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REVIEW ARTICLE

Development of Extemporaneously Prepared Captopril Oral Dosage Forms - A Comprehensive Chronological Study

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Abstract

Captopril is an Angiotensin-converting enzyme inhibitor, its effectiveness as an antihypertensive agent and in the treatment of several cardiovascular conditions in neonates and children has been proved clinically. Unfortunately, in many countries, it is available as a solid dosage form only. As this does not satisfy the needs of these patients in terms of dosage and pharmaceutical formulations, extemporaneously prepared formulations represent the only available solution for this situation. Many attempts have been made to study the different factors that may affect the stability of captopril in oral liquid formulations, aiming to design a formula with maximum stability profile. Although there is still debate about the effect of some factors on captopril stability, other factors have a clear role. Low storage temperature, acidic media (up to pH 4), use captopril powder, absence of heavy metals, increase drug concentration, sugar-free vehicle, decrease oxygen contents in the formulation, and excipients such as chelating agents and antioxidants are well known to increase captopril stability. Varies type of extemporaneously prepared dosage forms (liquid, powder, or tablet) with different formulations have been prepared and studied. Unfortunately, the stability of captopril in these preparations has been highly variable and sometimes conflicting results obtained, reflecting the sensitivity of captopril to a variety of factors that have not yet been completely identified. This review discusses these factors and extemporaneously prepared formulations in a comprehensive chronological way.

Keywords: *Captopril, extemporaneous preparation, Drug stability, Pharmaceutical formulation, Drug compounding.*

Introduction

Captopril is the first Angiotensin-Converting Enzyme (ACE) inhibitor available as an oral dosage form. As a result of this inhibitory activity, it prevents the conversion of angiotensin-I to angiotensin-II, making it an effective antihypertensive drug and can be used in the treatment of several cardiovascular conditions that affect adults and children [1, 2].

Since captopril is not commercially available in a liquid dosage form and the conventional tablets available in the market (12.5 mg, 25 mg, and 50 mg) do not satisfy the needs of infants and small children in term of low doses required by these group of patients and as a suitable pharmaceutical formulation, the extemporaneously prepared captopril oral powder or liquid dosage forms represent the only solution for this problem.

However, although extemporaneously prepared captopril oral preparations provide dose consistency, which warrants a proper adherent to the therapy plan, it also possesses some limitations such as; physicochemical stability of the prepared dosage forms as well as microbial contaminations, especially when it is prepared in a liquid dosage form. This review discusses the development of extemporaneously prepared captopril oral dosage forms and the limitations accompanied with each formula and preparation in a comprehensive systematic-chronological way.

Captopril as a Powder and Aqueous Dosage Forms

Although the use of extemporaneously prepared captopril oral solution appeared in the literature since 1983, in a letter sent to clinical pharmacy journal (*discontinued in 1993*) from Iafrate et al. [3], it is believed that its use was started before that time [4-6]. The first attempt to study the stability of captopril in the aqueous system was made by Timmins et al., by assessing the stability of captopril powder in acidic (pH 2) and alkaline (pH 8.5) aqueous solutions, its mode of degradation, the oxidative and hydrolytic degradation products under these conditions, and the effect of different buffers (pH range 2.1-5.6) on the rate of captopril oxidation.

Revealing that oxidation is the most predominant route of captopril degradation over a wide range of pH values, with maximum stability occurs at pH below 4. Also, they found that while antioxidants (e.g., Propyl gallate) and chelating agents (e.g., Sodium edetate) provide protection against captopril oxidation and are necessary in developing stable formulations, contaminant trace metal ions (e.g., copper and iron) in solution formulation increase oxidative degradation rate [7].

These results are confirmed after five years in a study done by Lee & Notari by studying the kinetics and the mechanism of captopril oxidation in aqueous solution under controlled oxygen partial pressure at a pH range of 6.6 to 8.0 at 32°C, with and without the addition of cupric ions [8]. Similar to what reported by Timmins et al. 1982 [7], this study pointed out that oxidation is the main pathway of captopril degradation with captopril disulfide is the only degradation product under all study conditions.

Furthermore, by studying the rate of captopril oxidative-degradation, it indicated that in addition to being pH-dependent, it also depends on the initial captopril concentration, presence of other trace metals, and oxygen partial pressure. Kinetically, this study proved that Captopril degradation shift from first-order kinetic to zero-order kinetic with the decrease in captopril concentration (The exact concentration at which this kinetic transition occurs is a function of different studied factors, such as; pH, oxygen partial pressure, and cupric ion concentration), increase oxygen contents in the prescription bottle, and presence of contaminant copper ions while the first-order degradation profile predominates as pH value increases.

Adding different chelating agents (EDTA and 8-hydroxyquinoline) to the captopril solution inhibits the oxidation process to 50 hours in comparison to the control that oxidized entirely in 10 hours [8]. The first clinical study conducted by using extemporaneously prepared oral captopril solution for treating hypertension in neonates was done by O'Dea et al. In which the treated patients administered captopril solution via nasogastric tube after dissolving the 25mg tablets in water. Because the prepared solution has a short half-life, he prepared a new solution just immediately before each dose [9].

As its use in clinical practice continues to present a promising result, especially in neonates and children [10-16], this created an increased need of individualized doses with more extended stability profile. Taketpmo et al. studied the stability of triturated Captopril 12.5 mg tablets in lactose powder papers to a final concentration of 0.02% (w/w) in three different storage containers stored at room temperature (25±2 °C), protected from light and analyzed at different time intervals for up to 24 weeks.

By using stability-indicating high-performance liquid chromatography method, all captopril powder papers stored in class "A" prescription vial and Moisture Proof Barrier bags were stable for the entire period of the study (24 weeks).

In comparison, captopril powder papers stored in plastic zip-lock bags showed a degradation product (captopril disulfide) in one sample at 24 weeks. However, none of the samples at all storage conditions lost more than 10% of its initial captopril contents during the first 12 weeks of the study [17].

Furthermore, after two years, Pereira and Tam used the Arrhenius plot to calculate the time required for captopril 1 mg/mL oral solutions to reach 90% of its original captopril concentrations. Solutions were prepared from tablets in tap water, stored at various temperatures (5, 25, 50, and 75°C), and analyzed for captopril concentration for up to 28 days using stability-indicating HPLC method.

Calculated shelf lives were 27, 11.8, 3.6, and 2.1 days, respectively. Although formulation was prepared using tap water, the authors did not study their microbial burden, and the used assay method was unable to detect captopril disulfide dimer, which represents the only degradation product of captopril under the conditions of the assay [18]. It's worth mentioning here that the results of this study cannot be universalized as the contents of tap water can vary significantly from one source to another, e.g., the concentration of heavy metals such as copper and iron, which are known to affect the stability of captopril in solution.

Also, in the same year, Pramar et al. during his search to determine the shelf life of Captopril 5 mg/mL in some aqueous systems stored for up to 27 days at 5°C and 25°C in amber-colored glass bottle analyzed using stability-Indicating HPLC method, discovered that captopril oral liquid prepared in water did not follow any known order of reaction kinetic and was more stable at both temperatures than captopril oral liquid prepared in syrup (follow first-order kinetic), with maximum stability occurred at 5°C.

Additionally, captopril oral liquid prepared using the powder in water was more stable than the one prepared using tablets with shelf lives of 27 days and 20 days, respectively, at 5°C. The author attributed this decrease in shelf life to the tablet's excipients that may adversely affect the stability of captopril in the solution [19]. In contrast to what was mentioned by Pereira and Tam [18], the developed assay method was sensitive and able to differentiate captopril disulfide.

Also, although captopril concentration was less than 90% of its initial concentrations, solutions prepared from the water had a foul odor and signs of fungal infection after 18 days of storage. These results vary from the results of Anaizi & Swenson who conducted an experiment to compare the stability profile of captopril 1 mg/mL solution prepared from Captopril 25 mg tablets in sterile water for irrigation and in the tap water for up to 28 days at 5°C protected from light, using a stability-indicating (HPLC).

In this experiment, they found that captopril degrades to captopril disulfide at a markedly faster rate in tap water than in sterile water for irrigation, and by using graphical analysis of the stability data, he calculated three days shelf life for captopril solution prepared in sterile water for irrigation at 5°C protected from light. Also, he found that adding citric acid at a concentration of 40 mg/mL to the captopril 1 mg/mL solution prepared in sterile water for irrigation stored at 5°C protected from light does not influence on the captopril stability [20].

As Lee & Notari reported that the stability of captopril powder in aqueous solution increases with increasing concentration [8], Chan et al. conducted an experiment to figure if this applies to captopril solution prepared from the tablet as well. In this experiment, they studied the stability profile of two captopril aqueous solutions prepared from Captopril 25 mg tablets at two different concentrations (0.1% and 1%) and once captopril aqueous solution (1%) prepared from captopril powder. All three samples were prepared in sterile water for irrigation, stored in sterile glass containers, and protected from light at (20-26°C). samples were analyzed for captopril and captopril disulfide for up to 28 days using stability-indicating HPLC method.

This experiment presents the first attempt where microbiological assay tests have been done for extemporaneously prepared oral liquid dosage forms in which the author tested the sample against two cultures (Acid-fast bacilli and fungal cultures) [21]. The results of this experiments varied from Lee & Notari's results, in which captopril solution prepared from the tablet at a concentration of 1% was less stable (< 90% of its initial

concentration at 14 days with crystal formation) than the solution prepared from the tablet at a concentration of 0.1% (≈98% of its initial concentration at 28 days) [8], the author referred this instability accompanied with a higher concentration of captopril prepared from the tablets to the presence of metal ions in the table excipients which were absent in captopril solution prepared from captopril powder. Captopril prepared from powder at a concentration of 1% maintains its stability all over the study period (≈ 100% of its initial concentration at 28 days). Regarding microbiological burden assay, all cultures were negative for bacterial and fungal growth [21].

Captopril in Simple Vehicles

Nahata et al. conducted two experiments to study the stability of captopril in four different liquid dosage forms; I. mixture of (Syrup: Methylcellulose, 1:1), II. Distilled water, III. Distilled water contains sodium ascorbate injection (as an antioxidant at a concentration of 5 mg/mL), and IV. And distilled water contains an ascorbic acid tablet (as an antioxidant at a concentration of 5 mg/mL). All formulas were prepared from 50 mg tablets at a concentration of 1 mg/mL and stored in glass bottles at 4°C and 21-23°C protected from light for up 91 days (formula IV stored for up to 56 days at the same conditions) and analyzed using stability-indicating HPLC.

The results revealed that captopril liquid preparations stored at 4°C have shelf lives of 7, 14, 56, and 56 days for formulations I-IV, respectively. In comparison, preparations stored at 21-23°C had a shelf life of 7, 7, 14, and 28 days, respectively [13, 22]. Also, Sornchaithawatwong et al. evaluated the stability of two extemporaneously prepared captopril formulations; **i.** *Captopril suspension* (1 mg/mL) prepared from captopril tablets with ascorbic acid 10% (from tablet) in suspension consisting of carboxymethylcellulose mucilage 14 mL, 70% sorbitol 20 mL, purified water 5mL, 10% methylparaben & 2% propylparaben in propylene glycol 0.8mL, and syrup qs to 100 mL and **II.**

Captopril powder for reconstitution (1 mg/mL) prepared from captopril tablets with ascorbic acid 10% (from the tablet) and stored as powder form in light-resistant bag, to be reconstituted upon opening with the same vehicle mentioned for captopril suspension.

Both formulations (along with the vehicle for captopril powder for reconstitution) stored in an amber bottle at 2-8°C and 25-28°C for 28 days, and analyzed for captopril concentration using HPLC method. Results showed that at 2-8°C, both formulations are stable for 28 days. While at 25-28°C, the suspension was stable for 28 days, while reconstituted powder for suspension was stable for seven days only.

The authors postulated the instability of captopril powder for reconstitution at higher temperatures to the higher surface area of powder particles, which make them highly exposed to moisture in the air, as well as powder for reconstitution stored in light-resistant polyethylene bags have some extent of oxygen permeability, which allows some oxygen to defuse inside these bags, which recommend storing dry powder in amber glass bottles as moisture and air can't pass through these glass containers.

As a side note, the authors did not specify the time between captopril powder for reconstitution preparation and the actual reconstitution time [2].After the invention of ready to use sweetening and suspending agents, Allen and Erickson studied the stability of captopril tablets 100 mg in three different liquid dosage forms; I. Mixture of Ora-Sweet and Ora-Plus (1:1), II. Mixture of Ora-Sweet SF and Ora-Plus (1:1), and III.

Mixture of Cherry syrup concentrate and simple syrup (1:4).All liquids prepared at a concentration of 0.75 mg/mL and stored in amber plastic polyethylene terephthalate prescription bottles with a low-density polyethylene foam cap lining at 5°C and 25°C. Samples were analyzed for captopril concentration by stability-indicating HPLC method for up to 60 days.

The results revealed less stability profile of captopril tablets in sweetened vehicles compared to the aqueous solutions (data from previous studies). In which prepared formulations retained ≥ 90% of its initial captopril concentration after 14, 10, and 2 days when stored at 5°C, and 7, 2, and 2 days when stored at 25°C for I, II, and III liquid dosage forms, respectively [23].

Later and after one year, Lye et al. studied the stability of fourteen different Captopril 1 mg/mL liquid formulations prepared from either powder or 12.5 mg tablets in I & II. Sterile water for irrigation (powder and tablets), III & IV. Highly purified water (Milli Q reagent water) (powder and tablets), V & VI.

Syrup (sucrose 85 % with preservative) (powder and tablets), VII & VIII. Sterile water for irrigation: syrup (50:50) (powder and tablets), IX & X. 2% Methylcellulose in sterile water for irrigation (powder and tablets), XI & XII.4% Methylcellulose in sterile water for irrigation (powder and tablets), XIII. Sterile water for irrigation: syrup (50:50) plus 0.1% (w/v) edetate disodium (from powder only), XIV.

2% Methylcellulose in sterile water for irrigation plus 0.1% (w/v) edetate disodium (from powder only).The liquids were stored at 5°C in amber glass containers. Since trace metals contaminants available in the vehicles (syrup and methylcellulose), e.g., iron and copper, are well known to affect the stability of captopril in liquid dosage forms, edetate disodium was added as a chelating agent in two of the formulation. Samples were assayed for captopril concentration by stability-indicating HPLC method for up to 30 days.

Also, they studied the influence of the degree of methoxy substitution in the methylcellulose on the stability profile of the captopril liquid (1 mg/mL) prepared from powder [24]. Strangely and vary from what was reported by Pramar et al. and Chan et al. [19, 21], formulas prepared from captopril tablets were more stable than formulas prepared from captopril powder. There was no significant difference in stability profile between formulas prepared in highly purified water (Milli Q reagent water) and formulas prepared in sterile water for irrigation.

Furthermore, the authors noticed that the formulation prepared in undiluted syrup was more stable than formulations, where water was part of its vehicle or formulas contained methylcellulose. The author referred the higher stability of captopril in undiluted syrup, comparing to the diluted one to the antioxidant effect of sucrose at higher concentrations, while low stability profile of captopril in methylcellulose formula referred to the direct chemical reaction between them or due to its metal contaminants.

Regarding methylcellulose type and concentration, after seven days analysis results revealed that liquids containing a higher concentration of methylcellulose or methylcellulose with higher methoxy substitution have less stability profile, this is due to the increased electron density around the oxygen of the methylcellulose's methoxy group which make captopril's sulfhydryl group more susceptible to nucleophilic attack. Additionally, it's markedly noticed that edetate disodium increases the stability of captopril, which explains the vital role of trace metals in captopril degradations.

The maximum stability of the formulas was 7, 10, 10, 15, 15, 15, 3, 3, unstable, 3, unstable, 1, 30, 30 days for formulations i-xiv [24]. In order to assess the hypothesis proposed by Lye et al. that captopril is more stable in undiluted syrup due to the antioxidant effect of its invert sugar contents (D-(+)-glucose and D-(-)-fructose) [24], Sam and HO conducted an experiment comparing the stability profile of captopril 1mg/mL prepared from powder in five different concentrations of invert sugar solution (0% (Milli-Q water), 1%, 10%, 30%, and 85% w/v) stored at 5°C.

Samples were analyzed for captopril concentration for up to 30 days using stability-indicating HPLC method. Results indicated that Captopril in Milli-Q water (0% of inverts sugar) was more stable compared to that in invert sugar solutions (1%, 10%, 30% w/v). In comparison, captopril in 85% invert sugar solution was more stable than Captopril in Milli-Q water (0% of inverts sugar). Although higher stability noticed with higher invert sugar concentration, the findings in this study did not support the hypothesis proposed by Lye et al.

As in general, antioxidants exert their effects at low concentrations, which not seen here with low concentrations of invert sugar. The authors attributed the differences in Captopril 1 mg/mL stability in solutions containing different concentrations of invert sugar to the dissolved oxygen contents in the formulation, which decreases (oxygen contents) as the water content of the formula decrease resulting in a more stable formulation.

Using initial rate constant to calculate the rate of Captopril 1 mg/mL degradation in invert sugar at 5°C resulted in (5, 3, 3, 4, 20 days) as a shelf life for formulas containing (0%, 1%, 10%, 30%, and 85% w/v) inverted sugar [25].

Consequently, as formulations containing a high concentration of sucrose have a harmful effect to the teeth of children and the possibility of its crystallization under refrigeration, and based on the findings by Chen et al. as that low concentration of citric buffer (0.03M) enhances the stability of captopril in liquid formulations, Liu et al. studied the stability of Captopril 1 mg/mL (prepared from powder) in twelve liquid formulations containing different concentrations of sucrose with/without citric buffer adjusted to pH=3 (i-viii) in the presence of glucose oxidase (antioxidant) adjusted to pH=4.5 (ix-xii), stored in an amber glass bottle at 5°C (i-x) and 32°C (xi and xii).

Formulations were analyzed for captopril concentration for up to 30 days (i-viii) and two days (ix-xii) using stability-indicating HPLC method. Results obtained indicate that citric buffer at low concentration (0.03M) has No apparent stabilizing effect on captopril's formulations do not contain sucrose or containing 30 % sucrose.

In comparison, the stabilizing effect was significant on captopril's formulation containing sucrose at a concentration of 10% and 85%. By using the degradation rate constant of captopril in formulation i-viii, the shelf lives have been calculated to be; 11, 13, 18, 29, 7, 10, 26, and 22 days, respectively. With maximum stability obtained for Captopril 1 mg/mL in 10% w/v sucrose in Milli Q reagent water with 0·03 M citric buffer. Captopril in formulations containing glucose oxidase (antioxidant) degraded very rapidly within the first day of preparation, signifying its destabilizing effect on captopril stability, although the results showed its strong capabilities to remove dissolved oxygen from formulations [26, 27].

Markoulina et al., used the stability-indicating HPLC method to assess the stability of ten Captopril 1 mg/mL formulations, stored in amber glass bottles at 2-8°C and 20-24°C for 30 days. Formulations were prepared from either captopril powder or tablets based on formulas mentioned in the literature and known to have a reasonable stability profile (sometimes with some modification) and were as following; I & II. Purified water containing 1 mg/mL disodium edetate (powder/tablet), III & IV.

Purified water containing 5 mg/mL sodium ascorbate (powder/tablet), V & VI. Purified water containing 1 mg/mL disodium edetate and 5 mg/mL sodium ascorbate (powder/tablet), VII & VIII. Mixture of Ora-Sweet and Ora-Plus (1:1) (powder/tablet), IX & X. Purified water only (powder/tablet) [13, 22-24, 26, 28-29]. All formulations were stable for all study period (3o days) at both storage conditions except formulations prepared in a mixture of Ora-Sweet and Ora-Plus (VII & VIII) were unstable at both storage conditions and formulation prepared from powder in Purified water containing 5 mg/mL sodium ascorbate (iii) stored at 20-24°C.

A formulation consisting of Captopril 1 mg/mL solution prepared from powder in purified water containing 1 mg/mL disodium edetate (i) showed the maximum stability after 30 days of storage and has been selected for long-term stability study conducted for two years at 2-8°C and 20-24°C, and one year at 38-42°C using the same analysis method.

Furthermore, the microbiological assay of these formulations has been conducted initially, after six months, and at the end of the study period. Results revealed that a modified formula (based on formula mentioned by Lye et al.) [24] consisting of Captopril 1 mg/mL solution prepared from powder in purified water containing 1 mg/mL disodium edetate (preservative and chelating agent) is chemically and microbiologically stable for up to two years in amber glass bottle stored at 2-8°C and 20-24°C, and 12 months at 38-42°C [30].

Additionally, Imre et al. in their attempts to study the stability of different captopril 1 mg/mL oral liquid formulations stored at 8 and 19-25°C for 38 days, they found that formulations containing ascorbic acid are physically, chemically, and microbiologically stable for seven days at both storage temperatures (No further information available) [31]. Furthermore, Geiger et al. studied the stability of captopril 0.8mg/mL prepared from powder in ready to use Syr

Spend SF suspending vehicle (Sorbitol-, sugar- and alcohol-free suspending agent) stored in low-actinic, protect from light plastic prescription bottle at 2-8°C for up to 32 days, using stability-indicating HPLC method. The results revealed that the captopril formulation remained stable for up to 14 days with captopril concentration around 95% of its initial concentration, while it decreased to 86% after 32 days of storage [32].

Captopril in Advanced Vehicles

Mulla et al. during their survey to determine the inter hospital consistency of extemporaneously prepared captopril oral solutions used to treat children with cardiac problems in 26 healthcare facilities based on United Kingdome, they reported the use of nine different captopril liquid formulations; *Three of the liquid formulations were procured from "special" manufacturer*, where concentrations vary, and the vehicle consisting of (i) fractionated coconut oil and Cab-o-sil (90 days expiry), (ii) Xanthan gum 1% and ascorbic acid (28 days expiry), (iii-a) suspension diluent containing (xanthan gum 1%, methyl hydroxybenzoate, and propylhydroxy benzoate) diluted in 1:1 ratio with water (8 days expiry), and (iii-b) suspension diluent containing (xanthan gum 1%, methyl hydroxybenzoate, and propylhydroxy benzoate) diluted in 1:1 ratio with water and favored with ascorbic acid (28 days expiry).

One formulation obtained from an NHS manufacturing unit with a concentration of 1, 5, and 12.5 mg/mL in a vehicle consisting of (iv) Xanthan gum 0.4%, methyl hydroxylbenzoate, and propylhydroxy benzoate (35 days expiry). *One formulation was imported from outside the country* with a concentration of 5 mg/mL in a vehicle consisting of (v) Citric acid, sodium citrate, disodium edetate, and sodium benzoate (28 days expiry). As well as *four formulations were extemporaneously prepared* where concentrations vary and the vehicle consisting of (vi) Ascorbic acid and water, (vii) suspension diluent containing (xanthan gum 1%, methyl hydroxybenzoate and propylhydroxy benzoate), (viii) OraPlus/OraSweet (1:1 ratio), and (ix) suspension diluent containing (xanthan gum 1%, methyl hydroxybenzoate and propylhydroxy benzoate) diluted in 1:1 ratio with water.

All these four formulations were stable for 14 days. Based on the author's investigation, none of the nine formulas suppliers (either manufacturer or hospital), except for the formulation imported from outside the country, had conducted stability study for their final product to support claimed shelf life [33]. For this review, Unfortunately, all nine mentioned formulas could not be traced to any valid stability study except for formulas used to prepare formulation vi&Viii. In order to come with a new formula with extended stability, Kristensen et al. studied the effect of different formulation properties on the chemical stability of captopril powder in acidic aqueous solutions at pH 3.

The studied factors were; (i) *captopril concentration*; the effect of captopril concentration on the stability profile of captopril in buffer-free water for injection at low pH stored at 25°C has been studied. Results showed that an increase in drug concentration from 1 to 5 mg/mL improves the chemical stability of captopril. Also, kinetically, the degradation reaction of captopril on pure aqueous solution follows zero-order kinetics at low captopril concentration, and will change at higher concentration (≥ 2.5 mg/mL) to a different model, apparently, does not fit well first-order kinetic model.

The shelf lives of the prepared solutions were; 7, 33, and 54 days for concentrations 1, 2.5, and 5 mg/mL stored at 25°C at pH 3. It is worth mentioning here that a black precipitate has been noticed after 57 days of storage for Captopril 5 mg/mL solution, and 73 days for captopril 1 and 2.5 mg/mL solutions stored at 25°C which expected to be captopril disulfide degradation product.

(ii) *Storage temperature*; the decrease in the storage temperature improved the chemical stability of the drug. As captopril 1 mg/mL prepared in aqueous solution found to be stable up to 26, 7, and 4 days at 2, 25, and 36°C storage temperatures, respectively. (iii) *Mechanism of drug degradation*; it has been postulated that the intramolecular proton transfer from the captopril thiol group to the carboxylic group represents the first step in the captopril oxidative degradation process. (iv) *different solvents*; by studying the effect of different solvents on captopril stability,

Kristensen and colleagues found that captopril stability depends on the amphiprotic properties of the solvent used, in which solvents with proton donor properties destabilize captopril. In contrast, solvents with proton acceptors properties stabilize it. Long-term stability (one year stored at 36°C) indicated that sugar alcohol solvents such as glycerol and Sorbitol have a destabilizing effect on captopril 1mg/mL aqueous solution adjusted to pH 3 (v) *Solvent polarity*; the results of the role of solvent polarity on the stability profile of captopril are not consistent, with no clears consensus about this factor. (vi) *solvent viscosity*; The authors studied the stability profile of captopril in different glycerol concentrations (0-80%) which represent different solvent viscosities and found that captopril degradation increase as the solvent viscosity increase up to glycerol concentration 50%, then decrease at higher concentration of glycerol which indicates that there are many factors more important than solvent viscosity able to affect captopril stability at glycerol concentration ≤ 50% before viscosity becomes an issue (≥ 50%) and reduce drug degradation rate. (vii) *Chelating agents*; Long-term stability (one-year study at 36°C) of captopril 1mg/mL aqueous solution adjusted to pH 3 indicated that Na-EDTA at a concentration of 0.1 mg/mL significantly stabilizes the formulation, which is a tenth of the concentration mentioned by Markoulina *et al.* [34]. (viii) *Salt contents*; increase salt contents in the prepared formulations will promote captopril degradation and formulation destabilization. (ix) *Buffer effect*; citrate buffer and phosphate buffer found to have a destabilizing effect on captopril solution at acidic media (pH 3). This destabilizing effect of citrate buffer is contradictory to what was mentioned by previous studies [20, 26-27].

Authors studied the effect of different concentrations of citrate buffer. They found that the stability effect of citrate buffer (as a chelating agent) is dose-dependent, in which at higher citrate concentration, it forms a complex formation with drug molecules rendering them unstable. (x) *Oxygen contents*; although oxygen content in water decrease as the temperature increase, it was found here that the degradation is independent on the oxygen level as temperature increase (xi) *combined effect*; In order to study the influence of combined factors on captopril 1 mg/mL aqueous solution stability in acidic media (pH 3), stored at 36°C for one year, an experiment has been conducted in the presence of Na EDTA (0.1 or 1 mg/mL), sorbitol (30-35 mg/mL), with/without purged with N_2-gas. The results revealed that Sorbitol destabilizes the captopril solution, while Na-EDTA 0.1 mg/mL in the presence of Sorbitol (35%) is sufficient to stabilize the formulation. Furthermore, purging prepared formulation with N_2-gas to remove dissolved oxygen before storage is not crucial as long as Na-EDTA is present. This step (purging with N_2-gas) becomes significant at a low level of Na-EDTA (0.1 mg/mL) combined with a higher level of Sorbitol (35%).

All Captopril 1 mg/mL formulations stored at 36°C in aqueous acidic solution (pH 3) containing Sorbitol (at a concentration of 0, 20 or 35%) and Na-EDTA (at a concentration of 0, 0.1 or 1 mg/mL) purged or not purged with nitrogen gas were stable for 365 days except for captopril 1 mg/mL aqueous acidic formulation pH 3 with sorbitol 35% and Na-EDTA 0.1 mg/mL and Not purged with nitrogen gas was stable for 188 days [35].

Based on these formulation properties and After one year, the same team designed a new extemporaneously prepared captopril 1 & 5 mg/mL oral liquid formulations, using captopril powder in sterile water for irrigation with Sorbitol (70%) 287 mg/mL, disodium edetate 0.1 mg/mL, and sodium benzoate 1 mg/mL. formulations were adjusted to pH<4 and stored in amber glass bottles with headspace air at 21.5-22.5°C for 12 months. captopril concentration was measured using stability-indicating HPLC method.

Furthermore, microbiological burden for bacteria, fungi, and the presence of *Escherichia coli* has been studied at 0, 6, and 12 months for 1mg/mL formulation, and at 0 and 12 months for 5 mg/mL formulations. Also, they studied the stability of Captopril 1 mg/mL (prepared using same constituents) after one month of simulated daily use, at the start and the end of the 12 months study period (from the start of the study to 1 month of storage and from the 11th to the 12th month of storage) stored at 2-8°C, as well as its microbiological quality.

Although the results revealed that all prepared captopril formulations were chemically (≥ 98.5% of initial captopril concentration) and physically stable without any evidence of microbial contamination during study periods at all mentioned storage conditions, captopril 5 mg/mL formulation showed a slightly sulfurous taste and smell. Also, results indicate that oxygen content in captopril formulation is not a factor in its stability, as air could access the solution during simulated one-month usage without any apparent effect [36].

Pabari et al. surveyed the extemporaneously prepared captopril liquid formulations in Irland. Then, The stability of the most commonly used formulation was evaluated and compared with a newly extemporaneously prepared fast-dispersing tablet using stability-indicating HPLC method.

i. xanthan gum, **ii.** Water, ascorbic acid, and xanthan gum, or **iii.** Ora-sweet: ora-plus, represent the most commonly used captopril formulations prepared from tablets. These formulations could be traced to a valid formula mentioned in the literature. Accordingly, The stability of captopril 1, 2.5, and 10 mg/mL liquid formulations prepared from the tablet in 0.4% xanthan gum suspension stored in an amber glass bottle at 2-6°C have been validated using Stability-indicating HPLC for 56 days. The results revealed that all captopril formulations were stable for up to 7 days, irrespective of the captopril concentration.

Where the concentration of captopril in all formulation was <90 at 14 days analysis, where the decrease in captopril concentration was inversely related to the starting concentration, it is worth mentioning here that prepared formulations had a slightly sulfurous to acidic odor, which starts to increase after seven days of storage and with an increase in drug concentration, and become a pungent smell after 14 days and last over the study period (56 days) making the formulation unpalatable.

Captopril fast-dispersing 2.5 and 10 mg tablet have been prepared using captopril tablet with mannitol 200 (171.4 mg and 123.4 mg, for 2.5 and 10 mg captopril fast-dispersing tablets, respectively), Crosslinked Polyvinylpyrrolidone 5% w/w (10 mg), Magnesium stearate 0.5% w/w (1 mg), and Raspberry flavor 0.8 w/w (1.6 mg). the total weight of each prepared tablet was 200 mg. Then tablets were compressed at 7 rpm and a compression force of 10 KN and stored at room temperature till the time of analysis. Fast-Dispersing tablets found to disintegrates in less than 32 seconds, with no sign of sticking or capping and no change in color or appearance with a consistent weight. Surprisingly, although Captopril 10 mg Fast dispersing tablets were stable all over the study period (56 days), Captopril 2.5 mg captopril fast-dispersion tablet showed less than 90% of captopril concentration after 28 days which indicate that the degradation of captopril in the solid dosage form is, also, dose-dependent.

Although the authors mentioned Fast-dispersing tablets as a doable technique to prepare captopril in the most stable formulation extemporaneously, this kind of formulations still needs the availability of some excipients and compressing machines that are not available in all hospitals [37]. Casas et al. Surveyed 20 hospitals in Spain for captopril formulations. Then, formulation with the maximum stability profile was selected to validate its physiochemical stability using stability-indicating HPLC method.

Accordingly, captopril 1 mg/mL liquid solution was prepared from powder in purified water with edetate disodium 0.1mg/mL, stored in amber glass bottles at 2-8, 23-27, and 38-42°C for up to 90 days. Results showed that captopril 1 mg/mL oral solution is more stable at 2-8°C than at the upper temperature. Also, Although all captopril formulations were stable for 30 days at all storage temperatures (Retained 100, 98, and 97% of its initial captopril concentration at 2-8, 23-27, and 38-42°C storage temperature, respectively), only formulation stored at 2-8°C retained its stability profile till 50 days of study (97, 86, and 82% of its initial captopril concentration at 2-8, 23-27, and 38-42°C storage temperature, respectively).

It worth mentioning here that after 50 days, captopril stored at 25 and 40 C showed signs of microbiological contamination. At the end of the study period (90 days), none of the prepared formulation maintained more than

40 % of its initial captopril concentration [38]. Sathapanapitagkit et al. studied the stability of four Captopril 1 mg/mL suspension prepared from the tablet in I. 80% simple syrup (preserved with sodium benzoate 1 mg/mL), II. 80% simple syrup (preserved with sodium benzoate 1 mg/mL) and citric acid (chelating agent and pH reducer agent) at a concentration of 20 mg/mL, III. 80% simple syrup (preserved with sodium benzoate 1 mg/mL) and ascorbic acid tablets (from 100 mg tablet as antioxidant) at a concentration of 4 mg/mL, and IV.

80% simple syrup (preserved with sodium benzoate 1 mg/mL) and ascorbic acid tablets (from 100 mg tablet as antioxidant) at a concentration of 5 mg/mL, stored in a. amber polyethylene terephthalate bottle and b. clear glass bottle protected from light by aluminum foil, at 2-8°C for 90 days, and at 30°C for 60 days, formulations were analyzed using the HPLC method.

The results revealed that adding citric acid reduced the pH of the suspension to 2.66. While ascorbic acid reduced the pH to 4.4 and 4.42 for 4 and 5 mg/ml, indicating that the increase in ascorbic acid concentration has no apparent effect on the pH of prepared formulations. Also, an increase in storage temperature has a destabilizing effect on all captopril formulations. At 2-8°C, the addition of citric acid or ascorbic acid (4 or 5 mg/mL) rendered captopril formulations stable for all study period (90 days), whereas formulation without stabilizers remained stable for 74 days.

At 30°C, all formulations showed drug stability up to 28 days except for the formulation with citric acid, which found to accelerate captopril degradation at this temperature [39]. This destabilizing effect of citric acid at this temperature varies from what was discovered by Chen et al [26].Which attributed to the differences in pH values of the studied formulations (pH 2.66 and 6). Furthermore, the increase in ascorbic acid concentration had no significant effect on captopril stability.

Goes et al. in their attempt to suggest favorable conditions for the development of stable captopril formulation, they studied the compatibility between captopril (powder) and some pharmaceutical excipients; EDTA, citric acid, dihydrate sodium citrate, and sucralose in a solid phase using thermal analysis methods; differential scanning calorimetry (DSC), differential thermal analysis (DTA) and thermogravimetry (TG) analysis. The results of this thermal analysis revealed that there is No interaction between captopril powder and both EDTA and dehydrate sodium citrate, while there is a possibility of interaction between captopril and two excipients; citric acid and sucralose (not conclusive, need further confirmation by other methods).

However, both excipients (sucralose and citric acid) are not determining factors for captopril stability in aqueous solutions, as presented later by the results of the stress test. Furthermore, they studied the influence of interaction between pH, quality of water, and chelating agent concentration (EDTA) in the stability profile of extemporaneously prepared captopril 5 mg/mL oral solution prepared from powder.

To do so, they prepared 12 different captopril 5 mg/mL formulations in; Distilled water (I-VI), or mineral water (VII-XII).Containing; 0.05 mg/mL EDTA (I-III & VII-IX), or 1 mg/mL EDTA (IV-VI & X-XII). At three pH values; 2.5 (I, IV, VII, and X), 4 (II, V, VIII, and XI), and 5.5 (Iii, VI, IX, XII). In addition, Sucralose (sweetener) was added based on the pH value of formulation (0.15, 0.17, and 0.2 %, for formulations have a pH value of 5.5, 4.0, 2.5, respectively).

All twelve formulations were stored at 58-62°C (stress test) and analyzed for captopril concentration using the HPLC method. The results of this stress test indicate that the decrease in the pH value (up to 4), increase EDTA concentration, and use of mineral water instead of distilled water render captopril formulations more stable.

Where higher stability obtained for Captopril 5 mg/ml in mineral water containing 1 mg/ml EDTA and kept at a pH value of 4. It is postulated that higher pH values enhance captopril degradation by promoting its ionization. While at low pH values (< 4), the degradation is independent of the ionization process and defined as acid-catalyzed degradation. Also, authors attributed the higher stability of captopril in mineral water to the presence of some ions in the water that can interact with metals ions able to degrade captopril through the oxidative degradation process.

It's worth mentioning here that by studying all factors collectively, results showed that increase in the concentration of EDTA (from 0.05 to 1 mg/mL) enhances the stability of captopril on the solution only when other factors are not supporting captopril stability, e.g., High pH values or using distilled water. Also, results showed that captopril degradation follows zero-order kinetics, which indicates that captopril degradation is independent of the captopril concentration in the solution [40].

Surprisingly, these results vary from what was mentioned by other studies [34-36]. Furthermore, sucralose, as a sweetening agent found to has no effect on captopril stability in aqueous solution. The t_{90} has been calculated to be around 6, 8, 2, 6, 14, 4, 13, 14, 5, 15, 16, and 4 days for formulations i-xii stored at 58-62°C, respectively. In conclusion, the authors assumed that captopril 5 mg/mL with EDTA 0.8 mg/mL and a buffering system consisting of anhydrous citric acid and sodium citrate dihydrate added to bring the pH to 3.85 possess the maximum stability profile.

Bioequivalence of Extemporaneously Prepared Captopril Formulations

Although there is No bioequivalence study available for extemporaneously prepared captopril oral formulations, one open-label crossover study assessed the bioequivalence of two ready to use captopril oral liquid preparations against tablet form in a group of 18 healthy adult volunteers. Results showed that both ready to use liquid formulations failed to be bioequivalent to captopril tablets or each other in terms of maximum plasma concentration (C_{max}) and area under the curve (AUC), indicating that formulation substitution should be done with care and may require close monitoring to the patients upon formulation substitution [33].

Conclusion

Although captopril is not available as ready to use Oral liquid preparations for neonates and children, it is still representing a corn stone in hypertension and other cardiac problems treatments in these groups of patients. Many attempts have been made to prepare it extemporaneously with a reasonable stability profile in various types of vehicles with different pharmaceutical excipients. Although researchers were able to do that, the inconsistency of stability results of the same formulation prepared by different teams represent the extent of sensitivity of this drug to a variety of factors. Till it become available as ready to use oral liquid formulation, these attempts will continue by researchers and pharmaceutical industries.

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References

1. Castro Díez C, Khalil F, Schwender H, Dalinghaus M, Jovanovic I et al (2019) Pharmacotherapeutic management of paediatric heart failure and ACE-I use patterns: a European survey. BMJ Paediatr Open. doi:10.1136/bmjpo-2018-000365
2. Sornchaithawatwong C, Chuemongkon W, Nunthanavanit P, Chaiporntrakulkit R, Nathong A et al (2018) Vehicle stability enhancement of Captopril extemporaneous preparation. Journal of Pharmacy Research, 12(7): 924-928.
3. Iafrate RP, Wall D, Lynch SM (1983) Oral captopril solution for neonatal hypertension. Clin Pharm., 2(5):395.
4. Bifano E, Post EM, Springer J, Williams ML, Streeten DH (1982) Treatment of neonatal hypertension with captopril. J. Pediatr., doi:10.1016/s0022-3476(82)80256-4
5. Friedman A, Chesney RW, Ball D, Goodfriend T (1980) Effective use of captopril (angiotensin I-converting enzyme inhibitor) in severe childhood hypertension. J. Pediatr., doi:10.1016/s0022-3476(80)80038-2
6. Oberfield, SE, Case DB, Levine LS, Rapaport R, Rauh W et al (1979) Use of the oral angiotensin I--converting enzyme inhibitor (Captopril) in childhood malignant hypertension. J. Pediatr., doi:10.1016/s0022-3476(79)80787-8

7. Timmins P, Jackson I, Wang Y (1982) Factors affecting captopril stability in aqueous solution. Int. J. Pharm., doi:https://doi.org/10.1016/0378-5173(82)90083-7
8. Lee TY, Notari RE (1987) Kinetics and mechanism of captopril oxidation in aqueous solution under controlled oxygen partial pressure. Pharm Res., doi:10.1023/a:1016406716989
9. O'Dea RF, Mirkin BL, Alward CT, Sinaiko AR (1988) Treatment of neonatal hypertension with captopril. J Pediatr., doi:10.1016/s0022-3476(88)80292-0
10. Bendig L, Temesvári A (1988) Indications and effects of captopril therapy in childhood. Acta Physiol Hung, 72(Supp l):121-129.
11. Moreno Villares JM, Barrio Andrés C, Gutiérrez Junquera C, Torres Mohedas J (1990) Captopril treatment of neonatal arterial hypertension. An Esp. Pediatr., 32(3):253-256.
12. Kaplan S (1990) New drug approaches to the treatment of heart failure in infants and children. Drugs. doi:10.2165/00003495-199039030-00005
13. Nahata MC, Morosco RS, Hipple TF (1994a) Stability of Captopril in liquid containing ascorbic acid or sodium ascorbate. Am J. Hosp. Pharm., 51(13): 1707-1708.
14. Schneeweiss A (1988) Cardiovascular drugs in children: angiotensin-converting enzyme inhibitors. Pediatr Cardiol., doi:10.1007/bf02083709
15. Shaw NJ, Wilson N, Dickinson DF (1988) Captopril in heart failure secondary to a left to right shunt. Arch Dis Child., doi:10.1136/adc.63.4.360
16. Stern H, Weil J, Genz T, Vogt W, Bühlmeyer K (1990) Captopril in children with dilated cardiomyopathy: acute and long-term effects in a prospective study of hemodynamic and hormonal effects. Pediatr Cardiol., doi:10.1007/bf02239543
17. Taketomo CK, Chu SA, Cheng MH, Corpuz RP (1990) Stability of Captopril in powder papers under three storage conditions. Am J. Hosp. Pharm., 47(8):1799-1801.
18. Pereira, CM,Tam, YK (1992) Stability of captopril in tap water. Am J. Hosp. Pharm., 49(3):612-615.
19. Pramar Y, Das Gupta V, Bethea C (1992) Stability of Captopril in some aqueous systems. J. Clin Pharm. Ther., doi:10.1111/j.1365-2710.1992.tb01291.x
20. Anaizi NH, Swenson C (1993) Instability of aqueous captopril solutions. Am J. Hosp. Pharm., 50(3): 486-488.
21. Chan DS, Sato AK, Claybaugh JR (1994) Degradation of Captopril in solutions compounded from tablets and standard powder. Am J. Hosp. Pharm., 51(9):1205-1207.
22. Nahata MC, Morosco RS, Hipple TF (1994b) Stability of Captopril in three liquid dosage forms. Am J. Hosp. Pharm., 51(1): 95-96.
23. Allen LV, Erickson MAI (1996) Stability of baclofen, Captopril, diltiazem hydrochloride, dipyridamole, and flecainide acetate in extemporaneously compounded oral liquids. Am J. Health Syst Pharm., doi:10.1093/ajhp/53.18.2179
24. Lye MY, Yow KL, Lim LY, Chan SY, Chan E et al. (1997) Effects of ingredients on stability of captopril in extemporaneously prepared oral liquids. Am J. Health. Syst. Pharm., doi:10.1093/ajhp/54.21.2483
25. Sam WJ, Ho PC (1998) Stability of Captopril in invert sugar solution. J. Clin Pharm Ther., doi:10.1046/j.1365-2710.1998.00190.x
26. Chen D, Chen H, Ku H (1995) Degradation Rates of Captopril in Aqueous Medium Through Buffer-Catalysis Oxidation. Drug Development and Industrial Pharmacy, doi:10.3109/03639049509026643
27. Liu J, Chan SY, Ho PC (1999) Effects of sucrose, citric buffer and glucose oxidase on the stability of captopril in liquid formulations. J. Clin Pharm Ther., doi:10.1046/j.1365-2710.1999.00213.x
28. Buchsein K, Wolkewitz B (2000) Stabilität einer wässrigen Captopril-Lösung. Krankenhaus Pharmazie, 8:432-434.
29. Loyd V. Allen J (1997) Captopril 0.75 mg/ml oral liquid. International Journal of Pharmaceutical Compounding, 1(5):322.
30. Markoulina B, Grégory P, Nicolas W, Stéphane G, Bernard T et al. (2007) The development of a stable oral solution of captopril for paediatric patients. European Journal of Hospital Pharmacy Science, 13(3):27-32.

31. Imre S, Vancea S, Muntean DL, Sipos E, Cociş A et al (2008) Stability of some medicinal solutions with captopril. Rev Med Chir Soc. Med. Nat Iasi, 112(3):848-855.
32. Geiger CM, Sorenson B,Whaley PA (2013) Stability of Captopril in SyrSpend SF. Int J Pharm Compd, 17(4):336-338.
33. Mulla H, Tofeig M, Bu'Lock F, Samani N, Pandya H (2007) Variations in captopril formulations used to treat children with heart failure: a survey in the United kingdom. Archives of disease in childhood, doi:10.1136/adc.2006.109389
34. Berger-Gryllaki M, Podilsky G, Widmer N, Gloor S, Testa B et al. (2007) The development of a stable oral solution of captopril for paediatric patients. EUR. J. HOSP. PHARM-S P, 13(3):27-32.
35. Kristensen S, Lao YE, Brustugun J, Braenden JU (2008) Influence of formulation properties on chemical stability of captopril in aqueous preparations. Pharmazie, 63(12):872-877.
36. Brustugun J, Lao YE, Fagernaes C, Braenden J, Kristensen S (2009) Long-term stability of extemporaneously prepared captopril oral liquids in glass bottles. Am J. Health Syst. Pharm., doi:10.2146/ajhp080542

