



## Stability of carbamide peroxide in gel formulation as prepared in Brazilian compounding pharmacies

### Estabilidade do peróxido de carbamida na formulação de gel como preparado em farmácias brasileiras de manipulação

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#### SUMMARY

Carbamide peroxide (CP) is a widely used tooth bleaching agent in Brazil. Although commercially available, CP is commonly synthesized in Brazilian compounding pharmacies to reduce costs. The aim of this work is to evaluate the stability of CP as raw material and its gel formulation. The CP was synthesized as made in compounding pharmacies, and its purity was determined by iodometric volumetry using the method described in USP. The prepared CP was maintained at 5 °C, 25 °C, 40 °C (closed flask) and 40 °C (open flask). A 10% CP gel formulation was prepared, and its stability was determined at 5 °C and 40 °C. The raw material was stable at 5 °C in closed flask, and at 40 °C in open flask. The gel was more stable under refrigeration (5 °C). The prepared CP is stable, and its gel formulation should be stored under refrigeration to maintain its stability.

**Keywords:** Drug stability, Tooth bleaching agents, Remedy expiration

#### RESUMO

O peróxido de carbamida (PC) é um agente de branqueamento dental amplamente utilizado no Brasil. Embora comercialmente disponível, o CP é normalmente sintetizado em farmácias magistrais visando a redução do custo final da formulação. O objetivo deste trabalho foi o de avaliar a estabilidade do CP, tanto como matéria-prima quanto na sua formulação magistral de gel. O PC foi sintetizado seguindo o procedimento usualmente utilizado em farmácias de manipulação e a sua pureza foi determinada por iodometria, utilizando o método descrito na USP. O CP preparado foi mantido a 5 °C, 25 °C, 40 °C (frasco fechado) e 40 °C (frasco aberto). Utilizando a mesma matéria prima, uma formulação de gel a 10% foi preparada e a sua estabilidade foi determinada a 5 °C e 40 °C. A matéria-prima mostrou-se estável em frasco fechado, quando mantida a 5 °C e a 40 °C em frasco aberto. Na forma de gel, a formulação mostrou-se estável sob refrigeração (5 °C).

**Palavras-chave:** Estabilidade de medicamentos, Clareadores dentários, Prazo de validade de medicamento

#### INTRODUCTION

Carbamide peroxide (CP) also called urea peroxide is among the most used dental bleaching agents in Brazilian dentistry. It is a product from the reaction of hydrogen peroxide and urea, resulting in a solid with higher stability than hydrogen peroxide itself (Taliensky, 2005). The bleaching action results from a chemical oxidative process involving the hydrogen peroxide and discoloured compo-

nents of enamel pores and dentine, through the formation of reactive oxygen species (ROS), as peroxide and hydroxyl anions and free radicals. These species attack and cleave chemical bonds of chromophores, leading to a whitening effect (Suliman, 2008). The urea, in theory, can help the bleaching process by its decomposition in carbon dioxide and ammonia, that increases the pH and improve

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the process (Sun, 2000).

Other uses of CP includes relief of minor inflammation of gums, oral mucosal surfaces and lips (Tartakow *et al.*, 1978; Etemadzadeh, 1991), emulsification and dispersion of ear wax and some formulations for endodontic treatments use the antiseptic properties of CP during the chemical-surgical preparation of root canal (Yamazaki *et al.*, 2010).

Although CP is commercially available, its low availability in Brazilian market and high cost in comparison to the starting material encourage the Brazilian compounding pharmacies to synthesize it when necessary for dental formulations, since it can be easily obtained and isolated with good purity and considerable yields. The CP can be prepared by recrystallization of urea in a 30% aqueous hydrogen peroxide solution. This method is widely used and described in literature (Taliensky, 2005; Lu *et al.*, 1941).

One of the concerns with pharmaceutical formulations produced in compounding pharmacies is the stability of the formulation, since the process is made in a laboratorial scale and usually stability tests are not performed as a routine or in an appropriate manner.

Considering that the peroxides are relatively unstable, mainly in aqueous environment, the main objectives of this work are evaluate the stability of CP as raw material obtained in Brazilian compounding pharmacies and its gel formulation intended to be used for dental bleaching.

## MATERIALS AND METHODS

All chemicals used in this work were obtained in its commercially available analytical grade. CP was synthesized according to the method below.

### Synthetic procedure

In a flame-dried flask, were added 103 mL of a 30% hydrogen peroxide solution (Synth Labs, Diadema, SP, Brazil) and heated to 45 °C. Thereafter 64 g of urea (Synth Labs, Diadema, SP, Brazil) and 1.7 g of sodium pyrophosphate (Synth Labs, Diadema, SP, Brazil) previously triturated were added to the solution. The resulting mixture was maintained under stirring in room temperature overnight. The solid precipitate was filtered off under reduced pressure in sintered funnel. The obtained crystals were dried and characterized as CP according to the literature data.

### Purity determination

The purity was determined by iodometric volumetry using the method described in United States Pharmacopeia (Pharmacopeial Convention, 2008). About 100 mg of the CP or equivalent amount of gel, accurately weighted was transferred to a 500 mL iodine flask with the aid of 25 mL of water, 5 mL of glacial acetic acid (Carlo Erba Reagents, Milano, Italy), 2 g of potassium iodide (Synth Labs, Diadema, SP, Brazil) and 1 drop of ammonium molybdate (Merck KGaA, Darmstadt, Germany) TS. The flask was closed and kept in dark for 10 minutes. The liberated iodine was titrated with 0.1 N sodium thiosulfate (Merck KGaA, Darmstadt, Germany).

The amount of CP was calculated considering that each

mL of 0.1 N sodium thiosulfate reacts with 4.704 mg of CP.

### Gel preparation

The gel composition was presented in table 1.

The sodium saccharin (Synth Labs, Diadema, SP, Brazil) and the EDTA (Merck KGaA, Darmstadt, Germany) were previously dissolved in water and the methylparaben (Merck KGaA, Darmstadt, Germany) and the mentol (Synth Labs, Diadema, SP, Brazil) in ethanol. The carbomer 940 (Lubrizol Advanced Materials, Cleveland, OH) was dispersed in water with the glycerin (Synth Labs, Diadema, SP, Brazil) and the pH was adjusted to 7.0 (+/- 0.2).

The CP was previously triturated and solubilized with enough amount of water, then added to the gel. The final product was packaged in 5 mL plastic disposable syringes as commercially available.

Table 1. Formulae of the CP gel

Component	Amount
Carbomer 940	3 %
Glycerin	5 %
Sodium saccharin	1 %
Methylparaben	0.15 %
EDTA	0.1 %
Menthol	0.1 %
Carbamide Peroxide	20 %
Purified Water	70.5 mL

### Stability test for the raw carbamide peroxide

The sample was divided in 4 groups: (A) that was maintained refrigerated at 5 °C (+/- 2 °C) in a sealed glass flask; (B) that was maintained at 25 °C (+/- 2 °C) in a sealed glass flask; (C) that was maintained at 40 °C (+/- 2 °C) in a sealed glass flask and (D) that was maintained at 40 °C (+/- 2 °C) in an open Petri dish. The CP content was determinate initially and at up to 50 days after the preparation.

### Stability test for the carbamide peroxide gel

The sample was divided in 2 groups: (E) that was maintained refrigerated at 5 °C (+/- 2 °C) and (F) that was maintained at 40 °C (+/- 2 °C). The CP content of the formulation was determined initially and during 49 days after the preparation.

## RESULTS AND DISCUSSION

The reaction yield for the carbamide peroxide was 48.9%, with average purity of 97.1% (figure 1). The CP content in the crystals determinate during the test is shown in the table 2. The CP contents in the gels during the stability test are shown in table 3.

CP is a complex formed between urea and hydrogen peroxide. There are several methodologies described in literature to prepare CP, most of them deposited as patents. However, these methodologies are based in a spontaneous complexation reaction between urea and hydrogen peroxide in solution (Taliensky, 2005). The crystal of CP was studied to determine the structure of the complex (Lu *et al.*, 1941). This complex is sufficient stable to provide

controlled release of hydrogen peroxide (Gonsalves *et al.*, 1991), becoming CP a suitable agent for several uses, as oxidizing agent in chemical reactions (Taliansky, 2005; Gonsalves *et al.*, 1991; Yu *et al.*, 2008), as antimicrobial and disinfectant agent (Bentley *et al.*, 1995; Lai *et al.*, 2003; Lazarchik & Haywood, 2010), and as bleaching agent in cosmetics and pharmaceutical products (Kowitz *et al.*, 1991; Fasanaro, 1992; Mokhlis *et al.*, 2000).



Figure 1. CP crystals obtained from synthetic procedure.

Table 2. CP content (expressed in % w/w) in the samples A (5 °C), B (25 °C), C (40 °C) and D (40 °C – open flask), during the stability test.

Day	CP content (%)			
	A	B	C	D
0	98.9	96.9	96.9	96.9
3	97.4	96.0	96.5	96.3
6	97.0	95.7	81.7	n.d.
13	96.7	95.6	21.2	n.d.
20	96.0	93.8	0.1	95.7
31	96.0	77.1	n.d.	95.0
48	95.3	71.1	n.d.	94.5

n.d. – not determined.

Table 3. CP content (expressed in % w/w) in the samples E (5 °C) and F (40 °C), during the stability test.

Day	CP content (%)	
	E	F
0	20.1	20.3
4	19.4	20.2
7	19.3	20.3
11	19.5	19.2
14	19.9	18.9
18	19.7	18.1
21	19.5	18.0
32	19.5	17.7
49	19.4	16.8

Although CP is commercially available in preparations for tooth bleaching as dental gels, several dentists in Brazil use compounding pharmacies services as an economical alternative or even to formulate products like Endo-PTC. However, stability issues were always a question in those formulations, since stability tests are not performed on these establishments. Thus, compounded products are very criticized, due to poor quality control and to the stability of the formulations. There are several reports of lack of

quality profiles in compounded products in literature (Pissatto *et al.*, 2006; Scheshowitsch *et al.*, 2007; Baracat *et al.*, 2009). Despite this, the evaluation of compounded formulations of CP is necessary to establish the benefits and/or problems of this kind of preparation.

Home bleaching treatment is preferred by patients and professionals when compared to the in-office method because the former technique required less chair time, in spite of the in-office method being under the dentist's control and less expensive. Home bleaching is a method whereby the patient fills a custom-designed tray with bleaching material (10% to 20% carbamide peroxide) (Auschill *et al.*, 2005), which can be obtained in compounding pharmacies or as industrialized product, being the former cheaper. When purchasing the bleaching agent, price might be a determining factor in the choice of the product to be applied. Sometimes, the patient does not take into consideration the quality of the formulation to be used (Martin *et al.*, 2007).

Martin *et al.* (2007), analyzing the concentrations of CP in 100 samples of 16% carbamide peroxide gel from 5 sources, being 4 compounding pharmacies and one industrialized product, found levels from 7.8 to 21.8 % of CP (48.8 to 136.2 % of the declared value). In this work, the CP levels had a wide variation and maybe stability could play an important role to explain these findings.

In the stability test of the CP, the predicted decomposition reaction would be as shown in figure 2. During the oxygen and water formation, various reactive intermediates are formed, being the basis of antimicrobial and bleaching activities of hydrogen peroxide and, hence, CP.

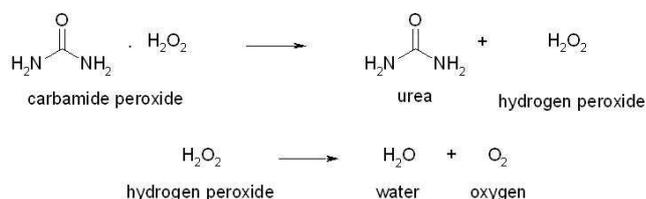


Figure 2. Chemical decomposition of CP in hydrogen peroxide.

In the early stages of the test, all samples of the raw material showed low degradation rates, but between the 3rd and 6th day, the sample C assumed a different behavior. The crystals got a wet aspect, maybe indicating degradation in some extent. The formed water was able to dissolve some of the CP thus accelerating the degradation rate. Same situation was observed with the sample B after 30 days in stability test. The figure 3 shows the degradation profiles of the samples A, B, C and D.

The CP amounts in samples A and D had lower degradation rates, showing better stability for 48 days and losing, respectively, 1.65% and 2.47% of its original amount. As sample A was maintained under refrigeration (5 °C), the degradation rate was lower than samples B and C. However, sample D showed relative stability even in higher temperature (40 °C). It could be attributed to the water evaporation, since it was maintained in an open flask. According to the results is reasonable to assume that the CP synthesized by the method described in this work is stable, under refrigeration, for 30 days after its preparation. However, as samples A, B and C were maintained in

closed flask, maybe these samples could be the same behavior of sample D, if it were maintained in open flask.

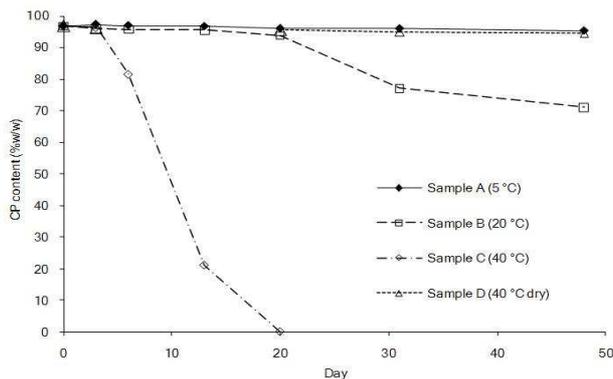


Figure 3. Content of CP in the raw material samples A, B, C and D, expressed as % (w/w) versus days in stability test.

As can be observed in figure 2, the water formation is due to CP degradation. The liquid water is formed in an extension capable to dissolve more CP of the sample, changing the degradation kinetics profile from that observed in solid state (more stable) to a kinetics of solution state (more reactive). Moreover, is widely known that the higher is the temperature, the higher is the velocity of chemical reactions. Regarding this, the differences between samples C and D can be rationalized. As sample C was maintained in higher temperature and in closed recipient, the formed water was condensed and kept with the sample, different to the condition in sample D, where the water was able to evaporate to the air.

The stability definition assumes that the shelf live is determined as the time were the original amount of the active ingredient decays 10% (Woolfe & Worthington, 1974; Connors *et al.*, 1986). In practical terms, the pharmaceutical industry considers lower values to determine the expiry date of the products, since 10% loss is a considerable limit. In the gel samples E and F, based on this criteria, the linear regression of the data gives 100 days of shelf life for the sample E (5 °C) and 24 days for sample F (40 °C), corroborating with the data obtained for the stability of the raw material. As the gel formulation contain high amount of water, the CP degradation rate seems to be higher. Figure 4 shows the content of CP in the samples E and F, the linear regression of the data and the correlation coefficient for the regression.

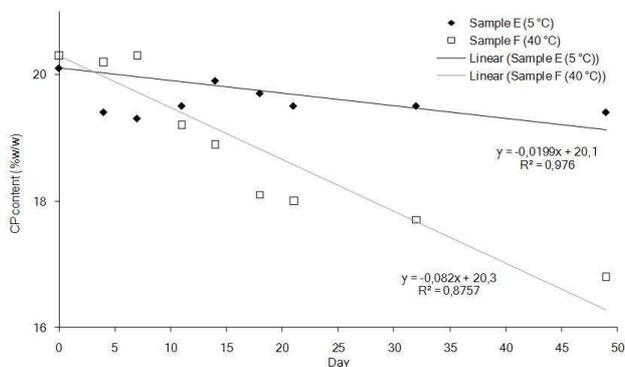


Figure 4. Content of CP in the gel samples E and F, expressed as % (w/w) versus days in stability test.

The influence of temperature in degradation of CP can be also observed in the samples E and F, where CP is introduced in a gel. In this condition, CP is dissolved in gel water, and its chemical behavior follows that observed in raw material in presence of the condensed water (sample C) with the difference that the lower concentration and the restricted diffusion of the formed oxygen affects the degradation velocity.

Auschill *et al.* (2005) verified the higher the concentration of the bleaching agents, the faster the stain is removed. Bleaching speed is related to the peroxide concentration and is time dependant (Martin *et al.*, 2007). A previous study showed that a 15% concentration of CP resulted in a faster and greater color change than 10% concentration during the treatment period in the first 2 weeks (Matis *et al.*, 2000). Thereby, the conditions of storage of the CP gel can influence in the clinical response due to degradation of active ingredient. The best storage conditions verified in this work is under refrigeration, since its shelf life is longer when compared to the storage in higher temperatures.

In summary, although CP is stable as raw material as obtained in the described method, its gel formulation prepared in compounding pharmacies should be storage in a properly manner to ensure the adequate clinical response.

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