2007 International Nuclear Atlantic Conference - INAC 2007
Santos, SP, Brazil, September 30 to October 5, 2007
ASSOCIAÇÃO BRASILEIRA DE ENERGIA NUCLEAR - ABEN
ISBN: 978-85-99141-02-1

STUDY OF THEOPHILLINE STABILITY ON POLYMER MATRIX

Kiriaki M. S. Rodrigues, Duclerc F. Parra, Maria José A. Oliveira, Oscar V. Bustillos, Ademar B. Lugão

Instituto de Pesquisas Energéticas e Nucleares (IPEN / CNEN - SP)
Av. Professor Lineu Prestes 2242
05508-000 São Paulo, SP
strassacapa@uol.com.br

ABSTRACT

Theophylline is a bronchodilator, commonly known and used as a drug model in the development of pharmaceutical formulations. The stability of the drug and the matrix, scope of this study, was evaluated in the solid formulation. Polymeric matrix based on PHB containing the drug (theophylline) was prepared and submitted to radiation sterilization at different doses of: 5, 10, 20 and 25 kGy using a Cobalt- 60 source. The modified drug release of theophylline sterilized tablets has been studied. Modern techniques of HPLC (High Pressure Liquid Chromatography), DSC (Differential scanning calorimetry) and TGA (Thermogravimetry analysis) were employed. The results have shown the influence of sterilization by radiation process in both the theophylline and the polymeric drug delivery matrix samples. The increasing of polymeric matrix crosslinking under radiation conditions retards the drug release while the theophylline structure is stable under the radiation.

1. INTRODUCTION

Polyhydroxybutyrate (PHB), structure presented at figure1, and its copolymers are melt-processable semi-crystalline thermoplastics made by biological fermentation from renewable carbohydrate feedstock and is biodegradable. Although quite stable under everyday conditions they degrade slowly in the body and when composted or in landfill sites.

Their chemical resistance is somewhat limited as they are attacked by acids and alkalis and dissolve in chlorinated solvents.

PHB homopolymer is a stiff and rather brittle polymer of high crystallinity, whose mechanical properties are not unlike those of polystyrene, though it is less brittle and more temperature resistant. Also, its degradation rate is quite high at its normal melt processing temperature.

Beyond its thermoplastics characteristics, that allow it to be molded or transformed in films for many applications, it is also biocompatible [1,2,3] with potential for medical applications, as sutures, support for tissues culture for implants, drug encapsulation for controlled release. [2,3,4]. The polymer is regarded as non-toxic, and the monomer is a normal constituent of human blood.

Theophylline is a methylxanthine, drug used in therapy for respiratory diseases such as COPD or asthma under a variety of brand names. As a member of the xanthine family, it bears structural and pharmacological similarity to caffeine (fig.2). The use of modified

release systems of theophylline is practical owing to its narrow therapeutic index, so its use must be monitored to avoid toxicity. It can cause nausea, diarrhea, increasing of heart rate, arrhythmias and CNS excitation. Its toxicity is increased by erythromycin, cimetidine and fluoroquinolones.

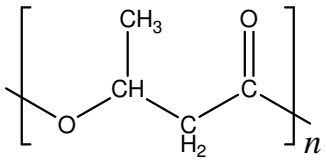

Figure.1: Chemical structure of PHB

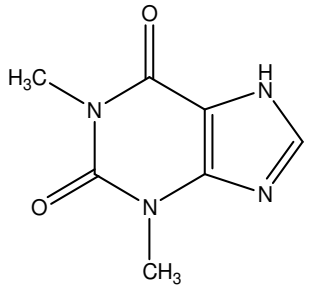

Figure 2: Chemical structure of theophylline

Tablets made with PHB matrix can be sterilized with gamma radiation. The aim of this work is the study of the effects of gamma radiation in the theophylline structure and in the drug release profile.

2. MATERIALS AND METHODS

2.1 HPLC (High Pressure Liquid Chromatography) assay

The determination had been carried through a LC-MS/MS system composed of mass spectrometer quadrupolar API4000TM, Applied Biosystem/MS/MDS Sciex, concord, CA), equipped with cell of collision LINAC® ionization turbo source VTM operated in the TurbolonSpray® way (electrospray), generator of gases PEAK Generator (PEAK Scientific Instruments, Scotland) and infusion bomb Harvard Apparatus (Holiston, MA, EUA). The spectrometer of masses was connected to a high efficiency liquid chromatograph, Agilent 1100 Series (Agilent Technologies, Waldborn, AL), equipped with quaternary bomb.

2.2 Calorimetric analysis

Samples of theophylline had been radiated with radiation gamma in doses of 5, 10, 20 and 25 kGy and the thermal properties were studied through the tests of DSC (Differential scanning calorimetry) and TGA (thermogravimetry).

2.2.1 Thermogravimetry by TGA

The thermal stability of samples of theophylline was determined by TGA techniques. In the TGA/SDTA-851e device Metter-Toledo the TGA assays had been carried, with samples of 10mg, under the conditions: heating of 30 at 650°C, with rate of heating of 5 º C/min, in N_2 atmosphere.

2.2.2 DSC (Differential scanning calorimetry)

With the DSC tests the temperatures of melting had been obtained. The assays had been carried through in the DSC-822e Metter-Toledo device, with samples of 10mg, under the following conditions: heating of -50 ° C at 200° C, with rate of heating of 10° C/min, in inert atmosphere of N_2.

2.2. 3 Dissolution assay

Preparation of the polymeric matrix processed the binary complex using 20% of theophylline and 80% of PHB following: 1)Solubilization of the compounds in agitating plate with heating (Corning PC-320) at temperature of 50 °C during 1 h; 2) evaporation of solvent in Rotaevaporator (Tecnal TE-210); 3) The drying of complexes was made in greenhouse with air circulation (Fabbe) during 12 h; 4) triturating in mill of knives (IKA – A11 basic) and 5) addition of the excipient and submitted to the compression.

The formulations used were: 500mg of complex, 250mg of cellulose microcrystalline PH 102 (Blanver). The tablets were submitted to cobalt-60 gamma radiation 10 kGy dose and 20 kGy and in sequence to dissolution assay.

The dissolution assay was made in Logan D800 - Dissolution tester (Logan Instruments Corp.) in accordance to the American Pharmacopeia (USP XXVIII): display 2 (paddle), 50 rpm, water, 900mL at 37°C , totalizing twenty and four hours of assay.

The quantification of the dissolved drug was carried out in spectrophotometer UVVIS (Beckman Coulter – DU 640), at 272 nm wavelength, in reference to calibration curve constructed.

3. RESULTS AND CONCLUSIONS

3.1 HPLC (High Pressure Liquid Chromatography) assay

In positive way ESI, the ion m/z 181,2 corresponds to theophylline molecule. The peaks at m/z 124 (123 + 1H+) , 96 (95+1), 69 (68+1) and 41,9 (40 +1) are typical fragments of Theophylline. The same spectrum of fragments was obtained to the radiated samples. It is observed that with the irradiation, the 181 ion is persistent, what characterizes the stability of the molecule under radiation conditions.

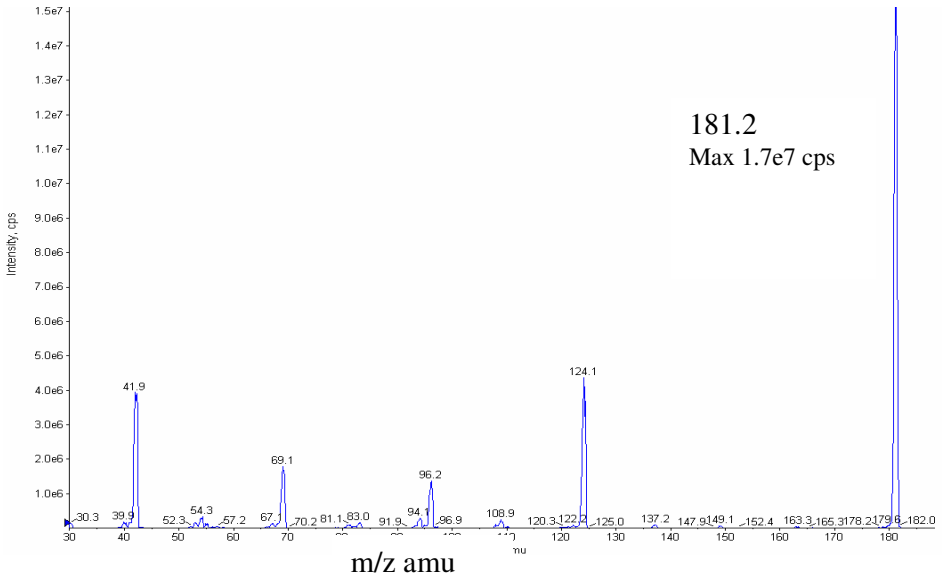

Figure 3: Mass spectra of theophylline obtained by HPLC MS/MS

3.2 Thermogravimetry by TGA

The DTGA (derivate thermogravimetry) profiles are shown in the fig.4. The curves presented differences in the values of temperatures of decomposition onset of the radiated samples in relation to theophylline not radiated.

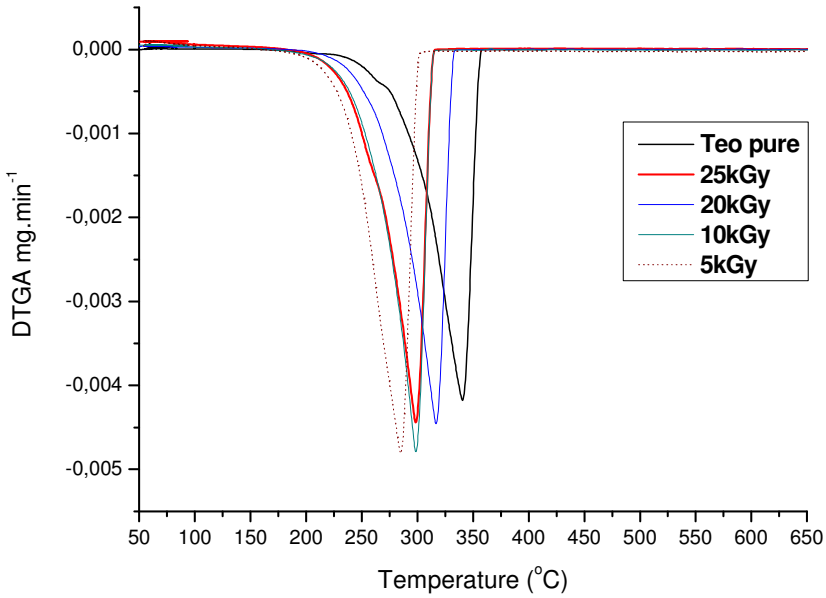

Figure 4: Results of theophylline TGA assay

3.3 DSC (Differential scanning calorimetry)

Figure 5 presents the DSC curves of theophylline samples (6-14mg) after radiation comprising 5 to 25 kGy. The melting points of the samples were considered the same of the original drug (276ºC) with variation at around ± 1ºC. Considering the DSC melting in the same temperature interval of T_{onset} of decomposition, it is observed that the theophylline melts under decomposition.

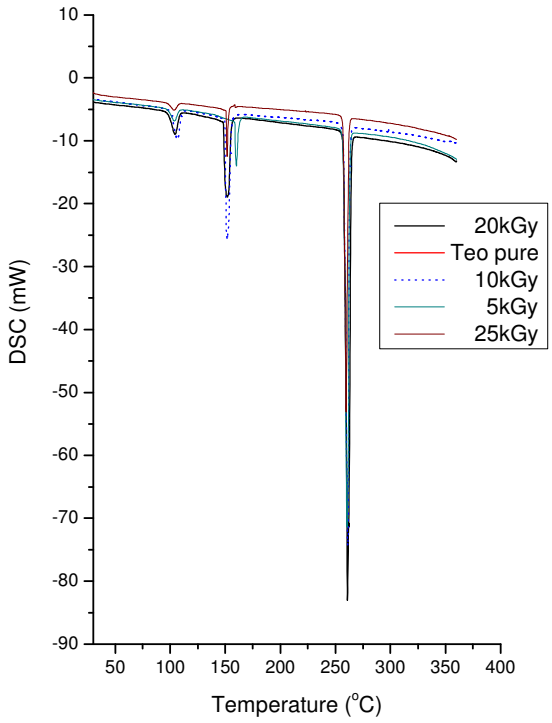

Figure 5: Results of theophylline DSC assay

In table 1 are reported the values of T_{onset}, T_{max} (temperature of maximum decomposition), T_{endset} and T_{m1} (melting temperature). It is verified that the samples melting occurs while decomposition starts then theophylline fusion occurs under decomposition. The variation of T_{onset} do not reveals difference in stability.

Table 1: Temperatures of the main events in TGA and DSC analysis

Dosage of radiation (kGy)	T_{onset} (ºC)	T_{max} (ºC)	T_{endset} (ºC)	T_{m1} (ºC)
0	259,6	335,0	341,8	277,4
5	252,2	291,4	298,0	277,1
10	263,1	305,0	310,0	276,1
20	276,9	323,6	327,3	276,0
25	261,1	306,9	310,4	275,4

Pina et al [5] reported theophyline DSC results showing its melting in the temperature interval of the decomposition and was observed melting shift in the theophylline complex with beta-cyclodextrin.

According to Wesolowski et al [6] the heating rate and mass of the sample influence the thermal decomposition of the purines, like theophylline. The author reported, in the similar condition of analysis, the decomposition of theophylline in the interval of 195-540°C while the melting point is at around 270-274°C.

3.4 Dissolution assay

The results obtained in dissolution assay are shown in figure 7. The irradiated samples retain the drug in comparison of the matrix not irradiated.

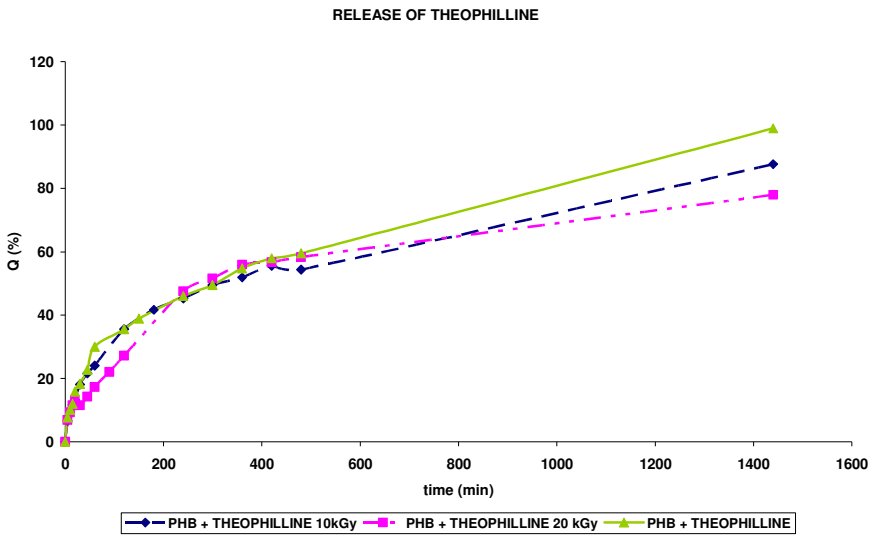

Figure 7: Release of theophylline in tablets made with polymeric matrix

In accordance with results obtained in dissolution assay is verified that the irradiated tablets present retardation in the drug release, when compared with the tablets that they had not received radiation, probably, to an increase of the reticulation of the polymeric matrix, having, thus, modification of the profile of dissolution of the same. The drug is stable under radiation conditions (10-20 kGy) owing to the strong resonance effect on the xanthine structure of the molecule.

ACKNOWLEDGMENTS

The authors thank to CNPq, IPEN/CNEN, FAPESP end CAPES.

REFERENCES

1. J. Borsa, "Irradiation Facilites: Machine Source Options and Considerations", *Food Irradiation Process Control School*, **11**, (1997).
2. E. Chielini; P. Cinelli; A. Corti. And E.R. Kenaway, **"**Composite films based on waste gelatin: thermal–mechanical properties and biodegradation testing**"** *Polymer Degradation and Stability*, **73,** pp.549-555 (2001).
3. S. J. Holland.;B. J. Tighe T; P. L. Gould. "Polymers for biodegradable medical devices. The potential of polyesters as controlled macromolecular release systems.*"* *Journal of Controlled Release*, **4**, pp. 155-68 (1986).
4. D. W. Cllegg.; A. Collyer. *Irradiation effects on Polymers*. Elsevier Applied Science, (1999).
5. M. E. Pina; F. Veiga. "The influence of diluent on the Release of Theophylline from Hydrophyilic Matrix Tablets", *Drug development and industrial pharmacy*, **26(10)**, pp.1125-1128 (2000).
6. W. Wesolowski and P. Szy. "Thermal decomposition of purine derivatives used in medicine", *Journal of Thermal Analysis and Calorimetry,* **65**, pp.599-605 (2001).