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Application of sorption–desorption moisture transfer modeling to the study of chemical stability of a moisture sensitive drug product in different packaging configurations

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Abstract

The sorption–desorption moisture transfer (SDMT) model was used to predict the effect of desiccant quantity, tablet quantity and tablet initial moisture content on the relative humidity inside high density polyethylene (HDPE) bottles containing a moisture sensitive drug product, roxifiban tablets. The effect of these variables on the stability of roxifiban tablets in the HDPE bottles was also evaluated. There was a good correlation between the calculated relative humidity values inside the package and stability results. Tablet degradant concentration increased with the increase in the relative humidity calculated by the SDMT model. Desiccant quantity was the most important factor in controlling degradation rate, which decreased as the quantity of desiccant in the bottle was increased. For a given desiccant quantity, degradation rate increased with an increase in the weight of tablets in the bottle. The inclusion of a desiccant in the package significantly reduced the effect of initial tablet moisture content on stability. Nevertheless, the effect of initial moisture content was still discernible. This study demonstrated the practical utility of the SDMT model in understanding the correlation between packaging variables and the stability of a moisture sensitive product.

Keywords: Sorption; Desorption; Moisture; Packaging; Stability; Humidity

1. Introduction

Moisture is frequently associated with chemical and/or physical instability of a pharmaceutical drug product. Package design is particularly critical for a moisture sensitive product since it must ensure that the product is adequately protected from moisture during its shelf-life. Desiccant is frequently included in the packaging configuration of these products in order to maintain low relative humidity inside the package and hence protect the product from moisture. The use of a sorption–desorption moisture transfer (SDMT) model was successfully used to predict moisture

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transfer between a solid product and desiccant inside a closed package (Kontny, 1988; Zografi et al., 1988). The SDMT model accounts for the initial mass, moisture content and moisture sorption behavior of the product and desiccant to predict the relative humidity inside the package. The SDMT model illustrated the utility of the desiccant in scavenging moisture from the product and in maintaining low relative humidity inside the package. Theoretical simulations extended the use of the SDMT model to take into account moisture permeation properties of the package (Kontny et al., 1992). Despite the success of the SDMT model in predicting moisture transfer within a closed package, no stability data was previously published, to the best of our knowledge, to demonstrate the utility of this model in designing packages that would extend the shelf-life of a moisture sensitive product. The practical usefulness of this model still needs to be demonstrated.

Table 1
Experimental design for the study of packaging variables on tablet stability

Run number	HDPE bottle size (cm^3)	Strength (mg)	Number of tablets	Silica gel desiccant (g)
1	30	0.5	50	1.0
2	60	2.0	50	1.5
3	30	1.0	100	1.0
4	30	0.5	100	2.0
5	60	1.0	50	3.0
6	30	1.0	50	2.0
7	60	1.0	100	1.5
8	60	2.0	100	3.0

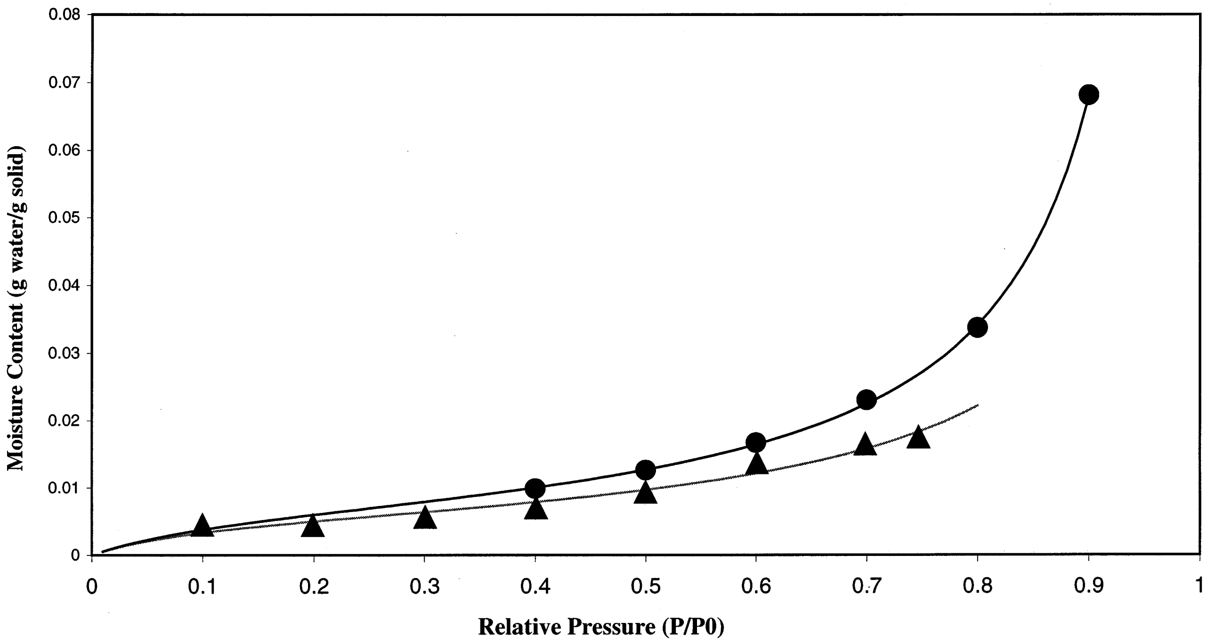

Fig. 1. Moisture sorption isotherm for the roxifiban formulation at (●) 25°C, and (▲) 40°C. Solid lines represent GAB fits to the data.

Table 2
Stability of tablets equilibrated at different relative humidities before packaging and subsequently stored in HDPE bottle without desiccant at 25°C/40% RH

RH for tablet equilibration (%)	% Increase in ester hydrolysis product after 3 weeks
<10	0.02
40	0.16
60	0.68

Table 3
Stability of tablets equilibrated at different relative humidities before packaging and subsequently stored in HDPE bottle with 3 g silica gel desiccant at 25°C/60% RH

RH for tablet equilibration (%)	% Increase in ester hydrolysis product	
	1 month	3 months
<10	0	0.03
31	0	0.04
47	0.02	0.05
60	0.04	0.09

Roxifiban (DMP 754), a prodrug of a platelet IIb/IIIa glycoprotein receptor antagonist, undergoes ester hydrolysis in the solid state and hence the stability of its drug product is sensitive to moisture (Badawy et al., 1999). The purpose of this work is to study the effect of various packaging configuration variables on the stability of roxifiban tablets. Theoretical calculations are performed using the SDMT model to predict the effect of package changes on relative humidity in the package and moisture content of the product. Stability studies are conducted to correlate the results of the SDMT calculations with the chemical degradation of roxifiban drug product.

2. Experimental

2.1. Methods

2.1.1. Stability studies

2.1.1.1. Effect of relative humidity on tablet stability. Roxifiban tablets were manufactured using commonly used pharmaceutical excipients and manufacturing processes. The effect of relative humidity on tablet stability was evaluated to demonstrate the extent of moisture sensitivity of this compound. Three tablet samples from the same lot were equilibrated at <10, 40 and 60% relative humidities for at least 24 h. Each tablet sample was then packaged in 30 cm^3 sealed high density polyethylene (HDPE) bottles without a desiccant. Bottles containing the tablets were capped, torqued, and induction sealed. The packaged HDPE bottles were stored in stability chambers at 25°C/40% RH. The bottles were pulled at different time intervals, and the contents were

Table 4
Stability data for the study of effect of packaging variables on tablet stability

HDPE bottle size (cm^3)	Strength (mg)	Number of tablets	Silica gel desiccant (gm)	Ester hydrolysis product at 40°C/75% RH (%)			
				Time zero	1 month	3 months	6 months
30	0.5	50	1.0	0.15	0.17	0.29	0.76
60	2.0	50	1.5	0.14	0.18	0.31	0.74
30	1.0	100	1.0	0.14	0.18	0.32	ND[a]
30	0.5	100	2.0	0.15	0.17	0.23	0.39
60	1.0	50	3.0	0.14	0.16	0.20	ND[a]
30	1.0	50	2.0	0.14	0.19	0.22	0.37
60	1.0	100	1.5	0.14	0.19	0.30	ND[a]
60	2.0	100	3.0	0.14	0.18	0.25	0.41

[a] No data.

Table 5
Calculated effect of bottle size on the relative humidity inside the HDPE bottles at 40°C/75% RH

Time (months)	60 cm^3 bottle[a]		30 cm^3 bottle[a]	
	Calculated relative humidity (%)	Calculated moisture content (%)	Calculated relative humidity (%)	Calculated moisture content (%)
0	6.7	0.26	6.7	0.26
1	7.6	0.28	7.5	0.28
2	8.5	0.30	8.3	0.29
3	9.4	0.32	9.2	0.31
4	10.4	0.34	10.0	0.33
5	11.4	0.36	10.9	0.35
6	12.3	0.38	11.8	0.37

[a] Three gram silica gel, 24 g tablets/bottle.

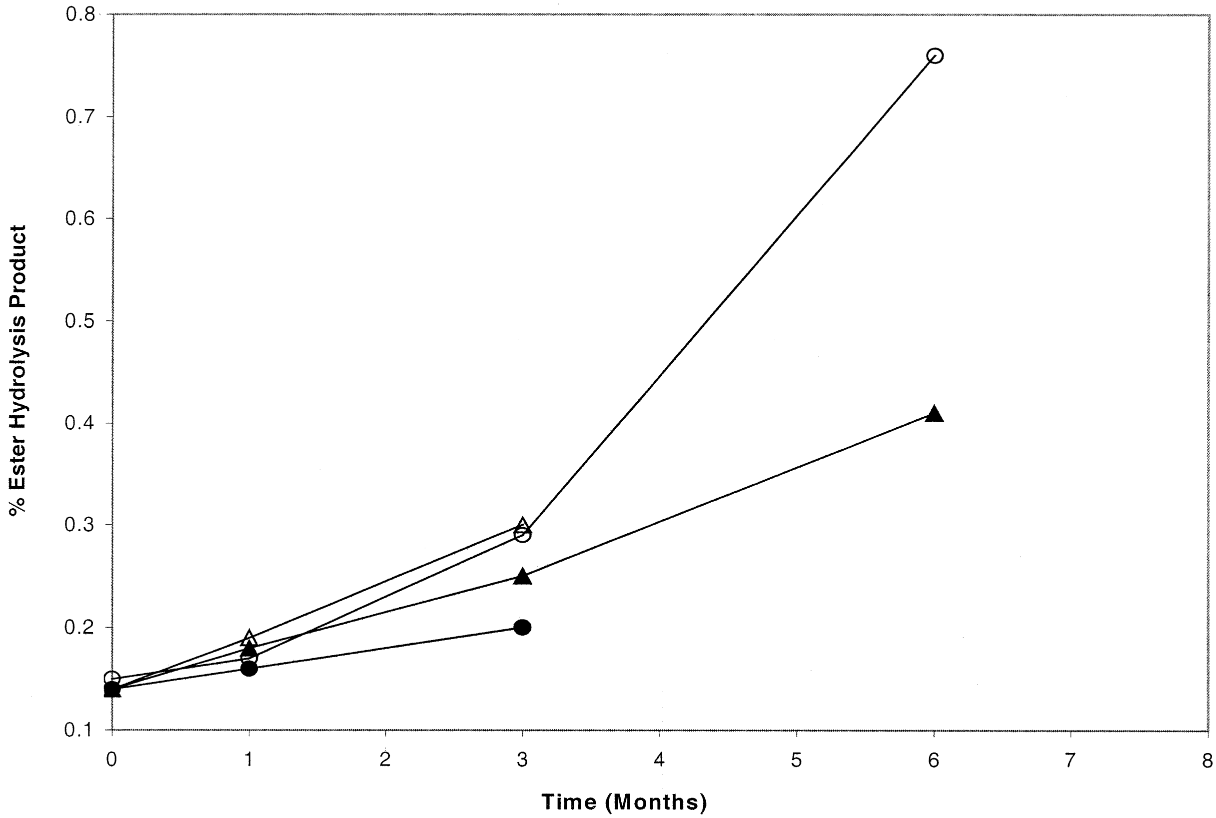

Fig. 2. Stability of tablets in 60 cm^3 HDPE bottles at 40°C/75% RH. (○) 1.5 g silica gel/bottle, 12 g tablets/bottle (50 tablets, 2.0 mg strength); (●) 3 g silica gel/bottle, 6 g tablets/bottle; (△) 1.5 g silica gel/bottle, 12 g tablets/bottle (100 tablets, 1.0 mg strength); and (▲) 3 g silica gel/bottle, 24 g tablets/bottle.

analyzed for the ester degradation product by a validated stability-indicating HPLC method. Ester hydrolysis in the tablets is expressed as area percent of the ester hydrolysis product relative to roxifiban. The limit of quantitation for the ester hydrolysis product using this method corresponds to 0.02% of the drug substance in the tablets (Badawy et al., 1999).

In another experiment, four tablet samples from the same batch were equilibrated at <10, 31, 47 and 60% relative humidities for 24 h. Each tablet sample was then packaged in 75 cm^3 sealed HDPE bottles with 3 g silica gel desiccant canisters (Sorb-it, United Desiccants, Belen, NM) and stored at 25°C/60% RH. Stability of tablets was determined as described above.

2.1.1.2. Effect of packaging configuration on tablet stability. Stability of tablets was evaluated in different packaging configurations involving HDPE bottles. Two HDPE bottle sizes, 30 and 60 cm^3, were used for these studies. Desiccant quantity, number of tablets per bottle, and tablet strength were changed among the different configurations. Different tablet strengths were manufactured using the same formulation by changing tablets weight (tablets compressed from a common granulation). An eight run fractional factorial nested design was used to study the effect of these variables (Table 1). The packaged HDPE bottles were stored in stability chambers at 40°C/75% RH. Tablets were analyzed for the ester hydrolysis product by the above HPLC method at different time intervals. Stability data was analyzed after 3 months using analysis of covariance in (SAS) Statistical Analysis System. A model was used, which allowed for separate intercepts for bottle size and strength within bottle, and separate slopes for the bottle size, strength within bottle size, desiccant within bottle size, number of

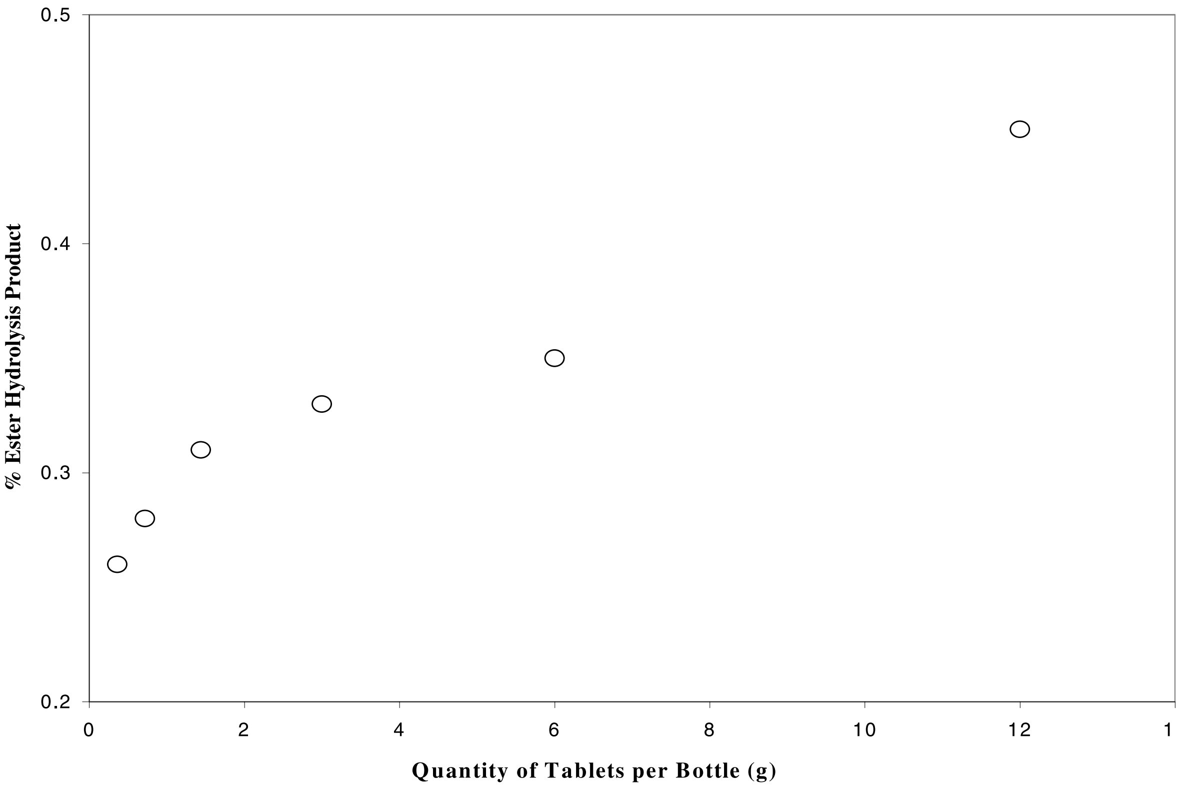

Fig. 3. Effect of tablet quantity per bottle on stability of tablets in 40 cm^3 HDPE bottle containing 0.6 g silica gel desiccant after 3 months at 40°C/75% RH.

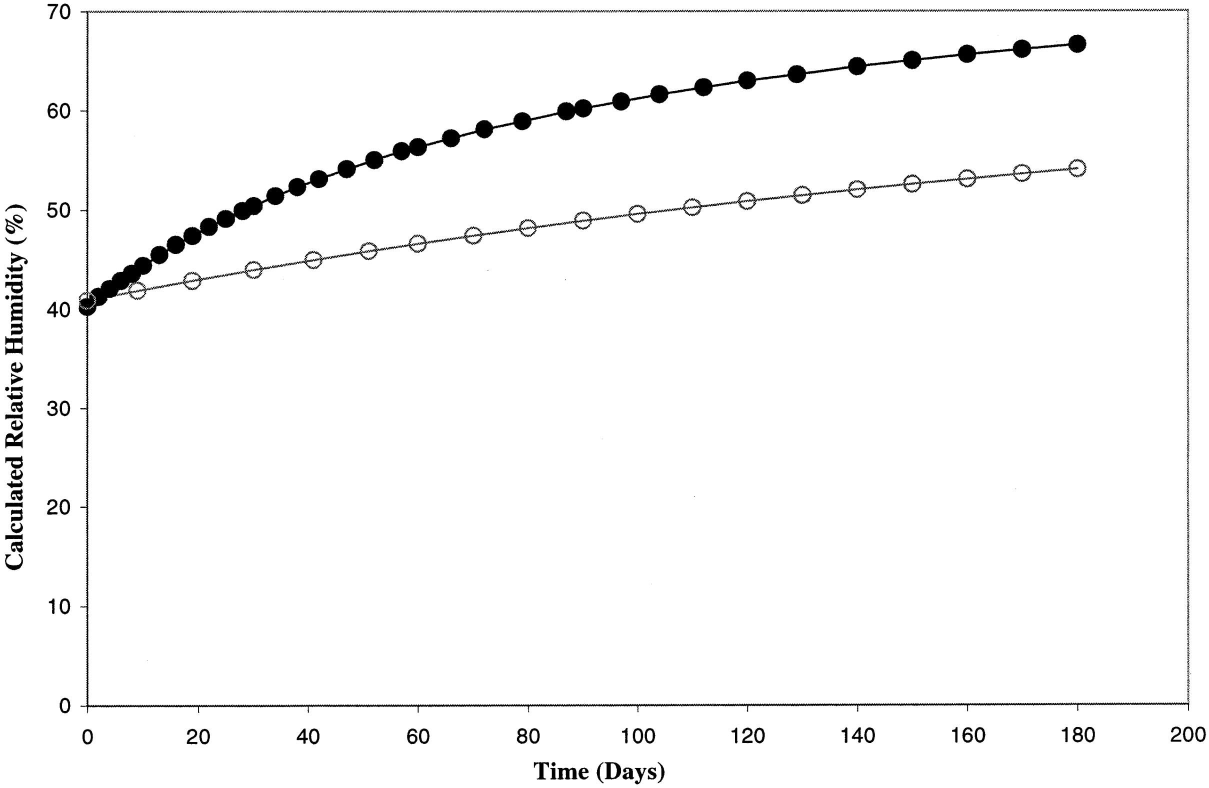

Fig. 4. Calculated effect of tablet fill weight on relative humidity inside the 60 cm^3 HDPE bottle stored at 40°C/75% RH without desiccant. (●) Six gram tablets per bottle, and (○) 24 g tablets per bottle.

tablets. A time-squared term was also added to allow for overall curvature in the model.

Stability of tablets was also evaluated in 40 cm^3 HDPE bottles. In this case, tablets were packaged in different counts in the 40 cm^3 bottle with 0.6 g silica gel desiccant (Sorb-it, United Desiccants). Weight of tablets in the bottles ranged between 0.36 and 12.0 g.

2.1.2. Simulated effect of packaging configuration variables on tablet moisture content and relative humidity inside the package

Tablet moisture content and relative humidity inside the package were calculated using a SDMT model (Kontny, 1988; Zografi et al., 1988; Kontny et al., 1992). The effect of packaging variables on the tablet moisture content and package relative humidity was calculated using the SDMT model. The model uses the moisture sorption isotherms for components inside the package (desiccant and tablets) and the total amount of moisture inside a closed package to predict relative humidity inside the package. Initial moisture content of the formulation was obtained by a loss on drying method at 105°C. The moisture sorption isotherm of the tablets was then obtained using VTI integrated microbalance (VTI Corporation) and the data was fitted to the Guggenheim, deBoer, and Anderson (GAB) equation by non-linear regression (Fig. 1). The GAB equation is as follows (Zografi and Kontny, 1986; Kontny and Mulski, 1989):

$$W = \{W_m C_g K(P/P_0)\}/\{[1 - K(P/P_0)] \times [1 - K(P/P_0) + C_g K(P/P_0)]\}, \quad (1)$$

where W is the weight of water sorbed per weight of dry solid at a relative vapor pressure P/P_0, W_m is the weight of water per weight of dry solid associated with primary binding sites, and C_g and K are constants related to free energy of sorption.

Equation constants determined for the tablets at 40°C were as follows: $W_m = 0.0057$, $C_g = 10.9$, and $K = 0.94$. The GAB equation was then used to determine the moisture content of the formulation at any given relative humidity. The shape of the silica gel moisture sorption isotherm is better described by the Langmuir equation:

$$W = \{W_m C_L(P/P_0)\}/\{1 + C_L(P/P_0)\}, \quad (2)$$

where W, W_m and P/P_0 are similar to the GAB equation and C_L is the Langmuir constant. The Langmuir equation constants for moisture sorption by silica gel were obtained from the literature ($W_m = 0.572$, $C_L = 1.78$; Zografi et al., 1988). The total moisture inside the closed bottle at time zero (t_0) was determined by adding the initial moisture content associated with silica, tablets, and bottle head space. Desiccant moisture content was arbitrarily chosen to be 1.5% based on an average moisture testing results for the desiccant. Similarly, the free initial moisture content of tablets was taken as 0.8% (unless otherwise stated), which corresponds to the equilibrium moisture content at $\approx 30\%$ RH and 25°C. The moisture associated with the bottle head space was determined using the ideal gas law at 40% RH and 25°C. Moisture contributed by the head space to the total moisture was insignificant compared to that contributed by the product and desiccant. An iterative method was used to determine the relative humidity inside the bottle at t_0 (40°C) that satisfies the sorption isotherms for the formulation and the desiccant and the total moisture content inside the package. Convergence was achieved when the difference between the two values was $< 10^{-4}$ g.

The quantity of moisture permeated into the package during a subsequent time interval, $t_1 - t_0$, was calculated using the following equation (Kontny et al., 1992):

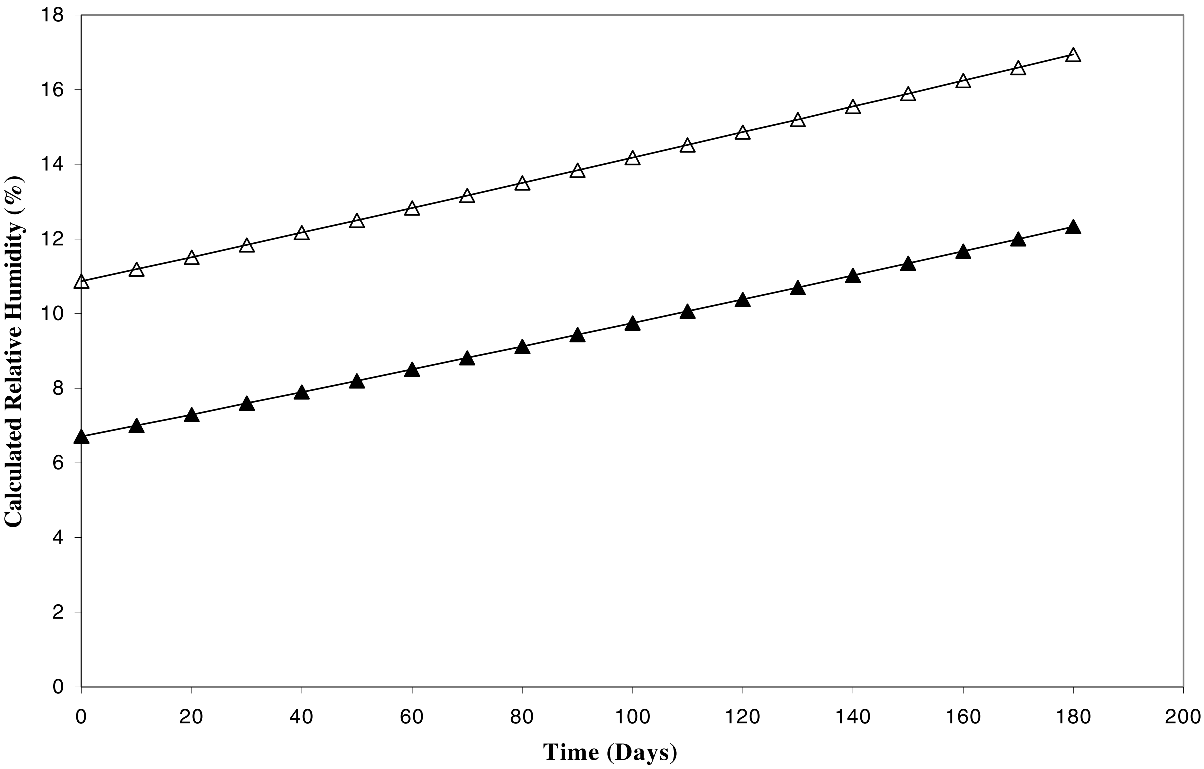

Fig. 5. Calculated effect of tablet initial moisture content on relative humidity inside the 60 cm³ HDPE bottle stored at 40°C/75% RH with 3 g silica gel desiccant. (▲) 0.80% free moisture, and (△) 1.27% free moisture.

$$\int P_m((P/P_0)_{out} - (P/P_0)_{in})\,dt, \quad (3)$$

where P_m is the permeability constant of the entire package, $(P/P_0)_{out}$ and $(P/P_0)_{in}$ are the relative humidity outside and inside the package, respectively, and dt is a time increment. Water vapor permeability constant for the entire package was calculated using the package permeation rates determined by the Mocon water vapor permeability tester (Mocon, Minneapolis, MN) at 40°C. The water vapor permeation rates, at 75% external relative humidity and 0% relative humidity inside the bottle, were 0.000975, 0.00088, and 0.000776 g/package per day for the 60, 30 and 40 cm^3 bottles, respectively. The quantity of moisture permeated during the time interval $t_1 - t_0$ was calculated using a $(P/P_0)_{out}$ value of 0.75 (75% external relative humidity) and was then added to the moisture content at t_0 to yield the total amount of moisture inside the package at t_1. The SDMT model was then used to determine the relative humidity inside the bottle at t_1. Moisture equilibration between package contents is assumed to be much faster than moisture permeation through the bottle. The calculation was then repeated for subsequent time intervals up to 6 months. The time interval was chosen so that the change in relative humidity inside the bottle during this interval is $< 1\%$. Because of the small change in the relative humidity inside the bottle during the time interval, the value of $(P/P_0)_{in}$ in Eq. (3) is assumed to be constant resulting in constant rate of water vapor permeation into the bottle during this time period.

3. Results and discussion

3.1. Effect of humidity on tablet stability

Stability of tablets was strongly dependent on the relative humidity. For tablets stored without desiccant, degradation rate increased exponentially as a function of the initial relative humidity to which tablets were exposed before packaging (Table 2). Since tablets were packaged without desiccant in this case, the calculated initial relative humidity inside the bottle closely approximates that to which tablets were exposed before packaging. Tablets pre-equilibrated at 60% RH showed 34-fold increase in the ester hydrolysis product compared to those stored at $< 10\%$ RH. The presence of desiccant in the packaging configuration lowered the relative humidity inside the package and significantly reduced the effect of initial humidity condition on tablet stability (Table 3). The presence of a desiccant in the packaging configuration minimized the differences in degradation rate between tablets initially exposed to the different humidities. However, the effect of initial humidity condition was still noticeable, particularly for tablets equilibrated at 47 and 60% RH. These tablet showed 1.7- and 3-fold increase in the ester hydrolysis product, respectively, compared to the tablets pre-equilibrated at $< 10\%$ RH. These results confirm the high sensitivity of this formulation to humidity and moisture.

3.2. Effect of packaging configuration on tablet stability

Stability results from the experiments for the fractional factorial nested design are shown in Table 4. Results showed that bottle size had no effect on tablet stability ($P = 0.70$). Although the 60 cm^3 bottle has slightly higher permeability than the 30 cm^3 bottle (0.000975 and 0.000880 g/day per package, respectively), the larger bottle size was not associated with increased degradation according to the experimental design results. The SDMT calculations showed very similar relative humidity values for the two bottles (Table 5), which is in agreement with the results from the experimental design.

Degradation rate decreased with the increase in amount of desiccant per bottle ($P < 0.01$), regardless of tablet quantity or strength (Fig. 2). This effect was predicted by the relative humidity calculations. The calculated relative humidity inside the bottle and tablet moisture content decreased as the desiccant quantity inside the bottle was increased (Table 6). The desiccant serves a dual role in the packaging configuration. The desiccant withdraws moisture from the tablets initially and creates low humidity in the bottle at time zero. Subsequently, the desiccant absorbs moisture that

Table 6
Effect of total desiccant plus tablet mass on tablet stability in the 60 cm^3 HDPE bottle at 40°C/75% RH

Time (months)	3 g Silica gel, 24 g tablets/bottle			1.5 g Silica gel, 12 g tablets/bottle		
	Calculated relative humidity (%)	Calculated moisture content (%)	% Degradant (experimental)	Calculated relative humidity (%)	Calculated moisture content (%)	% Degradant (experimental)
0	6.7	0.26	0.14	6.7	0.26	0.14
1	7.6	0.28	0.18	8.5	0.30	0.18
3	9.4	0.32	0.25	12.4	0.38	0.31
6	12.3	0.38	0.41	18.6	0.48	0.74

permeates through the package over time hence reducing the rate of humidity increase inside the bottle. Both initial tablet moisture content and the rate of increase in tablet moisture content with time decreased with the increase in desiccant quantity. It should be noted that the change in tablet moisture content is very minimal for the studied packaging configurations, particularly for those with high desiccant quantity. Because of the high moisture sensitivity of this product, this small increase in moisture content is still reflected on the concentration of the degradation product.

For a given desiccant quantity, degradation rate increased as the number of tablets in the bottle increased ($P = 0.02$). Since all tablets are compressed using a common formulation, the strength and number of tablets per bottle are two related variables that may be combined to yield the total weight of tablets, which is good measure of bottle fill. The increase in degradation rate with the increase in bottle fill was also observed for the stability studies conducted in the 40 cm^3 bottle (Fig. 3). In agreement with experimental data, the calculated relative humidity and tablet moisture content increased with the increase in tablet weight in the bottle for a constant desiccant quantity (Tables 7 and 8). The higher quantity of tablets in the bottle results in higher total moisture content inside the package at time zero. In the case of low bottle fill, the higher ratio of desiccant to tablet results in lower relative humidity and tablet moisture content, which are maintained during the study period. It is noteworthy that the bottle with lower tablet quantity shows higher rate of increase in relative humidity and moisture. However, because of the lower initial values, lower humidity and tablet moisture content are preserved during the study period. In the case of the 40 cm^3 bottle with low desiccant quantity (0.6 g), relative humidity for the low bottle fill eventually approached that for the high fill at the 6 months time point. It should be noted that, because of the higher slope in the case of bottle with low tablet fill, the relative humidity inside this bottle will eventually exceed that for the bottle with the high tablet fill, if the calculations are conducted for sufficiently long time period. The higher rates of humidity and moisture increase for the low tablet fill are attributed to the lower weight of tablets available for moisture distribution. This was shown in the calculations for bottles without desiccant (Fig. 4). In this case, moisture associated with the tablets at time zero is similar for the two tablet fills. The rate of increase in moisture content is again higher for the lower tablet fill resulting in higher moisture value at all time points. Thus, in absence of desiccant, the lower tablet fill is expected to have higher degradation rate, contrary to the finding in the case of bottles with desiccant.

Relative humidity and moisture content were calculated for tablets with higher initial moisture (1.27% free moisture). This moisture value corresponds to the equilibrium moisture content at $\approx 50\%$ RH and 25°C. Humidity and moisture numbers were compared to those tablets with lower initial moisture (0.8%). Weight of tablets was 24 g in both cases. Results showed that relative humidity at time zero is higher for the tablets with higher initial moisture due to the increased total moisture inside the package (Fig. 5). Subsequently, the rate of increase in relative humidity with time was similar in the two cases. However, higher humidity is maintained through out the study period for the tablets with increased initial moisture, due to the higher starting value at time zero. Thus, tablets with higher initial moisture are expected to have somewhat higher degradation rate, despite the presence of large quantity of desiccant (3 g silica gel per bottle).

4. Conclusions

This study emphasized the significance of package design to the stability of a moisture sensitive compound such as roxifiban. Desiccant quantity, tablet weight and initial tablet moisture content before packaging were found to have an effect on tablet stability. The use of theoretical calculations utilizing the SDMT model was shown to be useful in the understanding of packaging requirements for this product. Calculated relative humidity data corroborated experimental findings regarding the effect of the above variables on tablet stability.

Table 7
Effect of tablet fill weight on tablet stability in the 60 cm³ HDPE bottle at 40°C/75% RH with desiccant

Time (months)	3 g Silica gel, 24 g tablets/bottle			3 g Silica gel, 6 g tablets/bottle		
	Calculated relative humidity (%)	Calculated moisture content (%)	% Degradant (experimental)	Calculated relative humidity (%)	Calculated moisture content (%)	% Degradant (experimental)
0	6.7	0.26	0.14	3.0	0.14	0.14
1	7.6	0.28	0.18	4.0	0.18	0.16
3	9.4	0.32	0.25	6.0	0.24	0.20
6	12.3	0.38	0.41	9.2	0.31	ND[a]

[a] No data.

Table 8
Effect of tablet fill weight on tablet stability in the 40 cm^3 HDPE bottle at 40°C/75% RH with desiccant

Time (months)	0.6 g Silica gel, 6 g tablets/bottle			0.6 g Silica gel, 0.72 g tablets/bottle		
	Calculated relative humidity (%)	Calculated moisture content (%)	% Degradant (experimental)	Calculated relative humidity (%)	Calculated moisture content (%)	% Degradant (experimental)
0	7.8	0.28	0.14	2.5	0.12	0.14
1	11.4	0.36	0.20	6.5	0.25	0.16
3	19.2	0.49	0.35	15.7	0.43	0.28
6	31.6	0.66	1.23	31.0	0.65	1.04

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