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Research paper

Influence of formulation technique for hydroxypropyl-β-cyclodextrin on the stability of aspirin in HFA 134a

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Abstract

The objective of this study was to determine the influence of the formulation technique for 2-hydroxypropyl-β-cyclodextrin (HPβCD) on the stability of aspirin in a suspension-based pressurized metered-dose inhaler (pMDI) formulation containing a hydrofluoroalkane (HFA) propellant. HPβCD was formulated in a pMDI as a lyophilized inclusion complex or a physical mixture with aspirin. A pMDI formulation containing aspirin alone was used as the control. The chemical stability of aspirin in each pMDI formulation was determined over 6-months storage at 5, 25 and 40°C. The quantity of water taken up into the pMDI canister was determined by Karl Fisher titration after storage for 6 months. Differential scanning calorimetry (DSC) was used to confirm the formation of a complex between HPβCD and aspirin. Aspirin in the lyophilized inclusion complex exhibited the most significant degree of degradation during the 6-months storage, while aspirin alone in the pMDI demonstrated a moderate degree of degradation. Aspirin formulated in the physical mixture displayed the least degree of degradation. The water uptake study showed that water ingress occurred to the greatest extent for formulations containing aspirin and HPβCD physical mixture, and to the least extent for formulations containing aspirin alone. Finally, the DSC study indicated that an inclusion complex was formed in situ in the pMDI formulations containing the HPβCD and aspirin physical mixture. In conclusion, HPβCD may be used to enhance the stability of a chemically labile drug, but the drug stability may be affected by the method of preparation of the formulation.

Keywords: 2-Hydroxypropyl-β-cyclodextrin; Aspirin; Hydrofluoroalkane; pMDI; Stability; Formulation technique

1. Introduction

Cyclodextrins have been used extensively to form non-covalent inclusion complexes with many substances. The inclusion complex normally exhibits higher aqueous solubility and greater chemical stability [1]. In addition, it was shown that some cyclodextrin derivatives could sustain the release rate of drugs following subcutaneous [2] and oral administration [3]. However, α- and β-cyclodextrins cause severe nephrotoxicity and are unsafe for parenteral use [1]. 2-Hydroxypropyl-β-cyclodextrin (HPβCD), a chemically modified β-cyclodextrin, has a greater aqueous solubility and lower parenteral toxicity, compared with its parent compound, β-cyclodextrin, and is a potential ingredient in pharmaceutical dosage forms [1]. The possible advantages of including HPβCD in a dosage form include improved chemical stability, increased aqueous solubility and enhanced bioavailability of the therapeutic drug [1].

In this study, HPβCD was formulated in a pressurized metered-dose inhaler (pMDI) as a lyophilized inclusion complex or a physical mixture with the model drug, aspirin. Aspirin contains a substituted phenyl ester group which is a nucleophilic center susceptible to hydrolysis and other acyl transferring reactions [4]. Aspirin can undergo an acid-catalyzed ester hydrolysis, as well as a base-promoted ester

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hydrolysis. Under acidic conditions, the hydrolysis of the ester group is accelerated by the addition of a proton to the oxygen of the carbonyl group and the nucleophilic attack from a water molecule at the carbon in the carbonyl group, leading to the formation of salicylic acid (SA; Fig. 1). Whereas under alkaline conditions, the alkoxide ion directly attacks the nucleophilic center causing the detachment of the ester group and formation of salicylic acid as the hydrolysis product. Salicylsalicylic acid (SSA; Fig. 1) and acetylsalicylsalicylic acid (ASSA; Fig. 1) are also among the degradation products of aspirin and are esters produced from the carboxylic acid group of aspirin or SA reacting with the hydroxyl group of SA. The degradation products of aspirin in a solution aerosol formulation containing trichloromonofluoromethane in the presence of surfactants include SA, SSA and ASSA [5].

HPβCD was shown to form an inclusion complex with aspirin at a molar ratio of 1:1 in aqueous solution [6]. It was shown that this inclusion complex could accelerate or retard the hydrolysis reaction of aspirin depending on the chemical environment [6]. Retardation of the hydrolysis reaction was due to shielding of the functional ester group from the attacking nucleophile since the active site of the molecule was completely included within the cyclodextrin cavity [6]. Acceleration of the rate of aspirin hydrolysis was ascribed to only partial inclusion of the ester molecule within the cavity, leaving the active nucleophilic center sterically fixed in close proximity to the alkoxide ion from the hydroxyl group of the HPβCD molecule, which catalyzed the hydrolysis of aspirin molecules [6].

The objective of this study was to determine the influence of the formulation technique for HPβCD on the stability of the chemically labile drug aspirin formulated as a lyophilized inclusion complex or a physical mixture in a suspension-based pMDI formulation containing a hydrofluoroalkane (HFA) propellant.

2. Materials and methods

2.1. Materials

HPβCD (encapsin, molecular weight of 1309–1425 with an average substitution degree of 4–5) was purchased from the American Maize Products Company (Hamond, IN). Aspirin and SA were obtained from Sigma (St. Louis, MO). SSA and ASSA were obtained from Fisher Scientific (Houston, TX). All chemicals were used as received. 1,1,1,2-Tetrafluoroethane (HFA 134a; DymelÆ 134a; DuPont Chemicals, Wilmington, DE) was filtered through a refrigeration filter-drier (Type C082, Sporlan Valve, Washington, MO) prior to use to eliminate moisture.

Aluminum aerosol cans (Cebal S.A., Bellegarde, France) were used to contain the pMDI formulations. Continuous spray valves (Valois of America, Greenwich, CT) were used for the aerosol canisters.

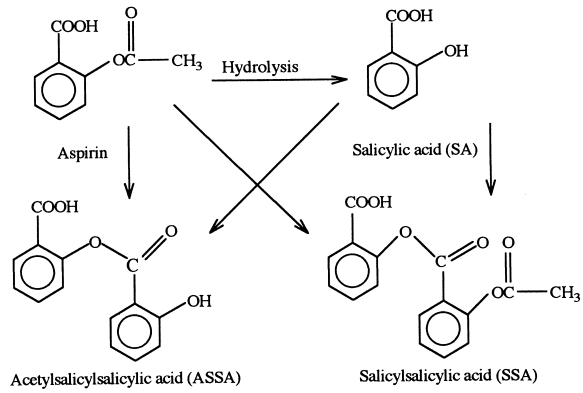

Fig. 1. Schematic illustration of the chemical structures of aspirin, SA, SSA and ASSA.

2.2. Methods

2.2.1. Analysis of aspirin and its degradation products

An HPLC method was developed and validated to quantitate aspirin and its degradation products. The HPLC was composed of a Shimadzu Liquid Chromatography system (Model LC-9A, Shimadzu, Columbia, MD) and a computer-based software program interfaced with the system (Class-VP, Shimadzu, Columbia, MD). The mobile phase was prepared by adding 12.5 ml of acetic acid to 450 ml of water and diluting with methanol to 1 l. A 250 × 4.1 mm 10 μ C18 column (Alltech Associates, Deerfield, IL) and a UV spectrophotometric detector (Model SPD-6A, Shimadzu, Columbia, MD) operating at 242 nm were employed. The flow rate was controlled at 1.0 ml/min with a run time of 15 min. System suitability was established prior to performing the analysis of each batch of unknown samples. The criteria for system suitability used in this study was: the linearity of standard curve should be greater than 0.990; the relative standard deviation (RSD) of five consecutive replicate injections should be less than 2%; the number of theoretical plates should be greater than 900 plates/column; the peak resolution should be greater than 2; and the peak asymmetry (i.e. tailing factor) should be less than 2.

2.2.2. Formation of the lyophilized inclusion complex

Aspirin and HPβCD were mixed in a molar ratio of 1:1 (7.5×10^{-3} moles of each) and dissolved in 500 ml of purified water to form an aqueous solution. The solution was subsequently submerged in dry ice to freeze, and lyophilized thereafter using a Labconco Freeze Dry System (Model 77510, Labconco, Kansas City, MO) for 72 h. The lyophilized samples were formulated into pMDIs or subjected to HPLC testing immediately following lyophilization. The degradation products were quantitated by HPLC following the preparation process of the inclusion complex.

2.2.3. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to confirm the formation of an inclusion complex between HPβCD

and aspirin using a Model 2920 Modulated DSC (TA Instruments, New Castle, DE). An accurately weighed amount of sample was placed in an aluminum pan which was then sealed with a hand-operated crimper (TA Instruments). The heating rate was controlled at 10°C/min over a temperature range of 20 to 160°C. DSC was performed for aspirin alone, the physical mixture of aspirin and HPβCD, and the lyophilized complex. The physical mixture was prepared by physically blending the aspirin and HPβCD together by geometric dilution.

2.2.4. Preparation of the pMDI formulation

A physical mixture of HPβCD and aspirin was prepared in a molar ratio of 1:1 for comparison with the inclusion complex. An accurately weighed aliquot of the inclusion complex, the physical mixture, or aspirin alone as the control, each containing equivalent amounts of aspirin, were placed in aluminum aerosol cans. The physical mixture was prepared by directly adding the aspirin and HPβCD into the aerosol cans. Continuous spray valves were crimped onto the aerosol cans using a propellant compressor pump (Pamasol Model P2005, Pamasol Wili Mader AG, Pfaffikon, Switzerland). Ten grams of HFA 134a was filled into the canister through-the-valve by a small scale pressure filling machine (Pamasol Model P2008).

2.2.5. Chemical stability of aspirin in pMDI formulations

The finished aerosol canisters were stored at 5, 25 and 40°C for up to 6 months, and the chemical stability of aspirin was monitored over the storage period. At the time of assaying, the pMDI canister was removed from storage. After the canister was cooled to 0°C in a freezer, it was immediately punctured at the neck position and the propellant was allowed to slowly evaporate off at 25°C. Aspirin was recovered from the canister and dissolved in the mobile phase for HPLC analysis. The method of recovery of aspirin from the canister was validated using a known standard.

2.2.6. Water content determination

Water uptake into the pMDI canister was determined by Karl Fisher titration (Aquatest 8, Photovolt, Indianapolis, IN) after storage for 6 months using the same procedure as reported previously [7]. Briefly, the titrator was blank titrated to less than 10 μg of water. Each pMDI canister was actuated five or ten times into the titrator, depending on the actual water content in the individual unit. The water content of HPβCD, aspirin and HFA 134a prior to the formulation was determined using the same method, respectively. The detection limit of the method utilized in this study was determined to be 10 ppm.

2.2.7. DSC study of the physical mixture recovered from the pMDI

pMDI formulations containing HPβCD and aspirin physical mixture at a molar ratio of 1:1 were prepared as described above. After storage of the pMDI formulations at 40°C for 3, 7 and 10 days, 2, 3 and 4 weeks, the physical mixture was recovered from the pMDI, and DSC was conducted using the same conditions as described above.

2.2.8. Statistical analysis

The data were compared using one-way ANOVA to evaluate the differences. The significance level was based on the 95% probability values ($P < 0.05$).

3. Results and discussion

3.1. HPLC analysis of aspirin and its degradation products

It was suggested that SA, SSA and ASSA were possible degradation products of aspirin [4]. SA is the primary product of the hydrolysis of aspirin, the most important reaction contributing to the instability of aspirin. SSA and ASSA are produced when aspirin and SA undergo further reactions in alkaline conditions [8]. HPLC methods were previously developed to quantitate aspirin and its degradation products in solid dosage forms [8–11]. In this study, an HPLC method was validated to quantitate the different components in the system. A typical chromatogram is shown in Fig. 2. The order of elution and retention times were aspirin (3.67 min), SA (5.17 min), ASSA (7.03 min) and SSA (11.73 min). Calibration curves were generated with working standard solutions for each batch of sample analysis. The linearity of the calibration curve for each compound was excellent for all batches, as indicated by the correlation coefficient of the linear regression ($r^2 > 0.99$, Table 1). A set of the system suitability data of a typical batch is summarized in Table 1. It was shown that the RSD of five consecutive replicate injections was less than 2% for each compound; the theoretical plate number was greater than 900 plates/column for each compound; the peak resolution, calculated with the first eluted peak (aspirin peak) as the reference, was greater than 2 for SA, ASSA, and SSA; and the peak asymmetry was less than 2 for all peaks. Therefore, system suitability was established, and the HPLC method was validated as a stability indicating method and used throughout the study to monitor the degradation of aspirin in pMDI formulations.

3.2. Formation of inclusion complex by lyophilization

An inclusion complex was prepared in this study by lyophilization. DSC was conducted on the lyophilized solid. The DSC thermograms of aspirin, HPβCD, the physical mixture of aspirin and HPβCD, and the lyophilized solid complex are shown in Fig. 3. The melting peak of aspirin alone (Fig. 3a) and in the physical mixture (Fig. 3c) occurred at 144°C. A broad endothermic peak of HPβCD (Fig. 3b) was found at 120°C, which was probably due to the loss of water molecules that were associated with HPβCD. This peak was shifted to a lower temperature (85°C) when

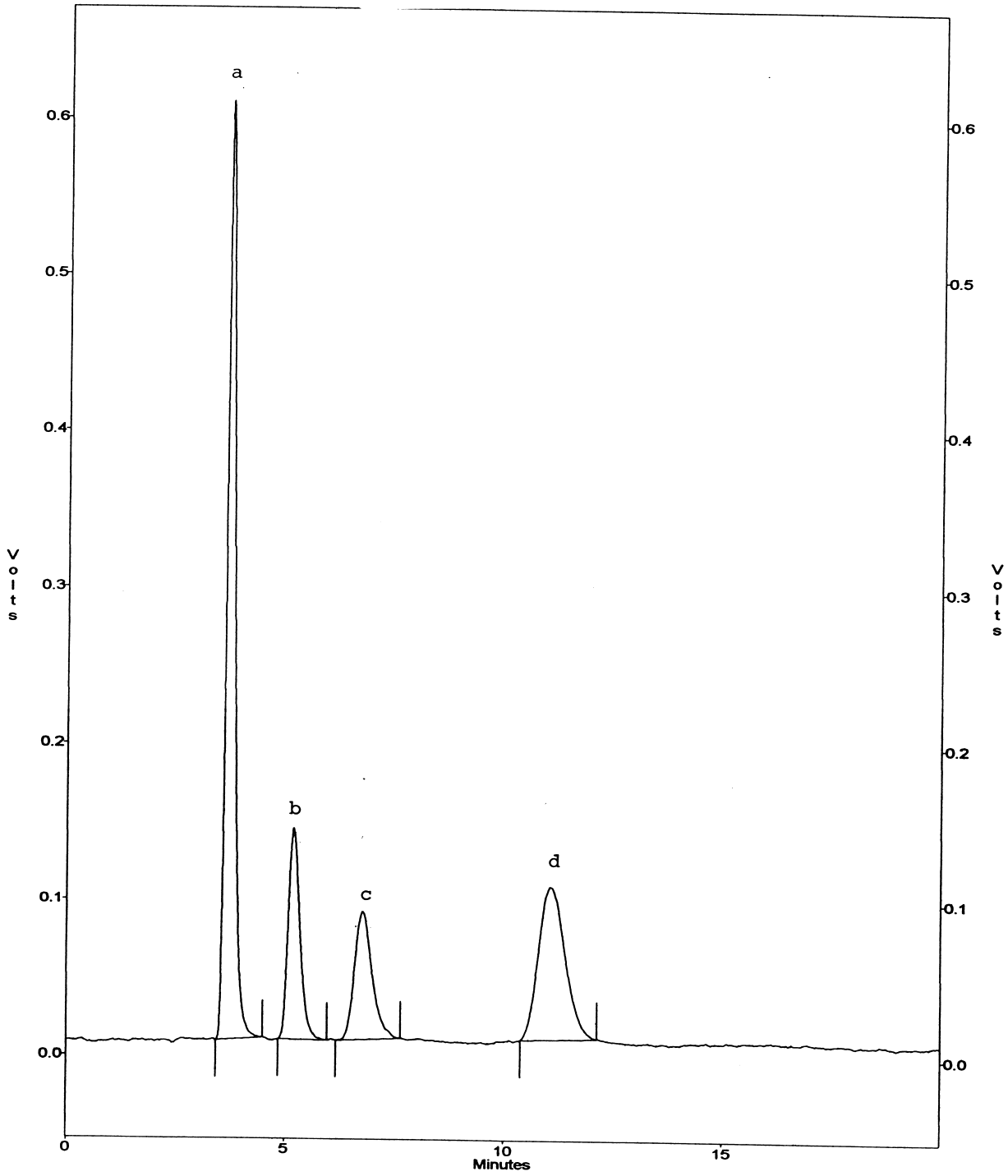

Fig. 2. HPLC chromatograms of aspirin and its degradation products. In the order of elution, the peaks are aspirin (a), SA (b), ASSA (c) and SSA (d).

HPβCD was mixed with aspirin either in the physical mixture or in the inclusion complex (Fig. 3d), indicating that adulteration of HPβCD by aspirin lowered the dehydration temperature. The thermogram of the physical mixture was a combination of HPβCD dehydration peak and aspirin melting peak. In the lyophilized solid, however, the melting peak of aspirin was not present, confirming the inclusion of aspirin in the HPβCD cavity at a molecular level. It was reported that aspirin and HPβCD forms an inclusion complex at a molar ratio of 1:1 in aqueous solution [6], in which each aspirin molecule occupies the cavity of one HPβCD molecule. Therefore, based on the DSC results obtained, it was assumed that a 1:1 inclusion complex was formed between aspirin and HPβCD after lyophilization in this study. The content of aspirin in the inclusion complex was determined by HPLC following lyophilization, and it was

Table 1

System suitability parameters for a typical HPLC analysis of aspirin and its degradation products

Parameter		Result
r^2 Of the calibration curve	Aspirin	0.995
	SA	0.999
	ASSA	0.999
	SSA	0.996
RSD of five consecutive replicate injections (%)	Aspirin	1.182
	SA	1.503
	ASSA	1.411
	SSA	1.109
Theoretical plate number	Aspirin	1.773
	SA	1.763
	ASSA	1.371
	SSA	1.630
Peak resolution (the first eluted peak, aspirin was used as the reference)	SA	3.344
	ASSA	3.416
	SSA	5.354
Peak asymmetry[a]	Aspirin	1.351
	SA	1.304
	ASSA	1.335
	SSA	1.208

[a]Tailing factor.
SA, salicylic acid; ASSA, Acetylsalicylsalicylic acid; SSA, salicylsalicylic acid.

determined that less than 2% of the original amount of aspirin was degraded into SA during the process of complex formation, which included exposure of aspirin to 25°C during the solution preparation and to –20°C during the lyophilization process.

3.3. Chemical stability of aspirin in pMDI formulations

A suspension-based pMDI formulation was obtained by mixing HFA 134a with the lyophilized inclusion complex, the physical mixture of aspirin and HPβCD in a molar ratio of 1:1, or aspirin alone as the control. The percent of aspirin remaining undegraded in the pMDI formulation over the storage period at 5, 25 and 40°C is shown in Fig. 4. It was evident that aspirin formulated in the lyophilized inclusion complex by HPβCD exhibited the most significant degree of degradation in the aerosol formulation at 25°C over the storage period of 6 months (13.0%), while the aspirin control in the pMDI demonstrated a moderate degree of degradation (6.3%), and aspirin formulated as a physical mixture

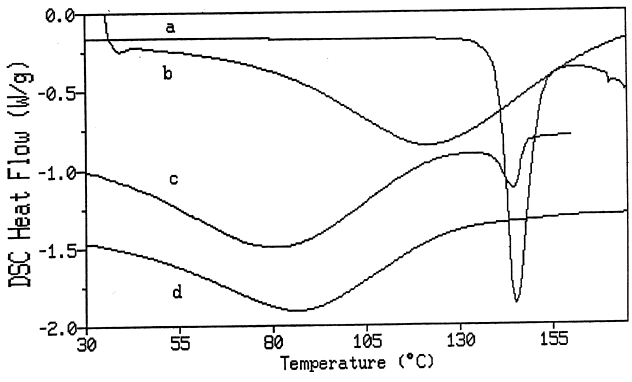

Fig. 3. DSC thermograms of aspirin (a), HPβCD (b), the physical mixture of aspirin and HPβCD in a 1:1 molar ratio (c), and the lyophilized solid from the aqueous solution of aspirin and HPβCD (d).

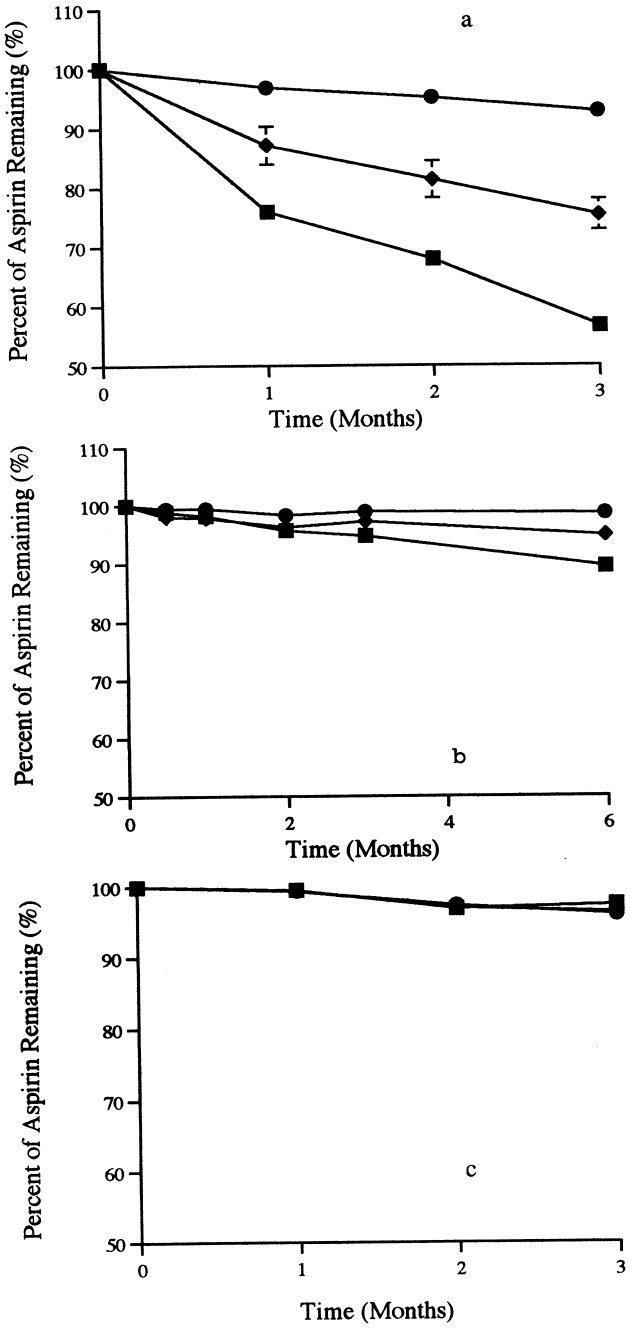

Fig. 4. Percent of aspirin remaining undegraded in the pMDI formulations containing the lyophilized inclusion complex (■), the physical mixture of aspirin and HPβCD at a molar ratio of 1:1 (●), and aspirin alone (♦) after storage at 40°C (a), 25°C (b) and 5°C (c).

with HPβCD remained the most chemically stable. A similar trend was found for the formulations stored at the accelerated stability condition, 40°C, except that the aspirin degraded at a much faster rate. The stability profiles of aspirin in the formulations at 5°C were used as the control, in which no significant difference in degradation rate of aspirin was observed for the different formulations. This stability study revealed that the inclusion complex accelerated the hydrolysis of aspirin in the pMDI formulation, but the presence of HPβCD in a physical mixture with aspirin retarded the hydrolysis rate and increased the long-term chemical stability of aspirin in the pMDI formulation. SA, produced from the hydrolysis reaction of aspirin, was the only degradation product detected from the pMDI formulation containing either the lyophilized inclusion complex or the physical mixture. SSA, ASSA, and SA were found as degradation products in the pMDI control formulation containing aspirin alone, which agreed with the results from a degradation study conducted for pMDI formulations containing aspirin, surfactants and trichloromonofluoromethane [5]. This indicated that further chemical reactions occurred between degradation products in addition to the hydrolysis of aspirin in the pMDI containing aspirin alone, whereas no further chemical reaction other than the hydrolysis of aspirin was detected in pMDI formulations in the presence of HPβCD. The mechanism by which HPβCD inhibits further chemical reactions of SA requires additional studies.

3.4. Water uptake determination

The water uptake into the pMDI canister prior to and after 6 months storage was determined and is presented in Fig. 5. The water content of HPβCD prior to formulation was 7836 ppm, and it contributed about 126 ppm of water to the final pMDI formulation. The water content of HFA 134a prior to use was 310 ppm, contributing the largest amount of water to the final pMDI formulation since it was present in the largest amount by weight. The water content of aspirin was below the detection limit of the method used, and it did not contribute significantly to the water amount in the final formulation. It was shown that the formulations with the inclusion complex and the physical mixture initially contained similar amounts of water (396 and 422 ppm, respectively), which mainly came from the propellant HFA 134a and HPβCD. The formulation with aspirin alone contained a significantly lower water content (296 ppm) due to the absence of HPβCD. After 6 months storage, the water ingress occurred to the greatest degree for the formulations containing the aspirin and HPβCD physical mixture (875 ppm at 5°C and 1097 ppm at 25°C), and to the least degree for the formulations containing aspirin alone (209 ppm at 5°C and 358 ppm at 25°C) (Fig. 5). The differences among the water contents of the pMDI formulations investigated were statistically significant ($P < 0.05$). In addition, it was shown that storage at a higher temperature promoted water ingress into the pMDI canister. Water present in the dosage

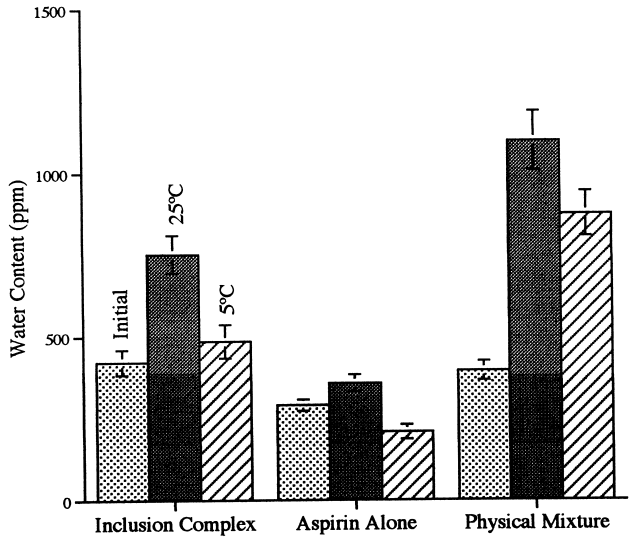

Fig. 5. Water content present in the pMDI formulations prior to and after storage for 6 months at 5 and 25°C.

form is a contributing factor to the instability of aspirin. This was one explanation to account for the greater stability of aspirin alone in the pMDI as compared with aspirin in the pMDI containing the inclusion complex since the water content was much lower for the pMDI containing aspirin alone. However, the pMDI containing the physical mixture presented the greatest chemical stability regardless of having the highest water content. Therefore, the presence of HPβCD in the physical mixture protected aspirin from the hydrolysis reaction and led to a greater stability of aspirin in the pMDI formulation.

The effect of cyclodextrins on the chemical stability of a guest molecule is dependent on the interaction and orientation between the host and guest molecules. NMR studies have indicated that a partial inclusion exists in the inclusion complex of β-cyclodextrin and aspirin at a molar ratio of 1:1 since the benzene ring of the aspirin molecule is located inside the cavity, but the acetyl ester group is protruding from the cavity [12]. Substituted cyclodextrins, such as HPβCD, have been shown to retain the complexing properties of the parent cyclodextrins [13]. Hence, it is assumed that the inclusion complex of HPβCD and aspirin possessed the same configuration as that of β-cyclodextrin and aspirin, with the benzene ring caged in the cavity and the ester group extending out of the cavity. In acidic conditions, the hydrolysis rate of aspirin is retarded due to the steric hindrance provided by the surrounding cyclodextrin structure to prevent the nucleophilic attack by the water molecules [6,12,14]. However, the ester group, protruding from the cavity and occupying the void space of the cyclodextrin molecule, is sterically fixed in a favorable position for the approach of the hydroxyl group from the cyclodextrin to the carbonyl group of aspirin under neutral or alkaline conditions, catalyzing the detachment of the ester group from the aspirin molecules [6,14]. The catalyzing effect of HPβCD on the hydrolysis reaction of aspirin was supported by the

significant degradation of aspirin in pMDI formulations in this study. Inclusion by lyophilization of a chemically labile drug, aspirin, in a complex with HPβCD did not enhance its stability in the pMDI formulation investigated. To the contrary, the long-term chemical stability of aspirin was decreased because a partial inclusion complex was formed and the hydrolysis of aspirin was accelerated by HPβCD molecules in the formulation.

3.5. DSC study of the physical mixture recovered from the pMDI

Although the lyophilized inclusion complex of aspirin in HPβCD decreased the chemical stability of aspirin in the pMDI formulation, the presence of HPβCD in a physical mixture with aspirin was shown to enhance the stability of aspirin. In order to understand the mechanism of stability enhancement of HPβCD in the physical mixture with aspirin, pMDI formulations containing the physical mixture of aspirin and HPβCD in molar ratios of 1:1 were prepared and stored at 40°C. The physical mixture was recovered periodically from the pMDI formulation and examined by DSC. The DSC thermograms of the mixtures recovered following 3 days, 2 weeks and 4 weeks of storage are shown in Fig. 6. A distinct melting peak of aspirin was observed for the recovered mixtures 3 days after the pMDI formulations were prepared (Fig. 6I). However, the aspirin melting peak disappeared following 2 weeks storage (Fig. 6II), and it remained absent from the thermogram for the mixtures recovered 4 weeks after preparation (Fig. 6III). The disappearance of the aspirin melting peak indicated the inclusion of aspirin into the cavity of HPβCD. Therefore, the DSC study revealed that an inclusion complex was formed in situ in the pMDI formulation.

The formation of an inclusion complex of cyclodextrins and guest molecules is almost always accompanied by a large negative enthalpic change, and the entropic change of this process can either be positive or negative [12]. Van der waals interactions are considered as the primary intermolecular forces involved in complex formation [12,13].

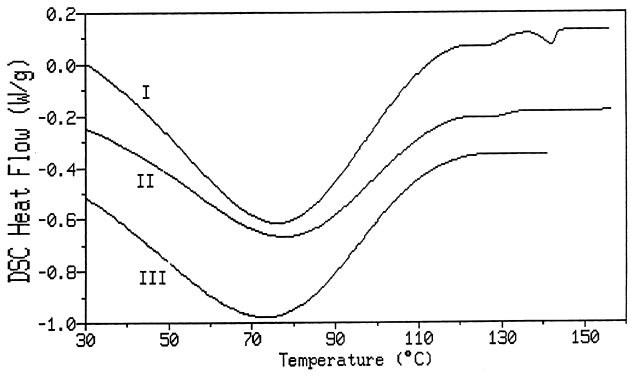

Fig. 6. DSC thermograms of the aspirin and HPβCD physical mixture at a molar ratio of 1:1 recovered from the pMDI formulations after 3 days (I), 2 weeks (II) and 4 weeks (III).

Water molecules are often viewed as the driving force in this process. The water molecules located inside the cyclodextrin cavity cannot satisfy the hydrogen-bonding potentials and possess a higher enthalpy. Consequently, the energy of the system is lowered when the enthalpy-rich water molecules in the cavity are replaced by more nonpolar guest molecules [12]. Therefore, in this study, the water present in the pMDI formulation containing the physical mixture of aspirin and HPβCD could provide water molecules as a driving force for the in situ formation of an inclusion complex.

The stabilizing/destabilizing effect of cyclodextrins on the included compound depends on the stoichiometric ratio between the host and guest molecules in the complex and the orientation of the host and guest molecules. For example, when the antiallergic drug, tranilast, forms a 2:1 (guest:host) complex with γ-cyclodextrin, the drug degradation was accelerated by approximately 5500-fold. However, 1:1 and 1:2 complexes are formed with increasing γ-cyclodextrin concentration, which decreased the rate of degradation [12]. A similar trend was found for the complex of bispilocarpine prodrugs and HPβCD, which existed as a 1:1 and a 1:2 complex, and the latter was shown to be more stable [15]. In this study, degradation of aspirin was retarded in the pMDI formulation containing the physical mixture of aspirin and HPβCD due to an inclusion complex formed in situ. However, it was shown that the complex formed between aspirin and HPβCD at a molar ratio of 1:1 after lyophilization decreased the stability of aspirin in the pMDI formulation. Therefore, the results suggested that the inclusion complex formed in situ occurred probably either in a different stoichiometric ratio or a different orientation of the molecules within the complex, whereby hydrolysis of aspirin was decelerated possibly by the complete inclusion of aspirin molecules into the cavity of HPβCD.

4. Conclusions

In conclusion, it was found that the degradation of aspirin was accelerated when aspirin was formulated as a 1:1 lyophilized inclusion complex with HPβCD in a pMDI formulation containing HFA 134a as the propellant. This was ascribed to partial inclusion of aspirin molecules in the HPβCD cavity. When aspirin was formulated in the pMDI formulation alone, it also underwent significant hydrolysis and produced SA, SSA and ASSA as the degradation products. Finally, the long-term chemical stability of aspirin was enhanced when it was formulated in a physical mixture with HPβCD in the pMDI. It was found that an inclusion complex was formed between aspirin and HPβCD in situ in the pMDI, which retarded the degradation rate of aspirin. Therefore, the formulation technique of incorporating HPβCD as an excipient in pMDI formulations to enhance the stability of chemically labile drugs should be investigated.

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