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COMMUNICATION

Effect of Packaging and Storage on the Stability of Carbamazepine Tablets

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ABSTRACT

The effect of packaging and storage on carbamazepine (CBZ) tablets was examined using Tegretol® and Tegral, dispensed in strip seals, and Finlepsin®, dispensed in bottles. Tegretol and Tegral tablets were stored in their original strips at 40°C, 50°C, and 60°C for 6 months, 3 months, and 1 month, respectively, at 75% relative humidity (RH). Also, tablets were removed from their strips, placed in bottles, and exposed daily to 97% RH at 40°C for 5 min for 30 days. Finlepsin tablets were exposed to 97% RH at 25°C or 40°C for 1 month by removing bottle caps daily for 5 min. Dissolution was used to assess in vitro tablet performance, and high-performance liquid chromatography (HPLC) was used to evaluate the chemical stability of CBZ. Results show that Tegretol tablets were not affected by the tested stress conditions. Tegral tablets, stored in their strips at 50°C or 60°C and 75% RH, showed increased disintegration and dissolution. The effect of 40°C/75% RH for 6 months was similar to 1-month storage at 40°C/97% RH; the tablets hardened and dissolved less than fresh Tegral tablets. Removal of Tegral tablets from their original strips resulted in only 7% dissolved in 60 min. For Finlepsin, the effect of 97% RH at 40°C was more profound than 97% RH at 25°C, but both conditions caused a decrease in dissolution, the extent of which was dependent on tablet position in the bottle. Stressed CBZ tablets, however, showed no change in the chemical stability of CBZ under all tested conditions.

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INTRODUCTION

Carbamazepine (CBZ), an iminiostilbene derivative, is a frequently prescribed anticonvulsant. It is practically insoluble in water (1) and exists as the anhydrous and dihydrate forms (2–4). Once the anhydrous form is in contact with moisture, it transforms to the more thermodynamically stable dihydrate (2,5), which is less soluble. Research conducted at Food and Drug Administration (FDA) laboratories in Washington, DC, and in FDA-funded laboratories at the University of Tennessee, College of Pharmacy in Memphis, showed that, when CBZ tablets were exposed to humidity, they hardened and dissolved poorly (6–10) and lost as much as one-third of their potency (6–9). The FDA is advising manufacturers to improve the product's packaging (6–8), and for patients using CBZ tablets, it is reemphasizing storing tablets in a tightly closed container in a dry location away from bathrooms, showers, and humidifiers (6–10). Also, physicians may not want to prescribe more than a 30-day supply to be dispensed in one container (10). The same observation was seen at the Pretoria College of Pharmacy in South Africa, where tablet dissolution rates decreased, and the dihydrate form of CBZ was identified in the tested CBZ tablets exposed to humidity (11). The research group recommended storing CBZ tablets with silica gel sachets.

These observations, as well as others (12,13), led to a study investigating the effect of humidity and temperature on in vitro dissolution of some marketed CBZ tablets (14). In vivo evaluation of CBZ tablets with a history of clinical failure was also conducted (15). Recently, a multinational survey of the quality of CBZ tablets conducted at 22 laboratories in 19 countries under the auspices of the Official Laboratories and Medicines Control Services (OLMCS) Section of FIP (Fédération Internationale Pharmaceutique) (16) showed marked differences in dissolution behavior, suggesting that not all CBZ tablet products are bioequivalent with each other. The effect of packaging was not considered in any of the studies. The objective of this work is to examine the effect of packaging and storage conditions on the in vitro performance of CBZ tablets. Tablets used were Tegretol® and the Egyptian generic, Tegral, presented in poly(vinyl chloride) (PVC)/aluminum strip seals inside a carton, and the German product, Finlepsin®, dispensed in bottles of 50 tablets. In vitro tablet performance was assessed through dissolution testing, and chemical stability of CBZ was assessed via high-performance liquid chromatography (HPLC).

EXPERIMENTAL

Materials

The CBZ was a gift from the manufacturer of Tegretol, Swisspharma (now Novartis Pharma). Tegretol 200-mg conventional tablets (batch 503), Tegral 200 (batch 126) from Chemical Industries Development, CID, Cairo, Egypt, and Finlepsin (batch B081069) from Arzneimittelwerk Dresden Gmgh, Radebeul, Germany, were used. Sodium lauryl sulfate (SLS), sodium chloride, and potassium sulfate were obtained from ADWIC, Egypt (under license from PROLABO), and methanol, HPLC grade, was obtained from Romil Chemical, England.

Treatment of Carbamazepine Tablets Under Stressed Conditions

Accelerated Stability Protocols

The temperature and relative humidity (RH) adopted for Tegretol and Tegral tablets were (*a*) 40°C and 75% RH for 6 months with sampling at 2, 4, and 6 weeks and 2, 3, 4, and 6 months; (*b*) 50°C and 75% RH for 3 months with sampling at 1, 2, 3, 4, and 6 weeks and 2 and 3 months; (*c*) 60°C and 75% RH for 1 month with sampling at 1, 2, 3, and 4 weeks. Tablets were stored in their original packages, and the desired relative humidity was attained by first dissolving the salt at a higher temperature and then cooling it to the desired temperature. The saturated solution was then transferred to a desiccator, a layer of salt was added, and it was kept overnight for further equilibration prior to use. Sodium chloride was used to obtain 75% RH.

Other Stress Conditions

For Finlepsin dispensed in bottles, conditions were adopted to mimic daily habits for tablet intake as described in an FDA study (14). Bottles were stored in 97% RH at 40°C; each day, the lids were removed for 5 min to expose the tablets. This procedure was done once daily for a period of 30 days. The same exposure protocol was adopted at 25°C and 97% RH. Potassium sulfate was used to provide 97% RH.

Effect of Packaging

Tegretol marketed in Egypt is dispensed in PVC/aluminum strip seals, as is Tegral. The effect of packaging was examined by removing Tegretol and Tegral tablets

from their strip seals, placing them in glass bottles, and storing them at 40°C /97% RH. Daily and over 1 month, tablets were exposed to the high humidity for 5 min by removing the bottle lids. For comparison, Tegretol and Tegral tablets in their original package were also stored under 40°C/97% RH.

Dissolution Testing

Dissolution studies were performed according to the USP monograph for CBZ tablets (17) on fresh and stressed CBZ tablets. Each of six vessels of the dissolution apparatus (Pharma Test, Germany) was filled with 900 ml of 1% SLS aqueous solution and equilibrated at 37°C for 1 hr. Six tablets were used in each run, and the paddle speed was 75 rpm. About 3-ml aliquot samples were obtained at 15, 30, 45, 60, 90, and 120 min and were filtered using Millipore® membrane filters (0.2-μm pore size). The absorbance was measured at the predetermined (λ_{max} of 285 nm (Shimadzu UV 240 Double Beam Spectrophotometer, Kyoto, Japan), and the concentration in each sample was calculated from a standard curve of CBZ in 1% SLS ranging from 2.5 to 20 μg/ml prepared along with each run. Linear regression was used to express absorbance as a function of CBZ concentration.

Determination of Carbamazepine Content

The effect of stress conditions on the chemical stability of CBZ was examined using HPLC. The method to determine drug content was obtained courtesy of the management of Swisspharma (now Novartis Pharma). The procedure for sample preparation was identically followed; however, the HPLC column and mobile phase were modified to suit our laboratory testing conditions. A Spherix C_{18}, 5-μm (250 mm × 4.6 mm) column and 45:55 methanol:water for the mobile phase were used, while other chromatographic conditions of flow rate (1.5 ml/min) and detection wavelength (254 nm) were maintained the same. The HPLC used consisted of Consta Metric® 4100 Solvent Delivery System, from LDC, Milton Roy, with a Spectro Monitor™ 5000 photodiode array detector (LDC, Milton Roy). Peak areas were calculated using an LDC Milton Roy integrator. The test and comparison solutions were prepared, and a 10-μl aliquot equivalent to 2 μg of CBZ active substance of each solution was injected in duplicate. The area of CBZ peak in the chromatograms of the test and comparison solutions was determined. The CBZ content was calculated as a percentage of declared content.

RESULTS AND DISCUSSION

Pharmaceutical stability is generally defined as the capacity of a drug product to remain within specifications established to ensure its identity, strength, quality, and purity (18). High temperatures of 50°C and 60°C were used to mimic uncontrolled conditions during product transport and/or storage exhibited in the summer for some areas in Egypt. The CBZ tablet performance was evaluated in vitro through dissolution testing, and HPLC was used to assess the chemical stability of CBZ.

Dissolution of Carbamazepine Tablets

The aim of this study was to assess the in vitro dissolution performance of stressed CBZ tablets in comparison with fresh tablets. The USP method (17) recommends using 1% SLS aqueous solution as the dissolution medium, which provides a bile-salt-like solubilizing effect on drugs of poor aqueous solubility such as CBZ (14). Statistical testing was performed on the 15-min and 60-min points of dissolution since the USP is considering a proposal to amend the USP dissolution test for CBZ tablets to include a measurement at 15 min, with *Q* between 40% and 70%, besides that at 60 min, in order to exclude products with very rapid or very slow dissolution rates (19).

Table 1 shows the dissolution profiles of Tegretol tablets, both fresh and stressed. Fresh tablets met the USP specification of 75% dissolution in 60 min (17). Statistical testing using unpaired Student *t* test to compare percentage dissolved from stressed tablets with fresh showed no significant differences at 15 and 60 min under all stress conditions, $p > .05$. Tested tablets stored in their original strip seals or removed from their package, placed in bottles, and exposed to 97% RH at 40°C daily for 30 days maintained their dissolution profiles and instantaneous disintegration in dissolution medium throughout the storage and testing period.

The dissolution profiles of fresh and stressed Tegral tablets are given in Table 1. Fresh Tegral tablets showed slower disintegration and dissolution than fresh Tegretol tablets throughout the 2-hr dissolution period. Also, different stress conditions greatly affected tablet performance, and 50°C/75% RH and 60°C/75% RH caused tablets to disintegrate faster, producing higher percentage dissolved at all points in time in comparison with fresh Tegral tablets, $p < .05$ using unpaired Student *t* test. After 2 months of storage at 40°C/75% RH, percentage CBZ dissolved at 15 min was not significantly different from that of fresh tablets, $p > .05$. However, at 60 min,

Table 1

Effect of Storage Conditions on the Dissolution of Tegretol, Tegral, and Finlepsin Tablets: Mean Percentage Carbamazepine Dissolved

Storage Conditions	15 min	30 min	45 min	60 min	90 min	120 min
Tegretol tablets						
Fresh	57 ± 6.8	69 ± 6.2	76 ± 7.4	84 ± 5.9	90 ± 5.2	95 ± 3.7
40°C/75% RH						
2 months	53 ± 11	63 ± 13	70 ± 13	78 ± 15	84 ± 11	92 ± 9.2
6 months	62 ± 5.8	73 ± 5.1	80 ± 7.5	85 ± 7.9	92 ± 5.5	96 ± 3.2
50°C/75% RH						
1 month	69 ± 6.2	78 ± 6.6	82 ± 8.0	85 ± 6.2	89 ± 4.2	91 ± 0.98
2 months	54 ± 5.1	66 ± 6.4	73 ± 7.7	76 ± 6.7	87 ± 5.9	87 ± 5.1
3 months	49 ± 7.1	59 ± 6.0	68 ± 8.3	74 ± 8.1	83 ± 4.9	90 ± 2.9
60°C/75% RH						
1 month	56 ± 3.5	64 ± 1.4	71 ± 2.1	75 ± 4.6	84 ± 5.0	90 ± 1.7
40°C/97% RH						
1 month[a]	56 ± 6.5	64 ± 5.4	72 ± 8.8	76 ± 8.3	85 ± 86	90 ± 7.2
40°C/97% RH						
1 month[b]	59 ± 3.2	72 ± 8.8	78 ± 2.2	80 ± 2.7	90 ± 1.6	94 ± 1.6
Tegral tablets						
Fresh	42 ± 4.6	54 ± 2.6	61 ± 6.0	63 ± 6.5	68 ± 7.1	72 ± 6.2
40°C/75% RH						
2 months	44 ± 5.1	71 ± 3.9	86 ± 3.9	91 ± 3.4	96 ± 3.0	102 ± 1.8
6 months	20 ± 3.2	30 ± 2.1	38 ± 4.3	42 ± 1.2	49 ± 0.84	55 ± 0.85
50°C/75% RH						
1 month	88 ± 3.2	94 ± 0.82	95 ± 0.86	95 ± 0.90	96 ± 0.64	97 ± 0.73
2 months	72 ± 1.3	92 ± 9.1	98 ± 4.6	100 ± 2.9	102 ± 1.6	101 ± 0.84
3 months	69 ± 6.7	93 ± 2.6	99 ± 1.1	99 ± 1.1	99 ± 1.3	99 ± 1.1
60°C/75% RH						
1 month	78 ± 9.5	92 ± 5.5	95 ± 3.5	97 ± 2.3	97 ± 1.9	97 ± 1.8
40°C/97% RH						
1 month[a]	20 ± 5.8	31 ± 7.6	38 ± 8.9	42 ± 9.2	49 ± 9.6	57 ± 6.9
40°C/97% RH						
1 month[b]	3.3 ± 0.83	4.3 ± 0.36	5.7 ± 0.86	6.6 ± 1.1	9.3 ± 1.5	12 ± 1.8
Finlepsin tablets						
Fresh	80 ± 3.5	89 ± 4.0	92 ± 3.2	93 ± 2.8	93 ± 2.3	94 ± 2.2
25°C/97% RH	46 ± 4.8	61 ± 4.5	68 ± 6.7	72 ± 7.4	82 ± 5.7	88 ± 6.4
40°C/97% RH						
Mean of 4	9.3 ± 2.8	14 ± 1.4	20 ± 3.4	25 ± 4.3	30 ± 3.2	33 ± 2.4
Mean of 2	41	66	77	86	91	93

[a]Tablets stored in their original package.
[b]Tablets removed from strips and placed in bottles.

stressed tablets exhibited higher dissolution rates when compared with the fresh. After 6 months of storage at 40°C/75% RH, tablets dissolved poorly and did not disintegrate throughout the 2-hr dissolution period. The same was observed with tablets stored at 40°C/97% RH for 1 month. The 1-month storage at 40°C/97% RH had the same effect as 6-month storage at 40°C/75% RH for Tegral tablets stored in their original strip seals. For Tegral tablets placed in bottles and exposed to 97% RH at 40°C daily for 30 days, only 7% was dissolved in 60 min.

For Finlepsin tablets, the stress testing protocol was different from that for Tegretol and Tegral, as mentioned in the Experimental section above. The dissolution rate

of fresh tablets met the USP requirement at 60 min. However, at 15 min, percentage CBZ dissolved was significantly higher than for fresh Tegretol tablets, 80% versus 57%, respectively. This value is higher than that amended by the USP (*Q* between 40% and 70% at 15 min). After 1 month of exposure to 97% RH at 25°C, dissolution was reduced; the average percentages dissolved at 15 and 60 min were 46% and 72%, compared to 80% and 93%, respectively, for fresh tablets. A drastic decrease in dissolution was observed when tablets were exposed to 97% RH at 40°C. Of the six tested humidity-exposed tablets, four gave a mean of 25% dissolved at 60 min, while the other two gave a mean of 86% at 60 min. This may be explained by differences in the degree of exposure to humidity with tablets on top suffering more damage. Results for Finlepsin tablets are also given in Table 1.

Chemical Stability of Carbamazepine

The chemical stability of CBZ was evaluated by HPLC. The decrease in the CBZ peak and/or appearance of new peaks were monitored in each run for all tested tablets, but only the CBZ peak was quantified. Chemical stability of CBZ in the stressed and fresh tablets of the tested CBZ products was examined against a CBZ reference standard, which was run simultaneously every time samples were evaluated. The results show that, for the tested tablets, CBZ ranged from 99% to 107% for Tegretol and 97% to 102% for Tegral, which fall within the acceptable USP limits of 92% to 108% (17).

CONCLUSION

In conclusion, this study examined the effect of storage and packaging on the performance of CBZ tablets. Although storage conditions examined in the study affected the disintegration/dissolution behavior of some CBZ tablet formulations, they did not have any significant effect on the chemical stability of CBZ. Tegretol tablets exposed to different stress conditions, in their original package or in bottles after removal from strips, showed no significant change in tablet performance. For Tegral tablets, high temperatures of 50°C and 60°C enhanced dissolution. Thus, such tablets may deliver high CBZ concentrations in a short time, which is similar to dose dumping. Failure in disintegration and a decrease in dissolution observed with Tegral tablets exposed to 97% at 40°C may lead to undermedication, and therefore therapeutic failure, as tablets would not deliver the labeled dose during their residence in the gastrointestinal tract. The PVC/aluminum strip seal packaging did not maintain optimum tablet performance, with the Tegral tablets stored in strips under 97% RH at 40°C giving a low percentage dissolved at 60 min (42%), which was still higher than those tablets placed in bottles and exposed to humidity, for which only 7% was dissolved in 60 min. For Finlepsin, tablets were affected to different degrees depending on their position in the bottle.

Therefore, it may be concluded that differences in tablet performance in vitro and the extent of the effect of storage are largely formulation dependent, with factors such as sensitivity to moisture of different excipients used, as well as the moisture content, play a major role in tablet performance (20).

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