAS01, GAS02 and GAS03 sodium starch glycolate samples without water. The samples showed various phase transition processes accompanied by complete decomposition at 280°C (A), 280°C (B) and 285°C (C). The first phase transition corresponds to a discreet movement of the sample, it is observed in the extremities and little dark points inside the sample, according to indication of the arrows, between $210\text{--}220^{\circ}\text{C}$ (A). Sample B presents the first phase transition that corresponds to mass loss and colour change of the samples at 180°C and showed the second one at 270°C which is representative to the expansion of the sample. It continues with the formation and evaporation of bubbles, according to the indication of the arrow. Sample C presents a first phase transition for mass loss and colour change of the samples occurring at 200°C and showed little dark points inside the sample, according to indication of the arrows, occurred at 225°C . At 285°C the expansion of the



Fig. 3 DSC photovisual of croscarmellose sodium samples without water: A – CRC01 samples, B – CRC02 samples and C – CRC03 samples

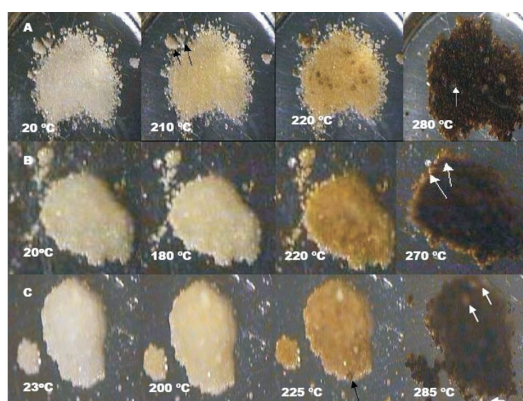


Fig. 4 DSC photovisual of sodium starch glycolate samples without water: A – GAS01 samples, B – GAS02 samples and C – GAS03 samples

sample was observed followed by bubbling according to the indication of the arrow.

Photovisual DSC studies showed meaningful differences in thermal behaviour between the three batches of croscarmellose sodium and the sodium starch glycolate disintegrants.

The technological quality parameters of the studied disintegrants obtained by infrared spectroscopy and Karl-Fischer titration method were in agreement with the specifications of the pharmaceutical industry. However, particle size distribution data and DSC analysis showed significant differences between the samples, which related to the water absorption capacity. This is an important factor since disintegrants may be used both in direct compression and wet-granulation processes.

Conclusions

The results of this study showed that only DSC cooling/heating technique was representative for the technological quality properties of different disintegrant samples.

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