WJPMR, 2025, 11(11), 275-284

Research Article

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Impact Factor: 6.842

ISSN (O): 2455-3301

ISSN (P): 3051-2557

Coden USA: WJPMBB

FORMULATION AND STABILITY STUDIES EVALUATION OF THE SELECTED CAPTOPRIL MOUTH DISSOLVING TABLETS

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DOI: https://doi.org/10.5281/zenodo.17538895

How to cite this Article: Ahmed Mohamed Othman, Mahmoud Mahyoob Alburyhi*, Ghada Hassan Al-Hadad. (2025). FORMULATION AND STABILITY STUDIES EVALUATION OF THE SELECTED CAPTOPRIL MOUTH DISSOLVING TABLETS. World Journal of Pharmaceutical and Medical Research, 11(11), 275–284.

Article Received on 07/10/2025 **Article Revised on 27/10/2025** **Article Published on 01/10/2025**

ABSTRACT

Captopril is a sulfhydryl-containing angiotensin-converting enzyme inhibitor which is the enzyme that converts angiotensin-I to angiotensin II and may also reduce the degradation of bradykinin. It is used in the management of hypertension, heart failure, myocardial infarction and in diabetic nephropathy. Therefore, it can be used as a model of mouth dissolving tablets MDTs as a more bioavailable form than conventional tablets. The main objective of the present study was to stability studies were performed to know the development of formulation and evaluation of Captopril mouth dissolving tablets MDTs to improve the bioavailability of Captopril. The selected stored Captopril MDTs F1 were evaluated for weight variation, uniformity of thickness, content uniformity, friability, hardness, disintegration time and wetting time at time intervals (1,2,3,4,5 & 6 months). Dissolution rate of F1 selected stored Captopril MDTs seemed to be slightly affected by storage conditions but still within acceptable range. Drug content of F1 selected stored Captopril MDTs was found to be 98.3% at the end of the six-months storage period which was complied with the pharmacopeial requirements. The percent of drug remaining of F1 selected stored Captopril MDTs was found to be 90.4% at the end of the 6 months. storage period which was complied with the pharmacopeial requirements. It was concluded that the F1 of Captopril MDTs was found to be stable at 40^{o}C/75%RH for 6 months.

KEYWORDS: Captopril, Stability Studies, Excipients, Development, Formulation.

INTRODUCTION

Compatibility and Stability Study[1-42]

The stability, chemical structure and bioavailability of an API are affected by interactions taking place between the API and the excipients. These alterations lead to a reduced therapeutic efficacy and safety. As a rule, solid dosage forms are less stable than the isolated API. Although it has already been established that API-excipient compatibility testing must always be carried out during the development of new dosage forms, a consensus on the test to be employed is still lacking. The most common signs of deterioration of an API are changes in color, taste, odor, polymorphic form, or crystallization (pharmaceutical incompatibility). These changes arise from chemical reactions with the excipient, leading to degradation of the API.

Thermo-analytical techniques have been developed to predict the suitability of the excipients to be employed in dosage forms in order to minimize undesired reactions (stability issues) between the API and the excipient. In this sense, physico-chemical interactions between the API and excipients can be readily evaluated by differential scanning calorimetry (DSC). Some authors claim; however, that the data obtained by thermal techniques are difficult to interpret and that the interactions observed at high temperatures during DSC assays may not be representative of those occurring under normal storage conditions. Isothermal stress testing-high performance liquid chromatography (IST-HPLC), The IST-HPLC involves storing the API-excipient blends at high temperature followed by the determination of the API content by HPLC.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. It should include the effect of temperatures (in 10°C increments (e.g., 50°C, 60°C, etc.) above that for accelerated testing), humidity (e.g., 75% RH or greater) where appropriate, oxidation, and photolysis on the drug substance.

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

Long term, accelerated, and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. The general case applies if the drug substance is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified. as shwon in Table 1.

Table 1: Stability Study Conditions.

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long Term	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

Importance of Drug-Excipient Compatibility

Studies of active pharmaceutical ingredient (API)-excipient compatibility represent an important study in the preformulation stage of the development of new dosage forms, stability of the dosage form can be maximized, any physical or chemical interaction between API, and excipient can affect bioavailability and stability of drug, it helps to avoid the surprise problem, by performing drug excipient compatibility studies (DECS) we can know the possible reaction before formulating final dosage form, DECS data is essential for IND (investigational new drug) submission, and now, USFDA has made it compulsory to submit DECS data for any new coming formulation before its approval.

The potential physical and chemical interactions between an API, and the excipients can affect the chemical nature, the stability and bioavailability of the former and, consequently, its therapeutic efficacy and safety, solid dosage forms are generally less stable than their API components and despite the importance of API-excipient compatibility testing, there is no universally accepted protocol to assess such interactions.

Pharmaceutical Excipients: Excipients are additive substances used to improve the bulkiness, disintegration, dissolution rate, and bioavailability of a formulation etc. Different dosage forms like powders, granules, capsules, tablets, oral liquids, injectable products, implants, eye products, nasal products, inhalers, topical creams, ointments, gels, transdermal patches and suppositories etc, contains different types of excipients. To make it acceptable and compatible various pharmaceutical excipients are added in pharmaceutical dosage form for their direct therapeutic action, manufacturing process, to protect, support or enhance stability, for bioavailability or patient compliance. These must be physiologically and chemically stable, must not have any incompatibility with the API, and must meet the standards of regulatory requirements.

Evaluation of Drug-Excipient Compatibility

The compatibility study of API and excipients is important to predict the stability of the API, in the final pharmaceutical product. It's the first time that API was compatible with excipients promoted physical and chemical compatibility studies was achieved by thermal and non-thermal methods. As a part of preformulation study, a compatibility study of API with the other excipients was carried out using physical blends in analytical techniques for the evaluation of drug-excipient interactions. The most commonly used pharmaceutical

analytical techniques include, thermal techniques such as Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA), Isothermal Microcalorimetry (IMC) and Hot stage microscopy (HSM) etc, and non-thermal techniques such as UV-Visible Spectrophotometric (UV), Infrared, Near-Infrared and Raman Spectroscopy (FT-IR), (NIR), Powder *X*-Ray Diffraction (PXRD), Solid-State Nuclear Magnetic Resonance Spectroscopy (ssNMR), Microscopic techniques: Scanning Electron Microscopy (SEM), Chromatographic techniques: Thin Layer Chromatography (TLC), and High-Performance Liquid Chromatography (HPLC) etc.

Preformulation Parameters: According to dosage form of API, mainly solid state, particle size, shape, pKa, pH determination, common ion effect, temperature, partition coefficient, solubility studies, dissolution rate, melting point, powder flow properties, crystallinity, polymorphism, hygroscopicity, stability study and drug-excipient compatibility etc. While other dosage forms according to important of preformulation parameters used in study before start in development of formulation.

Drug-excipient compatibility and formulation stability is not depended on API only but also its affected by excipient. Excipient play important role in dosage form but side by side it also increases compatibility problem so proper selection of excipient is very important in development of formulation. Incompatibility can be result mainly in any of following changes: Changes in organoleptic properties, changes in dissolution performance, decrease in potency, and increase in degradation rate etc.

Drug excipient physicochemical characterization is a systematic approach towards design of therapeutically active and stable dosage forms. The rapid advancements in novel drug delivery systems development have led to an interest by formulation scientists in the role and functionality of the excipients.

In the present study, it was proposed to stability studies of the selected Captopril Mouth Dissolving Tablets MDTs Formulation, safety, efficacy, quality of a formulation are major concepts of any API development process.

MATERIALS AND METHODS

Materials

Captopril (Wockhardt limited, India),. Microcrystalline cellulose “Avicel PH101” and Croscarmellose sodium “Ac-Di-Sol” (FMC co., Ireland). Aspartame (Asuka, Turkey). Lactose monohydrate, disodium hydrogen phosphate, Potassium di-hydrogen ortho phosphate, citric acid, maize starch and magnesium stearate (E.Merk, Germany). Mannitol (Roqette, France). Sodium starch glycolate “Explotab” (JRS pharma, Germany). Colloidal silicon dioxide “Aerosil 200” hydrophilic, Potassium chloride & sodium chloride (Kirsh Pharma, Germany). Sodium hydroxide (Riedel-de Haen, Germany). FD & C blue dye no.1(Symrise, Germany). Methanol, Phosphoric acid HPLC grade (SIGMA-ALDRICH, Germany). Other solvent and chemicals are of analytical grades. Most of the previous materials were kindly Supplied by YEDCO, Yemen which was the place of this research.

Equipment

Tablet press, IOTA press (India). Disintigration tester (Pharma test PT2S, Germany). Hardness tester (Pharma test PTB, Germany). Friability tester (ERWEKA TAR, Germany). Digital CALIBER 0-150mm(CHRIST, Germany). Dissolution tester (Hanson Research corporation SP8 SR11, USA). Spectrophotometer UV/Vis, (JASCO V-550, Japan). Membrane filter 0.45µm, (Gelman, sciences Inc., Germany). PH meter (sartorious, Germany). Hotplate magnetic stirrer (Stuart, U.K). Sensitive and electronic balance sartorious, Germany). Sonicator (Elma,Germany). Sieves sizes (0.3, 0.5 and 1.4mm). Oven (Manesty PETRIE, U.K).. Microliter syringe. C18[(dimensions 250mm×4.6mm) (particle size 5.0µm) HPLC column(Thermo, USA)]. Waters HPLC apparatus(Waters2707 autosampler,2489 U.V/Visible detector, 1525 binary HPLC pump and Empower2 software, USA).

Formulation and Evaluation Methods[1-69]

Based on evaluation for 16 captopril MTDs which we had done in a previous study[43], results showed least disintegration time more rapid and highest dissolution and, satisfactory weight variation, hardness, friability and thickness with F1 so it was selected for stability study and was kept in a stability chamber at 40°C± 2 / 75% ±5 RH for six months. Samples from formula were taken at 0, 1, 2, 3-, 4-, 5- and 6-months intervals and examined for:

Weight Variation Test

Twenty tablets were separately weighed and their average weight was calculated.

Uniformity of Tablets Thickness

The thickness of ten tablets were measured using [Digital CALIBER 0-150mm (CHRIST, Germany)] and the average value was then calculated.

Friability

Ten tablets from each formula were accurately weighed placed in the drum of the friabiliator (ERWEKA TAR, Germany) and rotated at 25 r.p.m for a period of 4 minutes, and then reweighed. The percentage loss in weights was calculated and taken as a measure of friability:

(Weight before –Weight after/Weight before) x100.

Hardness

The average breaking strength (in Kg) of ten tablets of each formula was determined by the hardness tester (Pharma test PTB, Germany).

In-Vitro Disintegration Time

A tablet was inserted in each of six cells of the disintegration apparatus (Pharma test PT2S, Germany). The immersion fluid used was simulated saliva fluid (SSF) of pH6.8 at a temp of 37± 0.5oC. Disintegration time was recorded at which the tablets disintegrated leaving behind no aggregates on the basket mesh. Simulated saliva fluid (SSF) (phosphate buffer saline), was composed from the following: sodium chloride(8gm), potassium chloride(0.19gm), disodium hydrogen phosphate(2.6gm) and potassium dihydrogen phosphate (0.2gm) in one liter of distilled water.

Wetting Time

The wetting time of the tablets was measured using a simple procedure. Circular tissue paper of 10-cm diameter were placed in a petri dish with a 10-cm diameter. Ten milliliters of water containing a blue water-soluble dye, were added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

In-Vitro Dissolution Profile

The wetting time of the tablets was measured using a simple procedure. Circular tissue paper of 10-cm diameter was placed in a petri dish with a 10-cm diameter. Ten milliliters of water containing a blue water-soluble dye, were added to the petri dish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. Wetting time corresponds to the time taken for the tablet to disintegrate when kept motionless on the tongue.

Content Uniformity

Twenty tablets were used in this test, where each one was crushed and dissolved in 100mL of the mobile phase (methanol: water: phosphoric acid ,55:45:0.05) in 100mL volumetric flask. The mixture was filtered by passing it through a 0.45µm membrane filter and degassed by mean of vacuum pump. The mobile phase was delivered into the HPLC apparatus at a flow rate of 1 ml/min, the detection was conducted at λmax 220nm.

Chemical Stability

The selected MDTs Captopril formula (F1) was stored in sealed tight amber glass bottles and chemical analysis of the stored captopril formula was carried out to:

I-Determine the Drug Content Using UV-Visible Spectrophotometer

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 10 mg of Captopril was dissolved in 100 ml of pH 6.8 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 205 nm using UV-Visible spectrophotometer (JASCO V-550, Japan).

II-Determine the Amount of Drug Remaining Using HPLC Stability Indicating Method

The HPLC Stability Indicating Method was carried out as followed:

Chromatographic Conditions according to USP

The mobile phase was a mixture of methanol: water: phosphoric acid (55:45:0.05). The mixture was filtered by passing it through a 0.45µm membrane filter and degassed by mean of vacuum pump. The mobile phase was delivered into the HPLC apparatus at a flow rate of 1 ml/min, the detection was conducted at λmax 220nm.

Preparation Stock, Working Standard and Sample Solutions

Captopril stock solution: 50mg of captopril powder was accurately weighed in a 50mL volumetric flask, 35ml of the mobile phase was added and Shaked for 25 minutes, completed to required volume with mobile phase and mixed and filtered through a 0.45µm membrane filter. Standard solution of Captopril powder 100µg/mL was prepared in the mobile phase.

Captopril Working Solution

10µg/mL in mobile phase, prepared by transferring one mL from stock Captopril to 10mL volumetric flask and completing to volume with mobile phase.

Sample Solution

20 tablets were weighed and finally powdered, powdered material equivalent to 50mg was transferred to 50ml volumetric flask, 35ml of mobile phase was added and Shaked for 25 minutes, completed to required volume with mobile phase and mixed and filtered through a 0.45µm membrane filter.

Preparations of Solutions Used for Assay Validation

For the study of Captopril response linearity, ten solutions were prepared in mobile phase at concentrations ranging from 1µg/mL to 10µg/mL.

Calibration Curve of Captopril Using HPLC Method

Standard samples were prepared to provide final concentration of Captopril ranging from 0.24 to 1.02 µg/mL, prepared by transferring from stock Captopril to 10mL volumetric flask and completing to volume with mobile phase. Then a sample of 20µL of each standard solution of Captopril was injected to into the column for prepare the standard plot. The peak areas of samples were plotted against Captopril concentrations. The least square linear regression analysis was used to determine the slope, Y-intercept, and the coefficient of determination of the standard plot. as shown in Table 2 & Figure 1.

Table 2: Calibration Curve of Captopril Using HPLC.

Sr.No	Concentration µg/ml	AUC µg/ml.hr
1	0.246	2110432.402
2	0.244	2093041.873
3	0.251	2153457.692
4	0.502	4342287.085
5	0.51	4409345.332
6	0.507	4385748.535
7	0.743	6440554.055
8	0.746	6459490.324
9	1.021	8859415.96
10	1.02	8853144.725

Formulation of Captopril MDTs by Different Methods

The following excipients were used for the preparation of Captopril MDTs. Magnesium stearate and aerosil 200 as lubricants, lactose monohydrate, avicel PH101 and mannitol as diluents, croscarmellose sodium (Ac-Di-Sol) and sodium starch glycolate (Explotab) as disintegrants, aspartame as a sweetener, citric acid and sodium bicarbonate as effervescent agents, maize starch as binder. The calculated dose of the drug and other excipients listed in Table 3.

Table 3: Formulation of Captopril Mouth Dissolving Tablets.

Ingredients (%) / Formulation Code	Captopril	Maize Starch	Avicel PH101	Lactose Mono-hydrate	Mannitol	Explotab (SSG)	Ac-Di-Sol (CCS)	Citric Acid	Sodium Bicarbonate	Aspartame	Aerosil200	Magnesium Stearate	Total
F1	13.9%	---	78.1%	---	---	5%	---	---	---	1%	1%	1%	**100%**
F2	13.9%	---	73.1%	---	---	10%	---	---	---	1%	1%	1%	**100%**
F3	13.9%	---	78.1%	---	---	---	5%	---	---	1%	1%	1%	**100%**
F4	13.9%	---	73.1%	---	---	---	10%	---	---	1%	1%	1%	**100%**
F5	13.9%	---	39.1%	---	39%	5%	---	---	---	1%	1%	1%	**100%**
F6	13.9%	---	26.1%	---	52%	5%	---	---	---	1%	1%	1%	**100%**
F7	13.9%	---	47.1%	31%	---	5%	---	---	---	1%	1%	1%	**100%**
F8	13.9%	---	44.1%	29%	---	10%	---	---	---	1%	1%	1%	**100%**
F9	13.9%	---	47.1%	31%	---	---	5%	---	---	1%	1%	1%	**100%**
F10	13.9%	---	44.1%	29%	---	---	10%	---	---	1%	1%	1%	**100%**
F11	13.9%	---	37.1%	---	37%	10%	---	---	---	1%	1%	1%	**100%**
F12	13.9%	---	24.1%	---	49%	10%	---	---	---	1%	1%	1%	**100%**
F13	13.9%	---	65.1%	---	---	---	---	8%	10%	1%	1%	1%	**100%**
F14	13.9%	9%	73.1%	---	---	5%	---	---	---	1%	1%	1%	**100%**
F15	13.9%	9%	68.1%	---	---	10%	---	---	---	1%	1%	1%	**100%**
F16	13.9%	---	78.1%	---	---	5%	---	---	---	1%	1%	1%	**100%**

Preparation of Captopril MDTs by Direct Compression Method

Formulae F1-F13 were prepared as the following: Accurately weighed quantities of Captopril, avicel PH101, aspartame and the superdisintegrant (Explotab or Ac-Di-Sol) or effervescence agents (as citric and sodium bicarbonate) were passed through a sieve mesh ≠60 and blended homogeneously. Then magnesium stearate and aerosil 200 were added to the mixture. The final mixture was converted into constant weight tablets by direct compression method using a single punch tableting machine (IOTA press, India) equipped with 8.5mm concave punch.

Preparation of Captopril MDTs by Indirect Compression (Wet Granulation Method)

Formulae F14-F16 were prepared as the following: Accurately weighed quantities of Captopril, avicel PH101, aspartame and the superdisintegrant were passed through 0.5 mm sieve and mixed in a glass mortar. The above blend was granulated with ethanol 95% as a non-aqueous granulating agent (with or without binder) and passed through a sieve (1.40 mm). The granules were air-dried, lubricated with magnesium stearate and aerosil 200 and compressed using a single punch tableting machine (IOTA press, India) equipped with 8.5 mm concave punch.

RESULTS AND DISCUSSION

Formula of Captopril tablets F1 were stored under accelerated conditions at 40°C and 75% relative humidity for 6 months. Concerning the physical stability, no change in color and appearance was observed throughout the storage period.

Concerning the weight variation test, there was no change in the weight of tablets during storage. An average weight was within the range 183.6 to 183.8mg as shown in Table 4. Also, there was no change in the thickness of tablets after the storage period as shown in Table 4.

It was found that, in general friability values were in satisfactory range. The stored formula showed percentages of fine within the range 0.19-0.24 % and also exhibited good breaking strength within the range from 4.5 to 5.1Kg, which were acceptable with the limit of conventional tablets as shown in Table 4. All tablets showed good breaking strength within the range from 4.5 to 5Kg, which were acceptable within the limit of conventional tablets as shown in Table 4.

The disintegration time of the tablet was not markedly affected during the storage conditions. SSG (explotab) was used within permissible concentration. The results of disintegration test revealed slightly increase of disintegration times in phosphate buffer PH6.8 for the tablets during the storage period as shown in Table 4. The average time for disintegration of about 11 seconds was recorded at the end of the storage period.

Results indicated slight increase in wetting time under the storage conditions, where the average time for wetting of about 13 seconds was recorded at the end of the storage period.

Concerning content uniformity test, all the tablets analyzed for their Captopril content were found to lie within the official acceptable range (not less than 85% and not more than 115% of the labeled potency) as obtained in Table 4 and Figures 2-7.

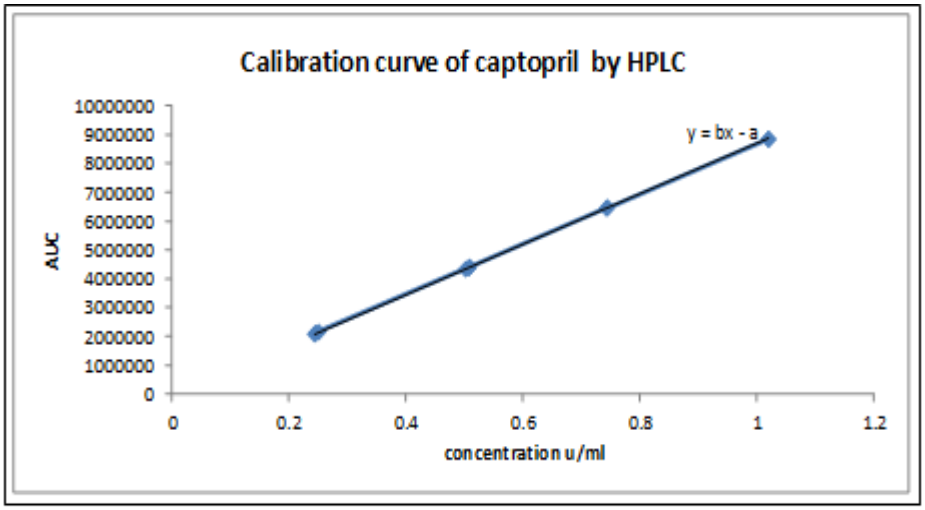

Fig. 1: Calibration Curve of Captopril Using HPLC Method.

Table 4: Physical Evaluation for the Selected Captopril MDTs F1 After Storage at 40°C/75%RH for Six Months.

Time (months)	Average Weight (mg)	Thickness (mm)	Friability (%)	Mean Hardness (Kg)	Disintegration Time (Sec)	Uniformity of Content (%)	Wetting Time (Sec)
1 Month	183.8	3.6	0.2	4.6	9	101.2	12
2 Months	183.6	3.6	0.2	4.5	9	100.9	12
3 Months	183.7	3.6	0.2	5.1	10	99.8	12
4 Months	182.8	3.6	0.2	4.8	10	99.2	13
5 Months	183.6	3.6	0.2	4.9	10	98.7	13
6Months	183.8	3.6	0.2	5	11	98.3	13

On the other hand, dissolution of Captopril from its selected MDTs formulation after storage at 40C^0/75% RH for 6 months revealed that the rate of dissolution of Captopril was slightly affected by storage, where the dissolution decreased under the storage conditions. Samples were taken after 1, 2, 3, 4,5 and 6 months, each sample was subjected to dissolution testing to study the effect of storage at elevated temperature on dissolution of Captopril from formula.

The selected tablet formulation showed acceptable results for dissolution (more than 87% was dissolute after 5 minutes) as reflected by Table 5.

Table 5: Dissolution Rate Percent of the Selected Captopril MDTs F1 after Storage at 40°C/75%RH for Six Months.

% Amount Dissolve				
Time(month)	**5 Min**	**10 Min**	**15 Min**	**20 Min**
0 Month	93.9%	93.5%	92.1%	91.6%
1 Month	93.1%	93%	92.5%	91.9%
2 Months	92.4%	88.7%	88.2%	87.9%
3 Months	90%	88.2%	86%	84.8%
4 Months	89.7%	85%	83.9%	82.8%
5 Months	88.3%	85%	83.2%	82.7%
6Months	87.5%	86%	83%	82.6%

In the determination of Captopril content tablets using UV-Visible spectrophotometer, results obtained were shown in Table 6.

Drug content of Captopril after 6 months storage at (40 °C /75% RH) was found to be 90.4% for F1, as shown in Table 6. This was complied with the pharmacopeial requirements.

Results of the chemical stability of the selected Captopril tablets formula F1 obtained from their U.V and HPLC analysis showed the followings:
Determination the amount of drug remaining using HPLC stability indicating method was as followed:

Samples were analyzed for the percent remaining of Captopril using stability indicating HPLC assay at time intervals of 1, 2, 3, 4, 6 months. The results of the accelerated stability testing of the drug from the prepared MDTs, F1, were presented in Table 6 & Figures 8-14.

Table 4 demonstrated the percent remaining of Captopril for F1 at 40°C/75%RH for 6 months which was found to be 98.3%. This was complied with the pharmacopeial requirements (Not less than 90% and not more than 110%).

Table 6: Drug content of the Selected Captopril MDTs(F1) after Storage at 40 °C /75%RH for Six Months.

Formula	**Content of Captopril Remaining after the Following Time Intervals in months**						
Months	**0**	**1**	**2**	**3**	**4**	**5**	**6**
F1	**96%**	**95.7%**	**94.6%**	**93.5%**	**92.5%**	**91.5%**	**90.4%**

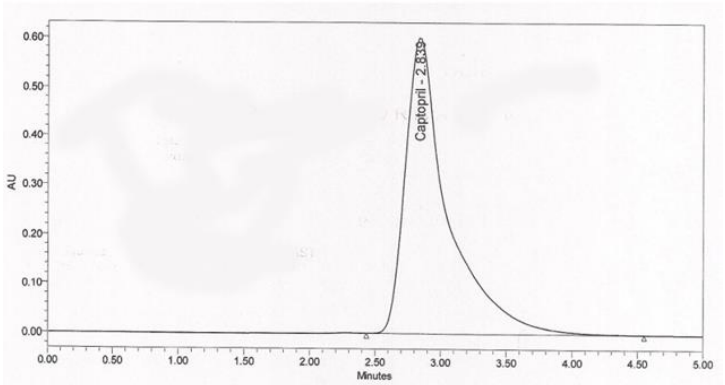

Fig. 2: Uniformity of Content for the Selected Captopril MDTs after Storage for One Month.

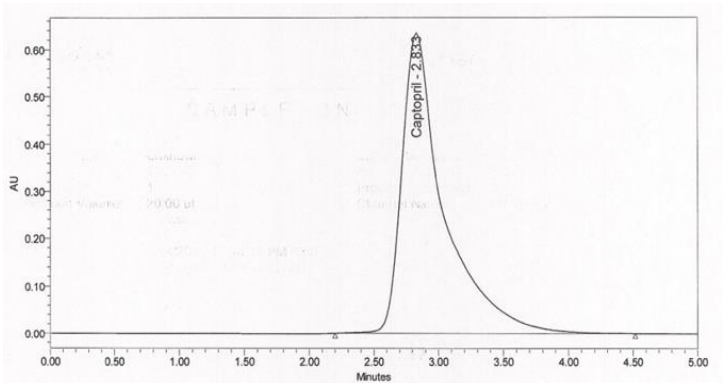

Fig. 3: Uniformity of Content for the Selected Captopril MDTs after Storage for Two Months.

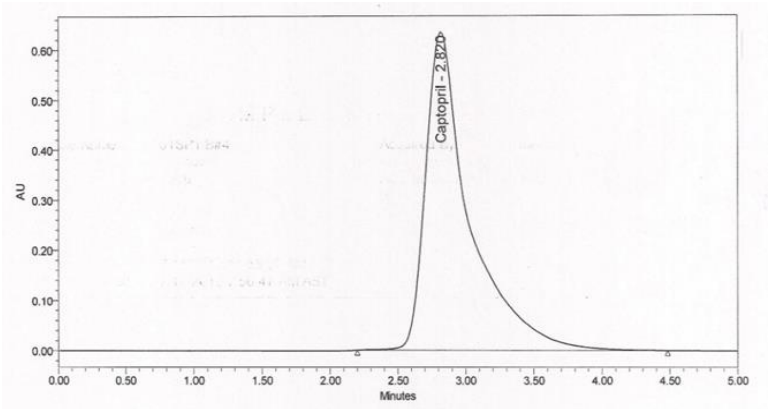

Fig. 4: Uniformity of Content for the Selected Captopril MDTs after Storage for Three Months.

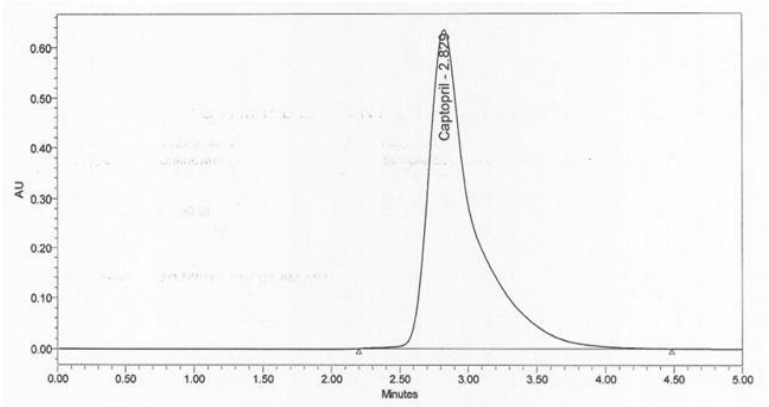

Fig. 5: Uniformity of Content for the selected captopril MDTs after Storage for Four Months.

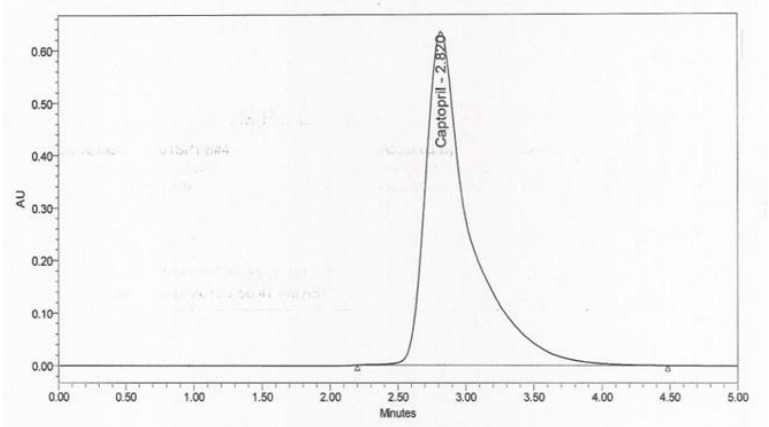

Fig. 6: Uniformity of Content for the Selected Captopril MDTs after Storage for Five Months.

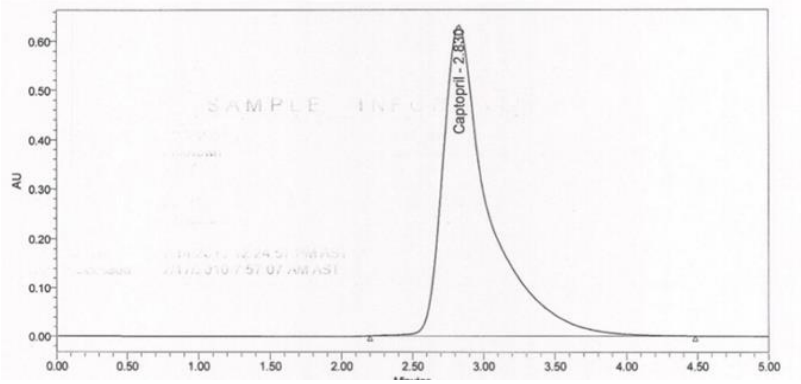

Fig. 7: Uniformity of Content for the Selected Captopril MDTs after Storage for Six Months.

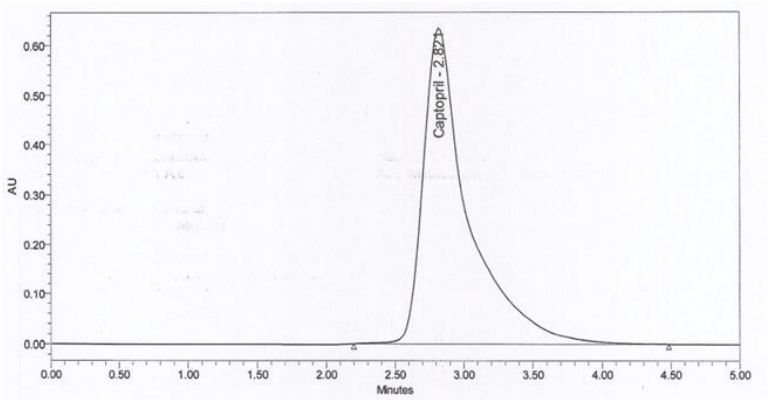

Fig. 8: HPLC Assay for the Selected Captopril MDTs before Storage.

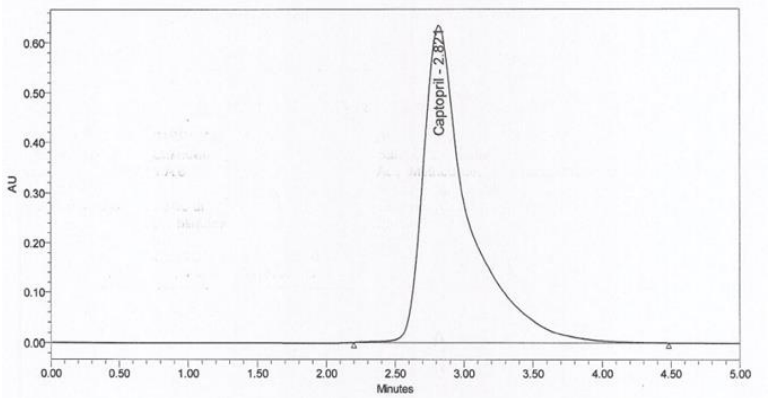

Fig. 9: HPLC Assay for the Selected Captopril MDTs after Storage for one Month.

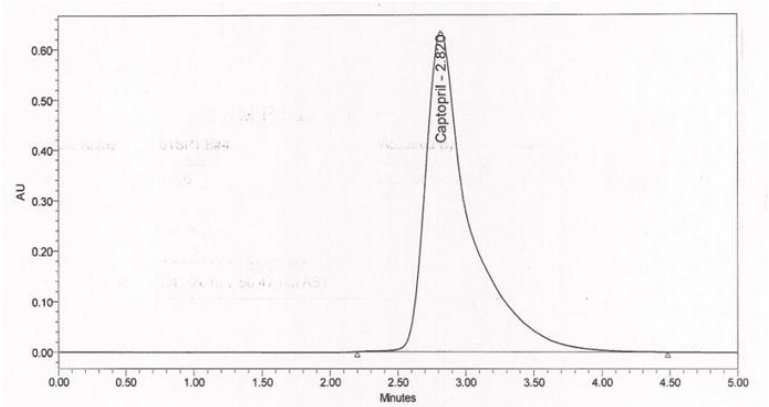

Fig. 10: HPLC Assay for the Selected Captopril MDTs after Storage for Two Months.

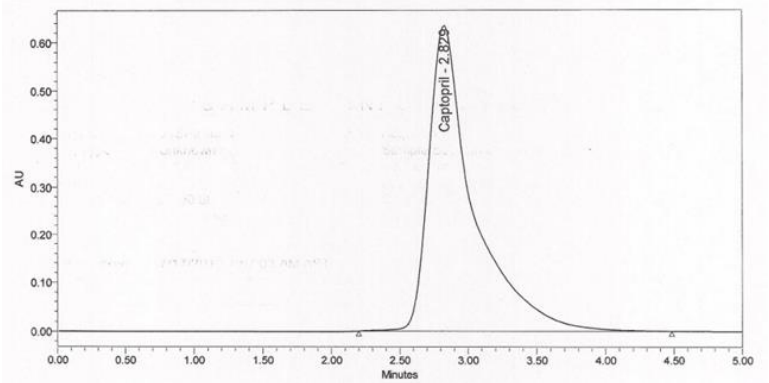

Fig. 11: HPLC Assay for the selected captopril MDTs after Storage for Three Months.

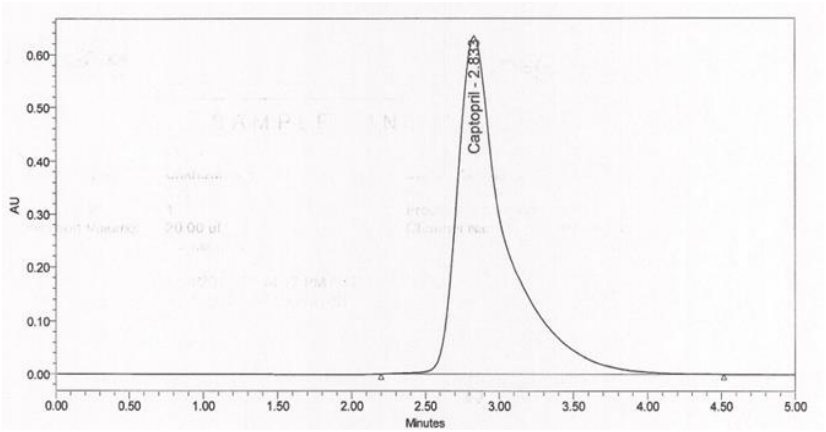

Fig. 12: HPLC Assay for the Selected Captopril MDTs after Storage for Four Months.

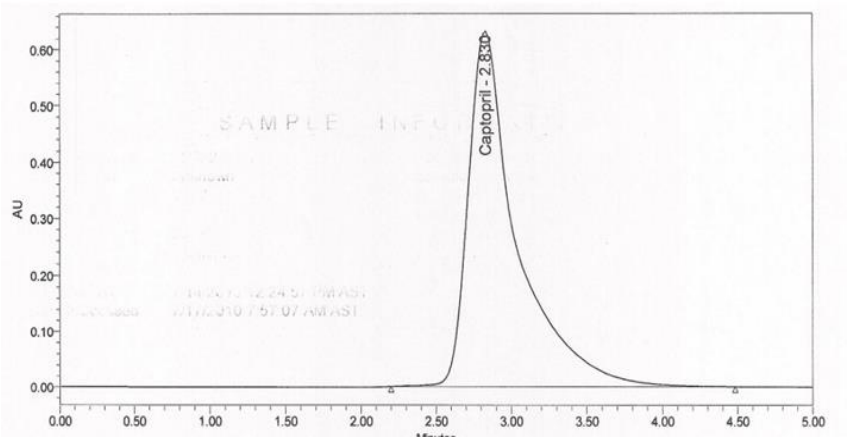

Fig. 13: HPLC Assay for the Selected Captopril MDTs after Storage for Five Months.

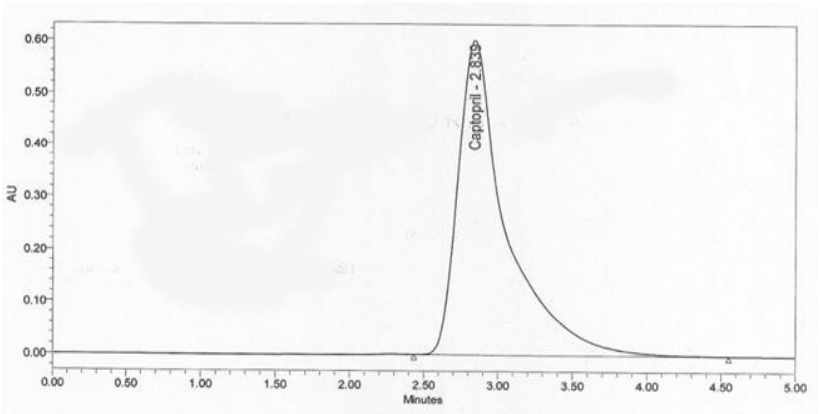

Fig. 14: HPLC Assay for the Selected Captopril MDTs after Storage for Six Months.

CONCLUSION

The formulation F1was the best Captopril MDTs formula, it has been chosen for accelerated stability testing at 40°C/75%RH for 6 months. Selected stored Captopril MDTs F1 were evaluated for weight variation, uniformity of thickness, content uniformity, friability, hardness, disintegration time and wetting time at time intervals (1,2,3,4,5 & 6 months). Dissolution rate of F1 selected stored Captopril MDTs seemed to be slightly affected by storage conditions but still within acceptable range. Drug content of F1 selected stored Captopril MDTs was found to be 98.3 % at the end of the six-months storage period which was complied with the pharmacopeial requirements. The percent of drug remaining of F1 selected stored Captopril MDTs was found to be 90.4% at the end of the 6 months. storage period which was complied with the pharmacopeial requirements. It was concluded that the F1 of Captopril MDTs was found to be stable at 40°C/75%RH for 6 months.

ACKNOWLEDGEMENT

The authors are thankful to YEDCO Pharmaceutical Industry Company-Yemen, for providing the research

facilities.

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