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MECHANISM OF GLASS AMPOULE BREAKAGE PREVENTION DURING THE FREEZE-DRYING PROCESS OF SODIUM THIOPENTAL LYOPHILIZATION PRODUCTS ON ADDITION OF SODIUM CHLORIDE

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Glass ampoule breakage during the freeze-drying process was prevented by the addition of sodium chloride to the formulation of lyophilization products of sodium thiopental. In order to clarify the ampoule breakage prevention mechanism, the physicochemical behavior of the freeze-drying process was monitored by simultaneous XRD-DSC measurements and thermal mechanical analysis (TMA). During the freezing process of formulated solution, the smaller heat of fusion of crystallized ice with the addition of sodium chloride was observed in comparison to that without sodium chloride. Although a greater amorphous portion remained, a higher crystal habit of hexagonal ice was reproducibly observed in the XRD patterns with the addition of sodium chloride during the freezing process. In the measurement of TMA, the scattering of the thermal expansion rate of formulated solution was significantly reduced by the addition of sodium chloride. These observations indicated that the addition of sodium chloride minimized the scattering of the thermal expansion rate and might be a cause for the inhibition of glass ampoule breakage during the freeze-drying process.

Keywords: *freeze-drying, sodium carbonate, sodium chloride, sodium thiopental, TMA, XRD-DSC*

Introduction

In the fierce competition for drug discovery, a number of substances with compounds that are extremely unstable and poorly absorbable in the gastrointestinal tract (GI-tract) have arisen as new clinical candidates. These candidates are generally chosen as injectable formulations, especially as lyophilized formulations [1–3]. Lyophilization, or freeze-drying, has been widely used as a technique in the production of pharmaceutical preparations (i.e. plasma components or antibiotics) since the 1960s [4].

Lyophilization formulations require sophisticated manufacturing technologies and know-how for many reasons, such as the techniques for aseptic manufacturing processes. Despite full utilization of these sophisticated technologies and the most meticulous care, the incidence of defective products is still not negligible. The principal cause of recall of lyophilization products is contamination with foreign matter, such as insects, hair, and glass splinters from ampoule breakage during production [5]. The defective products with glass splinter contamination are caused by incomplete washing processes or breakage during the freeze-drying process.

From the standpoint of process control, glass ampoule breakage in the freeze-drying process deteriorates process productivity, and poses risks of biological contamination caused by manual operation, product contamination with glass splinters, and production line contamination with drug substance. Thus, the breakage of glass ampoules in the freeze-drying process must be avoided by all means. This specific concern needs to be taken into consideration in the formulation development as well as in the manufacturing process design. However, few studies on glass ampoule breakage in the freeze-drying process have been made. Williams, *et al*. investigated glass vial breakage for frozen mannitol solutions [6–8]. In their patent publication, Arakawa *et al*. described a method for lyophilizing dextrans without glass vial breakage by vial shape modification [9]. Verma *et al*. investigated the relationship of fill ratio to ampoule breakage [10]. In our investigation on lyophilization products of sodium thiopental, it was found that anhydrous sodium carbonate added as stabilizer caused glass ampoule breakage in the freeze-drying process.

In the present study, the mechanism of ampoule breakage during manufacturing process of freeze-drying product was investigated using simultaneous measurement of XRD-DSC and TMA. XRD-DSC involves simultaneous measurement of X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC). TMA, thermomechanical analysis, is a temperature dependent technique used in the measurement of thermal expansion of materials. Instrumental analyses,

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such as XRD-DSC and TMA, are often applied to pharmaceutical research because the physicochemical properties of materials during the manufacturing process give us useful information for the rational design of high quality pharmaceuticals [11–15].

Experimental

Materials

Sodium thiopental was obtained from Tanabe Seiyaku Co. (Osaka, Japan) and used without further purification. Anhydrous sodium carbonate, sodium chloride, potassium chloride, mannitol, lactose, and other materials used in this study were purchased from Nacalai Tesque, Inc. (Kyoto, Japan).

Preparation procedure for freeze-drying product

Bulk solutions for sodium thiopental lyophilized products were prepared as follows: Sodium thiopental, were dissolved in distilled water for injection using a paddle mixer. Sodium hydroxide solution (1 mol L^{-1}) was added to adjust the pH of these solutions to 11.0. Distilled water for injection was then added to prepare 10% (*w*/*v*) sodium thiopental solution. The bulk solutions were filtrated through a membrane filter (pore size: 0.22 μm) and filtrates were collected in a glass or stainless steel vessel under nitrogen gas atmosphere to prevent crystallization of thiopental. Glass ampoules (12 mL) were filled with 4–5 mL of the bulk solution. The glass ampoules containing bulk solutions were stored in a drying chamber of lyophilizer. Either laboratory lyophilizer (KYOWAC RL-100BS, Kyowa Vacuum Engineering Co., Ltd., Tokyo, Japan) or small-scale industrial lyophilizer (KYOWAC RL-1115BS, Kyowa Vacuum Engineering Co., Ltd., Tokyo, Japan) was used for the preparation of freeze-drying product. The freeze-drying conditions were as follows: (A) Freezing process: the shelf temperature was decreased to –50°C and maintained for 3 h to freeze the components in ampoules completely. (B) First drying process: the shelf temperature was increased to 20°C and maintained for 48 h. The pressure in the drying chamber was evacuated to less than 100 mTorr. (C) Second drying process: the shelf temperature was increased to 60°C and maintained for 6 h. At the end of the freeze-drying process, nitrogen gas was introduced to the drying chamber to break the vacuum.

Methods

Simultaneous measurements of powder X-ray diffraction and differential scanning calorimetry (XRD-DSC)

The XRD-DSC measurements were performed with an X-ray powder diffraction system equipped with a differential scanning calorimetry system (Model XRD-DSC II, Rigaku Corporation, Tokyo, Japan). The XRD-DSC system includes an attachment for heating and/or cooling the sample with a vacuum pump, enabling the capability to monitor the freeze-drying process in situ. Bulk solutions were prepared as described above and samples (75 μL) were put into plastic cells. The samples were subjected to a temperature program that simulated the freeze-drying process. The solutions were cooled to less than –40°C at 1°C min^{-1} and maintained for 3 h, then heated to –30°C at a scanning speed of 5°C min^{-1} and maintained for 2 h. The sample temperature was then increased again at the scanning speed of 5°C min^{-1} until it was melted. X-ray diffraction scans were performed with CuKα radiation (50 kV·40 mA) at the scanning rate of 3°C min^{-1} between 2θ=5°–38° with a step size of 0.02°.

Differential scanning calorimetry (DSC)

The differential scanning calorimetry measurements were carried out with a PerkinElmer Model 7 DSC and a Shimadzu DSC-30. About 10 mg of each solution was weighed into an aluminum cell and sealed hermetically. The solutions were cooled to –50°C at a scanning rate of 5°C min^{-1}, then maintained for 20 min, after which the samples were heated to 20°C at a scanning rate of 5°C min^{-1}. Temperature calibration was made with reference materials: gallium (29.7°C), cyclohexane (6.5°C), undecane (–25.6°C), and water (0°C), before measurement.

Thermomechanical analysis (TMA)

The thermomechanical analysis was carried out with a Model Thermo Plus 2/ TMA (Rigaku Corporation, Tokyo, Japan). In this study, the expansion/compression mode was used to determine the thermal relative length change of samples. The sample was put into an aluminum cell (diameter: 6 mm, height: 5 mm) and covered with an aluminum lid. The sample was placed in the analyzer, then cooled to about –50°C at a scanning speed of 5°C min^{-1} before TMA measurements. The measurement probe was placed on the surface of the frozen solution, then the relative upward expansion length change of the frozen solution was monitored from –50 to –20°C under the scanning speed of 5°C min^{-1}. The linear expansion coefficient was obtained from the change of length between –50

to –20°C. At the same time, the expansion rate of frozen solution was monitored with the definition as d(Relative length change)/*d*(Time).

Results and discussion

Glass ampoule breakage of sodium thiopental lyophilized products during freeze-drying process

Sodium thiopental is generally used as anesthetic and officially published as 'Thiopental Sodium for Injection' in the Japanese Pharmacopoeia [16]. In the pre-formulation study, it was found that thiopental decomposed gradually under strong alkaline solution conditions, especially in the presence of sodium hydroxide. It was also found that the solution absorbed carbon dioxide from the atmosphere, which caused precipitation of water-insoluble thiopental crystals. The addition of sodium hydroxide in sodium thiopental solution was found to be very effective to prevent precipitation of thiopental crystals (data were not shown). On the basis of these physicochemical properties, tentative formulation for freeze-drying product was manufactured from bulk solution (Solution 1) as shown in Table 1. Anhydrous sodium carbonate and sodium hydroxide were added as stabilizing agents to prevent crystallization of thiopental. However, this formulation caused glass ampoule breakage during freeze-drying: the ampoule breakage ratio was found to be 8.34% (781 of 9632 ampoules).

In order to investigate the cause of the ampoule breakage during the freeze-drying process, freeze-drying was performed using bulk solution without anhydrous sodium carbonate in formulation (solution 1) as shown in Table 1. It was found that the breakage was completely inhibited without anhydrous sodium carbonate (Solution 2) as shown in Fig. 1. Thus, it was found that the main cause of ampoule breakage was due to addition of anhydrous sodium carbonate in the formulation. To investigate whether the ampoule breakage was prevented by the solution volume and/or thickness of ampoules, the freeze-drying was performed with different thicknesses of glass ampoule at higher concentrations of sodium thiopental (Solution 3 with different ampoule thickness types A – C). However, as shown in Fig. 1, ampoule breakage was not inhibited by the increase of ampoule thickness and/or decrease of solution volume. Thus, further formulation study was required to prevent the ampoule breakage, often the cause of trouble in large-scale manufacturing.

Investigation of prevention of ampoule breakage by the addition of pharmaceutical additives

Williams *et al*. [6–8] have reported that additives such as sodium chloride and lactose effectively prevented glass vial breakage during lyophilization of mannitol solutions. These additives were tentatively selected and used in parenteral preparations to pre-

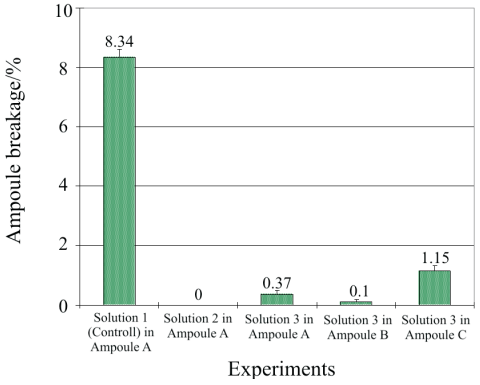

Fig. 1 Effect of drug concentration and glass thickness on ampoule breakage. Represents the mean ± SD of the three experiments

Table 1 Bulk solutions for freeze-dried sodium thiopental preparations

Ingredients Solution ID	Content/mg unit^{-1}		
	solution 1	solution 2	solution 3
Sodium thiopental	500	500	500
Sodium carbonate (anhydride)	30	–	30
Sodium hydroxide	q.s.	q.s.	q.s.
Distilled water for injection	q.s.	q.s.	q.s.
Total/mL	5	5	4
Drug concentration/%	10	10	12.5
Ampoule type	A	A	A,B,C

Several types of ampoules were used in this experiment, as follows:
Type A (external diameter 22.0 mm, wall thickness 0.55 mm)
Type B (external diameter 23.5 mm, wall thickness 0.57 mm)
Type C (external diameter 23.5 mm, wall thickness 0.55 mm, bottom thickness 0.7 mm)
Bulk solution was adjusted to pH 11.0 with 1M NaOH (1.2–1.6 mg NaOH/ampoule)

Table 2 Bulk solutions for freeze-dried sodium thiopental preparations containing various pharmaceutical additives

Ingredients Solution ID	Content/mg unit^{-1}					
	Solution 1	Solution 4	Solution 5	Solution 6	Solution 7	Solution 8
Sodium thiopental	500	500	500	500	500	500
Sodium carbonate (anhydride)	30	30	30	30	30	30
Lactose	–	5	–	–	–	–
Sucrose	–	–	5	–	–	–
Mannitol	–	–	–	5	–	–
Sodium chloride	–	–	–	–	5	–
Potassium chloride	–	–	–	–	–	5
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Distilled water for injection	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total/mL	5	5	5	5	5	5
Drug concentration/%	10	10	10	10	10	10
Ampoule type	A	A	A	A	A	A

Type A (external diameter 22.0 mm, wall thickness 0.55 mm)
Bulk solution was adjusted to pH 11.0 with 1M NaOH (1.2–1.6 mg NaOH/ampoule)

vent ampoule breakage during freeze-drying. Lactose, sucrose, mannitol, sodium chloride, and potassium chloride were usually used as additives for injections. Thus, these additives were selected as injection formulations and added to the control bulk solution (Solution 1) at a content of 0.1%, as shown in Table 2.

The ratios of ampoule breakage during freeze-drying are shown in Table 3. The addition of sodium chloride and potassium chloride completely prevented ampoule breakage. To clarify the effect of sodium chloride for ampoule breakage, different concentrations of additives were incorporated into Solution 1 (0.01% (1.67%), 0.05% (3.34%) and 0.1% (16.7%) of sodium chloride added to Solution 1, as shown in Table 4). The inhibition of glass ampoule breakage was found to depend on concentration of sodium chloride, as shown in Fig. 2. It was found that

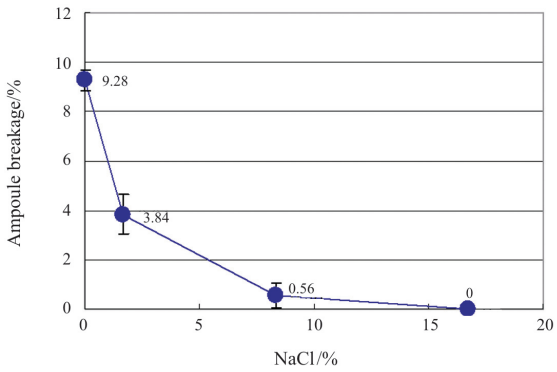

Fig. 2 Effect of the sodium chloride content on ampoule breakage prevention during freeze-drying of sodium thiopental bulk solution

Table 3 Effect of pharmaceutical additives on prevention of glass ampoule breakage

Additive	Experiment No.			Total	Breakage/%
	1	2	3		
	(Breakage / Total)				
Control	12/127	11/125	12/125	35/377	9.28
Lactose	7/180	6/183	8/184	21/547	3.84
Sucrose	6/180	7/180	7/180	20/540	3.71
Mannitol	7/180	9/180	9/179	25/539	4.64
Sodium chloride	0/180	0/180	0/180	0/540	0
Potassium chloride	0/180	0/180	0/180	0/540	0

Breakages (%) listed are the means of three experiments

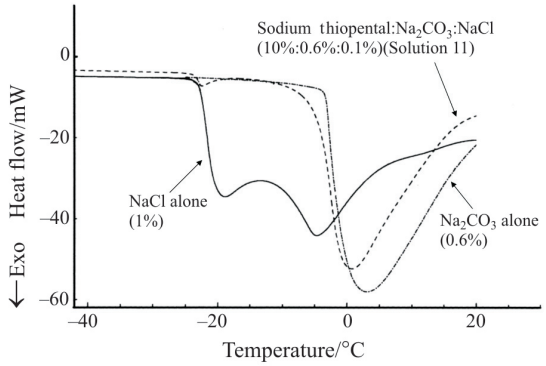

Fig. 3 DSC heating curves for frozen sodium carbonate solution, sodium chloride solution, and bulk solution with sodium chloride (Solution 11)

ampoule breakage was completely inhibited at a concentration of 0.1% (16.7% by mass based on dry sodium carbonate).

Measurements of DSC on bulk solutions for sodium thiopental lyophilized products

To clarify the cause of ampoule breakage during freeze-drying, DSC measurements for bulk solutions were performed. The DSC curves of anhydrous sodium carbonate solution (0.6 *w*/*v*%), sodium chloride solution (1 *w*/*v*%), and bulk solution (Solution 11 in Table 4) are shown in Fig. 3. In the DSC curve of anhydrous sodium carbonate solution, except for an endothermic peak due to melting of ice, no peaks were observed during the heating process. The sodium chloride solution showed an additional peak attributed to melting of sodium chloride dihydrate (at about –20°C) in addition to an endothermic peak due to melting of ice during heating. The DSC curve of Solution 11 showed no peaks due to sodium thiopental. From the results of these DSC curves, no remarkable phase change of sodium thiopental and/or sodium carbonate in the frozen bulk solution was observed during heating.

In the DSC curve of mannitol solution, the exothermic peak due to the phase change of mannitol crystal, was known to be observed in the heating process and the phase change of mannitol crystal was caused by the rapid generation of hexagonal ice crystal, which triggered the glass vial breakage [6, 17]. Thus, it was found that the ampoule breakage caused by thiopental injection formulation was not due to the phase change of sodium carbonate or sodium thiopental, as it was in the case of formulation containing mannitol. The DSC curves of two different bulk solutions (Solution 1 and Solution 11) are shown in Fig. 4. In the DSC curve of Solution 1 (without sodium chloride) and Solution 11 (with sodium chloride), the heat of crystallization of ice crystal and the heat of fusion of ice crystal were observed at about –20 to 25°C and –10°C, respectively. To evaluate the effect of sodium chloride addition on crystallized amount of ice crystal, the heat of fusion was calculated from the DSC curve of Solution 1 (without sodium chloride) and Solution 11 (with sodium chloride). Heat of fusion of Solution 1 (without sodium chloride) and Solution 11 (with sodium chloride) were 289 J g^{-1} and 250 J g^{-1}, respectively. The crystallized amount of ice crystal was greater for solution without sodium chloride. This may be partly due to the hydration of sodium chloride, reducing the free water in the solution. The crystallized amount of ice crystal, closely related to glass ampoule breakage, may be account for the effect of sodium chloride addition on the prevention of glass ampoule breakage be-

Table 4 Bulk solutions for freeze-dried sodium thiopental preparations containing various concentrations of sodium chloride

Ingredients Solution ID	Content/mg $unit^{-1}$			
	Solution 1	Solution 9	Solution 10	Solution 11
Sodium thiopental	500	500	500	500
Sodium carbonate (anhydride)	30	30	30	30
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.
Sodium chloride	–	0.5	1	5
Distilled water for injection	q.s.	q.s.	q.s.	q.s.
Total/mL	5	5	5	5
Drug concentration/%	10	10	10	10
Conc. of sodium chloride/%	0	0.01	0.05	0.1
Conc. of sodium chloride on sodium carbonate/%	0	1.67	3.34	16.7
Ampoule type	A	A	A	A

Type A (external diameter 22.0 mm, wall thickness 0.55 mm)
Bulk solution was adjusted to pH 11.0 with 1M NaOH (1.2-1.6 mg NaOH/ampoule)

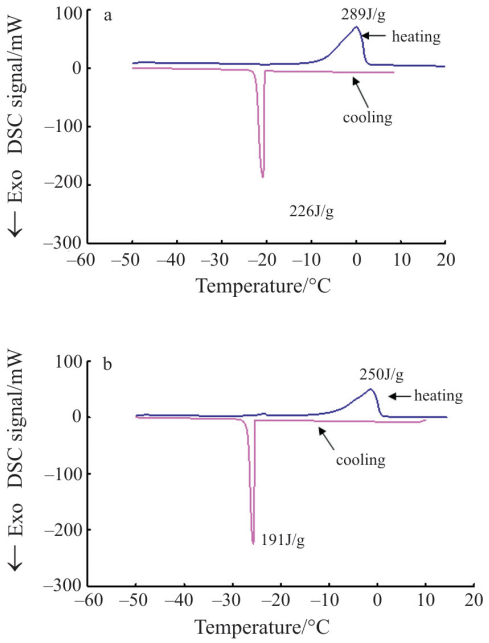

Fig. 4 DSC curves for a – bulk solution (Solution 1) and b – bulk solution with 0.1% sodium chloride (Solution 11)

cause sodium chloride decrease crystallized amount of ice crystal.

In a study of mannitol crystallization of frozen mannitol solution and relevant vial breakage, Williams *et al*. [6–8] measured an exothermic peak due to mannitol crystallization around –22.5°C in DSC urves of mannitol solution in the temperature-in - creasing process after rapid cooling. They described that the vial breakage occurred by the rapid volume expansion due to crystallization of mannitol and free water. The addition of a certain amount of sodium chloride or lactose could have prevented vial breakage, eliminating the exothermic peak due to transformation of crystal formation of mannitol in DSC, since the bulk solution with sodium chloride showed no exothermic peak due to crystallization of medicinal substance or excipient as found in mannitol solution in the heating process.

Simultaneous measurements of XRD-DSC on bulk solutions for sodium thiopental lyophilized product

The XRD patterns of both sodium carbonate (0.6 *w*/*v*%)/sodium chloride (0.1 *w*/*v*%) solutions and sodium carbonate (0.6 *w*/*v*%) solution are shown in Fig. 5. The distinctive sharp peaks due to hexagonal ice crystals were observed as indicated by arrows at 2θ = 22.8, 24.3, 25.9 and 33.6°. The sodium carbonate/sodium chloride solutions showed no marked difference in XRD peak patterns in comparison with sodium carbonate solution, except for a peak at 2θ = 16.5° due to sodium chloride crystal. However, the peak intensities due to ice crystals for sodium carbonate/sodium chloride solutions were greater than those of sodium carbonate solution.

The differences between Solution 1 and Solution 11 were observed in the XRD peak profiles. The XRD patterns of Solution 11 had reproducible distinctive sharp peaks due to hexagonal ice crystals during cooling process at 2θ = 22.8, 24.3, 25.9 and 33.6°, as shown in Fig. 6. On the other hand, the XRD patterns of Solution 1 indicated poorly reproducible ice crystal formation in both peak pattern and intensity, as shown

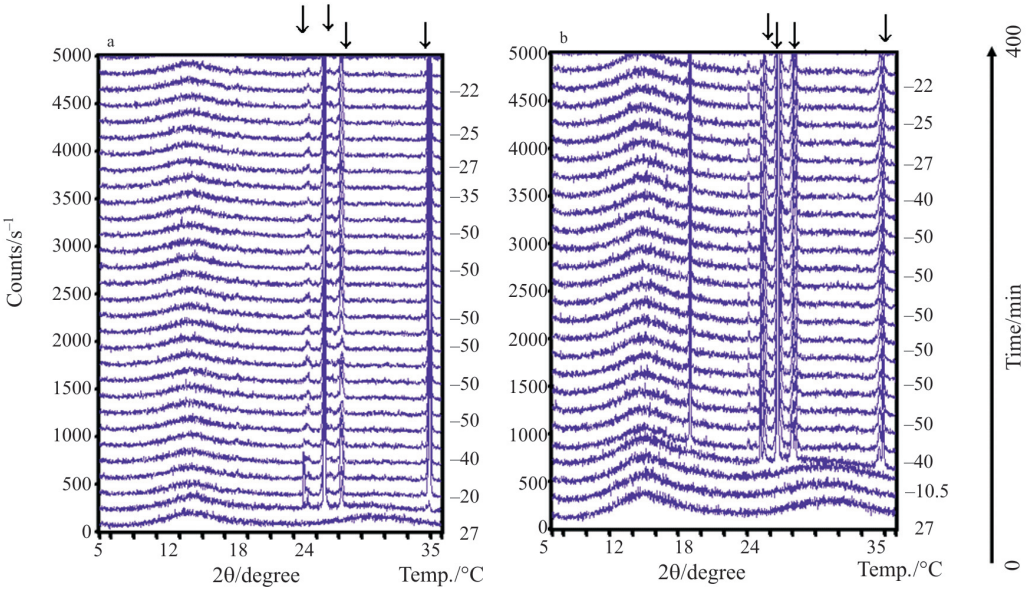

Fig. 5 XRD patterns of sodium carbonate solution and sodium carbonate/sodium chloride solution in the freezing process. a – 0.6% sodium carbonate, b – 0.6% sodium carbonate/0.1% sodium chloride solution. Arrows indicate peaks due to hex - agonal ice crystals

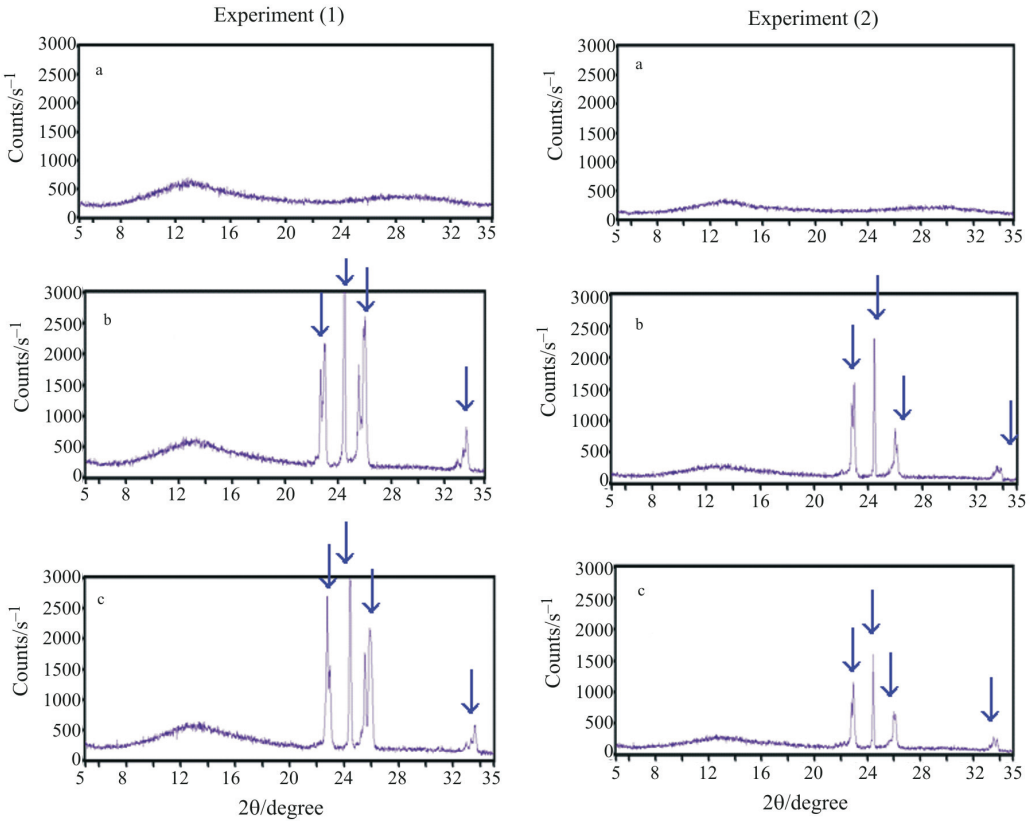

Fig. 6 XRD patterns of bulk solution with sodium chloride (Solution 11) for freeze-dried sodium thiopental preparations in the freezing process. a – before freezing, b – during freezing, c – after freezing. Arrows indicate peaks due to hexagonal ice crystals

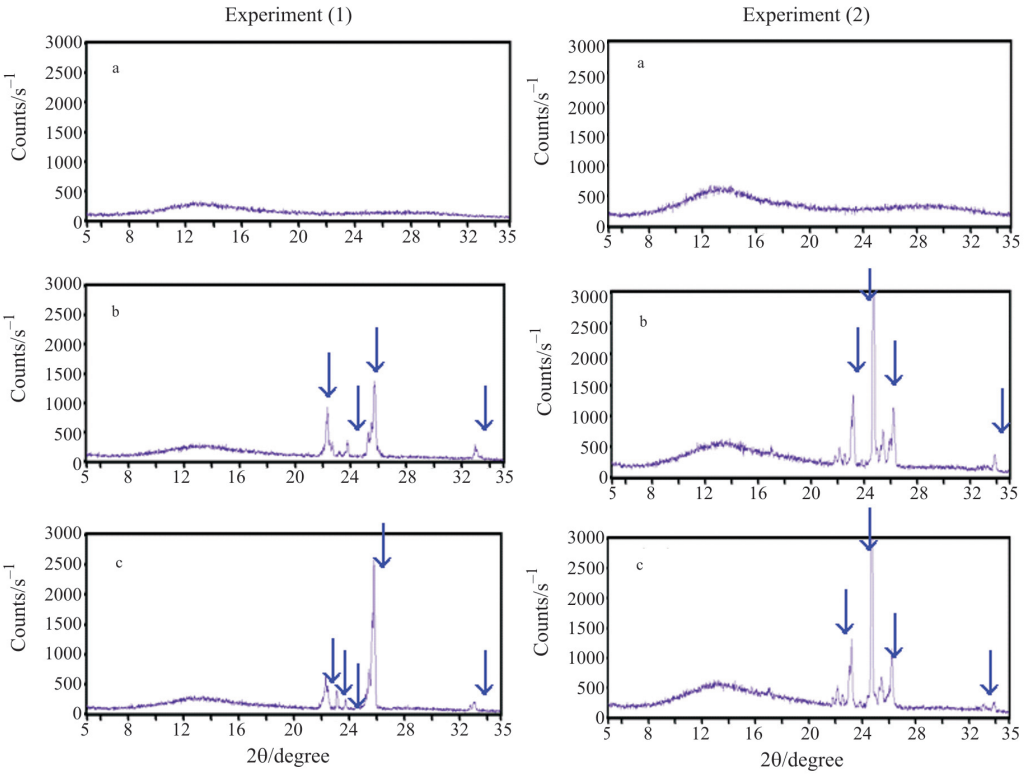

Fig. 7 XRD patterns of bulk solution without sodium chloride (Solution 1) for freeze-dried sodium thiopental preparations in the freezing process. a – before freezing b – during freezing c – after freezing. Arrows indicate peaks due to hexagonal ice crystals

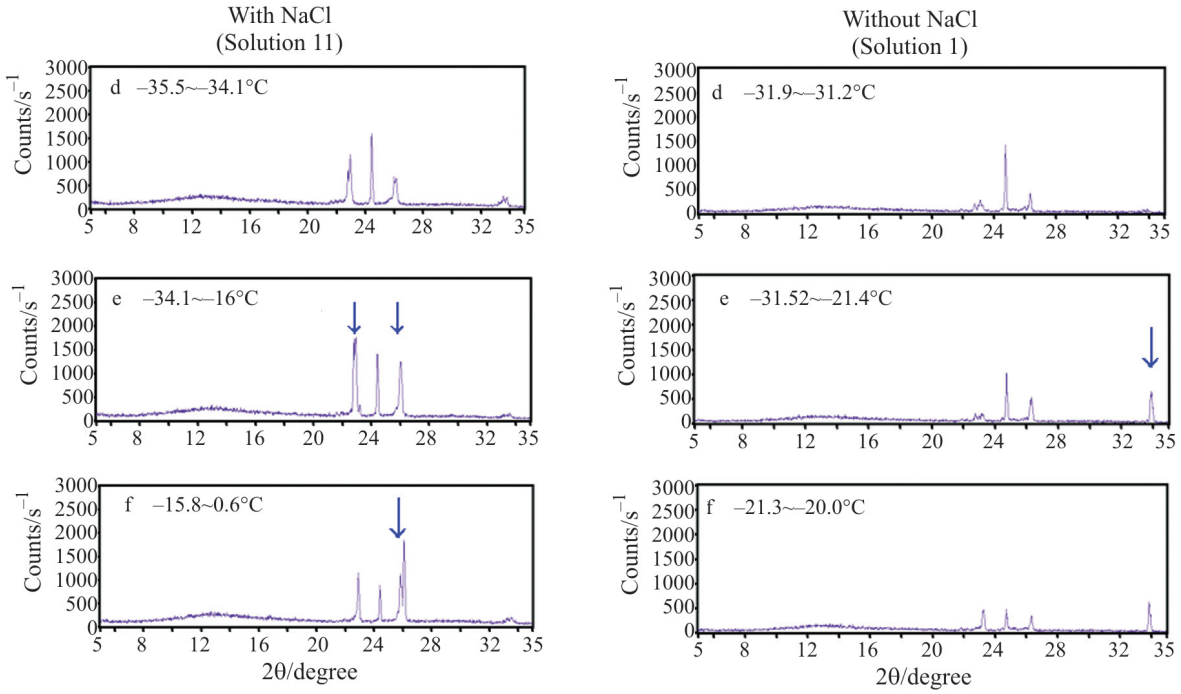

Fig. 8 XRD patterns for frozen sodium thiopental bulk solution with and without sodium chloride (Solution 1 and Solution 11) in the heating process. d – before heating, e – during heating, f – before melting ice crystals

in Fig. 7. Furthermore, for Solution 1 some peak intensities were increased during the heating process, suggesting heterogeneous crystal growth occurred during the heating process, as shown in Fig. 8.

These phenomena indicate that the crystal growth of hexagonal ice crystals were different during the cooling and heating processes in the absence and presence of sodium chloride. This clearly indicated that sodium chloride controlled the crystal habit of hexagonal ice crystal during both cooling and heating processes. As shown in Fig. 4, a smaller heat of fusion was observed in bulk solution with sodium chloride compared with that of bulk solution without sodium chloride. These results suggested that the sodium chloride affected the crystallization of bulk water in the formulated solution, that is, sodium chloride might assist control of the growth of hexagonal ice crystal (Figs 6 and 7).

TMA measurements for bulk solutions of sodium thiopental lyophilization products

Thermomechanical analysis (TMA) is able to determine dimensional changes of a sample while it is subjected to a vibration-free load and temperature programs. The linear expansion coefficient was then determined from the change in the height of frozen bulk solution in the cell during measurement. The linear expansion coefficient was $7.58 \cdot 10^{-5} \pm 6.53 \cdot 10^{-6}$ (n=6) in the absence of sodium chloride (Solution 1) and $7.46 \cdot 10^{-5} \pm 1.88 \cdot 10^{-6}$ (n=3) in the presence of sodium chloride (Solution 11), with no statistical signifi-

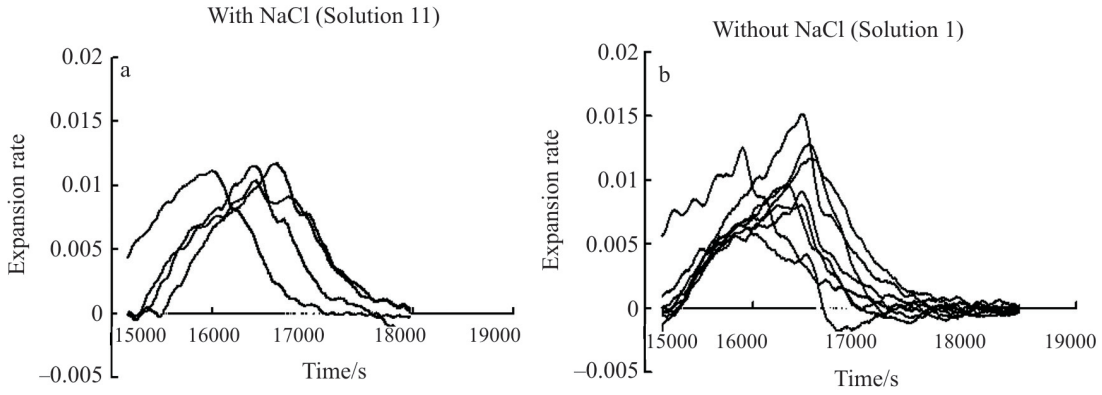

Fig. 9 Comparison of the volume linear expansion rate (d relative length change / d time) of bulk solution a – with, b – without sodium chloride (Solution 11 and Solution 1). Each line represents individual TMA measurement

Table 5 Linear expansion coefficient of sodium thiopental bulk solution with or without sodium chloride (Solution 1 and 11)

Sample	Linear expansion coefficient/$K^{-1}\cdot10^{-5}$	S.D. $\cdot10^{-6}$	Number of samples
Control (without NaCl)	7.58	6.53	6
NaCl added	7.46	1.88	3

There was no statistical significance among these samples

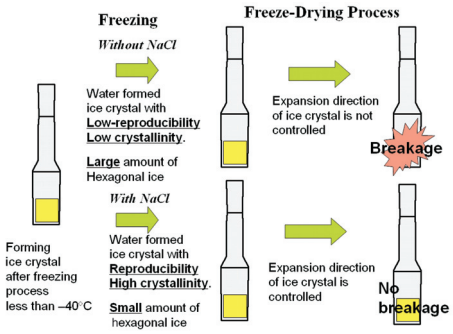

Fig. 10 Hypothesized illustration of the mechanism of glass ampoule breakage induced by sodium carbonate, and prevention mechanism of breakage by the addition of sodium chloride

cance observed, as shown in Table 5. It was assumed that ampoule breakage might not be caused by the rapid expansion of ice crystal. The expansion rate, (*d* Relative length change / *d* Time), was plotted *vs*. time as shown in Fig. 9. An almost constant expansion rate was observed in the presence of sodium chloride (Solution 11), however, a greater scattering of expansion rate was observed in the absence of sodium chloride (Solution 1). This might be the observation of greater crystal habit in Solution 11 compared to that of Solution 1. Therefore, the greater scattering of expansion rate and crystallization without crystal habit would be responsible for the breakage of ampoule due to less reproducible ice crystal formation as observed by XRD-DSC. These results indicate that glass ampoule breakage might be associated with the elimination of crystal habit of hexagonal ice during cooing and heating process.

Conclusions

On the basis of experimental data, we hypothesize a mechanism of glass ampoule breakage induced by sodium carbonate and a prevention mechanism by the addition of sodium chloride, as illustrated in Fig. 10. The different crystal habit of ice crystals and crystallization amounts of hexagonal ice by the addition of sodium chloride into sodium thiopental bulk solution might be responsible for ampoule breakage during the freeze-drying process. These results might account for the prevention of glass ampoule breakage on the addition of sodium chloride.

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