DESIGN AND OPTIMIZATION OF CAPTOPRIL SUBLINGUAL TABLETS: ENHANCEMENT OF PHARMACOKINETIC PARAMETERS IN HUMAN

BY

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Abstract

Oral mucous membrane of drug delivery is considered to be a promising alternative to the oral route. Sublingual route is a useful when rapid onset of action is desired than orally administered tablets. The objective of this study was to develop the sublingual tablet of captopril and improve its bioavailability. Captopril is the drug of choice in treatment of hypertension crisis or acute heart failure. Improvement of drug absorption and bioavailability was achieved by decreasing the pH of the mouth using citric acid. A 3^2 full factorial design was applied to optimize the formulations. Nine batches were prepared and evaluated to developing and optimizing sublingual tablets of water soluble drug (captopril). The optimization design was used to obtained the concentration of mixture superdisintegrants X_1 (crosscarmellose sodium, crosspovidone and sodium starch glycolate at 1:1:1 ratio) and using microcrystalline cellulose containing silicon dioxide (Prosolv-SMCC®) as a diluent (X_2). Disintegration time and t_{90} values used as dependent variables for optimization to obtain the desirable optimized formula. According to the results, the selected variables have a strong influence on disintegration time and T_{90} of captopril sublingual tablets. The lowest disintegration time (13.04 sec) and t_{90} (2.78 min) were showed by sublingual formulations composed of 7.82 % of superdisintegrants combination (X_1) with 30.50 % of prosolv-SMCC (X_2). So, this formula was chosen as the optimized formula. The F-optimized formula was compared with the marketed tablet pharmaburst® formula. It is clear from the result that the F-optimize formula had a very significant lower disintegration time than F-pharmaburst (12.2 and 16.3 sec respectively), and t_{90} (3.2 and 5.0 minute respectively). The pharmacokinetic parameter for the F-optimized showed a significant ($P \leq 0.05$) increase in maximum plasma concentration from 180.0 to 286.5ng/mL, and a shortening of the time taken to reach maximum plasma concentration to 45 min in comparison with the marketed tablet. Finally, the F-optimize improved oral absorption of captopril sublingual and a subsequent acceleration of clinical effect, which is favored for hypertensive crises and cardiac disorders.

Keywords: bioavailability, oral absorption, sublingual tablets, response surface design, Captopril, crosscarmellose sodium, crosspovidone, sodium starch glycolate, Superdisintegrant.

Introduction

Highly elevated blood pressure occurred in hypertension crisis, if not treated, can result in severe end organ damage or even death in a short period of time. In this case, reduction of blood pressure within few minutes is crucial (Chetty, Chen et al. 2001). Sublingual route is a useful method of administration when rapid onset of actions is required. The drug administration under the tongue lead to drug reaches directly to the blood stream through the ventral surface of the tongue and floor of the mouth. The absorption of the drug through the sublingual route is 3 to 10 times greater than oral route. Sublingual absorption is mostly rapid in action, but also short acting in duration (Narang and Sharma 2011). These dosage forms are of particular advantages in certain patient groups who have difficulty in swallowing such as pediatric, geriatric, and psychiatric patients (Suresh, Ranjit et al. 2011). The sublingual route is ease route of administration, patient compliance and improved bioavailability (Harris and Robinson 1992). To develop sublingual tablet with direct compression method, it was necessary to find suitable excipients with good compressibility and disintegrating ability. Although the superdisintegrants and type of diluent responsible for the effect of the disintegration rate, when used at high concentrations, they can also affect mouth feel, tablet hardness, and friability. Thus, several factors must be considered when selecting a superdisintegrant (Abdelbary, Elshafeey et al. 2009). The direct compression tablet disintegration and dissolution are based on the single or combined action of superdisintegrants and excipients. The choice of a suitable type and an optimal amount of superdisintegrants are paramount for ensuring a high disintegration rate (Dobetti 2000). In the new strategy for using the combination of three superdisintegrants (crosscarmellose sodium, crosspovidone and sodium starch glycolate) to make a synergistic effect for decreasing the disintegration time and improvement of the absorption and bioavailability of sublingual drug. Captopril is an angiotensin converting enzyme inhibitor which is used in management of hypertension, heart failure and myocardial infarction (Sweetman 2007). The physicochemical properties of Captopril are water soluble drug having plasma half-life of 2 hrs, make it suitable candidate to formulate buccal disintegrating tablets (Dumbare, et al. 2012). It has been reported that sublingual administration of captopril is an effective and safe method of lowering arterial blood pressure in patients with hypertensive emergencies (Longhini, Ansani et al. 1990, Ziller 1992, Wu, Lin et al. 1993). Oral and sublingual usage of captopril is quite common in emergency services. There are many studies showed the sublingual captopril reduces the blood pressure effectively in hypertensive crises (Öhman, Kågedal et al. 1985, Moldovan 2012). The citric acid was added to the formulations to elevate the acidic pH in the buccal cavity for enhancement the absorption and improving the bioavailability of captopril sublingual tablet.

In this study, a response surface design approach was used to optimize the concentration of ternary phase of superdisintegrants combination of crosscarmellose sodium, crosspovidone and sodium starch glycolate (X_1) and using Prosolv-SMCC® as diluent (X_2). Disintegration time (Y_1) and T_{90} values (Y_2) used as dependent variables for optimization to obtained the desirable optimized formula. Furthermore, it was compared with captopril pharmabrust sublingual formulation. Finally, the best formula was subjected to bioavailability study to compare with commercially available captopril oral tablets.

Materials and methods

Materials

Captopril was kindly supplied by EIPICO (10th of Ramadan City, Egypt). Sodium stearyl fumarate (Pruv®), crosscarmellose sodium (Vivasol®), sodium starch glycolate (Explotab®) and prosolv-SMCC were kindly supplied by JRS (Aalen, Germany). Crosspovidone and citric acid was received from Sigma for pharmaceutical Industries (Cairo, Egypt). Spray dried mannitol (Mannogem TM EZ) was kindly supplied by SPI (Grand Haven, MI, USA). Captopril tablets; Capoten^{R}, 25 mg from SmithKline Beecham, Egypt, an affiliated co. to *GlaxoSmithKline*. Methanol, HPLC grade; Merck. Darmstadt, Germany. Trichloroacetic acid, analytical grade; Merck Schuchardt, Germany.

Methods

Pre-compression tests

In a preliminary study, formulation of captopril listed in table 3 was subjected to micromeretic study. The angle of repose was measured by using funnel method (Cooper, 1986), which indicates the flowability of the granules. Angle of repose is defined as the maximum angle possible between the surface of a pile of powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose: $\tan\theta = \frac{h}{r}$

Where, θ is the angle of repose, h stands for the height of the pile and r represents the radius of the base of the pile (Suresh, Ranjit et al. 2011).

Bulk (BD) and tapped density (TBD) were measured using the formula:

$$BD = \frac{weight\ of\ the\ powder}{volume\ of\ the\ packing} \qquad TBD = \frac{weight\ of\ the\ powder}{tapped\ volume\ of\ the\ packing}$$

Hausner ratio (HR) is an indirect index of ease of powder flow. It is calculated by the following rule. $HR = \frac{TBD}{BD}$

Lower hausner ratio (< 1.25) indicate better flow properties than higher ones (>1.25).

Compressibility index (CI) of the powder formulation was determined by using the following rule (Rao and Kulkarni 2010):

$$CI = \frac{TBD\text{-}BD}{TBD} \times 100$$

Application of response surface experimental design

The response surface design (RSD) used to study the effects of different variables on the characteristics of the produced sublingual tablets. The process was optimized to obtain the minimum disintegration time, and rapid release pattern, a three-level, two-factor RSD was used. These variables are the amount of superdisintegrants mixture combination of crosscarmellose sodium (CCS), crosspovidone (CP), and sodium starch glycolate (SSG), 1:1:1 ratio (X_1) and diluents prosolv-SMCC® (X_2). The responses selected for evaluation and optimization were disintegration time (Y_1) and t_{90} of drug released after 30 minute (Y_2). The design was performed with Statgraphics

Plus® For Windows (Manugistics Inc, Rockville, MD, USA). The design suggests nine experimental runs. The dependent and independent variables with their intervals are shown in table 1 to perform RSD. The RSD is represented in table 2, while the tablet formulations are represented in table 3. The polynomial function represents how the components affect on the response. A polynomial model with fewer terms should be used. The RSD can be used to fit the following model**.** The response surface analysis is performed by using the fitted surface.

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_1 X_1^2 + \beta_2 X_2^2 + \beta_{1,2} X_1 X_2$$

Table 1. Variables in response surface design

Components				
Independent variables				
X_1	Superdisintegrants mixture of Croscarmellose Sod (CCS), Crospovidone (CP) and Sodium starch glycolate (SSG) at (1:1:1 ratio)			
Variable	**-1**	**0**	**+1**	**Unit**
	3	6	9	%
X_2	Prosolv® SMCC as diluents (microcrystalline cellulose containing silicon dioxide)			
Variable	**-1**	**0**	**+1**	**Unit**
	0	30	60	%
Dependent variables				
Y_1	Disintegration time (sec)			
Y_2	T_{90} (min)			

Table 2. Matrix Represented of Response Surface Design

Formulae	**Super disintegrants CCS, CP and SSG X_1**		**Diluent Prosolv SMCC X_2**	
F_1	**-1**	**3**	**-1**	**0**
F_2	**0**	**6**	**-1**	**0**
F_3	**+1**	**9**	**-1**	**0**
F_4	**-1**	**3**	**0**	**30**
F_5	**0**	**6**	**0**	**30**
F_6	**+1**	**9**	**0**	**30**
F_7	**-1**	**3**	**+1**	**60**
F_8	**0**	**6**	**+1**	**60**
F_9	**+1**	**9**	**+1**	**60**

Abbreviations: CCS, crosscarmellose sodium; SSG, sodium starch glycolate; prosolv-SMCC, prosolv silicon dioxide microcrystalline cellulose; CP, Crosspovidone

Table 3. Formulation of Captopril Sublingual Tablet

Formulae	Capto	SD	SMCC	Mannitol	SSF	TF	Citric acid	Sucralose	Menthol
F_1	25	3	0	66.5	1	1	2	1	0.5
F_2	25	6	0	63.5	1	1	2	1	0.5
F_3	25	9	0	60.5	1	1	2	1	0.5
F_4	25	3	30	36.5	1	1	2	1	0.5
F_5	25	6	30	33.5	1	1	2	1	0.5
F_6	25	9	30	30.5	1	1	2	1	0.5
F_7	25	3	60	6.50	1	1	2	1	0.5
F_8	25	6	60	3.50	1	1	2	1	0.5
F_9	25	9	60	0.50	1	1	2	1	0.5
Comparative study between F-optimize and F-pharmbrust									
F-optimize	25	7.82	30.5	31.18	1	1	2	1	0.5
F-pharmbrust	25			75.0	Total excipients formula				

Abbreviations

capto, captopril; SD, superdisintegrant; prosolvSMCC microcrystalline cellulose contining silicon dioxide; SSF, sodium stearyl fumarate; TF, tutty frutty.

Tablet manufacturing

These formulations mentioned in table 3 are designed to administer through the sublingual mucosa. The sublingual tablets are usually small, flat and compressed lightly to keep them soft. These tablets are designed in such a way that they must dissolve quickly in small quantity of saliva and allow the drug to be absorbed through the sublingual mucosa. Formulations of Captopril sublingual were prepared by the direct compression method. Nine formulations of 100mg total weight containing 25 mg Captopril with different ratios of tablet excipients were prepared according to the formulations given in Table 3. Mannitol was used as diluent; SSF was used as lubricant, TF, menthol and sucralose were used as sweetener and flavoring agent. The obtained blend was directly compressed by 6 mm flat round punches using a tablet machine (Royal Artist, Mumbai, India). The tablets were collected during compression for in-process testing (weight and hardness) and were stored in airtight high-density polyethylene bottles pending further testing (Mostafa, Ibrahim et al. 2013).

Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used for thermal analysis of captopril alone and captopril sublingual formulation (2 mg samples) using aluminum crucibles in a dynamic nitrogen atmosphere (flow rate 50 mL per minute) and at a

heating rate of 10°C per minute in the temperature range of 25°C–400°C (Dumbare, et al. 2012, Aljimaee, El-Helw et al. 2015).

Fourier transform infrared spectroscopy

Fourier transform infrared spectra were recorded on a Jasco FT IR-6100 spectrometer using KBr discs with a 2 cm-1 resolution in the range of 4,000–400 cm-1 (Aljimaee, El-Helw et al. 2015).

Evaluation of the Prepared Captopril Sublingual Tablets

The prepared Captopril sublingual tablets were evaluated for visual appearance, uniformity of content and weight, hardness, friability, and in vitro disintegration time according to US Pharmacopeia tests for tablets (Aljimaee, El-Helw et al. 2015).

Wetting time and wetting ratio

Ten milliliters of distilled water containing eosin, a water soluble dye, were placed in a Petri dish of 10 cm diameter containing circular tissue papers of 10 cm diameter. One tablet carefully placed in the center of the Petri dish and the time required for water to reach the upper surface of the tablet was noted as the wetting time. The test results are presented as mean value of three determinations ± SD (Jonwal, Mane et al. 2010). The complete wetted tablet was then weighed. Water absorption ratio (R) was determined according to the following equation:

$$Wetting\ ratio = \frac{tablet\ weights\ after - tablet\ weights\ before}{tablet\ weights\ before} \times 100$$

In vitro dissolution studies

In vitro drug release was performed for captopril tablets according to the (The United State s Pharmacopeia 2007) "Dissolution procedure" for immediate release dosage forms. A minimum of 6 tablets of each formula were tested. The USP 30 (apparatus 2) paddle method was used. Dissolution was carried out in 900 ml phosphate buffer pH 6.8 ± 0.05 to simulate saliva fluid. The paddle was rotated at 50 rpm at 37 ± 0.5 ºC. Samples were tested at specified time intervals (0.5, 1, 2, 3, 4, 5, 7, 10, 15, 20 and 30 min). Samples were adequately diluted and analyzed for captopril spectrophotometrically at wave length 211 nm (Dumbare, et al. 2012).

Comparing the optimized formula with pharmabrust formulation.

The optimized captopril sublingual formula was compared to captopril pharmabrust® formula a ready ODT system. Table (3) represents optimize sublingual formula and captopril pharmabrust formula. Disintegration time, T_{90} and dissolution profiles were evaluated for two compared formulae (Figures 1, 2 and 5**)**

In vivo and pharmacokinetic parameters

Sixteen healthy volunteers were enrolled in this study. The volunteers were informed about the objectives of the study and all the procedures were explained to them. A written consent form was signed by each agreement to participate in this study sixteen healthy male adult volunteers with age ranging from 18 up to 26 years, and their weight ranging from 60 to 85 kg were enrolled (non-obese). Physical examination showed that all the volunteers had no clinical evidences of chronic diseases. Volunteers with liver diseases, smokers, regular prescription medication and chronic diseases

(hypertension, diabetes, ischemic heart diseases), were excluded. The volunteers were instructed to never receive any medication (over the counter) for the 72 hours before the study. On the day before the study the volunteers were randomly divided to two groups, each 8 volunteers, and the first group received of F-optimized sublingual tablet, the second group received captopril 25 mg orally. Blood samples were obtained after captopril administration (Jankowski, et al., 1995).

The study protocol, which complied with the recommendations of the Helsinki Declaration, was fully approved and performed by the Egyptian Research and Development Company Ethical Committee (ERDC EC). The ERDC EC is organized and operated according to guidelines of the declaration of Helsinki, international conference of Harmonization ICH, and United States Codes of Federal Regulations (International Conference of Technical Requirements for the Registration of Pharmaceuticals for Human Use).

Blood samples (5 mL) were obtained by using vein puncture cannula after captopril administration at 10, 20, 30, 45, 60, 120, 150, 180, 200, 220, and 240 minutes, after captopril administration. All samples were collected in heparinized tubes (Maxi Mix II, Thermolyne Corporation, USA). Plasma was separated by centrifugation for 15 minutes at 4000 rpm (Minor 35, England) and then stored at -20 C^0 until analysis.

The assay of captopril by UV spectrophotometer (UV-1800 Shimadzu) was adopted and validated for analysis of captopril in plasma samples. To 3ml of each standard plasma samples, 2ml of 10 % trichloroacetic acid were added, for protein precipitation. The test tubes were shaken well for 2 minutes using vortex mixer, and then centrifuged for 15 minutes at 4000 rpm. The supernatant was filtered by membrane filter (0.45 mm) then, added to 1.5 ml filtrate 1.5 ml methanol, transferred to clean dry quartz cell, and its absorbance was measured at λ_{max} 225 nm. Unknown samples were treated exactly as the standard samples (El-Enany, et al., 2008).

Non-compartmental pharmacokinetic analysis was utilized to analyze the obtained results. The maximum plasma concentration (C_{max}) and the time of its occurrence (t_{max}) were determined from the concentration-time data. The area under the plasma concentration- time curve from 0 time to last sampling time (240 min) ($AUC_{0\rightarrow t}$) was calculated using the linear trapezoidal rule. The elimination rate constant (k) was estimated form the slope of the terminal phase of the captopril plasma concentration from the following equation:-

$$\text{Slope} = \frac{-k}{2.303}$$ The half-life is calculated from the elimination rate constant (k).

$$t_{1/2} = \frac{0.693}{k}$$

The other pharmacokinetic parameters such as Cl/F where Cl is the total body clearance, and F is the bioavailability was calculated.

$$Cl = \frac{FD}{AUC}\ ,\ \frac{Cl}{F} = \frac{D}{AUC}$$, where **D** is the dose.

The area under the curve was calculated utilizing the liner trapezoidal rule. The plasma concentration time profile was divided to trapezoids and the area of each trapezoid was calculated as follow:-

$$\text{Area of a trapezoid} = \left(\frac{C_n + C_{n+1}}{2}\right) \times (t_{n+1} - t_n)$$

The $AUC_{0\to t}$ was calculated by adding the area of all the trapezoids.

The pharmacokinetic parameters used for comparison were C_{max}, t_{max}, $t_{1/2,}$ k, $AUC_{0\to 240}$, and Cl/F. These pharmacokinetic parameters were calculated for each individual under each dosage form and the results were presented as the mean ± standard deviation (±SD) and were analyzed by Statistical Package for Social Science (SPSS) version 20. The Paired t-test was used. The level of significance was set at P value of 0.05 or less. The mean is the arithmetic average and can be calculated by;

$\bar{X} = \frac{\Sigma X}{n}$ Where Σx is the sum of all observations and n is the number of observations

Results and discussion

Evaluation of pre-compression parameters of sublingual tablets

The results of pre-compression parameters were represented in table 4 which were in between the optimum range and passes normal accordingly pharmacopeial. Depending these results, which are easy to use for direct compression tablet manufacture (table 4).

Evaluation of the prepared captopril sublingual tablets

The prepared sublingual tablet formulations were evaluated for the different parameters to ensure uniformity and compatibility of the prepared tablets with compendia requirements (Table 4). The weight of each tablet showed variability of no more than 2%, which met the specification of the USP limits. The average weight of the nine formulations were found to be in the range of 98.6–103.0 mg. Hardness, friability, wetting time and wetting ratio of all tablet formulations ranged from 2.6 to 3.1 kg/cm^2, 0.485 to 0.940%, 24.8 to 55.6 seconds and 36.5 to 95.0 %, respectively. According to the European Pharmacopoeia, so all the prepared tablets met the pharmacopeial requirement. Drug content of all the formulations was in the range of 97.50 to 99.90% which was within the acceptable limits. These results support the reproducibility of the captopril sublingual formulations and tableting process used in this study. The variables have strong influence on disintegration time and T_{90} of the captopril sublingual tablets. The disintegration time results were compatible with USP disintegration test for sublingual tablets. As per USP sublingual tablet must disintegrate completely within 2 minutes.

Table 4. Results of each experimental design of captopril sublingual tablet.

Formulae	Angle of repose	Hausner ratio	Carr's Index	Weight (mg)	Hardness (Kp ± SD)	Friability (%)	Drug content (%)	Wetting time Sec± SD	Wetting ratio (%± SD)
F_1	25.5	1.17	14.3	99.8±4.1	2.9±0.25	0.818±0.05	99.2±3.2	55.6±3.0	36.5±2.8
F_2	27.3	1.17	14.7	98.6±3.8	2.8±0.16	0.940±0.07	97.5±4.3	49.2±2.0	45.2±1.8
F_3	25.6	1.18	15.3	99.5±5.2	3.1±0.29	0.767±0.06	99.9±5.5	42.4±2.0	55.0±1.5
F_4	26.4	1.19	15.8	102.4±6.5	2.9±0.28	0.704±0.08	99.9±6.7	30.2±2.8	79.5±2.6
F_5	27.6	1.17	14.8	101.2±7.2	2.6±0.28	0.602±0.05	98.8±5.3	27.4±1.9	82.4±2.3
F_6	24.5	1.16	14.0	99.2±6.3	2.6±0.32	0.686±0.07	99.1±7.8	24.8±2.5	91.5±3.2
F_7	27.3	1.18	15.6	103.0±4.9	2.7±0.21	0.554±0.09	98.9±3.9	26.2±3.2	92.9±3.0
F_8	26.3	1.20	16.7	99.6±6.5	3.1±0.23	0.562±0.05	99.3±5.4	28.4±2.4	90.8±1.7
F_9	27.2	1.19	15.7	99.3±5.0	3.0±0.12	0.485±0.03	99.0±4.6	31.3±3.0	95.0±2.9
Comparative study between F-optimize and F-pharmbrust									
F-optimize	28.4	1.13	14.5	99.8±6.3	2.7±0.2	0.659±0.05	99.5±5.8	24.2±1.5	94.8±3.4
F-pharmabrust	26.2	1.17	12.5	99.8±5.0	3.00±0.15	0.635±0.04	99.8±4.8	33.5±2.0	90.6±2.3

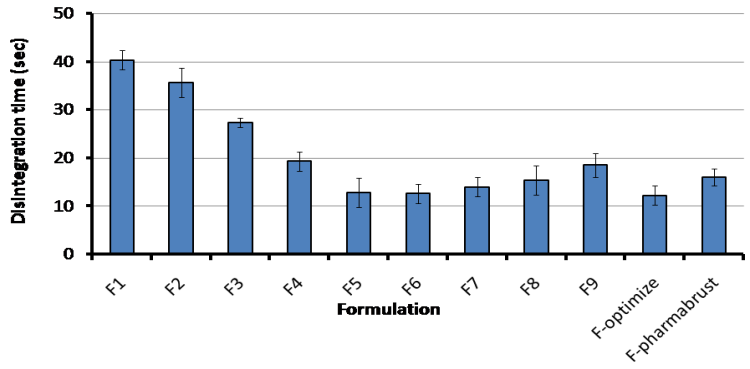

Figure 1. Histogram showing disintegration time (Y_1) of captopril sublingual tablets.

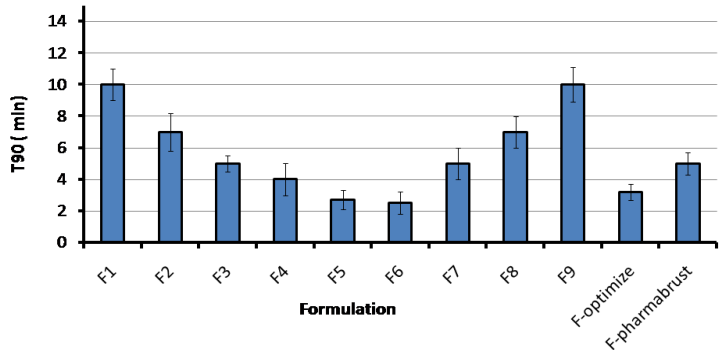

Figure 2. Histogram showing T_{90} (Y_2) of captopril sublingual tablets

Differential scanning calorimetry

DSC is a tool used to investigate the crystalline or amorphous nature of the drug within the developed formulations and to elucidate any possible interactions with other

ingredients. The thermal characteristic of pure captopril and F-optimized formula were shown in Figure 3. The differential scanning calorimetry thermogram of captopril indicates endothermic peak (T peak 103 to 107 °C) corresponding to its melting point, which is in agreement with values reported in the literature (Nogueira, Rego et al. 2011). Moreover, this characteristic peak was retained in also the F-optimize formulation. The above finding confirms compatibility of the formulation ingredients.

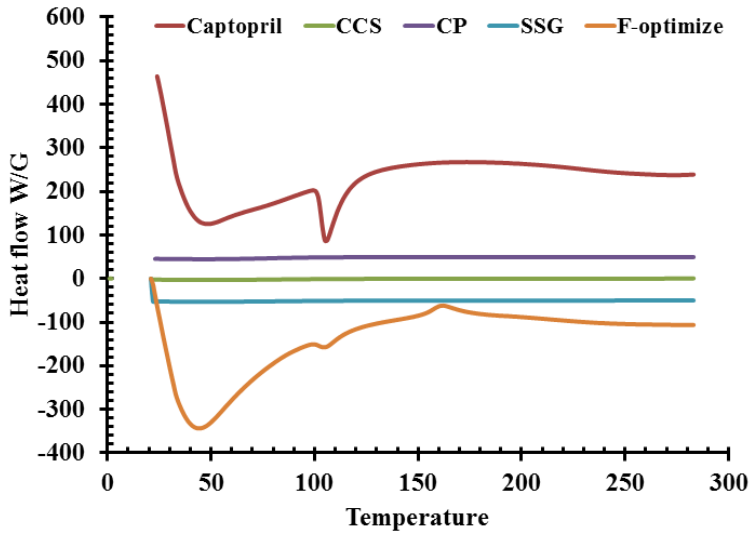

Figure 3. DSC thermogram of captopril pure drug and captopril sublingual tablet (F-optimize) formulation.

From figure 4, the FTIR spectrum of pure captopril showed S-H stretching bands at 2650 cm^{-1}, aromatic C-N vib bands at 1350 cm^{-1}, aromatic C-O stretching bands at 1200 cm^{-1}, and C–H stretching bands at 2983 and aliphatic O-H bands at 1322 cm^{-1}(Padmaja, Ramakrishna et al. 2014). The F-optimize formulation FTIR spectrum showed slightly change of some bands. This indicates that there was no interaction between drug and the Additives used in the study. Hence FTIR spectral analysis proved the compatibility of the drug and additives used. The presence of ingredients did not produce shift in the peaks of other ingredients. The above finding confirms compatibility of the formulation ingredients.

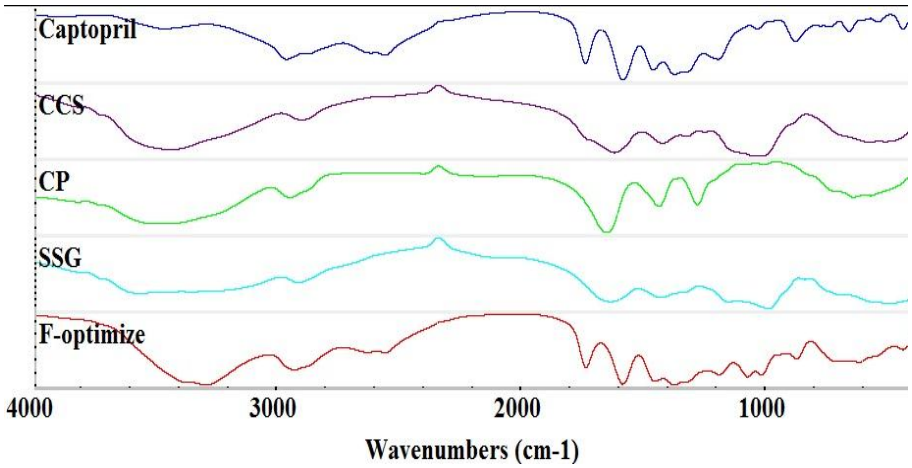

Figure 4. IR spectra of captopril pure drug and captopril sublingual tablet (F-optimized) formulation.

In vitro dissolution studies

The drug release profile was studied for all formulations following standard procedure and the results are showen in figure 5. According to the scientific literature, the amount of captopril dissolved from sublingual tablets must exceed 80% in 15 minutes (Das and Das 2004). The release of captopril sublingual was varied according to the amount of superdisintegrant and prosolv-SMCC diluents added. From cumulative drug release profile (Figure 5A) it was concluded that with zero concentration of prosolv-SMCC in the formulations (F_1 to F_3), the drug release rate from the tablet was found to be increased gradually with increasing the amount of superdisintegrant used. This may be attributed to increased hydration followed by increased swelling index of superdisintegrant with increasing its concentration. In contrast, the cumulative drug release with highest concentration of prosolv-SMCC in the formulations (F_7 to F_9), was found to be decreased in the start of drug release and the variation of release between formulae mainly depend on the concentration of superdisintegrant (Figure 5C).

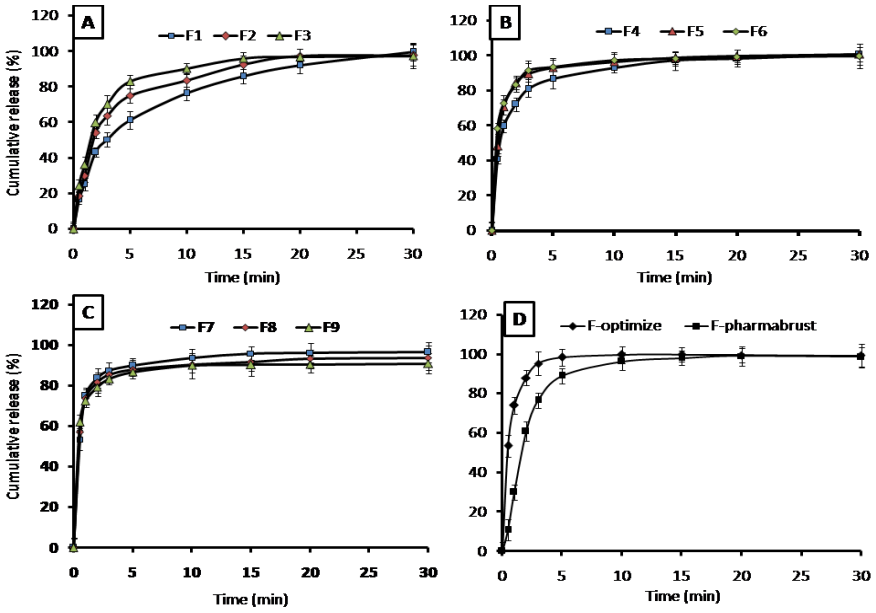

Figure 5. Dissolution profiles of different captopril sublingual formulations (A for F_1 to F_3), (B for F_4 to F_6), (C for F_7 to F_9) and (D for F-optimized and pharmabrust).

This may be attributed to increase of superdisintegrant with highest concentration of prosolv-SMCC that lead to increased swelling and gelling which retarded the drug release. The overall data on the in vitro dissolution studies closely indicated that among the nine formulations, the formulae F_5 and F_6 (Figure 5B) were found to be the best with optimum concentration of prosolv-SMCC and mannitol with the concentration of superdisintegrant from 6 to 9%. The F-optimize formula (Figure 5D) using the superdisintegrant (7.82 %) and prosolo-SMCC (30.46 %) ratio, the drug exhibited significant swelling properties with optimum release profile. Hence it can be concluded that the F-optimized will be suitable for sublingual administration for the treatment of hypertension.

Response surface design for optimization of captopril sublingual tablets

All tablet formulations were prepared according to the matrix of the design (Table 2) and according to formulae mentioned in Table (3). The responses measured (disintegration time "Y_1", and time for 90% (T_{90}) drug release "Y_2") were summarized in Figure 1 and 2. These results indicate that the selected variables have strong influence on disintegration time and T_{90} of the sublingual tablets. The resulting equations of analysis for each response variable were as follows:

$$\mathbf{Y_1} = 50.661 - 3.281\ X_1 - 1.284\ X_2 + 0.081\ X_1^2 + 0.0112\ X_2^2 + 0.048\ X_1X_2 \quad \mathbf{(1)}$$

$$\mathbf{Y_2} = 14.556 - 1.606\ X_1 - 0.451\ X_2 + 0.057\ X_1^2 + 0.0048\ X_2^2 + 0.028\ X_1X_2 \quad \mathbf{(2)}$$

Equations (1–2) reflect the quantitative influence of the formulation variables, i.e, percentage superdisintegrant (X_1) and diluent concentration prosolv-SMCC (X_2), and their interactions on the responses (disintegration time Y_1 and T_{90} Y_2). The main effect of process variables (X_1 and X_2) and their interaction (X_1X_2) on the responses (Y_1 and Y_2) were investigated. A positive sign reflects a synergistic effect while a negative sign stands for an antagonistic effect. It can be concluded, from regression equation 1, X_1 and X_2 has an antagonistic effect on the disintegration time (Y_1). X_2^2 and X_1X_2 has a synergistic effect on disintegration time (Y_1). Pareto charts and main effects plots (Figure 6A) are used to demonstrate the effect of the independent variables and their interactions on the dependent variables. In this case, 4 effects (X_1, X_2, $2X_2$ and X_1X_2) have P-values less than 0.05, indicating that they are significantly affected on the disintegration time.

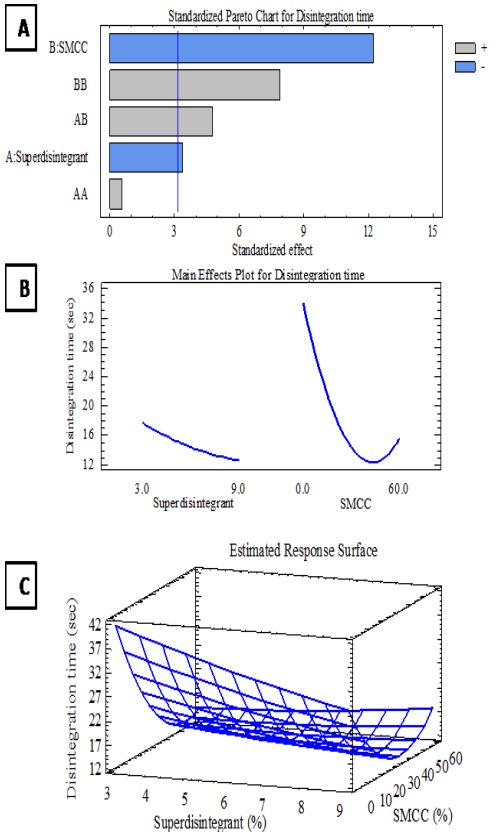

Figure 6. Estimated response surfaces of Standard pareto (A), plot (B), and contour plot (C) showing the effects of X_1 and X_2 on the dependent variable disintegration time (Y_1)

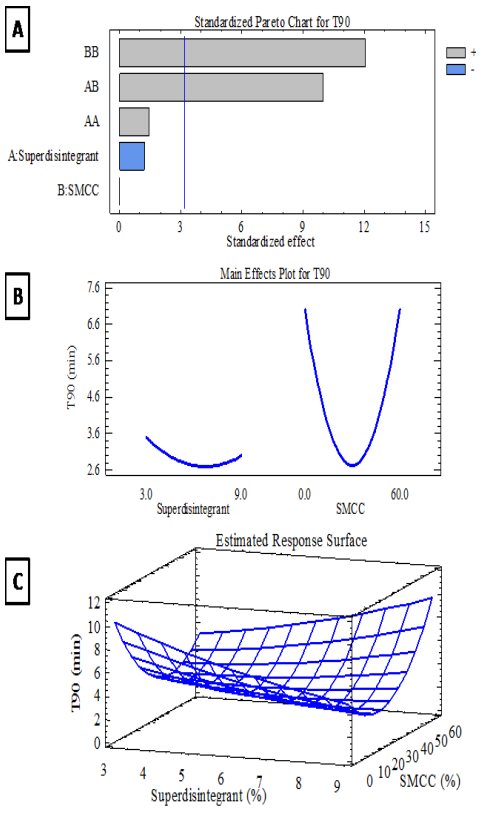

Figure 7. Estimated response surfaces of Standard pareto (A), plot (B), and contour plot (C) showing the effects of X_1 and X_2 on the dependent variable T_{90} (Y_2)

From regression equation 2, In this case, 2 effects ($2X_2$ and X_1X_2) have P-values less than 0.05, indicating that they are significantly affected on the T_{90} these were showed in Figure 7A. On the other hand, the variable X_2^2, X_1X_2 and X_1^2 has a significant effect on the Y_2 and X_1 has a synergistic effect on the T_{90}. Two-dimensional response surface plots and the contours of these estimated response surfaces (Figure 6 B,C and Figure 7 B,C) were determined graphically using the software to understand the relationship between the studied factors and the obtained responses. We concluded that tablets prepared with gradually increase the concentration of superdisintegrant from 3 to 9 % effect on disintegration time and T_{90} among tablets prepared by direct compression method (Zade, Kawtikwar et al. 2009 and Hossameldin, et al. 2016). On the other hand variation in the concentration of soluble (mannitol) and insoluble diluents (prosolv-SMCC) were showed increased disintegration time with increasing the concentration of soluble filler (mannitol). Moreover, water soluble filler causes an increase in viscosity of the penetrating power fluids which tends to reduce effectiveness of disintegrating agents and as they are water soluble, they are likely to dissolve rather than disintegrate the tablet (Gopinath, 2012). In case, when the concentration of insoluble diluent (prosolv-SMCC) around 30 % which tend to increase the effectiveness of superdisintegrants. In contrast, increasing the concentration of the insoluble diluent (prosolv-SMCC) to 60 % tend to increasing the viscosity and reducing the penetrating and effectiveness of disintegrating agents. From the composition of the multiple responses the optimized desirable formula was identified. The F-optimize formula was proposed to contain 7.82 % and 30.50 % of X_1 and X_2, respectively. This optimized formula was prepared and characterized for its disintegration time and T_{90}. The predicted values obtained from optimization were compared to the observed ones in which the residual was calculated and presented in Table 5 and figure 8. The F-optimized formula where further characterized and compared with captopril sublingual pharmabrust formulation (F-pharmabrust).

Table 5. Multiple response optimization of captopril sublingual formulations

Factor		**Low level**	**High level**	**Optimum level**
Superdisintegrants	X_1	3	9	7.82
Prosolv-SMCC	X_2	0	60	30.5
Response		**Predicted**	**Observed**	**Residual**
Disintegration time (sec)	Y_1	12.1	13.04	0.94
T_{90} (min)	Y_2	2.57	2.78	0.21

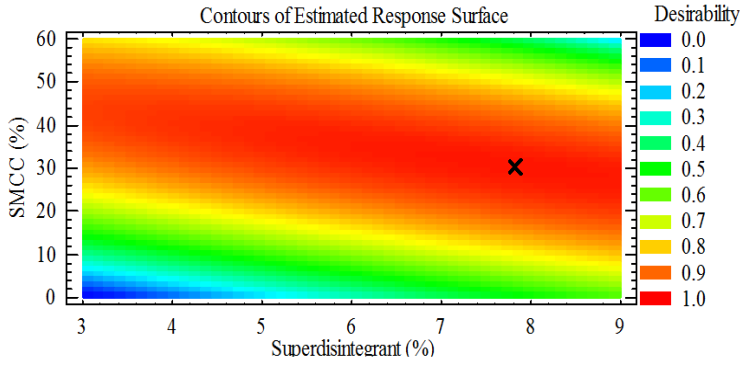

Figure 8. Contours of estimated response surface to determine the optimized formula

Comparative study between F-optimized and F-pharmabrust

Figure (1 and 2) showed the properties of both F-optimized and F-pharmabrust tablets. It is clear from the figures that the F-optimize formula had a very significant lower disintegration time than F-pharmabrust (12.2 and 16.3 sec respectively), and T_{90} (3.2 and 5.0 minute respectively). Additionally, it was clear from the dissolution profiles of both formulations that the F-optimize formula gave significant higher dissolution rate than F-pharmabrust formula that were shown in Figure 5D. This may be attributed to the F-optimize formulation had three superdisintegrants (CCS, CP and SSG 1:1:1 ratio) with the 30.50 % of prosolv-SMCC which cause enhancement of efficiency of superdisintegrants which lead to decrease disintegration time and T_{90}.

In vivo and pharmacokinetic evaluation in humans

An in vivo study was done to compare the pharmacokinetic parameters of captopril from the F-optimized sublingual formulation with those of the marketed captopril tablet. The mean plasma concentration time profiles of captopril after oral administration of a single dose (25 mg) for the F-optimized sublingual formulation and the marketed tablet are shown in Figure 9. C_{max}, t_{max}, $AUC_{0–240}$, half-life, Kel, and mean residence time for captopril from these formulations are summarized in table 6. On the other hand, the in vivo data showed that the oral absorption of captopril from the sublingual formulation was markedly higher than that of the marketed tablet. as a result of the significant improvement in C_{max} from 180.3 to 286.5 ng/mL for the marketed tablet and the F-optimized sublingual formulation obtained respectively (Figure 10). Moreover, the t_{max} of the sublingual tablet decreased to 45 min, compared with the t_{max} of 60 min for the marketed tablet. *In Table 6, the mean calculated area under plasma concentration time curve* (AUC_{0-240}) *for captopril that taken orally was 26132.5±231.8 (ng.min/ml). Whereas, the mean of* AUC_{0-240} *for F-optimized captopril taken sublingually (35858.44±281.95 ng.min/ml) was statistically significant increased by 37.21 %* ($P \leq 0.05$) *compared to captopril taken orally as shown in Figure 11.* These data indicate that the sublingual formulation was improved the bioavailability of captopril in comparison with the marketed tablet. This leads to acceleration of the onset of action for the sublingual tablet when compared with the marketed tablet. Based on these results, the F-optimized as well as its formulation as sublingual tablet is a promising method for enhanced the oral absorption and bioavailability of captopril.

Table 6. Pharmacokinetic parameters of captopril in the two groups each group eight volunteers when administration sublingual and oral tablets

Formulae	Pharmacokinetics Parameters				
	AUC (ng. min/ mL)	Cmax (ng/ml)	Cl/F (mL/min)	K (min^{-1})	$t_{1/2}$ (hr)
F-optimize sublingual	35858.44±281.95*	286.5±2.74*	0.6970±0.01	0.0057±0.00002	2.5
Captopril oral tab	26132.5±231.8	180±3.28	0.9567±0.01	0.00463±0.00001	2.0

Data are Mean ± SD

* Significantly different from captopril different dosage forms (Paired t-test, P < 0.05)

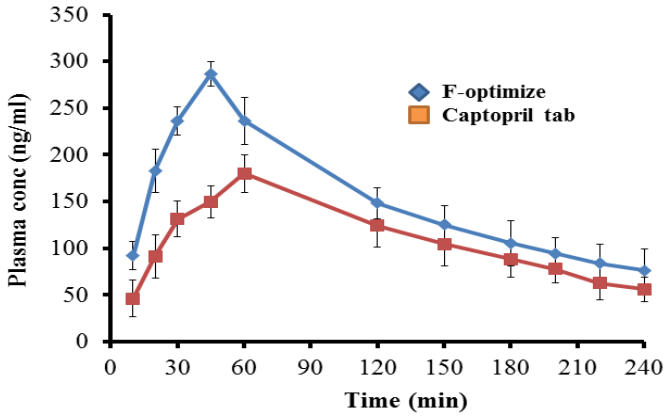

Figure 9. Mean plasma levels of captopril (ng/ml) in the two groups each 8 volunteers after administration of 25 mg F-optimized sublingual and captopril oral tablet using UV spectrophotometer at λ_{max} 225 nm.

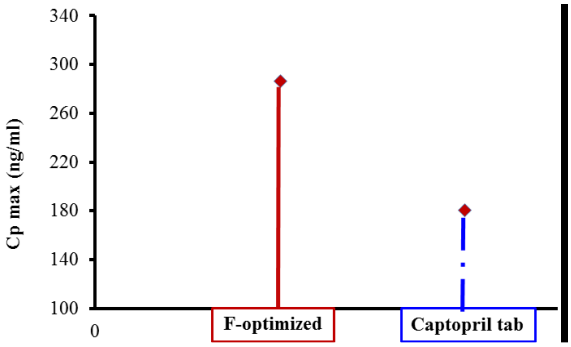

Figure 10. Cpmax resulted after administration of F-optimized sublingual tablet (▬) and captopril tablets (▬).

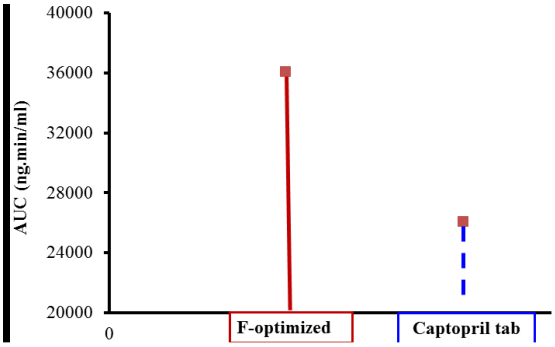

Figure 11. AUC resulted after administration of F-optimized sublingual tablet (▬) and captopril tablets (▬).

Conclusion

Captopril sublingual formulations were successfully prepared using direct compression method. The composition of sublingual tablet could be optimized using response surface design so as to obtain rapid disintegration time (12.2 sec) and T_{90} drug dissolution (3.2 min) along with acceptable tablets hardness and friability. In addition, the results of the optimization study showed that sublingual tablet containing water soluble filler (mannitol) and insoluble diluent (prosolv-SMCC) (31.18 and 30.5 mg respectively) can be formulated successfully using mixture of superdisintegrants at 7.82 % concentration. Furthermore, by comparing the F-optimized formula with F-pharmabrust it showed significant lower disintegration time and higher dissolution rate. Comparison of the pharmacokinetic parameters of the F-optimized captopril sublingual tablet with that of the captopril marketed tablet in healthy volunteers showed a significant improvement in the onset of action, drug absorption and hence bioavailability.

Conflict of interest

The authors report no conflict of interest in this work.

REFERENCES

Abdelbary, A., A. Elshafeey and G. Zidan (2009). "Comparative effects of different cellulosic-based directly compressed orodispersable tablets on oral bioavailability of famotidine." Carbohydrate polymers **77**(4): 799-806.

Aljimaee, Y. H., A.-R. M. El-Helw, O. A. Ahmed and K. M. El-Say (2015). "Development and optimization of carvedilol orodispersible tablets: enhancement of pharmacokinetic parameters in rabbits." Drug design, development and therapy **9**: 1379.

Chetty, D. J., L. L. H. Chen and Y. W. Chien (2001). "Characterization of captopril sublingual permeation: determination of preferred routes and mechanisms." Journal of pharmaceutical sciences **90**(11): 1868-1877.

Cooper. J, Gunn G.(1986). Powder flow and compaction, In; Tutorial pharmacy. New Dehli: CBS Publisers and distributers;.p.211- 233.

Das, N. G. and S. K. Das (2004). "Development of mucoadhesive dosage forms of buprenorphine for sublingual drug delivery." Drug delivery **11**(2): 89-95.

Dumbare, A.S*. Shelke, P. V., Gadhave, M.V., Gaikwad, D.D. (2012). "Formulation and evaluation of mouth dissolving tablets of captopril." Int. J. of Universal Pharmacy and Life sciences. 2 (3): 2249-6793.

Dobetti, L. (2000). "Fast-melting tablets: Developments and technologies." Pharm Technol Eur **12**(9): 32-42.

El-Enany, N., F. Belal and M. Rizk, (2008). Novel Spectrophotometric Method for the Assay of captopril in Dosage Forms using 2,6-dichloro quinone-4-chlorimide. Int. J. Biomed. Sci., 4(2): 147-154.

Gopinath, H., Shanmugasundaram, S. and Bada, P. (2012). "Disintegrants–a brief review." J. Chem. Pharm. Sci 5: 105-112.

Harris, D. and J. R. Robinson (1992). "Drug delivery via the mucous membranes of the oral cavity." Journal of pharmaceutical sciences **81**(1): 1-10.

Hossameldin, K., Alaa, Z., and Alaa, K. (2016). "Formulation and optimization of vardenafil hydrochloride oral disintegrating tablets: effect of superdisintegrants."Al-Azhar Journal of pharmaceutical sciences 53: 1110-1644.

Jonwal, N., P. Mane, S. Mokati and A. Meena (2010). "Preparation and in vitro evaluation of mouth dissolving tablets of domperidone." Int. J. Pharm. Pharm. Sci **3**: 975-1491.

Longhini, C., L. Ansani, G. Musacci, D. Mele, M. Vaccari, E. Baracca and P. Sgobino (1990). "The effect of captopril on peripheral hemodynamics in patients with esential hypertension: Comparison between oral and sublingual administration." Cardiovascular Drugs and Therapy **4**(3): 751-754.

Merkel, Sacerdoti D, Rondana M, Gatta A. Arch Intern Med. (1991); 151: 678–682." The Journal of Emergency Medicine **10**(3): 383.

Moldovan, Z. (2012). "A spectrophotometric method for captopril determination by using fluorescein sodium-bromide system." Rev. Roum. Chim **57**(7-8): 721-727.

Mostafa, H. F., M. A. Ibrahim and A. Sakr (2013). "Development and optimization of dextromethorphan hydrobromide oral disintegrating tablets: effect of formulation and process variables." Pharmaceutical development and technology **18**(2): 454-463.

Narang, N. and J. Sharma (2011). "Sublingual mucosa as a route for systemic drug delivery." Int J Pharm Pharm Sci **3**(Suppl 2): 18-22.

Nogueira, R., E. C. P. d. Rego, M. V. B. Sousa, W. Wollinger, T. E. d. Silva, G. F. Moreira, J. S. Barin, L. V. Laporta, M. F. Mesko and C. F. Bittencourt (2011). "Development studies of captopril certified reference material." Brazilian Journal of Pharmaceutical Sciences **47**(2): 339-350.

Öhman, K. P., B. Kågedal, R. Larsson and B. E. Karlberg (1985). "Pharmacokinetics of captopril and its effects on blood pressure during acute and chronic administration and in relation to food intake." Journal of cardiovascular pharmacology **7**(1): S20-S24.

Padmaja, B., R. Ramakrishna and S. Sravani (2014). "Formulation and Evaluation of Fast Dissolving Tablets of Captopril." Journal of Pharmacy Research Vol **8**(7): 963-968.

Rao, N. and U. Kulkarni (2010). "Development of Carbamazepine fast dissolving tablets: Effect of functionality of Hydrophillic carriers on solid dispersion technique." Asian. J. Pharma. Clinical Res **3**(2).

Suresh, V. K., K. Ranjit, S. R. Basavaraj, B. Ramesh and K. Ashok (2011). "EFFECT OF SUPERDISINTEGRANTS ON FORMULATION OF TASTE MASKED FAST DISINTIGRATING LISINOPRIL TABLETS." Int J curr Pharm Res **3**(1): 11-14.

Suresh, V. K., K. Ranjit, P. Nikunj, R. Someshwara, B. Ramesh and K. Aashok (2011). "Formulation and evaluation of fast disintigrating Meloxicam tablets and its comparison with marketed product." International Journal of Pharmacy and Pharmaceutical Sciences **3**(1): 134-139.

Sweetman, S. (2007). "Immunosupressants." Martindale, The complete drug reference. 35th ed. Pharmaceutical Press: New York: 1660-1689.

The United State s Pharmacopeia, U. (2007). The National Formulary, NF 25 (USP30-NF25). The dissolution procedure: development and validation, Mack Printing Rockville.

Wu, S.-G., S.-L. Lin, W.-Y. Shiao, H.-W. Huang, C.-F. Lin and Y.-H. Yang (1993). "Comparison of sublingual captopril, nifedipine and prazosin in hypertensive emergencies during hemodialysis." Nephron **65**(2): 284-287.

Zade, P., P. Kawtikwar and D. Sakarkar (2009). "Formulation, evaluation and optimization of fast dissolving tablet containing tizanidine hydrochloride." Int J Pharm Tech Res **1**(1): 34-42.

Ziller, A. B. (1992). "Comparison of sublingual captopril and nifedipine in immediate treatment of hypertensive emergencies: A randomized, single-blind clinical trial: Angeli P, Chiesa M, Caregaro L, J. of Emergency Medicine, 5(6): 91-98.

تصميم و استمثال اقراص الكابتوبريل تحت اللسان وذلك لتعزيز حركية الدواء في الإنسان

للسادة الدكاترة

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يعتبرامتصاص العقارعن طريق الغشاء المخاطي الفمي بديلا واعدا عن امتصاصه عن طريق الفم. وكذلك يعتبرامتصاصة عن طريق تحت اللسان اسرع منه عن طريق الفم. وكان الهدف من هذه الدراسة هو تطوير أقراص تحت اللسان من كابتوبريل وتحسين التوافر البيولوجي . إن كابتوبريل هو الدواء المفضل في علاج أزمة ارتفاع ضغط الدم أو قصور القلب الحاد .وقد تحقق تحسن من امتصاص الدواء والتوافر الحيوي عن طريق خفض درجة حموضة الفم باستخدام حمض الستريك.وقد تم إعداد تسعة تحضيرات، وذلك باستخدام RSD لدراسة تأثير المتغيرات على خواص الأقراص تحت اللسان المحضرة. وذلك لتقييم وتطوير وتحسين أقراص كابتوبريل تحت اللسان عن طريق استخدام المواد عالية التفتت بتركيزات مختلفة وكذلك المواد المضافة. وقد استخدم وقت التفتت والوقت اللازم لانطلاق العقار كمتغيرات لتعظيم الاستفادة من الحصول على الصيغة الأمثل المرغوب فيها من أقراص تحت اللسان لعقار الكابتوبريل. وقد أظهرت النتائج ان أدنى مستوى لوقت التفتت هو (١٣.٠٤ ثانية) و (٢.٧٨ دقيقة T_{90}) من خلال صيغ تحت اللسان٠ وتتكون الصيغة المثلى من ٧.٨٢٪ من مزيج المواد عالية التفتت (X_1)مع ٣٠.٥٠٪ من المواد المضافة (X_2) . وتمت مقارنة الصيغة المثلى مع صيغة الفارمابروست ويتضح من النتائج أن الصيغة المثلى كانت أقل وقتا فى التفتت من(١٢.٢ ثانيه و ١٦.٣ ثانية على التوالي)، والوقت اللازم لانطلاق العقار هو (3.2و ٥.٠ دقيقة على التوالي)عن الصيغة المحتوية على الفارمابروست. وقد أظهرت النتائج أن الصيغة المثلى قد نتج عنها زيادة في تركيز البلازما من ١٨٠.٠ إلى ٢٨٦.٥نانو مل، وتقصير الوقت الذي يستغرقه للوصول إلى أقصى تركيز البلازما إلى ٤٥ دقيقة مقارنة مع أقراص كابتوبريل التسويقيه .وأخيرا، فإن الصيغة المثلى من كابتوبريل قد تحسن امتصاصها عن طريق تحت اللسان والذي بدوره يفضل لأزمات ارتفاع ضغط الدم واضطرابات القلب.