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Captopril fast disintegrating tablets for children: formulation and quality control by HPLC

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Abstract

Captopril is an angiotensin converting enzyme inhibitor, which is used in hypertensive crises and heart failures as an emergency medication especially in pediatrics. Due to difficulty in swallowing of tablets and capsules, pediatric compliance for medication usage is a big challenge in formulation. Considering captopril instability in oral liquid media, it should be formulated as a solid dosage form. Using fast disintegrating tablets (FDTs) is an attractive strategy for solving this problem. According to captopril ultra violet absorption spectrum, high performance liquid chromatography (HPLC) seems to be an accurate, reproducible, and precise method for analysis. Captopril HPLC method was developed and validated for linearity, accuracy, and precision. Because of captopril unacceptable taste especially for children, Eudragit E was used as a taste masking polymer to prepare granules. Crospovidon and Ac-Di-Sol were used as super-disintegrants to reduce tablet disintegration time. Flavoring agents are important ingredients in formulating FDTs for children. Different FDT formulations were prepared by direct compression and granulation-compression method. Quality test of tablets such as thickness, weight, friability, hardness, disintegration time, dissolution profile, and taste masking power were also examined. HPLC validation was confirmed by r2=0.9994, accuracy of 97.4±2.3%, and inter and intra-day precisions of 97.6±1.2 and 97.3±2.1, respectively. The optimized tablets showed suitable friability (0.85%), hardness (4.1 N), and disintegration time (40 sec) with a desirable taste related to presence of Eudragit E. An appropriate and complete dissolution profile within 30 min was also achieved. Results confirmed that captopril taste-masked FDTs would be a pleasant alternative for the available tablets in the market for using in children.

Keywords: Captopril, Eudragit E, Fast disintegrating tablet, HPLC.

1. Introduction

Hypertensive crisis is an emergency situation, which requires medications with fast action and minimal side effects (1). Captopril is an angiotensin converting enzyme inhibitor, which is used as an emergency medication (e.g. sublingual tablet) in hypertensive crises and congestive heart failure especially in pediatrics (2). Captopril maximum effect is observed within 1 to 2 hr after administration of oral doses. Considering the risk of damages and side effects induced by the uncontrolled hypertension crisis, it is better to regulate blood pressure within 1 hr. Therefore, rapid onset drug delivery systems such as sublingual tablets seem to be suitable options (3). Previous reports showed an intense drop in blood pressure within 30 min after administration of an initial low dose of captopril (0.5-1.4 mg/kg) (4). Additionally, sublingual captopril was reported as a safe and ef-

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fective medication with a sustained response (1, 5). For congestive heart failure in children, captopril is used as an oral dose of 0.5-6 mg/kg (6). According to the available dosage forms in the market, adjusting the dose for children is very tedious. On the other hand, difficulty in swallowing tablet and capsules decreases pediatric compliance for medication usage (7). Considering all these points, it seems that liquid dosage form is the most suitable form for pediatrics that shows a very fast effect. Unfortunately, captopril instability in oral liquid media is a big challenge (8). Meanwhile, many studies reported that captopril is most stable in solution at pH values less than 3.5 (mostly pH 1.2) and increasing pH to 4 and higher causes a huge rise in degradation rate constant (9). FDTs are almost novel dosage forms designed to replace extemporaneous preparations of drugs that are unstable in liquid media. These dosage forms are prepared by granulation or direct compression methods using the excipients that facilitate and accelerate disintegration of the tablet upon contact with saliva (10). Rapid disintegration leads to fast release of the active ingredient without need to chewing or additional water (11, 12). Particles resulting from the disintegration of the tablet could be granules or microparticles coated with taste masking polymers (13). FDTs seem a suitable oral dosage form for captopril to be used in children. Considering captopril bitter taste (14), the aim of this study was to prepare taste masked captopril FDT for children by coating drug granules with Eudragit E. The formulations were then characterized for physical properties and taste. An efficient HPLC method was also developed and validated for studying assay and drug release profile of formulations as well as to assure the stability of drug in different processes.

2. Material and methods

Captopril, Eudragit E, Avicel, Crospovidone, and Ac-Di-Sol were kindly gifted by Exir Pharmaceutical Co. (Iran). Aspartam, vanillin, sorbitol, sodium saccharin, potassium hydrogen phosphate, acetone, methanol, ethanol, isopropanol, and acetonitril were purchased from Merck Chemicals (Germany). All other used materials and solvents were of the highest grade available from commercial sources.

2.1. HPLC analysis of captopril

HPLC system equipped with UV/V is detector (detection wavelength 220nm) was used for captopril assay. A RP-HPLC column C18 (25×4.6 mm) and a mobile phase consisted of 50:50 (%v/v) degassed mixture of phosphate buffer and acetonitrile was used. The flow rate of the mobile phase was maintained at 1.0 ml/min within a run time of 15 min. The injection volume was 20 µl.

2.2. Standard solution preparation

Stock standard solution (0.4 mg/mL) of captopril was prepared by dissolving 40 mg captopril in distilled water. The stock standard solution was diluted, as necessary to give five standard solutions with different concentrations of captopril (3.125, 6.25, 12.5, 25, and 50 µg/mL), which were used for the construction of calibration curve.

2.3. HPLC method validation

2.3.1. Linearity

Five series of standard solutions of captopril were selected for determining the linearity range. The concentration levels of these five series of standard solutions ranged from 3.125 to 50 µg/ml. All linearity level solutions were injected in triplicate. % RSD of peak response in triplicate injections for each level was calculated. A regression line of average peak areas of captopril solutions versus concentration of the captopril was plotted and the coefficient of correlation r, slope, and y intercept were determined.

2.4. Accuracy

Accuracy was evaluated by assaying, in triplicates, samples of known concentrations spiked with three different concentrations of standard solution (10.0, 20, and 40.0 µg/mL) at three different levels. Recovery (%) was calculated from differences between the peak areas obtained for spiked and unspiked solutions.

2.5. Precision

Repeatability (inter and intra-day precision) was evaluated by measuring area under the curve of five concentrations. Three times within a day and on three separate days, totally, five

different samples at concentrations range from 3.125 to 50 µg/ml were analyzed under the same experimental conditions. Precision (repeatability and intermediate precision) was expressed as relative standard deviation [RSD (%)].

2.6. Tablet preparation

Different FDT formulations were prepared by direct compression and granulation-compression method using a single punch tablet press machine (Erweka, AR400, Germany). Based on the data available for children usual oral dose, captopril amount was set to 5 mg in all tablets (4). Direct compression and wet granulation by the taste masking polymer, Eudragit E was applied to mask the bitter taste of the drug (14). Different solvents (acetone, methanol, ethanol, and isopropanol) were examined for dissolving Eudragit E and preparing the granulation solution.

Avicel was employed as disintegrant in tablets by two different intra granular and extra granular methods. In the first method, Avicel was mixed homogenously with the other ingredients and pressed in order to form a tablet. In the second method, half part of Avicel was applied in granule preparation, while the rest was used externally. The formulation ingredients used for different tablet formulations are presented in Table 1.

2.7. Evaluation of tablets

2.7. Thickness and weight uniformity

Thickness of ten tablets was measured using micrometer screw (Erweka, Germany). For evaluating weight variation, twenty tablets of optimum batches were selected randomly and weighed individually and all together. The weight average and the deviation percentage were calculated (12).

2.8. Hardness

The compression force (in Newton) applied diametrically to crush 6 tablets from each formulation batch was determined using a hardness tester (Erweka, Germany) and the average of readings was determined (12).

2.9. In vitro disintegration time

The tablets were placed in the center of a petri dish containing 5 ml of water at 25 °C and the time required for the tablet to completely disintegrate was noted (12).

2.10. Friability

Twenty tablets of each formulation batch were weighed precisely and tested in the friabilator (Erweka, Germany), which was rotated 4 min at 25 rpm. Tablets were then dedusted, reweighed, and the percentage of the weight loss of each formulation was calculated by the following formula (12)(Eq. 1):

$$F = 100 \times \frac{\text{initial weight} - \text{final weight}}{\text{initial weight}} \qquad \text{(Eq . 1)}$$

Table 1. Composition of different formulations of captopril FDTs.

	F1	F2	F3	F4	F5	F6	F7
Captopril (mg)	5	5	5	5	5	5	5
Eudragit E%	-	-	-	2	2	2	2
Intra granular Avicel%	-	-	-	-	35	20	15
Extra granular Avicel%	-	-	-	-	-	-	15
Sorbitol%	75	65	42	40	20	27	23
Crospovidone%	20	30	25	25	18	23	20
Ac-Di-Sol%	-	-	25	25	18	23	20
Vanillin %	2	1	2	1	1	2	2
Sodium saccharin %	-	1	-	-	-	1	1
Aspartam %	-	-	3	4	4	-	-
Direct Compression	+	+	+				
Granulation & Compression				+	+	+	+

2.11. Taste masking evaluation

Different formulations was tasted by 6 volunteers to evaluate the taste and the volunteers were asked to score the taste of the formulations as -- very bitter, - bitter, and + desirable taste.

2.12. Drug content determination

Ten tablets were randomly selected and crushed in a mortar. Then, an accurately weighed amount was transferred to 100 ml volumetric flask and diluted in phosphate buffer pH 6.8 and stirred for 1 hr. The mixtures were centrifuged and after appropriate dilutions were used for drug content determination using the validated HPLC method.

2.13. In vitro dissolution study

In vitro dissolution time of optimized tablet formulation was determined by USP dissolution apparatus II (Erweka, DT70, Germany). Dissolution media consisted of 900 ml 0.1 N HCl maintained at 37±0.5 °C and was stirred at 50 rpm. Samples (5 ml) were withdrawn at specified intervals and analyzed for drug content using a validated HPLC method. The volume withdrawn at each interval test was immediately replaced with equal fresh quantity of dissolution medium.

3. Results and discussion

Eudragit E is a common polymer, which is used for taste masking due to its solubility in acidic pH (pH<5). Eudragit E can mask the drug bitter taste in buccal cavity, since it is insoluble in pH range 5.8-7.4 (15). Eudragit E has been used as the taste masking polymer in many studies especially for drugs that lack an oral liquid dosage form for children (16, 17).

Designing a pleasant-taste formulation that could be used in children is needed for captopril, because of its low stability in liquid media. Therefore, FDTs of captopril with Eudragit E, as the taste masking polymer, were prepared and evaluated.

3.1. HPLC analysis of captopril

HPLC method of determination was very fast and selective for analysis of captopril with a short run time. As seen in chromatogram presented

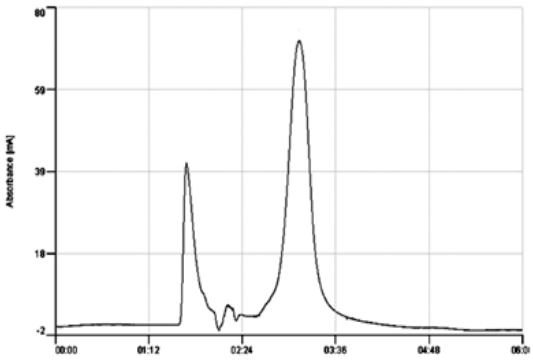

Figure1. Chromatogram of captopril solution (50 µg/ml)

in Figure 1, the captopril peak was appeared at 3 min with no excipient interference.

3.2. HPLC method validation

Calibration curve was constructed in the range of the expected concentrations of 3.125 to 50 µg/mL as shown in Figure 2. The peak area of captopril solutions exhibited linear relationship with concentration. Correlation coefficient (r^2) of the standard curve (0.9994) indicated linear relationship at a selected range of captopril concentrations. The determined accuracy from three different concentrations was 97.4±2.3%. The intra- and inter-day variations of the method were determined using five replicate injections at five different concentrations, which were prepared and analyzed on the same day and on three different days, respectively. The average of inter and intra-day precision was 97.6±1.2 and 97.3±2.1, respectively. These data (Table 2) indicate a considerable degree of precision and reproducibility of the method during one analytical run and different runs.

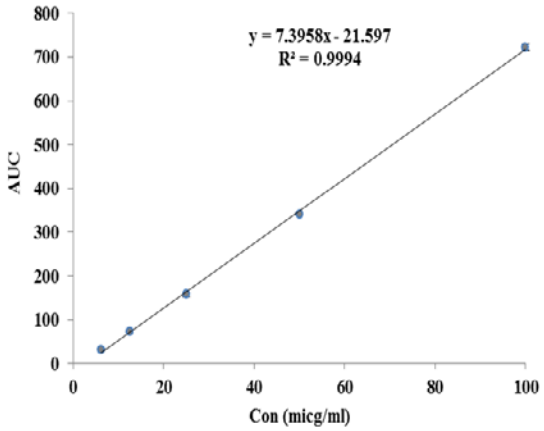

Figure 2. Calibration curve of captopril (n=5).

Table 2. Intra-day and inter-day precision of HPLC method of captopril.

Con. (µg/ml)	Intra-day precision%	Inter-day precision%
3.125	96.2±0.6	97.1±0.6
6.25	94.5±1.7	96.1±1.3
12.5	99.1±0.7	99.5±0.7
25	99.8±0.8	97.5±0.8
50	97.1±3	97.7±2.5

3.3. Tablet evaluation

3.3.1. Thickness and weight uniformity

The average thickness and weight of the examined tablets were 3±0.01 mm and 244±5 mg, respectively.

3.4. Hardness

The hardness values of different formulations are reported in Table 3. The hardness of fast disintegrating tablets prepared in this study was in the range of 30-50 N, which was lower than that of conventional tablets as reported in the previous studies on FDTs (18, 19). Hardness of F1 and F2 formulations were out of the acceptable range. Other formulations (F3-F7) showed acceptable hardness, which may be due to the presence of superdisintegrant Ac-Di-Sol (20).

3.5. In vitro disintegration time

The *in vitro* disintegration time of different formulations are summarized in Table 3. Avicel is a common filler in tablets; however; it can also act as a disintegrant in tablets. Crospovidon and Ac-Di-Sol are superdisintegrants usually used in tablet formulations and were reported to provide more satisfying effects in decreasing disintegration time, especially when used in mixture. In combination, superdisintegrants draw water into tablets rapidly and accelerate tablet disintegration due to their suitable "wicking property" (20). This effect was also confirmed in our study. F3-F7 formulations showed more suitable disintegration times due to presence of the both mentioned superdisintegrants. Presence of Avicel in addition to these superdisintegrants in F5, F6, and F7 decreased the disintegration time even more.

3.6. Friability

Friability is another index of strength of tablets that reflects the resistance of tablets against abrasion. The friability of a tablet must be less than 1% (11, 19). The friability values of different formulations are reported in Table 3. All formulations showed high friability except F7. Previous reports also indicated reduced friability results from using Ac-Di-Sol and crospovidon combination (19), which is consistent with our results.

3.7. Taste masking evaluation

Results of taste masking test is reported in Table 3. As it is seen, both F6 and F7 formulations showed desirable tastes. Considering other quality control tests, F7 was selected as the optimized

Table 3. Results of evaluation of tablets quality.

	Disintegration time (sec)	Hardness (N)	Friability	Taste
F1	150±10	8±1	2%<	--
F2	120±6	7.6±0.8	2%<	-
F3	90±10	4.5±0.7	2%<	-
F4	90±6	3.8±0.3	2%<	-
F5	80±6	5.1±0.4	1%<	-
F6	60±7	4.5±0.1	1%<	+
F7	40±8	4.1±0.3	0.85	+

(Scoring taste: -- very bitter, - bitter and + desirable taste).

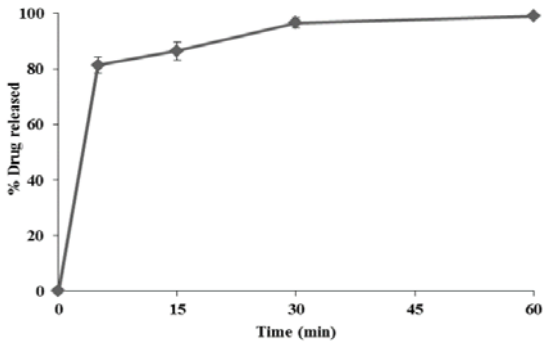

Figure 3. Dissolution profile of formulation F7 in HCl 0.1 N.

formulation and was evaluated in further tests.

3.8. Drug content determination

Drug content in tablets of F7 formulation was determined and showed captopril presence in tablets in a range of 101.3±6.4 %.

3.9. In vitro dissolution profile

As observed in Figure 3, almost 80% of captopril in tablets was dissolved within 5 min and the dissolution was completed at 30 min. This profile is satisfactory for FDTs containing Eudragit E and provide evidence that the drug would be bioavailable 30 min after oral intake.

4. Conclusion

FDTs are one of the suitable options for administration of captopril to children as the drug is unstable in liquid media. The present study indicated that HPLC was an efficient and validated method for determination of captopril fast disintegrating tablets quality. The most optimized captopril fast disintegrating tablet formulation presented a suitable friability (0.85%), hardness (4.1 N), and disintegration time (40 sec) with a desirable taste, which completely dissolved within 30 min. This FDT formulation could be a suitable choice for treatment of hypertension and heart failure in children.

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Conflict of Interest

None declared.

5. References

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