Stability of an alternative extemporaneous captopril fast-dispersing tablet formulation versus an extemporaneous oral liquid formulation.

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Comparing the stability of an alternative extemporaneous captopril fast dispersible tablet and extemporaneous oral liquid formulation

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ABSTRACT

Background: Administration of medications to paediatric patients is challenging as many drugs are not commercially available in appropriate dosage forms and dosage strength. Consequently, these drugs are prepared extemporaneously as oral liquid (OL) using marketed tablets or capsules. Unfortunately, these extemporaneous preparations often have no documented stability studies which impact on the safety of these preparations. An alternative extemporaneous solid formulation such as fast dispersible tablets (FDTs) can offer enhanced stability as well as dosing flexibility as these can be administered as orodispersible tablets or as reconstituted suspension/solution. While FDTs are available increasingly as patient friendly oral dosage forms and their simple method of manufacture can be applied to extemporaneous formulations, such applications have not been explored to date.

Objective: The use of extemporaneous captopril OL formulations in Irish hospitals was surveyed and the stability of the most commonly used captopril formulation was investigated and was compared with that of a novel extemporaneous fast dispersible tablet (FDT) formulation.

Methods: A survey was carried out regarding the use of captopril OL formulations in 120 hospitals in the Republic of Ireland. The stability of the most commonly used formulation was compared against a novel extemporaneous captopril FDT preparation. Captopril content of the formulations was measured by HPLC analysis. Formulations were also monitored for changes in appearance, colour, odour and pH (OLs).

Results: The survey showed that extemporaneously prepared captopril OLs were extensively used particularly in specialist childrens hospital. The most commonly used preparation was Keltrol® based oral suspension. Analysis of these OL preparations showed the OLs to be stable up to day 7 but captopril concentration decreased to 72-84% at day 14

and 59-68% at day 56 and this was accompanied by a pungent odour suggestive of captopril oxidation. In contrast FDT formulations demonstrated longer stability with 96% of captopril present at day 56.

Conclusions: The results of this study support only a 7 day stability for the currently dispensed captopril OL in Irish hospitals. In contrast a long stability of at least 56 days was shown for the FDTs. The FDTs present an alternative and convenient oral solid extemporaneous preparation for captopril and potentially for other extemporaneous paediatric medications.

Key words: captopril, paediatric, extemporaneous compounding, unlicensed preparations, oral liquid, fast dispersible tablets

INTRODUCTION

The majority of oral preparations are available as solid dosage forms such as tablets and capsules which present advantages such as patient convenience and compliance and high chemical and microbiological stability compared to liquid dosage forms.[1] However, conventional tablets are inappropriate for use by certain patient populations including elderly and paediatric patients as tablets are designed to be swallowed and corresponding liquid preparations are often not commercially available due to many factors including lack of market size.[2-4] Therefore pharmacists in both hospital and community settings are often challenged to extemporaneously prepare oral liquid (OL) preparations to allow ease of dose administration in particular to paediatric patients. It is reported that such extemporaneous OLs constitute about 40% of preparations administered to paediatric patients.[3] Captopril, an ACE inhibitor, is commonly used to treat paediatric hypertension and heart failure.[5-9] It is used as an unlicensed preparation in children as captopril is only approved for use in adults.

Captopril is generally available in doses ranging 12.5 mg - 100 mg for administration to adults. The doses recommended for children are generally lower than 12.5 mg; the BNF for Children (2012-13) recommends a maximum dose of 300 mcg/kg daily for neonates and 6 mg/kg daily for children aged 1 month–12 years, administered in divided doses. Since the paediatric dose is lower than the dose administered by adults, paediatricians have to instruct parents to crush tablets and administer the medication mixed in food or else instruct pharmacists to compound extemporaneous suspensions which offer advantages of titratable individualised doses.[5,11,12] Extemporaneous formulations are usually prepared from commercially available oral solid dosage forms by simply crushing tablets or opening capsules and subsequent addition of water or other diluents. In certain cases, unlicensed preparations can also be procured from a 'specials' manufacturer or imported from outside the EU. However in most cases limited stability data exists for these preparations.[3,4,6] In addition as there is often no consistency in compositions from various hospitals, health centres, pharmacies and specials manufacturers, these raise issues regarding the efficacy and toxicity of these preparations.[8-10]

As a solid, captopril is stable, however in solution it undergoes free radical oxidation to yield captopril disulphide as the major degradation product.[13] This degradation is complex, concentration and pH dependent with highest stability at pH 3.5.[13] The aqueous stability of captopril was reported to be determined by the quality of the water. When prepared in tap water from Edmonton, Alberta, captopril was reported to be stable for 27 days at 5°C, while in tap water from Rochester, New York, captopril was extremely unstable.[14-17] In sterile buffered water (pH 3 and pH 5), 1 mg/mL captopril solution made from triturated tablets was found to be stable for at least 28 days at 4°C.[18,19] Enhanced storage stability of >56 days at 4°C was reported when antioxidants such as ascorbic acid or sodium ascorbate

was added to aqueous solution of captopril.[2,6,10,20,21] On the contrary, Berger et al[22] reported that solutions of commercial captopril tablets in purified water containing ascorbate and/or EDTA-Na showed limited stability of less than one month, related to the presence of metal ions in the tablets to catalyse oxidation.

A major issue with extemporaneous OL captopril preparation is its stability profile and the variety of formulations which are used between different hospitals and dispensing centres in addition to 'specials' preparations which are also dispensed. This may result in patients dispensed with formulations which are inconsistent regarding their stability and shelf-life and therefore efficacy and toxicity.[8,9,23]

Oral powders individually packaged or filled into capsules have been used as an alternative extemporaneous preparations for administration mixed with feeding liquid or appropriate food and as the drug is in solid state, these dosage forms are more stable and generally are given a shelf life of 28 days. However such formulations are not favoured in England, Ireland, Norway and Sweden where liquid formulations are predominantly used.[6] Fast dispersible tablets (FDTs), in particular oro-dispersible tablets introduced for patients with difficulty in swallowing tablets can offer an alternative extemporaneous formulation with various advantages such as prolonged stability as the drug is in solid state, dosing flexibility as reconstituted suspensions or solutions for infants or enteral feeding or as oro-dispersible tablet to elderly patients and older children. Despite their popularity as commercial preparations and their ease of manufacture by a one-step direct compression process, these formulations have not been explored for extemporaneous dispensing. With the availability of a variety of directly compressible (DC) sugars and single station tablet press, such formulations can be easily prepared in a hospital pharmacy setting.

The objective of this study was to survey the type of captopril extemporaneous formulations that are dispensed in hospitals in the Republic of Ireland and to evaluate the stability of the most commonly prepared extemporaneous captopril formulation. A novel captopril fast dispersible tablet formulation was extemporaneously formulated as an alternative preparation and its stability was compared with that of the most commonly prepared captopril OL formulation.

MATERIALS AND METHODS

Materials

Captopril was purchased from Sigma-Aldrich Ireland. Captopril tablets; Capoten® 25 and 50 mg, Captor® 50 mg, xanthan gum 0.4% w/v (Keltrol®, Victoria Pharm.) were purchased from United Drug Ireland. All analytical solvents and reagents were of HPLC grade. Mannitol 200 (Parteck®) was purchased from Merck KGaA (Norman Lauder, Dublin, Ireland), Kollidon® CL-SF was a gift from BASF, Cheshire, UK and magnesium stearate was received from JMB, UK.

Survey of hospitals

A survey was carried out to evaluate extent of dispensing of captopril oral liquid (OL) formulations in approximately 120 hospitals in the Republic of Ireland. The questionnaire was designed to determine the route of administration i.e. oral or nasogastric, the source i.e. whether extemporaneously prepared or procured from external source "specials manufacturer", and the identity of the external source. In addition, the survey asked for any data available on the composition and properties of the extemporaneously prepared OLs in the hospitals; vehicle, other excipients, pH, stability and shelf life.

Extemporaneously prepared captopril OLs

Captopril OLs were extemporaneously compounded at three strengths of 1, 2.5 and 10 mg/mL in Keltrol®. Capoten® 50 mg tablets were used to formulate the 1 and 2.5 mg/ mL suspensions while Captor® 50 mg tablets were used for the 10 mg/mL suspensions. Captopril tablets, Captor® or Capoten® were ground to a fine uniform powder using a mortar and pestle. A small amount of the Keltrol® was added to form a paste, before adding further portions and transferring to a 100 ml volumetric flask. The formulation was made up to final volume of 100 mLs and transferred to an amber glass bottle. Formulations were prepared in triplicates and stored in amber glass bottles at 2-6 ^{o}C. The formulations were analysed at days 0, 1, 4, 7, 14, 21, 28 and 56 for "opened" bottles and at days 0, 1, 14, 28, 56 for "unopened" bottles. The formulations were shaken vigorously prior to sampling to ensure a homogenous suspension.

Formulation of extemporaneous captopril FDTs

Captopril FDTs were prepared at two strengths, 2.5 mg and 10 mg, using a simple blending of the formula outlined in Table I and a direct compression tableting process.[24,25] Briefly, an appropriate number of Captor® 25mg tablets were powdered and blended with Mannitol 200, Kollidon® CL-SF and raspberry flavour for 5 minutes in a plastic bag; subsequently magnesium stearate was added and blended for a further 2 minutes. Tablets were compressed using a Piccola tablet press at a low speed of 7 rpm and compression force of 10 kN. Tablets were stored in securitainers at room temperature until sampled for analysis.

Characterisation of FDTs

Uniformity of tablet weight was carried on n=10 tablets, taken randomly and weighed individually on a Sartorius balance, Model CP225D, Bradford, MA, USA. The average

weight of the tablets +/- standard deviation was calculated. Hardness of the tablets was carried out individually on n=3 tablets using a pre-calibrated PTB 411E Tablet hardness tester (PharmaTest Germany). Individual tablets was placed between the jaws and the force (Newtons) needed for the diametrical crushing of the tablets was recorded (BP 2009)[26]. The average hardness ± standard deviation was calculated. Disintegration tests on FDTs (n=3) were performed in deionised water maintained at 37˚C ± 2˚C, using a pre-calibrated Pharmatest PTZ Auto, PTFE Disintegration tester, (PharmaTest Germany). One ODT at a time was placed into the disintegration apparatus and the time taken (seconds; s) for the tablet to fully disintegrate was recorded. The average DT +/- standard deviation were calculated.

pH testing, visual appearance and organoleptic property

The pH of all formulations was measured in triplicates using a calibrated pH meter (CyberScan 510, Lennox, Dublin, Ireland) immediately after their preparation and on each sampling days.

The colour of the captopril OL was analysed by observing a sample of the OL in a clear beaker against a black background. The odour of the OLs was recorded. Keltrol® was used as the control. FDTs were visually observed for appearance and colour.

HPLC analysis of captopril formulations

On each sampling day, 100 µl of the OL formulations was withdrawn for analysis of captopril content by the stability indicating HPLC method as described in the BP 2009 for "Captopril oral solution, related substances"[26]. Samples were diluted with an appropriate volume of mobile phase consisting of 0.5: 500: 500 mixture of orthophosphoric acid, water and methanol and were analysed using a Perkin Elmer HPLC system (PE Series 200)

equipped with “Total Chromatogram Navigator” software and UV detector adjusted at 220 nm. The stationary phase was a Waters Spherisorb® C8 column (5 µm particle size, 4.6 x 250 mm [PSS831815]). A flow rate of 1.0 mL/min was used. Results were statistically analysed using Student’s t-test, with a statistically significant difference represented by a p value less than 0.05.

RESULTS

Identification of hospitals and Data collection

The survey questionnaire was sent to a total of 120 hospitals in the Republic of Ireland. A response rate of 79% was obtained. Of these, 8 hospitals dispensed extemporaneous captopril liquid formulations for oral or nasogastric use. In 6 of the 8 hospitals, captopril liquid formulations used were either compounded in-house or imported from a “specials” manufacturer. One hospital used only imported “specials” formulations while another only used extemporaneously compounded formulations.

The unlicensed "specials” captopril liquid formulations used varied in source between the hospitals and were from Specials Lab, Martindale, Nupharm Labs and Nova Laboratories. One hospital used a formulation of captopril liquid by Bristol-Myers Squibb (Australia) which is licensed in Australia only.

The survey showed that in the previous 12 months (2009/2010) one hospital catering specifically for sick children dispensed “hundreds” of captopril liquid for both oral and nasogastric use while the other hospitals dispensed captopril liquid for oral use, 2 of which also dispensed it for nasogastric use to <10 patients.

Of the 8 hospitals dispensing extemporaneous captopril preparations in the Republic of Ireland, 7 hospitals, including the hospital catering for sick children, dispensed

compounded captopril OLs which varied in their source of captopril tablets as well as the diluent used. A total of 3 formulations were used; 6 hospitals powdered and dissolved captopril tablets, Captor® 25mg tablets in Keltrol® (xanthan gum 0.4 % w/ v), one hospital used Capoten® 25mg tablets, powdered and dissolved in water, ascorbic acid and Keltrol® and one hospital suspended powdered Capoten® 25mg tablets in OraPlus® and OraSweet®. None of the 8 hospitals dispensed captopril dissolved in water alone for oral use although this may be used for nasogastric administration.

The stability and shelf life of the captopril OLs also varied. The captopril "specials" formulations used had shelf lives of 1-3 months,[10] whereas extemporaneous OLs were given a shelf-life of 7-8 days when stored at 2-6^{o}C. The hospital using ascorbic acid in the vehicle allowed a shelf life of 28 days. Apart from the Bristol-Myers Squibb formulation, no other manufacturer or hospital had conducted comprehensive stability studies on their finished OL product to support the stated shelf-life of 28 days.[9]

Although the majority of extemporaneous captopril OLs used in the Irish hospitals are prepared using Keltrol® based diluents and hence are assigned a 7 day stability, there is a lack of safety and efficacy data available to support its use.[27] As one of the aims of the present study, the stability evaluation of this most commonly extemporaneously compounded captopril OL was measured and was compared with an alternative oral solid extemporaneous preparation of captopril, a fast dispersible tablet.

Stability of extemporaneously prepared captopril OLs

pH profile of captopril OLs

The pH of all captopril OLs in Keltrol® was found to be <4 (Fig 1) and was inversely proportional to the captopril concentration. Over the 56 days studied, the pH of the captopril OLs increased slightly by 0.057-0.12 pH unit.

Odour and colour of captopril OLs

The odour of 1 and 2.5 mg/mL captopril OLs was slightly sulphurous, whilst the 10 mg/mL samples had a noticeably acidic odour. After 7 days the intensity of smell increased. At day 14 a pungent smell was apparent and this increased in intensity with increase in captopril concentration. This odour remained intense over the 56 days of the study, making the formulations unpalatable. No change in colour of the captopril OL was observed throughout the 56 days of the study. Keltrol® diluents also remained colourless and translucent throughout the course of this study.

Stability of captopril oral liquid

The concentration of captopril present in the OLs was greater than 90% of the initial amount at days 1, 4 and 7, regardless of the captopril concentration (Fig 2). At day 14, the captopril concentration in the OLs fell below 90% for all captopril strengths. The decrease in the captopril concentration was dose dependent; the 1 mg/mL showed a lower captopril concentration of 80%, while at the higher doses of 2.5 mg/mL and 10.0 mg/mL the captopril concentrations were higher at 86%. The captopril concentration of the OLs continued to decrease over time, the decrease being higher at the lowest concentration. At day 56, the amount of captopril was 57%, 59% and 68% respectively in the 1, 2.5 and 10 mg/mL OLs. Interestingly, a lower rate of degradation was observed for captopril OLs over the first 28 days from unopened bottles although at day 56, the extent of captopril degradation was found to be similar for OLs from unopened and opened bottles (Fig 3a-c).

Stability of extemporaneously prepared captopril FDTs

FDTs formulated showed no sticking and capping and were found to be uniform in weight with a low variability of < 2%. The hardness of the 2.5 mg captopril FDTs was higher compared to the 10 mg captopril FDT (Table II). The hardness of the tablets did not change significantly over the 56 days. The FDTs disintegrated rapidly in less than 32 seconds. The DTs of the FDTs was found to decrease particularly over the first 15 days for both, 2.5 mg and 10 mg FDTs. No change in appearance or colour of FDTs was observed over the 56 days.

At day 1, the captopril content of the FDTs was high at 98% of starting captopril, similar to the captopril concentration (92-99%) detected in the OL of various concentrations (Fig 4). Captopril FDTs showed higher stability compared to corresponding captopril OL formulations. Interestingly, no significant decrease ($p > 0.05$) in the captopril concentration for the 10 mg captopril FDTs was observed over the 56 day stability period, while the captopril concentration of the 10 mg/mL OL decreased significantly to 68.1% at day 56. The amount of captopril of the 2.5mg FDTs decreased from 98.7% at day 1 to 86.4% at day 28. Subsequently no significant ($p > 0.05$) decrease in captopril concentration was observed. As expected a larger decrease in captopril concentration to 59.2% was observed at day 56 for the corresponding captopril OL formulation.

DISCUSSION

The survey carried out in 120 hospitals in the Republic of Ireland showed that 8 hospitals which dispense captopril OL formulations were dispensing various captopril OLs, extemporaneously prepared by the hospital pharmacists or procured from 'specials manufacturers'. The variations in extemporaneous formulations used between and within

individual hospitals are a concern as previously Mulla et al[8,9] reported that unlicensed captopril formulations were not bioequivalent to each other and not bioequivalent to the licensed tablet form. This raises concern over optimal captopril dosing and may give rise to potential toxicity.[18] Therefore substitution of one formulation with another should be carried out with care and may require increased monitoring. Additionally, once the patients are discharged, their supply of captopril OL formulations may change as they then receive their captopril OLs from their community pharmacies. Of the 8 hospitals dispensing extemporaneous captopril OLs, only two hospitals would contact the relevant community pharmacy to support continued use of the OL captopril preparations dispensed by the hospital.

Another important variation is the stability and shelf life of the various extemporaneous OL captopril formulations. "Specials" OL formulations had a longer shelf of 1-3 months[10] compared to the extemporaneously prepared OL formulations dispensed in hospitals that were given a shelf life of 7-8 days when stored at 2-6^{o}C. In the present study our data support a 7 day stability of the most commonly prepared captopril OL in Irish hospitals, irrespective of the concentration of captopril. After day 7 the captopril content decreased significantly over the 56 days period. Of importance however is that the intervals at which the stability of the captopril OLs was evaluated does not simulate the "in use" opening frequency which would be daily as a multi-dose regimen. Captopril OL bottles that were opened at much lesser intervals 'unopened bottles' showed a lower rate of degradation. An increase in opening frequency of the bottles such as during in use by the patient most probably decreases the shelf life of captopril OLs related to the increased exposure to atmospheric oxygen.

A small increase in pH of the OLs and an increase in the intensity of sulphurous odour from day 7 to day 56 was observed, relating to the presence of increasing concentration of oxidised captopril (captopril disulphide). There was no change in colour of the OLs over the 56 days. Interestingly, Berger et al[22] reported the formation of a yellow colour within three weeks for 1 mg/mL liquid captopril solution prepared in buffered "Ora" preparations (pH 4.2).[22]

In comparison, extemporaneously prepared novel captopril FDTs were stable over a longer time of at least 56 days for the 10mg FDTs as the captopril was present as a solid. It is expected that as individually packaged blisters their stability may be further enhanced making these more convenient for both pharmacists and patients. Due to the amphoteric nature of captopril, FDTs when administered as oro-dispersible tablets, may facilitate the absorption of captopril across the lipid membranes of the buccal mucosa and result in enhanced absorption and reduced bioavailability differences as observed with other OLs.[8,9,28]

CONCLUSION

To date, the use of captopril in treating children is unlicensed and the only commercially available captopril is a tablet formulation licensed for use in adults. As a result patients receiving captopril (off label) are given an unlicensed liquid preparation or a crushed tablet dissolved in water. The survey carried out in Irish hospitals showed that 8 hospitals were dispensing extemporaneous liquid captopril either compounded in-house or procured from 'specials' manufacturers. The products used varied in stability and shelf life. The most commonly used extemporaneous captopril OL was prepared in Keltrol® with an assigned arbitrary shelf life of 7 days when stored at 2-8^{o}C. The results of stability testing of 3

concentrations of this OL formulation performed in this study demonstrated a 7 day stability although this was dependent on the frequency of opening the bottle.

In comparison, a novel FDT demonstrated a higher stability without the requirement of refrigerated storage. Due to its fast dissolving property, these tablets could be directly administered to suitable paediatric patients or easily reconstituted to captopril OL for infants or enteral administration. Such a formulation would also facilitate patients receiving chronic therapy to be maintained on the same formulation for the duration of the treatment as various captopril OL cannot be assumed to have therapeutic equivalence.[8,9,29] Such a solid extemporaneous formulation can therefore result in standardisation of captopril therapy through its improved stability, homogeneity and ease and flexibility of dose administration.

Funding: None

Competing interests: None

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Figure 1 pH of Captopril OL formulations at 1, 2.5 and 10mg/mL in Keltrol® stored at 2-6 ^{o}C over 56 days. (n=3 +/- SD)

Figure 2 Percent captopril remaining in captopril OLs at 1, 2.5 and 10mg/mL in Keltrol® stored at 2-6 ^{o}C over 56 days (n=3 +/- SD)

Figure 3 Percent captopril remaining in captopril OLs (a) 1 mg/mL, (b) 2.5 mg/mL, (c) 10 mg/mL stored at 2-6 ^{o}C opened vs unopened. (n=3 +/- SD)

Figure 4 Stability profiles of extemporaneously prepared captopril OLs and FDTs at two dosage strengths (a) 2.5 mg and (b) 10 mg. (n=3 +/- SD)

Figure 1

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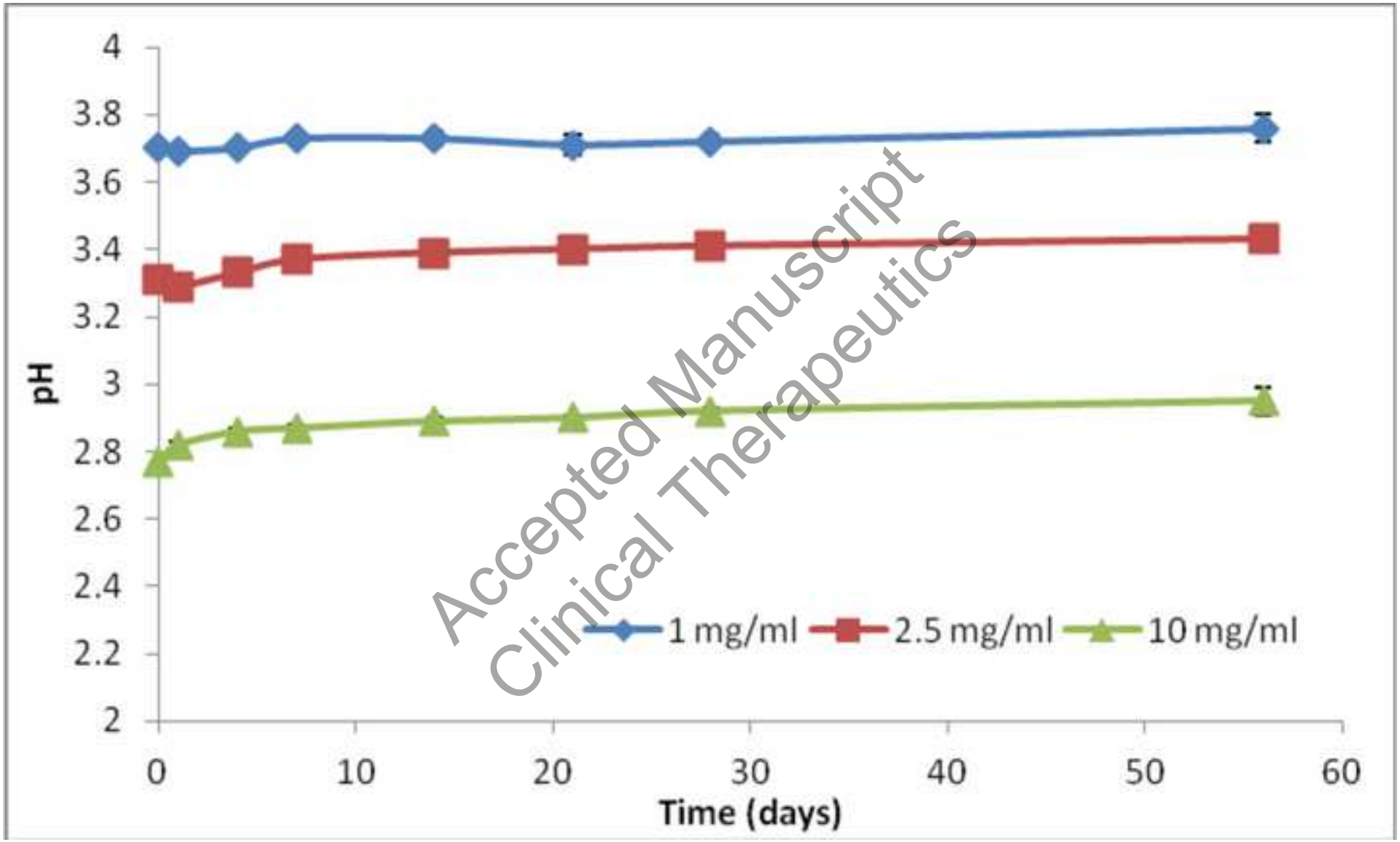

Figure 2

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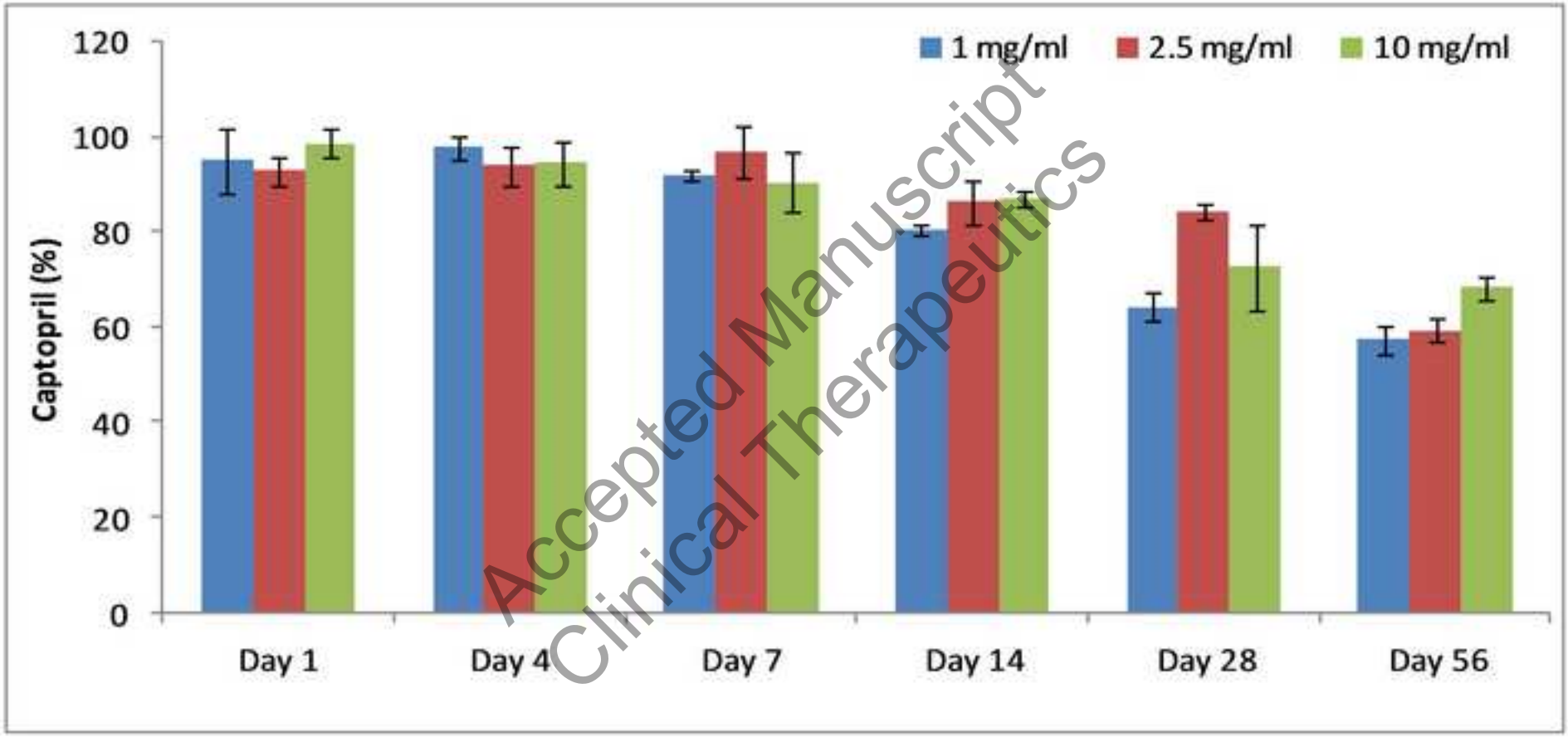

Figure 3

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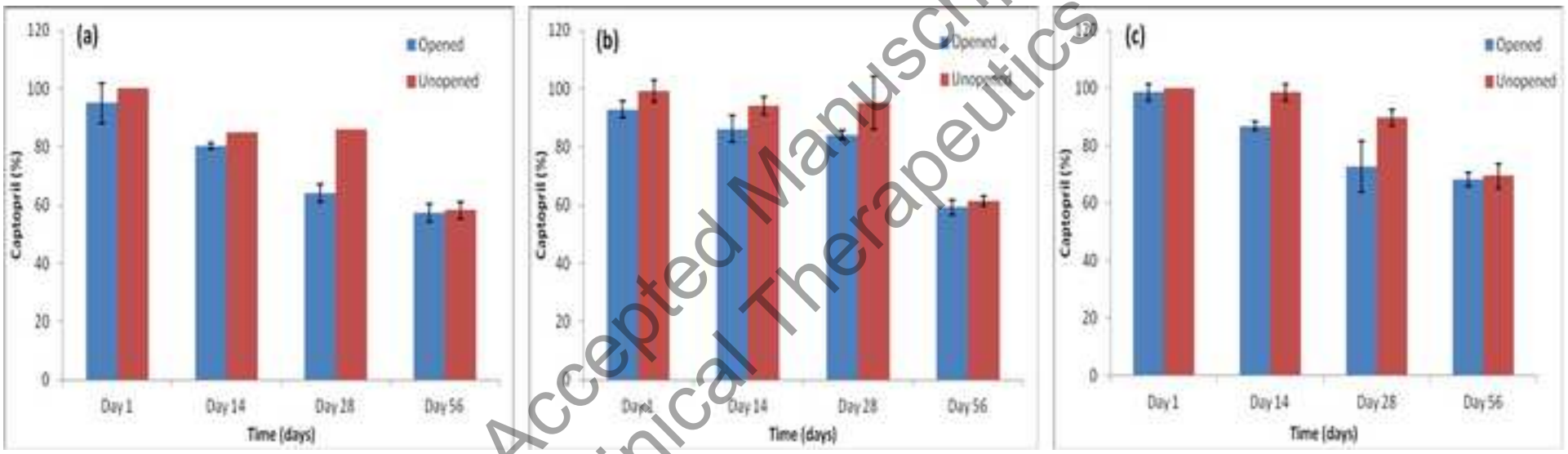

Figure 4

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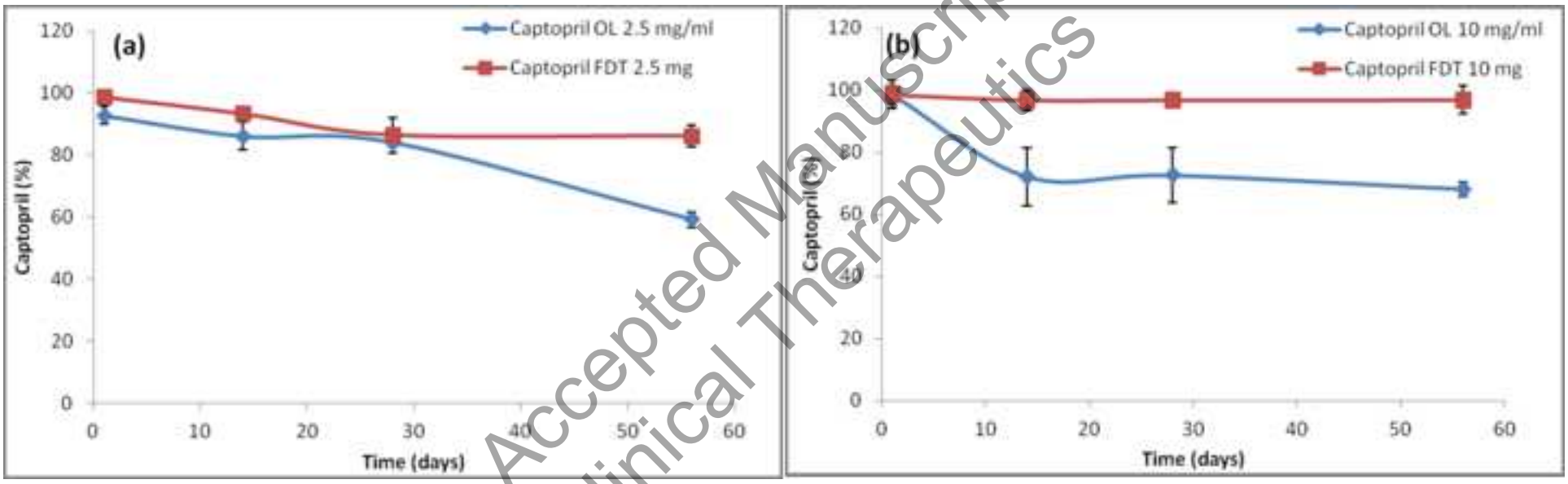

Table I Formulation composition for extemporaneously prepared captopril fast dispersible tablets (FDTs)

Formulation composition/ tablet	**2.5 mg captopril FDT**	**10 mg captopril FDT**
Ground Captopril 25mg tablets (Captor®)	16 mg	64 mg
Mannitol 200 (Parteck®)	171.4 mg	123.4 mg
Kollidon CLSF (5 %w/w)	10 mg	10 mg
Magnesium stearate (0.5 %w/w)	1 mg	1 mg
Raspberry flavour (0.8 %w/w)	1.6 mg	1.6 mg
Total tablet weight (mg)	200 mg	200 mg

Table II Physical characteristics of extemporaneous captopril FDTs

Time (days)	Captopril	Weight (mg)	Hardness (N)	DT (seconds)
Day 1	2.5 mg	198.16 ± 1.08	75.91 ± 0.72	23.6 ± 1.53
Day 15	2.5 mg	198.10 ± 0.96	74.11 ± 3.28	19.33 ± 1.53
Day 56	2.5 mg	198.43 ± 1.88	76.41 ± 2.30	17.67 ± 2.08
Day 1	10 mg	204.31 ± 2.11	54.54 ± 4.37	32.0 ± 3.46
Day 15	10 mg	205.20 ± 2.75	53.59 ± 1.79	24.67 ± 3.21
Day 56	10 mg	203.25 ± 1.10	53.82 ± 7.70	23.67 ± 1.53