ejpmr, 2024, 11(1), 18-28

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULTION AND EVALUATION OF CAPTOPRIL MOUTH DISSOLVING TABLETS

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Article Received on 27/10/2023 **Article Revised on 16/11/2023** **Article Accepted on 07/12/2023**

ABSTRACT

Pharmaceutical technologists have developed a novel oral dosage form known as Orally Disintegrating Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms. 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 as a more bioavailable form than conventional tablets. The objective in the present study was to formulate and evaluate of Captopril mouth dissolving tablets (MDTs) used antihypertensive drug. Several formulations of Captopril MDTs were prepared using the drug with the selected fillers (microcrystalline cellulose(avicel), lactose and mannitol) in addition to disintegrates (sodium starch glycolate (explotab) and croscarmellose sodium (Ac-di-sol) or effervescence agents (sodium bicarbonate & citric acid), glidant, sweetening agent and magnesium stearate as a lubricant (starch as a binder in some formulae). They were prepared by direct compression and wet granulation and compressed into tablets using a single punch machine equipped with 8.5mm concave punch. From these results it can be noted that formulae containing SSG or effervescence agents as disintegrants and Avicel PH101 as fillers (F1, F2, F3&F13) showed relatively higher dissolution, where 93.9%, 93.1%, 93.1% and 93 of the labeled dose were dissoluted after 5 minutes whereas 54.4%, 45.8% and 74.33% drug dissolution from marketed products (Captopril-Denk®, Capotal® 25 and Farcopril ®, respectively). Kinetic Analysis of the dissolution data of Captopril from different tablet formulations were determined using linear regression according to zero-order, first-order and Higuchi diffusion model, the coefficient of determination (R^2) was determined in each case. The highest value of R^2 yields the best fit. Therefore, predominant mechanism of Captopril MDTs was zero–order kinetics and only few were found to follow Higuchi diffusion model. It was concluded that F1 is the best formulation of prepared Captopril MDTs in order to increase onset of action and bioavailability of drug.

KEYWORDS: Captopril, Mouth dissolving tablets, Disintegrates.

INTRODUCTION

For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost-effective dosage forms.[1-4]

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration[1,5], owing to its several advantages and high patient compliance compared to many other routes. Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected. To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Orally Disintegrating Tablets (ODTs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need to take with water.[1,6-11] Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be

significantly greater than those observed from conventional dosage forms.[5-11]

A quick-dissolving tablet (also known as a fast-dissolving, fast-dissolving multiparticulate, rapid-dissolving, mouth-dissolving, fast-melting, or orodispersing tablets) is an oral tablet that does not require water for swallowing. The tablet dissolves within 60 seconds when placed in the mouth. The active ingredients are absorbed through mucous membranes in the mouth and GIT and enter the blood stream. A fraction of pregastric drug absorption may bypass the digestive system and metabolism by the stomach acids and enzymes. In general, the tablets are physically robust and can be packaged in multidose containers.[1]

The orally disintegrating dosage forms could be suitable for neuroleptics, cardiovascular agents, analgesics and antiallergics.[12] ACE Inhibitors (ACEIs) are considered as second line agents to thiazide diuretics and β blockers in patients with uncomplicated hypertension.

They may be preferred in patients with diabetics to help slow progression of kidney damage. In addition, ACEIs may be preferred as first line antihypertensives in patients with diabetes or congestive heart failure to decrease the development of heart failure. Examples of ACE inhibitors include Captopril, Enalapril, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril, Trandolapril and Benazepril.[13]

Captopril

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.[14-17]

Chemical data: Formula C9H15NO3S & mol. mass 217.29. Solubility profile: White to off white, crystalline powder, which may have a characteristics sulfide like-odour, melts in positive range of 104 to 110 and freely soluble in water, in methanol, in ethanol (95 percent) and in chloroform.

Pharmacokinetic Data

It is largely excreted in the urine, 40 to 50% as unchanged drug, the rest as disulphide and other metabolites. The elimination half-life has been reported to be 1 to 3 hours. It has been reported, that the duration of antihypertensive action after a single oral dose of Captopril is only 6–8 h, so clinical use requires a daily dose of 37.5–75 mg to be taken three times. About 60 – 75% of a dose of Captopril is absorbed from the gastrointestinal tract and peak plasma concentrations are achieved within about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30-40%.[15,18,19] The maximum effect of Captopril is produced within 1 to 2 hours after oral doses administration that limits the value of Captopril in the treatment of hypertension crisis or acute heart failure. Greatly elevated blood pressure occurred in hypertension crisis can result in severe damages or even death in a short time period, if not treated. In this case, reduction of blood pressure within minutes to 1 hour is necessary.[20-22]

Therapeutic Indications:[19] Hypertension: Captopril is indicated for the treatment of hypertension. Heart Failure: Captopril is indicated for the treatment of chronic heart failure with reduction of systolic ventricular function, in combination with diuretics and, when appropriate, digitalis and beta-blockers. Myocardial Infarction: - short-term (4 weeks) treatment: Captopril is indicated in any clinically stable patient within the first 24 hours of an infarction. - long-term prevention of symptomatic heart failure: Captopril is indicated in clinically stable patients with asymptomatic left ventricular dysfunction (ejection fraction 40%). Type I Diabetic Nephropathy: Captopril is indicated for the treatment of macroproteinuric diabetic nephropathy in patients with type I diabetes.

A recent research focused on the formulation of Captopril sublingual tablets where it was done by direct compression and tablets were stable for three months at accelerated conditions (45°C/75%RH).[22] A literature review revealed that previous researches were done on Captopril, where results clearly indicate a promising potential of the Captopril floating system as an alternative to the conventional dosage form. However, further clinical studies are needed to assess the utility of this system for patients suffering from hypertension. [24] Another research revealed that an oral formulation of Captopril for paediatric use can be prepared with ease by qualified professionals and is stable for at least two years at room temperature and allows individualized dosage and easy administration even to newborn patients.[17]

The objective in the present study was to formulate and evaluate of Captopril mouth dissolving tablets (MDTs) used antihypertensive drug.

MATERIALS AND METHODS

Captopril (Wockhardt limited, India), Microcrystalline cellulose “Avicel PH101”, 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, 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), Captopril denk 25 (Batch no.15227P), Capotal® 25 (Batch no.81064A), Farcopril® (Batch no.287), Capotril®

EIPICO (Batch no.081933) and Capocard®25 (Batch no.479E), Other solvent and chemicals are of analytical grades. Most of the previous materials were gift from (YEDCO Pharmaceutical Industry Company-Yemen).

Equipments: Tablet press, IOTA press (India). Disintegration 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 (Sartorius, Germany). Hotplate magnetic stirrer (Stuart, U.K). Sensitive and electronic balance Sartorius, Germany). Sonicator (Elma, Germany). Sieves sizes (0.3, 0.5 and 1.4mm). Oven (Manesty PETRIE, U.K). Infrared spectrophotometer (Shimadzu FTIR8900, Japan). 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).

Calibration Curve of Captopril in Phosphate Buffer pH 6.8

Serial concentrations of Captopril in phosphate buffer pH6.8 containing 2,6,10,14,20 and 22µg/mL were prepared. The absorbance of the prepared solutions was measured spectrophotometrically at λ max 205nm against phosphate buffer pH 6.8 as a blank. The absorbance was plotted against the concentrations and the procedural constant (K) was calculated from the best fitting straight line using linear regression analysis as shown in Table 1 & Figure 1.

Table 1: Calibration Curve of Captopril in Phosphate Buffer PH6.8.

Absorbance (nm)	Concentration(µg/ml)
0.28	2
0.41	6
0.55	10
0.68	14
0.84	18
0.98	22

R=0.9995266**, Slope**= 0.0351429**, Intercept**= 0.2016190**, K**= 28.5**.**

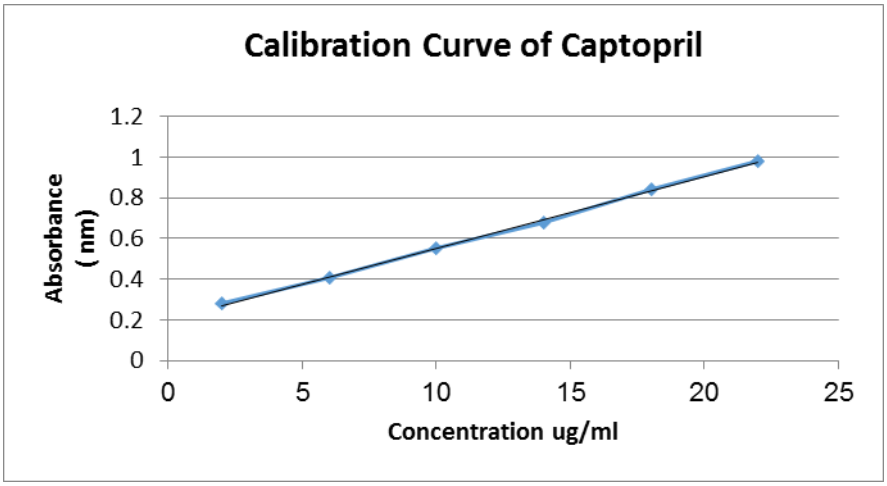

Fig. 1: Calibration Curve of Captopril in Phosphate Buffer pH6.8.

Formulation of Captopril MDTs by Different Methods[24]

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 2 & Figure 1.

Preparation of Captopril MDTs by Direct Compression Method

Table 2: 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%**

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.

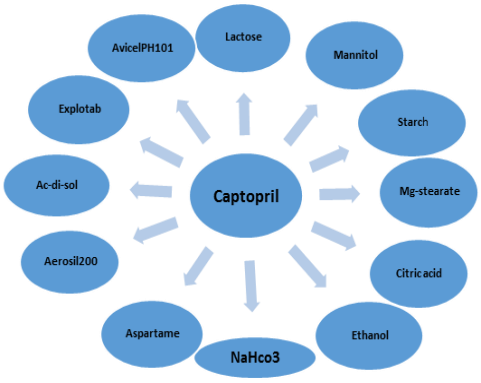

Fig. 2: Formulation of Captopril MDTs.

Evaluation of Captopril MDTs

Physical Evaluation of the Prepared MDTs

Weight Variation Test[25-27]

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

Uniformity of Tablets Thickness[30]

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

Friability[6,9,28,29]

Ten tablets from each formula were accurately weighed placed in the drum of the friabiliator (ERWEKA TAR, Germany) and rotated at 25rpm 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 Test[20,24,28]

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**[9,30,32,37]

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± 0.5^{o}C. 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[28,30,32-35]

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.

***In –Vivo* Disintegration Time**[9,10, 33,36,37]

Ten healthy human volunteers were selected and their consent was obtained. Each volunteer randomly took one tablet and kept on the tongue. The time taken for complete disintegration of the tablet on the tongue was noted. It was expressed in seconds. After the test, mouth was washed with distilled water. Two trials were performed, the first trial with F1 and the second for F13.

***In-Vitro* Dissolution Profile of Captopril Formulations MDTs**[1,2,6,11,20,24,26,29,38-40]

The dissolution of Captopril from different tablet formulations was tested by using USP dissolution tester, apparatus (2) [Hanson Research corporation SP8 SR11, USA]. The paddle was made to rotate at 50 rpm

(revolution per minute), the dissolution medium was 900mL phosphate buffer pH 6.8 maintained at 37± 0.5°C. At predetermined time intervals (5,10,15 & 25 minutes), aliquots of the dissolution medium were withdrawn and properly diluted and analyzed for Captopril content by measuring the absorbance at λmax 205nm, using phosphate buffer pH 6.8 as a blank. The withdrawn samples were replaced by equal volume of phosphate buffer pH 6.8. All results were run in triplicates.

Kinetic Analysis of the Dissolution Data of Captopril from Different Tablet Formulations[41]

To determine the mechanism of the dissolution of Captopril from its different tablet formulations, the dissolution data were analyzed using linear regression according to zero-order, first-order and Higuchi diffusion model, the coefficient of determination (R^2) was determined in each case and the highest value of R^2 yielded the best fit. Where the equations used were:

C- C^0=-Kt for zero order, LogC=LogC^0- Kt / 2.3 for first order, and Q=KH.t½ for Higuchi diffusion model.

RESULTS AND DISCUSSION

Table 3: Evaluation of Captopril Formulations MDTs.

Formulation Code	Average Weight (mg) ±S.D	Thickness (mm) ±S.D	Friability (%) ±S.D	Hardness Mean (Kg)±S.D	Wetting Time (Sec) ±S.D	*In-Vitro* Disintegration Time (Sec) ±S.D	*In-Vivo Disintegration Time (Sec) ±S.D*
F1	183.5±1.5	3.64±0.02	0.2±0.003	5 ±0.1	7±1	9±0.84	15±0.6
F2	178.8±2.3	3.49±0.02	0.3±0.002	5.2±0.2	7±1	10±0.89	-
F3	177.9±1.5	3.54±0.02	0.2±0.002	4.8±0.1	9±1	13±0.87	-
F4	179.4±0.7	3.52±0.02	0.3±0.004	4.7±0.1	11±0. 6	12±0.85	-
F5	180.7±2.7	3.17±0.02	0.3±0.004	3.9±0.1	18±0. 6	22±0.89	-
F6	180±0.6	3.12±0.01	0.3±0.003	3.7±0.2	22±1	26±0.88	-
F7	177.7±2.6	3.23±0.01	0.2±0.003	4.5±0.1	24±1	45±0.83	-
F8	183.3±1.7	3.26±0.01	0.2±0.003	4.5±0.1	23±0.6	46±0.85	-
F9	177.8±1.4	3.32±0.02	0.2±0.002	3.5±0.2	32±1	56±0.84	-
F10	176±2.4	3.27±0.02	0.1±0.002	4.1±0.2	30±1	55±0.84	-
F11	182.7±1.6	3.19±0.03	0.2±0.002	3.5±0.2	14±0.6	23±0.87	-
F12	181.2±0.7	3.15±0.03	0.3±0.004	3.2±0.2	21±1	28±0.88	-
F13	175.4±0.7	3.46±0.01	0.2±0.002	4.5±0.1	5±1	9±0.85	11±0.6
F14	177.5±0.7	3.55±0.03	0.1±0.001	3.6±0.1	22±1	36±0.84	-
F15	186.5±0.7	3.62±0.03	0.3±0.001	3.9±0.1	31±1	34±0.84	-
F16	177±1.5	3.56±0.01	0.1±0.001	5.8±0.1	28±1	75±0.87	-
Captopril denk®	100.8±0.7	2.52±0.02	0.2±0.002	7.6±0.1	350±1	381±0.84	-
Capotal ®25	151.3±0.7	2.33±0.02	0.3±0.001	5.5±0.2	130±1	420±0.85	-
Farcapril®	156±1.5	2.6±0.03	0.1±0.002	5.7±0.1	35±1	110±0.86	-
Capocard®	200±2.3	3.59±0.02	0.4±0.002	7.9±0.1	30±1	210±0.84	-
Capotril®	120.5±0.7	2.00±0.03	0.3±0.002	3.5±0.1	74±1	114±0.84	-

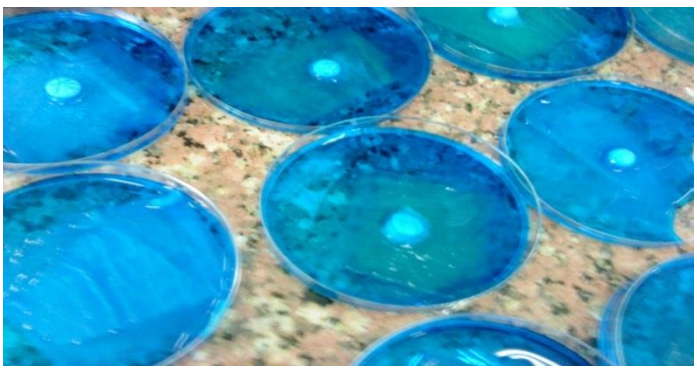

Fig. 3: Wetting Time of Captopril MDTs.

Table 4: Dissolution Rate Percent of Captopril Formulations MDTs.

Formulation Code	%Dissoluted after 5min.	%Dissoluted after 10 min.	%Dissoluted after 15 min.	%Dissoluted after 20 min.
F1	93.9%	93.5%	92.1%	91.6%
F2	93.1%	93%	92.5%	91.7%
F3	93.1%	91.45	90.7%	90.5%
F4	90.9%	91.2%	89.5%	89%
F5	92.4%	92.9%	90.3%	89.7%
F6	91.2%	91.8%	89.9%	89.5%
F7	91.8%	91.5%	91.5%	91%
F8	91.1%	93.2%	91.6%	91.5%
F9	91.2%	93.2%	91.3%	91.2%
F10	90.2%	93%	91.3%	91 %
F11	91.9%	93%	91.3%	91%
F12	90.8%	92.6%	91.4%	91.2%
F13	93%	92.2%	90.5%	90.3%
F14	71.3%	74.4%	71.2%	70.8%
F15	73.2%	71.2%	69.5%	68.7%
F16	40.1%	78.9%	80.1%	79.9%
Captopril denk®	54.4%	70.7%	91.2%	98.1%
Capotal ®25	45.8%	59.9%	80.5%	94.4%
Farcapril®	74.3%	89.2%	96.2%	99.3%

Table 5: Linear Regression Analysis of the Dissolution Data of Prepared Captopril MDTs in Phosphate Buffer PH6.8.

Formulation Code	Coefficient of Determination (R^2)		
	Zero	**First**	**Diffusion**
F1	0.947	0.920	0.960
F2	0.984	0.976	0.960
F3	0.960	0.736	0.960
F4	0.925	0.889	0.912
F5	0.949	0.957	0.978
F6	0.914	0.884	0.903
F7	0.949	0.929	0.906
F8	0.812	0.762	0.760
F9	0.677	0.629	0.607
F10	0.523	0.494	0.432
F11	0.679	0.575	0.610
F12	0.672	0.653	0.569
F13	0.857	0.815	0.927
F14	0.692	0.575	0.579
F15	0.901	0.897	0.966
F16	0.260	0.216	0.377

Table 6: Kinetic Parameters of Dissolution of Prepared Captopril MDTs in Phosphate Buffer PH6.8.

Formulation Code	Order	Intercept	Slope	(R^2)	K (min^{-1})	$T_{1/2}$(min.)
F1	Diffusion	96.95	-1.233	0.960	1.233	17.88
F2	Zero	93.77	-0.094	0.984	0.094	4.95
F3	Diffusion	95.14	-1.067	0.960	1.067	19.10
F4	Zero	91.66	- 0.112	0.925	0.112	4.10
F5	Diffusion	93.99	-0.913	0.978	0.913	21.20
F6	Zero	92.09	-0.116	0.914	0.116	3.93
F7	Zero	93.46	-0.119	0.949	0.119	3.88
F8	Zero	93.1	-0.091	0.812	0.091	5.05
F9	Zero	92.68	-0.081	0.677	0.081	5.63
F10	Zero	92.19	-0.076	0.523	0.076	5.93

F11	Zero	92.54	-0.079	0.679	0.079	5.77
F12	Zero	92.36	- 0.075	0.672	0.075	6.05
F13	Diffusion	94.74	-0.90	0.927	0.90	22.24
F14	Zero	73.2	-0.10	0.692	0.10	35.65
F15	Diffusion	76.17	-1.56	0.966	1.56	4.39
F16	Diffusion	46.05	-5.00	0.377	5.00	0.03

The Results of Evaluation for Captopril MDTs

Table 1, illustrated the absorbance determined at λ_{max}205nm in phosphate buffer pH6.8 at λ_{max}205nm for serial concentrations of Captopril. Figure 1, illustrated that a linear relationship between the absorbance at the specified λ_{max} and the concentration was obtained within the range of 2 to 22µg/mL. The procedural constant (K) was calculated and found to be 28.5 for phosphate buffer pH6.8.

On the other hand, several formulations of Captopril MDTs were prepared using 13.9% of the drug with 68-78% of the selected fillers in addition to 5-10% disintegrant such as SSG or CCS and 8-10% effervescence agents (citric acid & sodium bicarbonate), 1% glidant, 1% sweetening agent and 1% magnesium stearate as a lubricant, formulations were listed in Table 2 & Figure 2. The prepared tablets were evaluated for pharmaceutical parameters such as weight variation, thickness, friability, hardness, wetting time, disintegration and dissolution test. Table 3 & 4, showed the results of the all performed physical tests of the prepared Captopril MDTs.

Regarding, weight variation of formula (according to the Eur. Ph. and B.P.) complied with the test if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates by more than 10%. All the prepared tablets showed acceptable weight variation range from 175.4± 0.7 to 186.5± 0.7 as shown in Table 3.

Results of thickness showed uniformity in the prepared tablets where it was clear that the average thickness 3.4mm as shown in Table 3. In general friability values were within satisfactory range (not more than 1%). All formulations, showed percentages of fine less than 0.31% as illustrated in Table 3, and all tablet formulations showed good breaking strength within the range from 3.2 to 5.8 Kg, which were acceptable within the limit of conventional tablets as shown in Table 3.

Therefore, all the formulations, except F16, complied with the disintegration time requirement of less than 60 sec. for orodispersible (mouth dissolve) tablets as per European Pharmacopoeia. Regarding the disintegration test, most formulae had short disintegration time from 9 to 36 seconds, while formulae F7, F8, F9 and F16 showed longer disintegration time ranged between 45 and 75 seconds in comparison with 420, 381, 210, 114 and 110 seconds for Capotal 25®, Captopril denk®, Capocard®25, Capotril ® and Farcopril®, respectively. Results revealed that formulae prepared with SSG (explotab) as disintegrant exhibited the shortest disintegration time and those with higher disintegrant concentrations exhibited almost the same disintegration time of those of lower disintegrant concentrations or even longer disintegration time. F1 & F13 had the least disintegration time Table 3.

The optimization of tablet disintegration is commonly done by mean of the disintegration critical concentration. Below this concentration the tablet disintegration time is inversely proportional to the disintegrant concentration. Above the critical concentration, the disintegration time remains approximately constant or even increased[42] and this interpreted the previous results.

Lactose is very soluble in water and the excipients least soluble in water are the most appropriate for the formulation of orodispersible tablets. Both mannitol and lactose are water-soluble fillers that are supposed to dissolve at the pores upon contact with water allowing water penetration into the rest of excipients resulting in fast tablet disintegration. Nevertheless, lactose might have higher water-solubility than mannitol; therefore, it dissolves more quickly forming viscous saturated solutions at the pores, the increased viscosity act as a brake (barrier) against water penetration to the tablet constituents resulting in retarded tablet disintegration.[24,43] This clearly interpreted the shorter disintegration time exhibited by formulae with avicel PH101 alone as filler in comparison to those with (avicel PH101+lactose) and (avicel PH101 + mannitol) as fillers. This also explained the longer disintegration time exhibited by formulae with 2:1 (mannitol: avicel PH101) in comparison to shorter disintegration time exhibited by formulae with 1:1 (mannitol: avicel PH101).

Regarding the wetting time, results showed that most Ccaptopril MDTs formulae had short wetting time ranging from 7-28 seconds as compared with 30-350 seconds for Capotal 25®, Captopril denk®, Capocard®25, Capotril ® and Farcopril® (the marketed Captopril). Results also revealed that formulae F1 & F13 had the least wetting time as illustrated in Table 3 and Figure 3**,** so they were selected for *in –vivo* disintegration time and acceptable taste feel using 10 humans of 20-30 old where the recorded disintegration time was 15sec, & 11sec, for F1 & F13, respectively.

In-vitro dissolution profile of Captopril from its tablet Formulations was conducted. Ideally, physiological conditions at the site of administration should be considered when selecting the *in-vitro* dissolution/release test conditions. The saliva ordinarily maintains the pH of

mouth between 5.6 and 7.6. Therefore, in the dissolution studies, phosphate buffer that has a pH of 6.8± 0.5 was adopted as a dissolution medium.[24] Additionally, performed dissolution studies on orally disintegrating tablets used either SSF or purified distilled water. Results of the dissolution test of Captopril mouth dissolve tablets were shown in Table 4. Most formulae showed acceptable dissolution, where more than 91% of the labeled dose was dissoluted in 10 minutes. From these results it could be noted that formulae containing SSG (explotab) or effervescence agents as disintegrants and avicel PH101 as fillers (F1, F2, F3&F13) showed relatively higher dissolution, where 93.9%, 93.1%, 93.1% and 93 of the labeled dose were dissoluted after 5 minutes on the other hand different brands of Captopril namely Captopril-Denk®, Capotal® 25 and Farcopril ® exhibited 54.4%, 45.8% and 74.33% drug dissolution within 5 minutes, respectively. As mentioned before the least soluble excipients in water are the most appropriate for the formulation of orodispersible tablets[24] and avicel also showed some disintegrating property.[43] This might interpret the rapid dissolution of formulae with avicel alone as filler as compared to slow dissolution of formulations prepared with a mixture of avicel PH101 and lactose or avicel PH101 and mannitol.

The kinetic analysis of the dissolution data of captopril from its fresh tablets was illustrated in Tables 5&6. The highest coefficient of determination was chosen as the best fit and its kinetic treatments of Captopril in the fresh tablets and the kinetic parameters of most Captopril formulae were found to follow zero–order kinetics while only few formulae were found to follow Higuchi diffusion model.

CONCLUSION

Captopril, an ACEI, was selected as model drug for preparation of mouth dissolving tablets by direct compression and wet granulation techniques. Several formulae of Captopril MDTs have been prepared utilizing different excipient. All the prepared MDTs were evaluated for weight variation, uniformity of thickness, friability, hardness, wetting time, disintegration time, dissolution time and kinetic studies of dissolution data. All Captopril MDTs formulae (except F16) showed disintegration time less than 60 seconds. Captopril MDTs formulae F1 prepared with 78% avicel PH101 as a diluent, 5% explotab as a disintegrant, 1% Aerosil 200 as gildant, 1% magnesium stearate as lubricant & 1% aspartame as a sweetener) & F13(65% avicel PH101 as a diluent, (8:10) citric acid: sodium bicarbonate as effervescent agents, 1% Aerosil200 as gildant, 1% magnesium stearate as lubricant & 1% aspartame as a sweetener) showed the short disintegration time of almost 9 sec. All of the prepared Captopril MDTs showed wetting time less than 60 seconds and the least wetting time was observed from formulations F1 & F13. Dissolution profiles of most the prepared MDTs showed that more than 90% of drug dissolution within 5 minutes whereas 55-73% of drug dissolution were obtained from different brands of Captopril tablets. Captopril MDTs of F1 showed that 94% the highest extent of drug dissolution within 5 minutes. The kinetic analysis of Captopril dissolution from most tablets exhibited zero order mechanism. It was concluded that F1 is the best formulation of prepared Captopril MDTs in order to increase onset of action and bioavailability of drug.

ACKNOWLEDGEMENT

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

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