The use of polyhydroxybutyrate (PHB) matrices and their blends with polyetilenoglycol (PEG) in controlled release of theophylline

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Polyhydroxybutyrate (PHB) is considered a biodegradable, biocompatible and non-toxic polymer. PHB matrix has been discussed as systems for the controlled release of drugs. Theophylline as a methylxanthine drug is used in therapy for respiratory diseases such as chronic obstrutive pulmonary disease or asthma and due to a narrow therapeutic index the use of modified release systems is of vital importance to monitor the action and avoid the toxicity. A polymeric system of PHB is modified with polyethyleneglycol (PEG). Changes in the morphology showed loss of crystallinity and changes in mechanical and physical properties. The aim of this work is to study the release of theophylline (TEO) in PHB-PEG-theophylline and PHB- theophylline tablets.

Introduction

During the last two decades, significant advances have been made in the development of biocompatible and biodegradable materials for biomedical applications.[1]

One area of intense research activity has been the biocompatible polymers for controlled drug delivery[1, 2, 3]. The goal of the controlled release devices is to maintain the drug in the desired therapeutic range with just a single dose[4, 5 ,6].

Poly(3-hydroxybutyrate) (PHB) is a biodegradable[7,8] polyester produced by a number of bacteria as a reserve of carbon and energy. It has many special properties such as biocompatibility and biodegradability. In the biomedical area, PHB can be used as surgical sutures, bone implant material, drug release system and scaffold for tissue engineering[9]. Unfortunately, PHB is fragile, hydrophobic and, for applications in which a biodegradable material is required, its degradation time is long. Many efforts have been employed, including chemical copolymerization with polyethyleneglicol. [10,11]

PEG (polyethyleneglycol) is a synthetic polymer known to be highly hydrophilic, biocompatible and flexible. In order to satisfy different requirements, especially to address the need for biomedical materials, PHB and PEG blends have been investigated. The incorporation of low molecular PEG into a PHB matrix can improve the hydrophilic character, flexibility and degradation time by increasing the availability of water with the matrix.[10]

Theophylline is a drug chemically known as 1, 3-dimethylxantine, bronchodilator.[12] and frequently used as molecular model in the development of solid formulations. Theophylline relaxes the smooth muscle of the bronchial respiratory ways and pulmonary sanguineous vases to alleviate bronchospasm and increase the flow and vital capacity.

In this work,a study of a modified release of theophylline in time through the production of binaries and ternary complexes of Teo/PHB and Teo/PHB/ PEG was accomplished. As for the evaluation of drug/polymer complex tablets release, it has been prepared by adding micro crystalline cellulose to process. The tablets were submitted to the dissolution assays. The reference to the fulfilment of the present work ,was the replacement of the complex by lactose.

Experimental

PHB from (Usina da Pedra), chloroform (Merck), theophylline (EMS) and PEG of 4000MW from Oxiteno (Brazil) have been used.

The binary complex was prepared in the following ratio: 20% of theophylline and 80% of PHB and ternary from 20% of theophylline, 10% of PEG and 70% of PHB.

Also ternary complexes had been confectioned with 20% of theophylline 5% of PEG and 75% of PHB.

The complexes were made by solubilization of powders in agitating plate with heating (Corning PC-320) to a temperature of 60 °C during 1 h, followed by evaporation of the solvent in Rotaevaporator (Tecnal TE-210). The drying of the complexes was performed in a greenhouse with air circulation (Fabbe) during 12 h.

After the drying, the complexes were triturated in mill of knives (IKA – A11 basic), and added to the excipients (microcrystalline cellulose and magnesium stearate)

for subsequent compression.

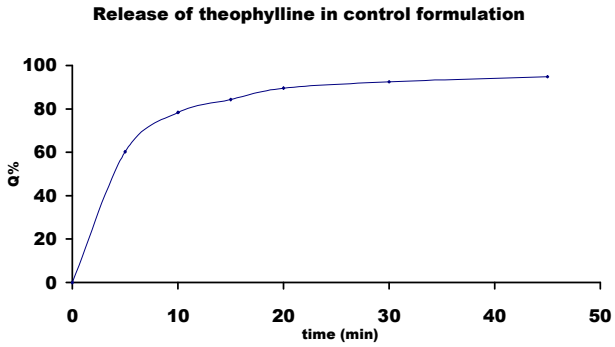
The used formulations have been:

- formulation 1- tablets containing 100mg of theophylline , with 50%of cellulose microcrystalline and 1% of magnesium stearate
- formulation 2 - tablets containing 100mg of theophylline and 25 mg of PEG 4000, with 50%of microcrystalline cellulose and 1% of magnesium stearate
- formulation 3 - tablets containing 100mg of theophylline and 50 mg of PEG 4000, with 50% of microcrystalline cellulose and 1% of magnesium stearate
- control formulation – tablets containing 100 mg theophylline, 500 mg lactose 200 mesh

The dissolution assays were performed in Logan D800 - dissolution tester (Logan Instruments Corp.), in accordance with the conditions established in the American Pharmacopoeia (USP XXVIII): display 2 (padle), 50 rpm, water, 900 mL at 37°C. The collection times have been differentiated between the formulations, being the control formulation submitted the tests of 45 minutes, in accordance with USP XXVII and the formulations 1, 2 and 3 for longer periods of time, totalizing twenty four hours of assay.

The dissolved drug quantifying was carried out in spectrophotometer UV-VIS (Beckman Coulter – DU 640), wavelength of 272 nm, in solutions of the drug in water after calibration.

Results and Discussion



The controlled formulation presented the expected profile: more than 80% of theophylline dissolved in 45 min (fig 1); while the complexes formulations had resulted in release of 80% in more than 480 min (fig.2).

Fig 1 . Curve of theophylline releasing in the control formulation

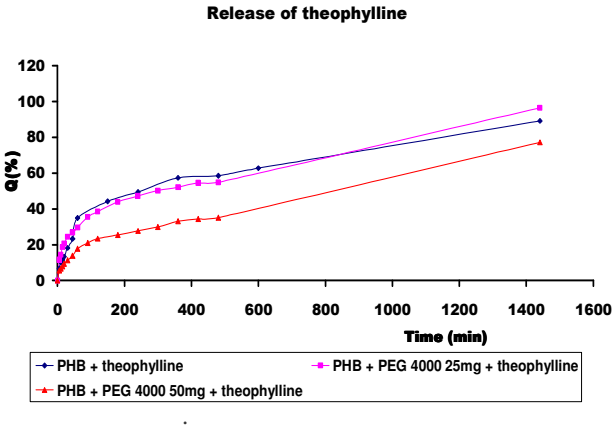


Fig. 2: Release of theophylline in binary complexes formulation 1(PHB/Teo) and ternary complexes of formulation 2 (PHB/PEG4000-5%) and formulation 3 (PHB/PEG4000-10%)

The release of theophylline in binary complex is slower than in the controlled formulation (lactose).

In the ternary complex with PEG the release of theophylline in correspondence with binary complex (PHB- theophylline) is slower.

Were performed a statistical analysis of the release curves (f1 and f2 factors) which results are showed in tables 1,2 and 3.

These two factors are, in reality, two equations that evaluate the difference between the percentage of dissolved drug in time between a test product and another one as reference. Two release curves are considered seemed if f1 values are between 0 and 15 and if f2 values are more of 50.

Table 1. Statistical analysis applied to formulations 1 and 2.

	time	Form1 (%)	Form2 (%)	f1	result	f2	result
1	5,00	6,7	11,65	73,88	NO	64,84	OK
2	10,00	10,1	14,33	54,64	NO	75,06	OK
3	15,00	11,51	18,7	57,82	NO	65,41	OK
4	20,00	13,28	20,74	57,30	NO	62,27	OK
5	30,00	18,25	24,34	50,00	NO	61,88	OK
6	45,00	23,25	26,83	40,32	NO	63,00	OK
7	60,00	34,97	29,62	32,91	NO	63,03	OK
8	240,00	49,47	47,18	24,56	NO	64,17	OK
9	360,00	57,31	52,23	20,56	NO	64,18	OK
10	480,00	58,5	54,9	17,58	NO	64,72	OK
11	1440,00	89,14	96,49	15,35	NO	63,65	OK

Table 2 . Statistical analysis applied to formulations 1 and 3.

	time	Form1 (%)	Form3 (%)	f1	result	f2	result
1	5,00	6,7	5,57	16,87	NO	91,07	OK
2	10,00	10,1	6,68	27,08	NO	79,11	OK
3	15,00	11,51	7,98	28,54	NO	76,08	OK
4	20,00	13,28	9,41	28,73	NO	74,18	OK
5	30,00	18,25	11,34	31,52	NO	68,39	OK
6	45,00	23,25	13,82	34,05	NO	62,96	OK
7	60,00	34,97	17,82	38,49	NO	54,17	OK
8	240,00	49,47	27,68	40,13	NO	48,10	NO
9	360,00	57,31	33,11	40,66	NO	44,17	NO
10	480,00	58,5	35,13	40,52	NO	42,01	NO
11	1440,00	89,14	77,19	34,03	NO	42,33	NO

Table 3. Statistical analysis applied to formulations 2 and 3.

	time	Form2 (%)	Form3 (%)	f1	Result	f2	Result
1	5,00	11,65	5,57	52,19	NO	60,52	OK
2	10,00	14,33	6,68	52,85	NO	62,98	OK
3	15,00	18,7	7,98	54,72	NO	55,76	OK
4	20,00	20,74	9,41	54,69	NO	52,92	OK
5	30,00	24,34	11,34	54,34	NO	50,54	OK
6	45,00	26,83	13,82	53,00	NO	49,20	NO
7	60,00	29,62	17,82	50,33	NO	48,74	NO
8	240,00	47,18	27,68	48,14	NO	45,90	NO
9	360,00	52,23	33,11	45,68	NO	44,21	NO
10	480,00	54,9	35,13	43,92	NO	42,88	NO
11	1440,00	96,49	77,19	38,10	NO	41,99	NO

In accordance with the stastistical analysis, the formulations 1 and 2 are seemed and the formulations 1 and 3 are different, and 2 and 3 are different.

Conclusions

Despite of the hydrophilic character of PEG, the complex formed with PHB has modified the drug release. One would expect that permeability through the blend would facilitate the theophylline dissolution.

Comparing the ternary complexes, TEO/PHB/PEG 5% has released a higher amount of theophylline than TEO/PHB/PEG 10%. Therefore the achieved order of the matrices can be described as: PHB/PEG(4000)10%<PHB/PEG(4000)5%<PH B. In accordance with the stastistical analysis, the formulations 1 and 2 are seemed and the formulations 1 and 3 are different or 2 and 3 are different.

To conclude it was verified that in relation to the control formulation, the complexes retard the drug release.

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References

1. P.L Gould; S. J. Holland; B. J. Tighe,1987, *Internatioal Journal of Pharmaceutics*, *38*, 231-237.
2. C. M. Lopes; J. M. S. Lobo; P. F. Costa, P *Rev. Bras. Cienc Farm*. 2005, *41*(2),
3. C. Pouton; S. Aktar.,Advanced Drug Delivery Reviews,1996, *18,*133-162,.
4. A. Gallardo; B. Vasquez, B. et al, ***Faenza*** *Editrice Iberica S.I.*,2004 *1*, 449-71.
5. L. B. Peppas. *Int J Pharm*, 1995 *116*, 1-9.
6. L. Brannon-Peppas. L *Medical Plastics and Biomaterial*, 1997, *4*, 34-44.
7. K. V. de Velde , P. Kiekens. *Polymer Testing*.2002, *21*, 433–442.
8. G. Cheng, Z. Kai, L. Wang. *Journal material science: materials in medicine* .2003, 1073-1078.
9. Z. J . Cai and G. X. Cheng, *J. Mater. Sci. Lett. 22* (2003) 153.
10. J. A. F. R. Rodrigues.; D. F Parra; A. B. Lugão, *Journal of Thermal analysis and Calorimetry,* 2005 , *79,* 379-381.
11. J.A.F.R. Rodrigues; D. F. Parra,;A. B. Lugão.2005, *Journal of Thermal analysis and Calorimetry* , *79*, 379-381.
12. R.G, Barr; B.H, Rowe; 2005 “Methyl-xanthines for exacerbations of chronic obstrutive pulmonary disease” , 1;CD002168