ELSEVIER

International Journal of Pharmaceutics 144 (1996) 153–158

international journal of pharmaceutics

Dissolution instability of encapsulated marketed tablets

D.S. Desai*, S.A. Ranadive, R. Lozano, S.A. Varia

Bristol-Myers Squibb Co., P.O. Box 191, New Brunswick, NJ 08903-0191, USA

Received 28 June 1996; revised 30 August 1996; accepted 5 September 1996

Abstract

For blinding purposes, 20 mg potency marketed tablets with some lactose monohydrate were encapsulated in size # 0 blue opaque capsule shells. After prolonged room temperature storage in HDPE bottles containing cotton and heat activated film seal, some of the capsule lots showed slower dissolution. No loss in potency was observed in these lots. When the contents of the capsules exhibiting the slower dissolution were transferred into fresh capsule shells, the original dissolution rate was observed. However, when aged tablet and fresh lactose monohydrate were transferred into the aged capsule shells, slower dissolution was observed. These observations indicated that the changes occurring in the capsule shells, rather than the capsule contents, were responsible for the decrease in dissolution. When the slow-dissolving capsules and 'as is' tablets were analyzed by HPLC, a peak corresponding to butylated hydroxy-toluene (BHT) was observed. This BHT was probably an impurity in butylated hydroxyanisole (BHA), which was used in the marketed tablet formulation as an antioxidant. The amount of BHT detected in the encapsulated tablet formulation was significantly lower than the amount detected in 'as is' marketed tablets. BHT can degrade in the presence of oxygen and moisture to form 2,6-di-tert-butyl-4-hydroxy-benzaldehyde as the main degradant product. It is hypothesized that this aldehyde product cross linked the gelatin of the capsule shell resulting in the observed decrease in the dissolution of the encapsulated product. On the other hand, the encapsulated lot showing no decrease in dissolution showed comparatively less BHT, and the amount of BHT detected in capsules and 'as is' tablets were not significantly different. Copyright © 1996 Elsevier Science B.V.

Keywords: BHA; BHT; Dissolution; Stability; Capsule; Tablet

1. Introduction

For many blinded clinical studies, competitor's product appearance is modified to make it indistinguishable from a product of interest. For a tablet dosage form, methods used to disguise

* Corresponding author.

PII S0378-5173(96)04740-0

competitor's products include encapsulation of the whole or broken tablet or grinding of the tablet and recompression. To disguise 20 mg potency marketed tablets for blinded clinical trials, the tablets were encapsulated with some lactose monohydrate in size # 0 blue opaque hard gelatin capsule shells. For stability evaluation, these capsules were packaged in HDPE bottles with cotton, and heat activated filmseal and stored at room temperature. After storage of more than a year, some of the encapsulated product lots showed significant decrease in dissolution. However, no such decrease in dissolution was observed for 'as is' marketed tablets stored under similar conditions. The decrease in the dissolution was not accompanied by loss in potency. Studies were conducted to investigate the causes for the slowdown in dissolution of the capsules. The results of these studies are reported in this article.

2. Materials and methods

2.1. Materials

The following ingredients were used as received from the suppliers: lactose monohydrate (Foremost Whey, Baraboo, WI), size # 0 blue opaque capsule shells (Shionogi, Indianapolis, IN), butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) (Sigma Chemicals, St. Louis, MO), 37% (w/w) formaldehyde and chromotropic acid disodium salt (Fisher Scientific, Springfield, NJ).

2.2. Equipment

The following equipment were used in this study. Conway diffusion cells (Fisher Scientific, Springfield, NJ), Vanderkamp 600 six spindle dissolution tester (Vankel Industries, Edison, NJ), and 8451A diode array spectrophotometer (Hewlett-Packard, Palo Alto, CA), Waters 712 WISP injector (Waters, Morristown, NJ), ABI 783A UV detector (Applied Biosystems, Foster City, CA) and sinkers for capsules (part no. 12-3050, VanKel Industries, Edison, NJ).

2.3. Encapsulation of marketed tablets

A capsule cap was separated from the body. A marketed tablet was cut into two halves. Both halves of the marketed tablets were placed in the capsule body. The void spaces were filled with lactose monohydrate. The ratio of lactose to tablet was 3:2. The capsule cap was attached to the body and closed. The entire operation was performed manually.

2.4. Dissolution stability studies

For dissolution stability evaluation, the capsules were packaged in HDPE bottles containing cotton and heat activated filmseal and stored at room temperature (RT). The 'as is' tablets were also packaged similarly and placed on storage at RT. Samples were withdrawn at various time points and analyzed for potency, and dissolution using the method described in the USP XXIII. The dissolution samples were taken at 10, 20, 30, and 60 min time points and concentration of dissolved active component was determined using the HPLC method given in the USP XXIII (50 rpm paddle speed and 900 ml of dissolution medium). Sinkers were used to prevent capsules from floating in the dissolution medium. Sinkers are a three prong assembly unit which prevent capsules from floating in the dissolution vessels.

2.5. Extraction procedure for capsule content

A capsule was opened and capsule contents were transferred into a mortar. The contents were ground using a pestle and were then transferred into a ten milliliter volumetric flask. Four milliliters of methanol was added to the contents. After sonicating the flask for 20 min, the solution was cooled to RT. The flask volume was made up to the mark using methanol and filtered through a 0.45 μm Nylon 66 (Acrodisc®) filter. Forty microliter aliquot of this solution was injected onto the HPLC system.

2.6. HPLC analysis

An HPLC method capable of separating the active component of the marketed product, BHA,

and BHT in a single chromatogram was developed by modifying a previously published method (Beker and Lovrec, 1987). The following conditions were used. Stationary phase 3 μm YMC A302-3 (150 mm × 4.6 mm); mobile phase, methanol: water (95:5); flow rate 0.9 ml/min; UV detection wavelength, 238 or 280 nm. The retention times for BHA, the active component, and BHT were 2.4, 2.9, and 3.6 min, respectively.

2.7. Formaldehyde detection

Degradation of BHT and BHA in the environment of high temperature and presence of moisture was simulated using the Conway diffusion cell. Two grams of BHT or BHA were placed in the outer ring of a Conway diffusion cell and 0.8 ml water, which was previously boiled to remove dissolved gases, was added to the BHT or BHA. In the inner ring of the cell, 3 ml of chromotropic acid reagent was placed. The cells were sealed and placed in an oven set at 60°C for 3 h. It was previously established that 3 h was sufficient time for reaction to reach completion under the experimental conditions. The chromotropic acid solution was then removed, placed in a vial, sealed, and incubated in an 80°C water bath for 30 min. Vials were then cooled and the absorbance of the solution was measured at 570 nm (Manius et al., 1993).

3. Results and discussion

In Table 1, dissolution data on the two capsule lots, N94A003C and N94E073C and corresponding 'as is' marketed tablets, lots A and B respectively, are shown. There was a significant decrease in dissolution of the capsules after 365 days and beyond compared to initial dissolution values. In contrast, no such decrease in dissolution was observed for 'as is' marketed tablets at these time points. As shown in Table 2, the other two lots of capsules, CON-250-H/H1 and CON-250-H/H2, and corresponding 'as is' marketed tablet, lots C and D, did not show any decrease in dissolution after 273 days and 813 days on storage at 30°C and 25°C, respectively. In all of the lots tested, there were no losses in potency on stability storage (data not shown).

In order to determine the cause for the decrease in the dissolution of the encapsulated product, the contents of the aged capsules of lot N94E073C were transferred into fresh capsule shells. Dissolution of these capsules were similar to the initial dissolution of the capsules of this lot (Table 3). However, when aged 'as is' tablet of lot B and fresh lactose monohydrate were placed in capsule shells retrieved from aged lot N94E073C, there was a significant decrease in dissolution (Table 3). These data indicate that the changes occurred in the capsule shells during storage were responsible for the decrease in dissolution.

Of the four capsule lots that were studied for dissolution, two lots exhibited slower dissolution compared to their respective initial assays, and the other two lots did not show any significant decrease in dissolution. During the dissolution runs of capsules exhibiting slower dissolution, it was observed that capsule shells appeared spongy and remained undissolved during the dissolution run. Based on our previous experience (Desai et al.,

Table 1
Dissolution of 20 mg potency encapsulated marketed tablets, and the corresponding 'as is' tablets (storage temperature: 25°C)

Lot #	Time point (days)	% Dissolved in minutes			
		10	20	30	60
Encapsulated tablets					
N94A003C	Initial ($n = 12$)	64	82	90	98
	365 ($n = 3$)	41	60	72	95
	485 ($n = 6$)	38	53	66	85
N94E073C	Initial ($n = 12$)	69	85	92	99
	365 ($n = 12$)	29	44	57	82
'As is' tablets					
A	Initial ($n = 6$)	66	80	86	94
	365 ($n = 3$)	87	96	99	99
	485 ($n = 6$)	68	87	96	99
B	Initial ($n = 6$)	72	92	98	101
	365 ($n = 6$)	67	89	97	100

Table 2
Dissolution of 20 mg potency encapsulated marketed tablets, and the corresponding 'as is' tablets

Lot #	Time point/Temperature	% Dissolved in minutes			
		10	20	30	60
Encapsulated tablets					
CON-250-H/H1	Initial ($n = 12$)	64	81	89	99
	273 days/30°C ($n = 3$)	55	76	85	96
CON-250-H/H2	Initial ($n = 12$)	68	87	94	100
	813 days/25°C ($n = 6$)	83	96	99	81
'As is' tablets					
C	Initial ($n = 6$)	68	83	90	98
	273 days/30°C	ND	ND	ND	ND
D	Initial ($n = 6$)	80	90	92	96
	813 days/25°C ($n = 6$)	94	99	100	101

ND, not determined.

1994) and other reported instances (Carstensen and Rhodes, 1993; Schwier et al., 1993; Hartauer et al., 1993; Digenis et al., 1994), such a phenomenon indicates interaction between gelatin of the capsule shell and aldehyde.

One capsule lot exhibiting dissolution instability, lot N94A003C, and one capsule lot with satisfactory dissolution stability, lot CON-250-H/H2, were selected for further studies. Capsule contents of these two lots and their corresponding 'as is' marketed tablets (lots A and D, respectively) were analyzed using HPLC. A typical chromatogram is shown in Fig. 1.

Table 3
Dissolution of 20 mg potency marketed tablets after re-encapsulation in old and new capsule shells

Vessel #	% Dissolved in minutes			
	10	20	30	60
Old encapsulated tablets[a]/Old filler[a] (lactose)/New shells				
1	67	79	87	97
2	77	89	95	100
3	77	87	92	97
Mean	74	85	91	98
Old 'as is' tablets[b]/New filler (lactose)/Old shells[a]				
1	56	70	80	94
2	43	52	62	88
3	59	71	80	94
Mean	53	64	74	92

[a] Lot # N94E073C.
[b] Lot # B.

In all four lots, along with active component of the marketed product and BHA, which is used as an antioxidant in the tablet formulation (Physicians' Desk Reference, 1988), a peak corresponding to the same HPLC retention time as BHT was detected (Table 4). Based on the similar retention time, it suggested presence of BHT which can be an impurity in the BHA used (Scheme 1; Wade and Weller, 1994). The amount of BHA was not significantly different ($P > 0.4$) in both capsule lots and their corresponding 'as is' marketed tablets (Table 4). Interestingly, the amount of BHT detected in 'as is' marketed tablet lot A was about twice that detected in 'as is' marketed tablet lot D (Table 4). Additionally, there was no significant difference ($P = 0.23$) in BHT amount between 'as is' marketed tablet lot D and its corresponding capsule lot CON-250-H/H2 (Table 4). However, the BHT amount detected in capsule lot N94A003C was about one seventh less ($P < 0.001$) than that detected in its corresponding 'as is' marketed tablets, lot A (Table 4). These results indicated that the amount of BHT in the batch of encapsulated tablets which exhibited a dissolution instability was high in the 'as is' marketed tablet and upon encapsulation and storage it had probably degraded.

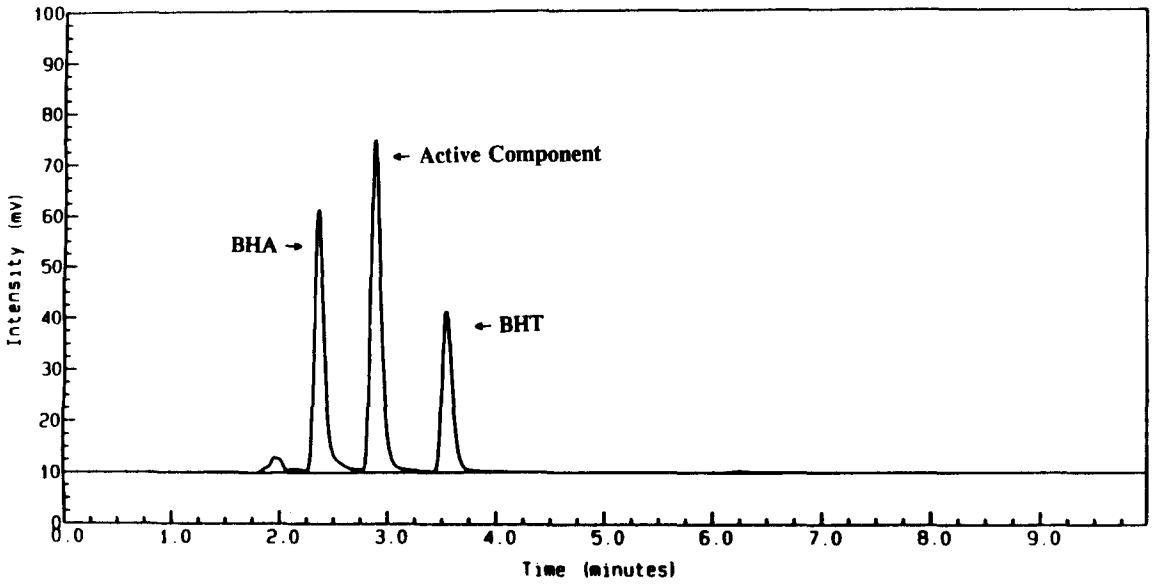
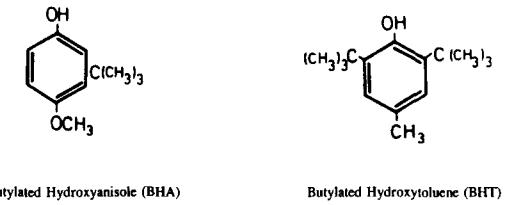


Fig. 1. A typical chromatogram showing a separation of the active component of the marketed tablet, BHA, and BHT.

Using the Conway diffusion cell and the method described in the experimental section, BHA and BHT were investigated for their potential to generate an aldehyde in an environment of moisture and heat. BHA did not generate any aldehyde under the experimental conditions. However, BHT did generate aldehyde under similar experimental conditions. The 4-methyl group of 2,6-dialkyl-4-methylphenols can often be oxidized selectively to an aldehyde group (Helmut and Bayer, 1991). It is hypothesized that a similar reaction must be taking place with BHT, in the presence of oxygen and moisture from lactose monohydrate and the capsule shell, forming 2,6-di-tert-butyl-4-hydroxybenzaldehyde on storage. The aldehyde formed can cross-link with the gelatin to form an insoluble compound, resulting in a decrease in dissolution of the capsules (Merck Index, 1976; Schwier et al., 1993).



Butylated Hydroxyanisole (BHA) Butylated Hydroxytoluene (BHT)

Scheme 1. Structures of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT).

Table 4
HPLC analysis of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) in encapsulated marketed and 'as is' tablets

HPLC assay[a]	Peak area units (mV)	
	'As is' tablets	Encapsulated tablets
	Lot # A	Lot # N94A003C
BHA content	295.2 ± 82.3	233.3 ± 84.3
BHT content	56.5 ± 4.51	8.4 ± 1.87
	Lot # D	Lot # CON-250-H/H2
BHA content	281.3 ± 91.1	262.4 ± 89.6
BHT content	30.5 ± 1.96	23.8 ± 7.91

[a] Average ($n = 3$).

Acknowledgements

The contribution to this study by Ms. Beth Lang is gratefully acknowledged.

References

Beker, D. and Lovrec, V., Determination of butylated hydroxytoluene in poultry premix by high-performance liquid chromatography. *J. Chromatogr.*, 393 (1987) 459–461.

Desai, D., Rubitski, B., Bergum, J. and Varia, S., Effects of different types of lactose and disintegrant on dissolution stability of hydrochlorothiazide capsule formulations. *Int. J. Pharm.*, 110 (1994) 257–265.

Carstensen, J.T. and Rhodes C.T., Pellicule formation in gelatin capsules. *Drug Dev. Ind. Pharm.*, 19 (1993) 2709–2712.

Digenis, G., Gold, T. and Shah, V., Cross-linking of gelatin capsules and its relevance to their in vitro–in vivo performance. *J. Pharm. Sci.*, 83 (1994) 915–921.

Hartauer, K., Bucko, J., Cooke, G., Mayer, R. and Sullivan, G., Effect of rayon coiler on the dissolution stability of hard-shell gelatin capsules. *Pharm. Tech.*, May 17 (1993) 78–80.

Wade, A. and Weller, P. (Eds.), *Handbook of Pharmaceutical Excipients*, American Pharmaceutical Association, 1994, pp. 45–48.

Helmut, F. and Bayer, A., Phenol Derivatives. In Elvers, B., Hawkins S. and Schulz, G. (Eds), *Ullmann's Encyclopedia of Industrial Chemistry*, Vol. A(19), VCH publishing, New York, 1991, pp. 316.

Manius, G., Wen, L. and Pauling, D., Three approaches to the analysis of trace formaldehyde in bulk and dosage form pharmaceuticals. *Pharm. Res.*, 10 (1993) 449–453.

Merck Index, 9th edn, Merck, Rahway, NJ, 1976, pp. 545.

Physicians' Desk Reference (PDR), 42nd edn, Medical Economics Company, 1988.

Schwier, J., Cooke, G., Hartauer, K. and Yu., L., Rayon: source of furfural-reactive aldehyde capable of insolubilizing gelatin capsules, *Pharm. Tech.*, June 17 (1993) 76–83.