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DRUG-EXCIPIENT INTERACTIONS OF SEPROXETINE MALEATE HEMI-HYDRATE: ISOTHERMAL STRESS METHODS

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ABSTRACT

Seproxetine maleate hemi-hydrate was originally formulated with pregelatinized starch, to provide 1 and 20 mg free base equivalent gelatin capsule dosage forms for storage at 25°C and 40°C. HPLC analysis after 3

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months revealed the formation of a 1,4 Michael addition adduct in each case. No additional degradation products were detected. To pursue a less interactive formulation, 5 mg formulation equivalent mixtures of seproxetine maleate hemi-hydrate were prepared with pregelatinized starch, lactose, and talc; thus, three distinctly different excipient classifications. These were evaluated in additional isothermal stress experiments at 25°C, 40°C, and 50°C. The results indicated that each excipient interacted with the drug in a unique chemically and thermally dependent manner. Thus, the drug-pregelatinized starch data may be represented by an Arrhenius type relationship, with activation energy of 32 kcal/mol, and formation of the previously described adduct. However, the drug-lactose data suggest reaction with an impurity in which the equilibrium is temperature dependent. Finally, the drug-talc data correspond to either sigmoid kinetics or a threshold temperature which must be exceeded for formation of an amide. A final choice of excipient is thus complicated by having to project these three solid state reactions, of different thermal characteristics, to the shelf life of the product.

INTRODUCTION

For efficient processing on large scale equipment, it is normally necessary to incorporate several types of excipients in a pharmaceutical formulation. These will include diluents, binders, lubricants, glidants, and disintegrants. However, these excipients have the potential to interact with the active drug substance and thus may have an adverse effect on an important property, such as stability or dissolution profile. For efficient operation, it is necessary for a pharmaceutical company to develop accelerated procedures for determining whether a significant interaction

between formulation components can occur. The structure of a generalized preformulation testing program, which includes accelerated testing methods, has been described.[1] As one example, these methods have been focussed to the determination of the most excipient compatible salt of mefenidil.[2] In a separate study, the effects of various excipients on the lactose browning reaction were investigated.[3] A mechanism for this reaction has been postulated and Arrhenius-type plots have been used to extrapolate elevated temperature stability data to room temperature stability.[4] Elevated temperature data is of greatest utility when a clear relationship with room temperature data can be established. In one case, an attempt was made to correlate excipient-drug data of ten days at 55°C with 17-27 months at 25°C.[5] In more definitive experiments, one month at 60°C was determined to be a more severe condition that two years at 25°C.[2] A further study elucidated the circumstances under which data obtained in three weeks at 55°C may be extrapolated to a five year shelf life at 20°C.[6]

In previous experiments, seproxetine maleate hemi-hydrate (SMH) stored at 40°C or 50°C for one month was determined to be stable. However, increased quantities of the 1,4-adduct were detected in a stability study of SMH as 1 and 20 mg capsules in a pregelatinized starch (PGS) formulation stored at 25°C and 40°C. Since starch may contain 7-15% surface water,[7] and excipient associated moisture can affect solid state drug stability[8,9], the free water was suspected to be of significance to the degradation reaction, either directly or catalytically.

To pursue a less interactive excipient, three excipients were selected for incorporation with SMH in isothermal stress evaluations: SMH was selected as the reference excipient; lactose was included as it contains only water of crystallization; talc was selected since it is hydrophobic and

contains neither surface water nor water of crystallization.[7] The objective was to establish a mechanistic understanding of the solid state reactivity of SMH. In this manner, the applicability of isothermal stress data to reformulation options could be appropriately assessed.

METHODS

SMH was supplied by Eli Lilly and Company (Indianapolis, Indiana) as pharmaceutical grade bulk chemical. Pregelatinized starch (PGS) and lactose were NF quality. Talc was USP grade. Pregelatinized starch-dried (PGS-D) was prepared by drying PGS for two hours in a vacuum oven at 60°C. All materials were passed through a 20-mesh sieve. For the isothermal stress experiments, 12 g batches containing 2.2% drug (free base equivalent) were prepared; this corresponds to a 5 mg formulation equivalent, geometrically intermediate to the original 1 and 20 mg capsule data. One gram samples of these batches were placed into 10 mL amber glass containers and tightly sealed. These drug-containing samples, along with samples of the individual excipients, were placed in 40°C and 50°C storage ovens. Individual containers were removed after one, two, or four weeks for analyses. Water content of the excipients and mixtures was determined by Karl Fisher analysis using the AquaStar C1000 system. The SMH samples were analyzed by HPLC using a Hewlett Packard series 1050 system with an ABI 1000S diode array detector. Analyses were accomplished using a reversed-phase HPLC system equipped with a DuPont RX-C8 (25 cm x 4.6 mm ID) column, UV detection at 215 nm (0.2 AUFS), and mobile phase comprising 40% acetonitrile/ 60% triethylamine buffer (99% water, 1% triethylamine, pH adjusted to 6.0 with phosphoric acid). A flow rate of 1.0 mL/min and sample injection of 20 microliters were used. These HPLC conditions separate all process intermediates, formulation

components, and known degradation products from seproxetine. Additionally, no interfering peaks were found from excipients that had been stored at 65°C for two weeks. Quantitation of individual degradation products was achieved using the high/low approach.[10] Variability analysis was conducted for the 1,4-adduct using samples that averaged 0.06% and 1.60% of this component; the coefficient of variation was 19% and 3.6%, respectively. Sample preparation for assay of the 5 and 20 mg formulations was accomplished by emptying the contents of one capsule (or weight equivalent of one capsule) into a 10 mL vial; either 3 mL (for 5 mg) or 10 mL (for 20 mg) of mobile phase was pipetted onto the material, after which the vial was capped and hand-shaken. The solution was filtered through an Acrodisc® syringe filter (0.2 μm). For the 1 mg formulation, the contents of four capsules were emptied into a 10 mL vial; 5 mL of acetonitrile was pipetted onto the material, after which the vial was capped and hand-shaken. The solution was filtered through an Acrodisc® syringe filter (0.2 μm) and the acetonitrile evaporated to dryness. The residue was reconstituted with 2 mL of mobile phase and filtered through a Acrodisc® syringe filter. Two replicates per sample were used for the 5 mg compatibility studies; six replicates per sample were used for the 1 mg and 20 mg formulations.

Solution storage experiments were used to identify potential degradation products. For this purpose, solutions were stored for two to four weeks in pH 8 buffer, 0.1 N HCl, or pH adjusted water.

RESULTS

Solution Storage

In mildly alkaline conditions (pH 8 buffer at 40°C for one month) HPLC analysis reveals one major degradation peak, the 1,4-adduct, with no

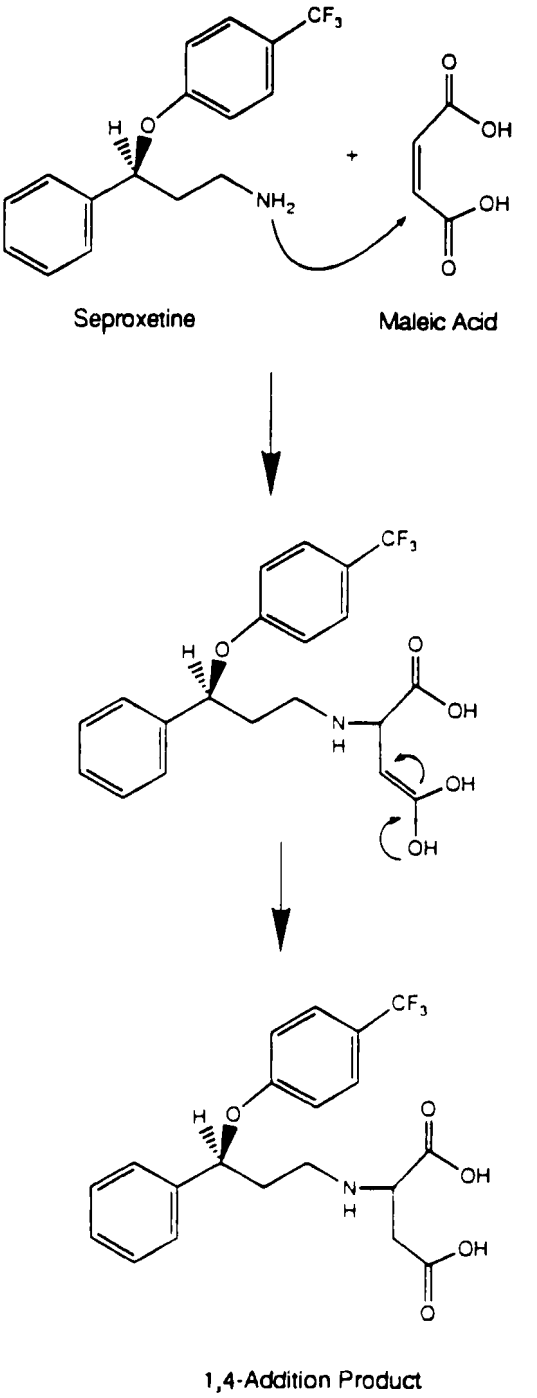

FIGURE 1. Degradation mechanism of seproxetine maleate hemihydrate via 1,4 Michael addition.

increase in other impurities. The reaction scheme is illustrated in Figure 1. A further study of SMH in pH adjusted water (stored at 40°C for two weeks) indicated that optimum adduct formation occurred in the pH range of 5.5 to 8.5, with no formation below pH 3. Increased concentrations of fumaric acid (the trans isomer of maleic acid) were found with increased levels of 1,4-adduct formation. This increase in fumaric acid suggests an equilibrium in which maleic acid can either convert to the trans isomer or react with seproxetine to form the adduct. Storage of SMH at acidic conditions (0.1N HCl at 40°C for one month) yields different degradation impurities, as illustrated by the reaction scheme of Figure 2 (ether cleavage and dehydration). Additional experiments, in which 1,4-adduct reference sample was stored in pH adjusted water at either room temperature or 40°C for 2 weeks, showed this adduct to be stable with no reverse degradation to SMH or maleic acid.

Formulation Stability

In previous experiments, bulk material stored at 40°C or 50°C was found to be stable. However, increased quantities of the 1,4-adduct were detected in a stability study of SMH as 1 and 20 mg capsules in a PGS formulation stored at 25°C and 40°C. The three month storage results, quantifying the 1,4-adduct and total related substances for these capsules, are given in Table I; initial analyses were conducted only for the bulk material, not for any of the formulations.

Several significant features may be observed from this data. First, the difference between the three month 20 mg capsule data at room temperature and the zero time bulk material data reflects the combined effects of formulation processing and three month storage. From the limited degree of degradation, it may be concluded that the processing factors are not significant to degradation (in this case). Second, for the

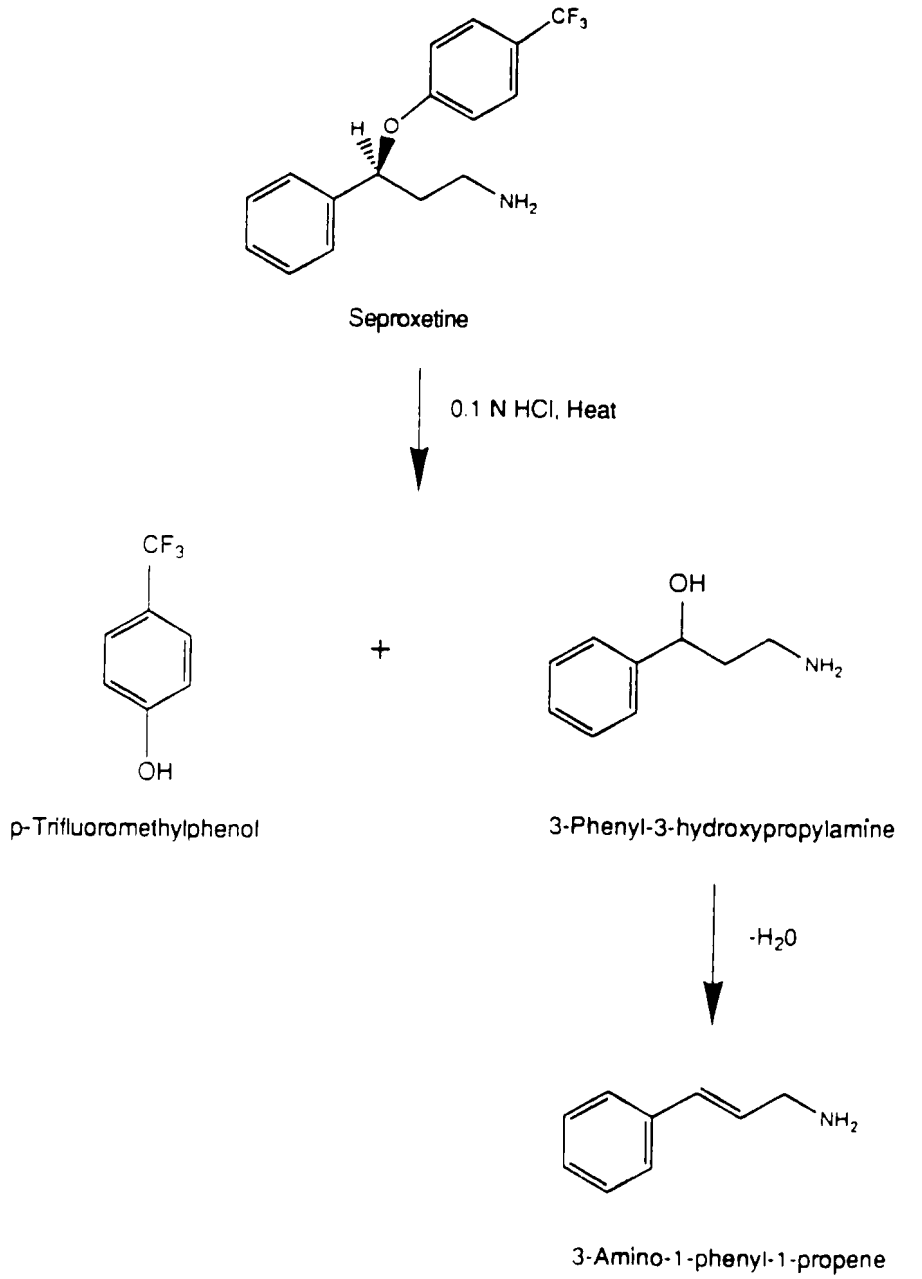

FIGURE 2. Degradation scheme of seproxetine in acidic solution.

TABLE 1. DEGRADATION PRODUCT FORMATION IN FORMULATED SEPROXETINE MALEATE CAPSULES AFTER THREE MONTHS STORAGE

CAPSULE	1,4-ADDUCT		TOTAL DEGRAD PRODS	
DOSE	25°C	40°C	25°C	40°C
1 mg	1.22%	17.34	1.80%	17.95
20 mg	0.21	1.57	0.71	2.05

Initial bulk material assays: 0.07% 1,4-adduct, 0.55% total degradation products.

four sets of data (two capsule strengths stored at two storage conditions), the difference between total related substances and 1,4-adduct is constant; this indicates that the single reaction mechanism has been identified (Figure 1). Finally, the rate of formation of 1,4-adduct is increased at the higher storage temperature. This rate increase, along with a defined reaction mechanism, satisfies the basic requirements for appropriate utilization of isothermal stress testing methods.

Excipient Compatibility Studies

At each storage interval, separate samples were removed for titrimetric water analysis. The data is shown in Figure 3. For PGS, there appears to be a slight decrease in water content with storage temperature. This may be attributed to a weakening in the aluminum cap seal with increased vapor pressure build up.

The storage stability data for the experiments of this study are represented in Figures 4-6. The specific data for PGS and PGS-D are shown in Figure 4. As expected, reducing the water content of the starch resulted

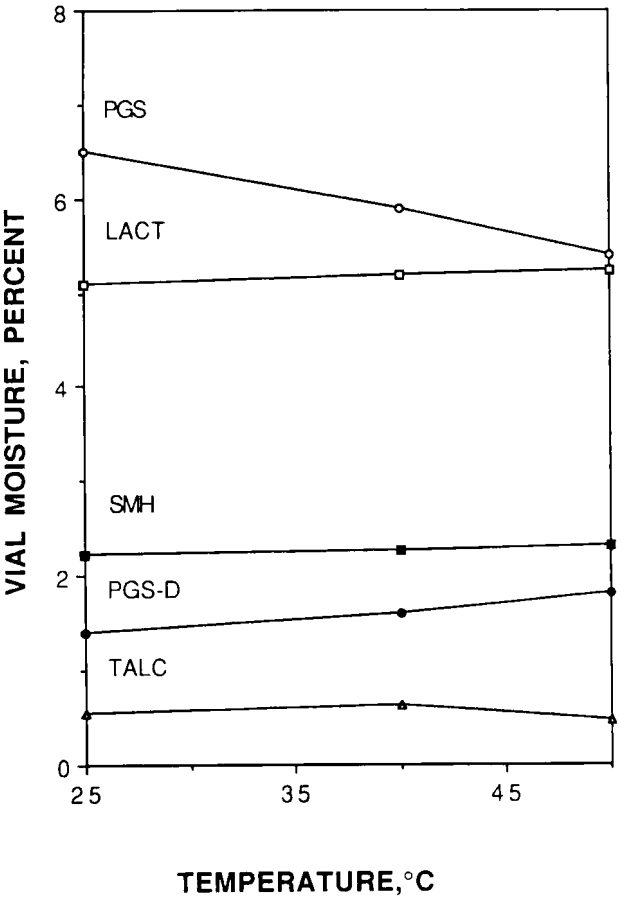

FIGURE 3. Influence of storage temperature on vial moisture content.

in improved stability. Also, the degradation product was determined to be the 1,4-adduct in each case.

The degradation product for the talc-SMH mixtures was identified as an amide, which is the condensation product of SMH (Figure 5). This data is given in Figure 6.

The degradation product found in the drug-lactose mixture was not identified. However, lactose has been known to react with primary amines via the hydroxyl groups, resulting in the formation of yellow-brown pigments.[3,4] This is commonly referred to as the Maillard (or lactose

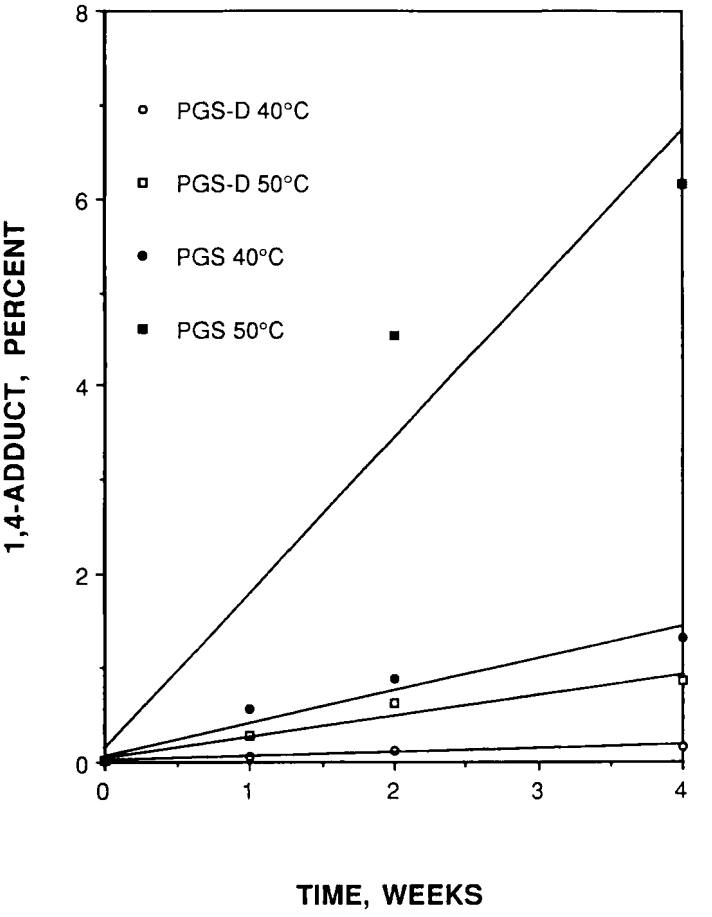

FIGURE 4. Effect of time and temperature on degradation products of seproxetine maleate hemihydrate - pregelatinized starch mixtures.

browning) reaction. Yellow discolorization of the samples of the current study was observed after one week storage, thus physically suggesting the Maillard reaction. The data is given in Figure 7.

DISCUSSION

This study was initiated when it was determined that there was a solid state interaction between SMH and PGS, resulting in the exclusive

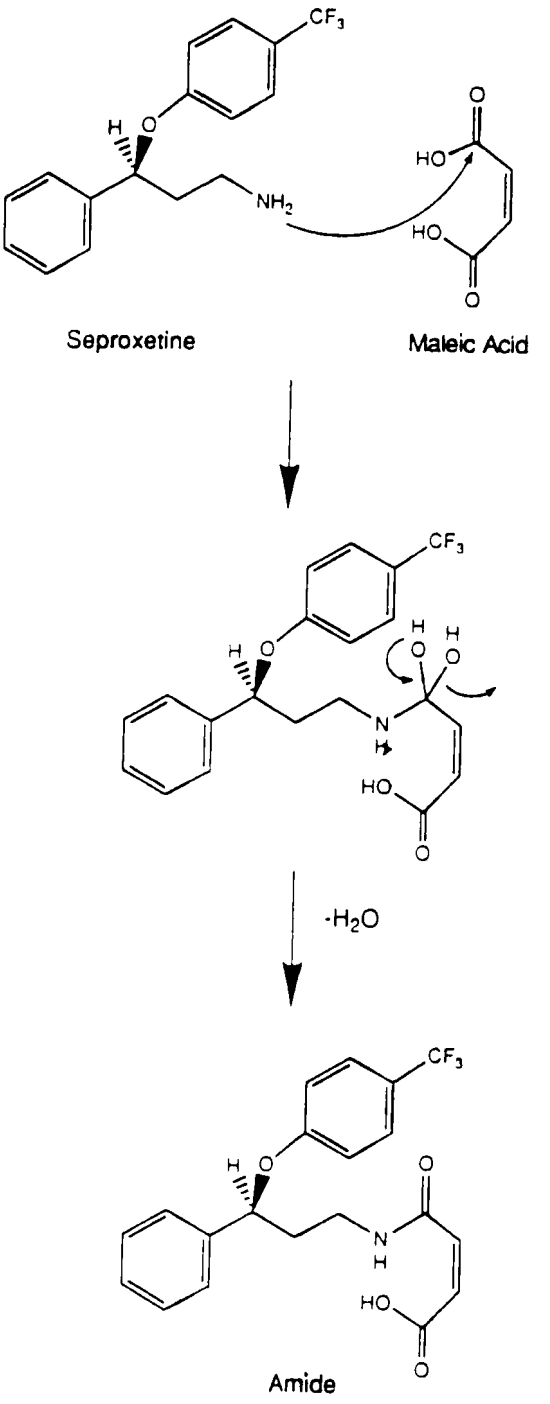

FIGURE 5. Degradation mechanism of seproxetine maleate hemihydrate via carbonyl attack.

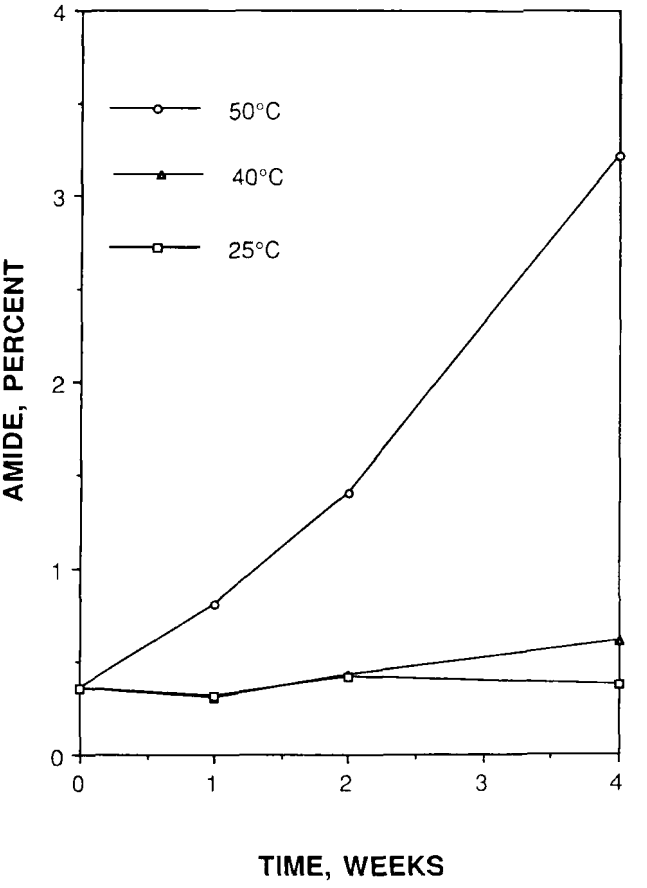

FIGURE 6. Effect of time and temperature on degradation products of seproxetine maleate hemihydrate - talc mixtures.

formation of a Michael addition adduct. As non-bound water from starch was suspected to be involved in this interaction, a basis for alternative excipient selection was suggested. Isothermal stress experiments involving PGS, these alternative excipients, and SMH, indicated the alternative excipient selection process to be considerably more complex, as additional interaction products were formed in the solid state. The data of Figure 4 is specific to the formation of 1,4-adduct for the starch based excipients. For both PGS and PGS-D the reaction is assumed to be zero order, and the ratio

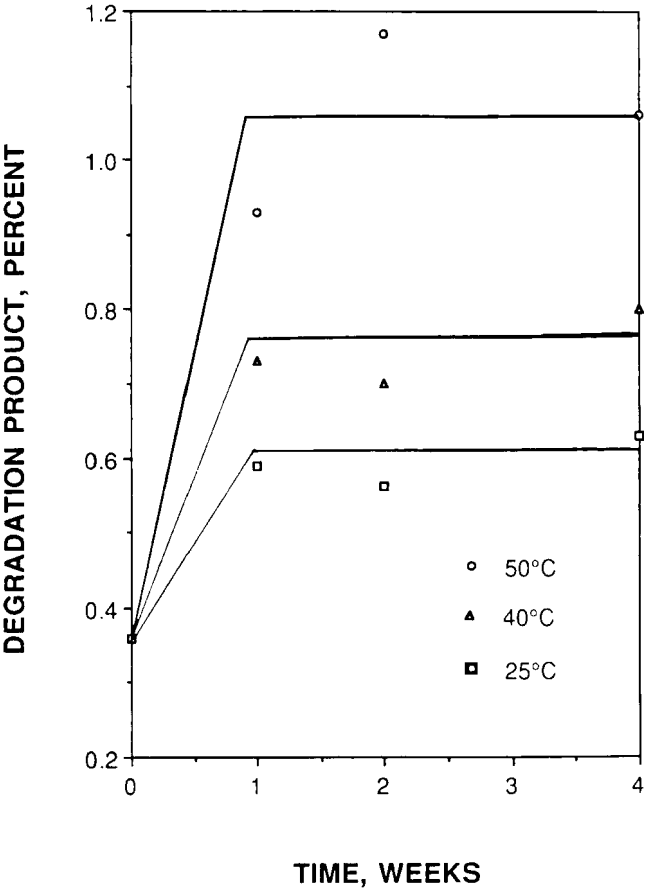

FIGURE 7. Effect of time and temperature on degradation products of seproxetine maleate hemihydrate - lactose mixtures.

of 50°C reaction rate to 40°C reaction rate is computed to be approximately five. To establish a basis for extrapolation of data to room temperature, the assumption is made that the variation of reaction rate constant with temperature may be represented by an Arrhenius type relationship. Thus, in differential form,

$$\frac{d \ln k}{dT} = \frac{E_a}{RT^2}, \qquad \text{(Eq. 1)}$$

or, in integrated form,

$$\log_{10}\frac{k_2}{k_1} = \frac{E_a\,(T_2 - T_1)}{2.303\,R\,T_1T_2}\,. \qquad \text{(Eq. 2)}$$

From Eq. 2, E_a is determined to be 32 kcal/mol. Substituting this value for E_a back into Eq. 2, the reaction rate ratio of 40°C to 25°C is extrapolated to be 13.6. The original capsule formulation data of Table I may be used to verify these computations. Thus, the ratios of the 40°C to 25°C increase in 1,4-adduct at three months for the one and twenty mg capsules are calculated to be 15.0 and 10.7, respectively, in close agreement with the extrapolated figure. This interrelates the original three month data at 25°C and 40°C for filled capsules (Table I) with the one month excipient compatibility data at 40°C and 50°C (Figure 4). A practical manner of interpreting this data is that one month at 40°C is predictive of one year at room temperature, and that one month at 50°C projects to five years at room temperature.

The talc-drug interaction data represented in Figure 6 reveals a different pattern of interactive behavior. The talc data at 25°C does not detect an interaction; however, this is approaching the sensitivity of the instrument. The talc data at 40°C suggests a lag time for degradation reaction, with amide increasing by 0.25% in four weeks. However, the 50°C data shows a 2.86% amide increase, and the reaction may still be in the accelerative phase at the end of the test period. These data may be reconciled in either of two manners. The first would be that 40°C is the threshold reaction temperature; in this case the amide reaction would not be expected to occur at room temperature storage conditions. The second would be that the mechanism is characterized by sigmoid kinetics; in this

case, following a temperature dependent induction period, a room temperature reaction would occur.

The lactose data of Figure 7 suggest a temperature dependent leveling off of Maillard product. Leveling off patterns have been attributed to reaction with surface impurities[5] (the presence of monosaccharide impurities in lactose has been suggested[3]). However, in that case the equilibrium was shown to be temperature independent, whilst in the current study the equilibrium is temperature dependent. One explanation of the current results would be that the reaction between lactose-associated-impurity (or lactose itself) and drug is reversible and endothermic.

CONCLUSION

In the course of this study three solid state reaction patterns of SMH with excipients have been shown to occur, with the following characteristics:

1. The Michael addition reaction occurs with PGS and PGS-D, though to a greatly reduced extent with the dried material. The data may be fit to a zero order reaction equation with activation energy of approximately 32 kcal/mol. In practical terms, one month at 40°C thus corresponds to one year at 25°C and one month at 50°C thus corresponds to five years at 25°C,
2. An amide formation reaction takes place with talc . From the limited data, it is not possible to distinguish whether this reaction follows sigmoid kinetics, or exhibits a threshold temperature of about 40°C. The differentiation is significant as in the former case, after a lag phase, the reaction would be expected to occur at room temperature;

however, in the latter case the reaction would not be expected at room temperature,

3. A Maillard reaction occurs with lactose only. The data is suggestive of a drug-impurity reaction, with the equilibrium being temperature dependent

From this discussion, it is clear that a single isothermal stress condition will inherently bias the results to the temperature selected. Thus, appropriate selection of the 'best' excipient for SMH first requires a determination of solid state reactivity of the drug, then an assessment of the relative influence of the various solid state reactions over a projected shelf life.

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