

Design and Evaluation of Single and Multi-unit Sustained Release Dosage Forms of Captopril

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Abstract

Background: Multi-unit dosage forms such as microcapsules and microspheres offer the advantage of better control over the release and lesser chances of dose dumping. This is critical for drugs with high dose, and no comparative study between single and multi-unit forms for controlled release was done previously. **Objectives:** To explore the utility of using a combination of almond gum and gelucire for preparing sustained-release (SR) matrix tablets. To employ a novel technique of microencapsulating the alginate beads of captopril for SR. **Materials and Methods:** Almond gum, gelucire (43/01), and ethyl cellulose were the major polymers used. Direct compression and emulsion solvent evaporation methods were employed to prepare the matrix tablets and microcapsules. The prepared products were evaluated for drug release and characterized by scanning electron microscopy, differential scanning calorimetry (DSC), and infrared spectroscopic studies. Accelerated stability study was performed, and drug release was studied before and after stability test. **Results and Discussion:** Drug release from the matrix tablets could be modified by changing the proportion of gelucire or almond gum in the formulation. The combined use of almond gum and gelucire is found to be more effective in giving a slow, and complete release spread over 12 h. Infrared spectroscopic and DSC studies revealed that there are no interactions of captopril with the various polymers. The microcapsules of alginate beads prepared employing ethyl cellulose are found to be free flowing and had an average size in the range of 750-850 μ . The matrix tablets of captopril are found to be giving more controlled release for a longer period of 12 h compared to the microcapsules. **Conclusion:** Entrapping the drug in a lipophilic material such as gelucire or beeswax and preparing the calcium alginate microspheres which are subsequently microencapsulated is a promising new approach to obtain the SR of highly water soluble drugs such as captopril.

Key words: Alginate beads, captopril, gelucire, matrix tablet, microcapsules, stability, sustained release, swelling index

INTRODUCTION

Captopril, an antihypertensive agent, is used for the treatment of hypertension and congestive heart failure.^[1] The usual dose is 25 mg 2-3 times a day, and in uncontrolled hypertension, the dose can be raised up to 100 mg 3 times a day. It has a very short biological half-life of 2 h.^[2] For ensuring optimal drug therapy, captopril needs to be administered in sustained-release (SR) dosage form 2 times a day with 12 h duration of drug release from the product. The SR dosage forms ensure a constant plasma concentration for extended periods of time. For delivering

drugs orally in a sustained manner, the matrix tablets and microcapsules are the commonly employed approaches.

There are some investigations on the formulation of SR dosage forms of captopril.^[3,4] The studies employed

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microparticles and floating tablets for the control of drug release. However, no systematic comparative evaluation was made on the efficacy of the microcapsules and matrix tablets in controlling the release of captoril. Microcapsules are reservoir systems with a rigid rate controlling membrane surrounding the core of a drug. In matrix tablets, the drug is intimately mixed with a network of polymers. Due to the inherent difference in the physical structure of the two types of dosage forms, the release of the drug from the two different forms is expected to be different.

In this investigation, single unit (matrix tablet) and multi-unit (microcapsules) dosage forms of captoril were developed. Matrix tablets of captoril employing new hydrophilic polymer, almond gum, are prepared. Almond gum is a natural gum having good swelling property, extracted from the bark of the tree *Terminalia catappa*. This relatively less explored gum is not employed previously to prepare SR dosage forms of captoril. There are only a few reports of the use of the almond gum in the development of SR formulations.^[5,6] A lipophilic polymer gelucire (43/01) is also employed in the formulation of single unit matrix tablets. Gelucires are a family of relatively inexpensive materials, comprising mixtures of mono-, di-, and triglycerides and also poly (ethylene glycol) esters of fatty acid. Gelucires are available with a range of properties depending on their hydrophilic/lipophilic balance (1-18) and melting point (33-65°C) range.^[7] Gelucires containing only polyethylene glycol (PEG) esters (gelucire 55/18) are generally used in the preparation of fast-release formulations, while gelucires containing only glycerides or a mixture of glycerides and PEG esters (gelucire 54/02, 50/13, 43/01) are used in the preparation of sustained-release formulations. There are some reports on the use of gelucires in the development of SR products.^[8]

Multi-unit forms are developed by initially preparing calcium alginate microspheres of captoril, which are subsequently used as a core to prepare the microcapsules employing ethyl cellulose as the coat material. This novel technique of microencapsulating the alginate microspheres is not reported earlier.

MATERIALS AND METHODS

Materials

Captopril (Sample provided by Julphar Gulf Pharmaceutical Industries UAE.), Gelucire (43/01) (Gel) [Gattefosse, France - sample provided by GenovaLife Sciences, Bengaluru, India], Almond gum (Hare Krishna Herbals, India), hydroxypropyl methylcellulose (K15M) [Nisso], ethyl cellulose - (having an ethoxyl content of 47.5% by weight and a viscosity of 22 cps in a 5% concentration at 25°C) [Acros Organics, New Jersey], Beeswax (BW), Heavy Liquid Paraffin (Olita Scientific), all other excipients, chemicals and solvents are of analytical grade and were purchased commercially.

Methods

Preparation of single unit (matrix tablets) forms

Matrix tablets (single unit forms) of captoril were formulated using a combination of hydrophilic polymers such as almond gum, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, and hydrophobic polymers like gelucire (43/01).

Six different formulae were developed (F1, F2, F3, F4, F5, and F6) according to the type and amount of polymers and other excipients used. Details of the formulations are given in Table 1. The granules are prepared by wet granulation. All the powder ingredients were initially passed through Sieve No. 80 to obtain fine powder and blended uniformly. Now small amounts of distilled water were added and the mixed well until sufficient cohesiveness is obtained. The mass is now passed through sieve No. 10 to form the wet granules. The wet granules were dried in a hot air oven at 37°C. The dried granules were now passed through sieve No. 35/50 to obtain a more uniform size of granules. These granules were now lubricated with talc and magnesium stearate and then are compressed into tablets.

Preparation of granules using hydrophilic polymers and gelucire (43/01)

The required quantity of gelucire (43/01) was weighed and melted in a china dish by heating on a hot plate. In the molten gelucire captoril was dispersed uniformly and allowed to cool by keeping on ice in a freezer. The frozen mixture of gelucire and captoril was scrapped and removed from the china dish and was powdered and mixed uniformly with other formulation ingredients. The resulting mass was now wet granulated by adding required quantity of water, and the granules were prepared as above. The resulting mass was now lubricated with talc and magnesium stearate and then was compressed into tablets.

Evaluation of matrix tablets

The prepared single unit matrix tablets are evaluated for drug content, hardness, friability, weight variation, swelling index, and drug release.

Swelling index study

The initial weight of a tablet of each of the formulation is noted. The tablets from each batch are taken into different baskets of a dissolution rate test apparatus, and it is immersed in 0.1 N hydrochloric acid, and the basket is rotated for 6 h. At regular intervals of every 30 min - the basket is removed, and the weight of the swollen tablet is measured. And at the end of 6 h, the swelling index is calculated from the formula given below:

$$\text{Swelling index} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

The details of drug content, hardness, friability, and weight variation are given in Table 2 and shown in Figure 1.

Drug release studies

The drug release study from the prepared matrix tablets was performed by employing USP dissolution rate test apparatus type 1 employing a basket stirrer. The drug release study was performed in 0.1 N hydrochloric acid for first 2 h and in phosphate buffer of pH 7.4 for the remaining 10 h. Samples of the dissolution medium were withdrawn at regular intervals and replaced by fresh medium, and the absorbance

of the filtered samples was measured at 205 nm. The results of the drug release study are given in Table 3 and shown in Figure 2.

Design of multi-unit (microcapsules) forms

Our initial studies on the preparation of calcium alginate beads of captopril resulted in beads which had very low drug content. This could be because of the high water solubility of the drug captopril. Hence, the development of multi-unit forms was done in 2 stages - (a) preparation of alginate beads by employing gelucire or BW entrapped drug and (b) microencapsulation of the resulting beads.

Table 1: Composition of different formulations of matrix tablets of captopril

Ingredient (mg)	F1	F2	F3	F4	F5	F6
Captopril	120	120	120	120	120	120
Almond gum	150	75	75	75	-	-
Gelucire (43/01)	-	-	75	120	-	-
HPMC (K15M)	125	125	125	125	160	120
Ethyl cellulose	45	120	45	-	45	45
Sodium CMC	-	-	-	--	40	30
MCC	-	-	-	-	75	125
Talc	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5

HPMC: Hydroxypropyl methylcellulose

Preparation of alginate beads by employing gelucire (43/01) or BW entrapped drug

The wax or gelucire loaded alginate microspheres are prepared by employing an intimately mixed mixture of drug and a lipophilic carrier at a ratio of 1:1.

About 1000 mg of gelucire (43/01) or BW is dissolved in 20 ml of dichloromethane in a mortar. The drug captopril 1000 mg is dissolved in the solution. Now to the resulting dispersion 1000 mg of microcrystalline cellulose is added and uniformly mixed. The mixture is stirred until all the dichloromethane is completely evaporated. The resulting powder consisting of BW or gelucire embedded captopril is now taken further to prepare the alginate microspheres.

Table 2: Characteristics of various matrix tablets

Formulation	Characteristic				
	Drug content ^a (%)	Hardness ^b (kg/cm ²)	Average weight ^c (mg)	Friability ^d (%)	Swelling index ^e (%)
F1	100.06±0.87	6.45±0.54	451.87±0.66	0.47±0.09	5.71±0.32
F2	99.84±1.12	6.92±0.41	450.25±0.63	0.38±0.12	4.77±0.66
F3	100.4±1.32	5.77±0.28	449.21±0.46	0.66±0.11	4.40±0.29
F4	99.25±1.56	5.27±0.31	449.47±0.74	0.71±0.21	4.20±0.47
F5	100.91±0.37	6.66±0.47	450.91±0.21	0.51±0.14	3.30±0.68
F6	100.66±0.45	6.88±0.72	450.55±0.37	0.29±0.17	3.18±0.57

^an=10, ^bn=5, ^cn=20, ^dn=20, ^en=3

Table 3: Drug release characteristics of various matrix tablets

Formulation	Correlation coefficient (r^2)			K_1 (h ⁻¹)	K_H (mg.h ^{-1/2})	Korsmeyer Peppas (n value)
	First order	Higuchi	Korsmeyer –Peppas			
F1	0.9916	0.9873	0.9927	0.1155	23.06	0.693
F2	0.9524	0.9926	0.9917	0.2857	30.18	0.507
F3	0.9266	0.9437	0.9705	0.1984	27.43	0.616
F4	0.9867	0.9854	0.9849	0.0944	22.18	0.881
F5	0.9651	0.9948	0.9774	0.3477	35.51	0.473
F6	0.9618	0.9839	0.9952	0.4098	35.56	0.401

The powder obtained in the above step is now added to 25 ml sodium alginate solution (2.5% w/v) and thoroughly mixed to disperse the added. This dispersion is now added drop wise to 50 ml of 5% w/v calcium chloride solution under continuous stirring. Stirring was continued for 30 min. The obtained microspheres were filtered and washed with purified water and then dried for 6 h at 40°C.

Preparation of ethyl cellulose microcapsules

The calcium alginate microspheres prepared by employing a mixture of wax dispersed drug as core are further microencapsulated using ethyl cellulose by employing emulsion solvent evaporation technique.^[9]

Microcapsules were prepared in a core: Coat ratio of 9:1 or 8:2. Ethyl cellulose (100 or 200 mg) is dissolved in 8 ml of acetone and the core (900 or 800 mg) comprising the gelucire or BW embedded captopril - is now dispersed the polymer solution. The resulting mixture is now added as a thin stream to liquid paraffin (agitated by Remi stirrer Model No. RQ 126 D) to disperse the added mixture as fine droplets. The mixture is agitated for 2 h under vacuum to remove the acetone completely. The microcapsules with the rigidized coat are now separated by centrifugation and filtration. The microcapsules are then washed with petroleum ether and air dried to obtain discrete free-flowing microcapsules. The details of various microcapsules prepared are given in Table 5.

Characterization of prepared microspheres

The microspheres are evaluated for the following characteristics:

1. Drug content
2. Size analysis
3. Scanning electron microscopy (SEM)
4. Drug release.

Determination of drug content

From each batch, four samples of 10 mg each of microspheres were taken and analyzed for captopril content. The weighed microspheres were taken into a 25 ml volumetric flask. 20 ml of distilled water was added, and contents were thoroughly mixed to extract captopril from the microspheres. The solution was made up to volume with distilled water and after filtration was suitably diluted with phosphate buffer of pH 7.4 and assayed for captopril content by measuring absorbance at 205 nm using phosphate buffer of pH 7.4 as blank. The results are given in Table 5.

Size analysis

For the size distribution analysis, different sizes in a batch were separated by sieving employing a range of standard

sieves and the amounts retained on different sieves were weighed. The results of the size analysis are given in Table 5.

SEM

The shape and surface features of the naproxen microcapsules were investigated by employing (SEM, Hitachi, model SU 1510). The microcapsules were mounted onto the SEM sample stub and are observed under reduced pressure employing an acceleration voltage of 15 KV. The SEM photograph of the microcapsules and microspheres are shown in Figure 3.

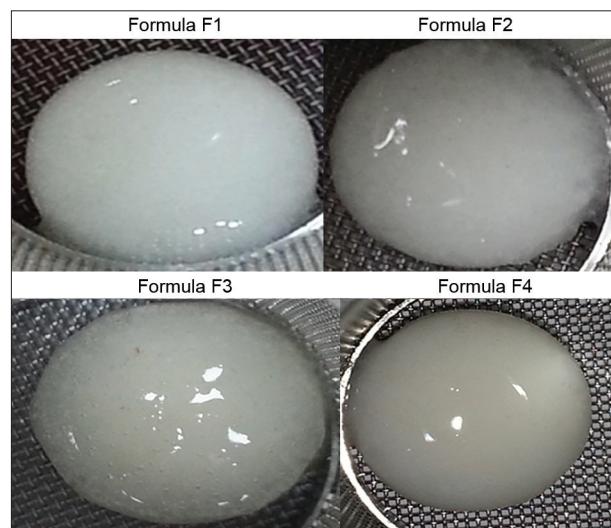


Figure 1: Swelling index study of matrix tablet formulations

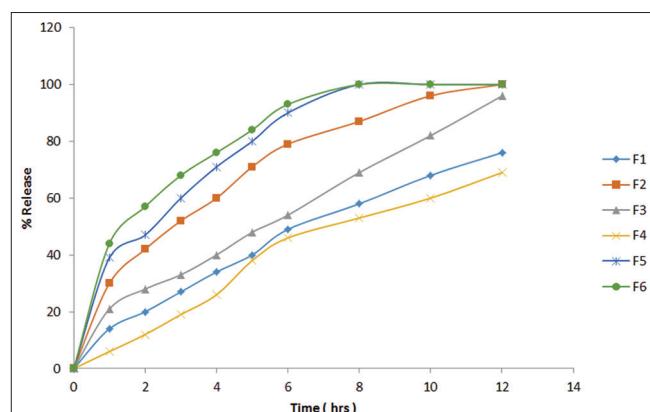


Figure 2: Drug release profiles from various single unit (matrix tablets) forms

Table 4: Drug content of alginate microspheres prepared by employing gelucire or BW embedded captopril

Microspheres	Drug content (%)	
	Theoretical	Actual
MS1 (Gelucire-MCC embedded)	2.75	2.24±0.17
MS2 (BW-MCC embedded)	2.75	2.62±0.21
BW: Beeswax		

Drug release studies

The drug release study from the various microcapsules was performed by employing USP dissolution rate test apparatus type I employing a basket stirrer. The drug release study is performed in 0.1 N hydrochloric acid for first 2 h and in phosphate buffer of pH 7.4 for the remaining 10 h. Microcapsules equivalent to 120 mg of captopril are taken for the study and samples of the medium are withdrawn at regular intervals and replaced by fresh medium, and the absorbance of the filtered samples was measured at 205 nm. The results of the drug release study are given in Table 6 and shown in Figure 4.

Fourier transform infrared (FTIR) studies

Captopril and its physical mixtures with gelucire (43/01), almond gun, and hydroxypropyl methylcellulose were subjected to FTIR analysis using FTIR spectrophotometer (Agilent Model Cary 630). Attenuated total reflectance sampling interface was used to obtain the spectra. The IR spectra are shown in Figure 5.

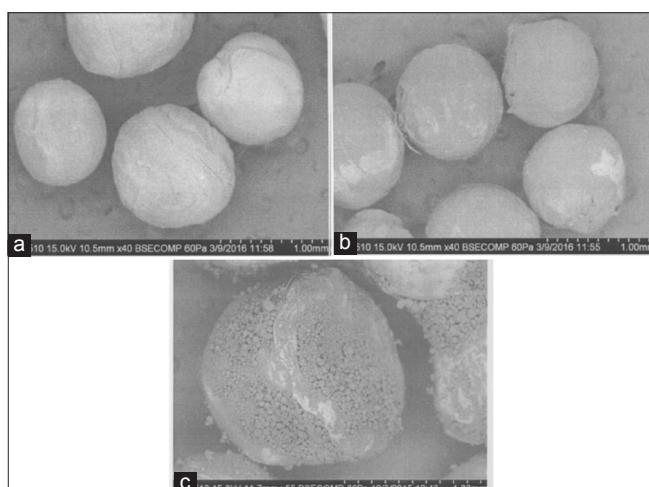


Figure 3: Scanning electron microscopy photographs of ethyl cellulose coated microcapsules (a and b), uncoated alginate microspheres (c)

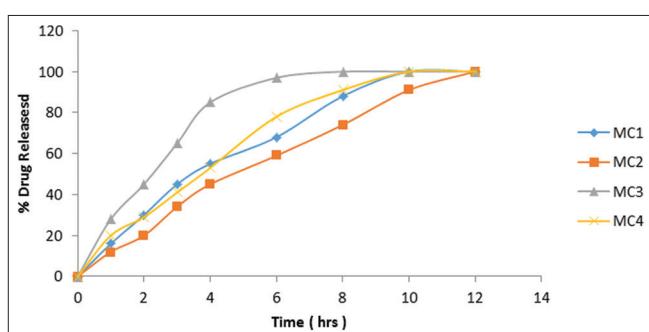


Figure 4: Drug release profiles of microcapsules

Differential scanning calorimetry (DSC) studies

Captopril and its physical mixtures with gelucire (43/01), almond gun, and hydroxypropyl methylcellulose were subjected to differential scanning calorimetric analysis to know about any interaction between the drug and the excipients. The calorimeter (TA Instruments, Bangalore Model Q 20) was operated at a scanning rate of 10°C/min and heated between 25°C and 250°C. The samples were sealed in aluminum pans and heated in a constant inert atmosphere maintained by purging nitrogen gas at a flow rate of 10 ml/min. The thermograms obtained on various products are shown in Figure 6.

Stability testing

Of the 6 formulations of tablets of captopril, the 3 formulations F2, F3, and F4 which showed slow and controlled release are subjected to stability study. The products are kept in glass bottles which are closed with a rubber closure and kept in a stability chamber and are exposed to a temperature of 45°C and humidity of 70±5% for 3 months. At the end of 3 months, the products are removed and evaluated for drug content and drug release. The details of the stability study are shown in Table 7. Similarly, of the 4 formulations of microcapsules of captopril, the 2 formulations MC2 and MC4 which showed slow and controlled release are also subjected to stability study.

RESULTS AND DISCUSSION

Preparation of single unit form - matrix tablets of captopril

Captopril used as antihypertensive drug captopril is a highly water soluble drug. Designing an SR dosage form for a highly water soluble drug is always challenging. This is because the drug due to its high solubility will diffuse out of the dosage form very rapidly. Hence, matrix tablets and microcapsules of captopril are developed employing a combination of different polymers to evaluate their suitability for obtaining an SR of captopril. 6 formulations are developed employing different hydrophilic and hydrophobic polymers. The details of various formulations are shown in Table 1.

Evaluation of matrix tablets

The post compression properties of the tablets formulated were evaluated. The various prepared tablets were evaluated with respect to their hardness, friability, drug content, and weight uniformity and the respective values are shown in Table 2. The hardness of tablets of all formulations was in the range of 5.77-6.92 kg/cm². The friability of tablets of

Table 5: Characteristics of microcapsules of captopril

Microcapsule	Core	Core coat ratio	Drug content (%)		Encapsulation efficiency (%)	Average size (μ)
			Theoretical	Actual		
MC1	C-Gel-MCC	9:1	20.16	18.12	89.88	754.99
MC2	C-Gel-MCC	8:2	17.92	16.54	92.29	844.68
MC3	C-BW-MCC	9:1	23.58	20.71	87.82	758.41
MC4	C-BW-MCC	8:2	20.96	18.98	90.55	844.54

BW: Beeswax, Gel: Gelucire

Table 6: Drug release characteristics of various microcapsules

Formulation	Correlation coefficient (r^2)			K_1 (h^{-1})	K_H ($\text{mg.h}^{-1/2}$)	Korsmeyer–Peppas (n value)
	First order	Higuchi	Korsmeyer–Peppas			
MC1	0.9831	0.9965	0.9947	0.4546	37.19	0.8108
MC2	0.9876	0.9989	0.9640	0.3201	30.04	0.8905
MC3	0.9138	0.9412	0.9768	0.4539	42.47	0.7294
MC4	0.9307	0.9856	0.9896	0.4219	40.08	0.7605

Table 7: Characteristics of tablets and microcapsules after stability testing

Formulation	Characteristic				
	Drug content (%)	Hardness (kg/cm^2)	Friability (%)	Swelling index (%)	K_1 (h^{-1})
F2	97.52 \pm 0.75	6.77 \pm 0.74	0.41 \pm 0.15	0.45 \pm 0.22	0.2857
F3	98.67 \pm 1.27	5.65 \pm 0.41	0.55 \pm 0.21	0.71 \pm 0.19	0.1984
F4	102.25 \pm 0.54	5.81 \pm 0.37	0.61 \pm 0.29	0.75 \pm 0.6	0.0944
MC2	101.81 \pm 1.31	-	-	-	0.3417
MC4	97.68 \pm 0.94	-	-	-	0.4325

all formulations was <1%. The tablet formulations in all the prepared batches contained captopril within $100 \pm 5\%$ of expected content. As such, all the batches of the formulated tablets were of good quality with regard to hardness, friability, and drug content. All tablets are found to be uniform in weight with low standard deviation.

Swelling index study

The SR tablets are expected to remain non-disintegrating throughout the drug release process. They may undergo swelling, and this extent of swelling depends on the nature of polymers employed. The presence of hydrophilic polymers increases the swelling of the matrix tablets. Tablets that are showed more swelling exhibit more retarding effect on the drug release process. This is because with increased swelling the distance that the drug has to traverse to get released will be more. Furthermore, the hydrophilic polymers which show more swelling form a gelatinous layer around the tablet and drug diffusion becomes more difficult through the viscous swollen layer. As expected in this study formulation F1 which has a higher amount of almond gum showed the highest swelling index of 5.71% (shown in Table 2 and Figure 1) compared to other formulations. This F1 matrix tablet also

has a high retarding effect on the drug release (discussed in more detail under drug release). However, no perfect correlation between swelling index and the release rate could be seen. This is because in F4 formulation where the extent of swelling is smaller than F1, contrary to the expected higher release, there is observed more retarding effect. This is because of the presence of gelucire (43/01) in F4 which being a lipophilic polymer will arrest the ingress of water into the matrix and thereby retarding the release of the drug.

Drug release studies

All the six formulations of matrix tablets showed slow and SR. Tablet formulations are prepared with almond gum as the major release retarding polymer. Changes in formulation are made with a view to verify the influence of gelucire (43/01) a lipophilic excipient. The combined effect of almond gum and gelucire on the release process is verified (formulations F3 and F4). Initially, formulation F1 with no gelucire and a high amount of almond gum is prepared. This formulation showed a very high sustaining effect resulting in only 76% drug release at the end of 12 h. Hence, in formulation F2 when the almond gum quantity is reduced by half - the release was faster with nearly 90% of the drug release being complete

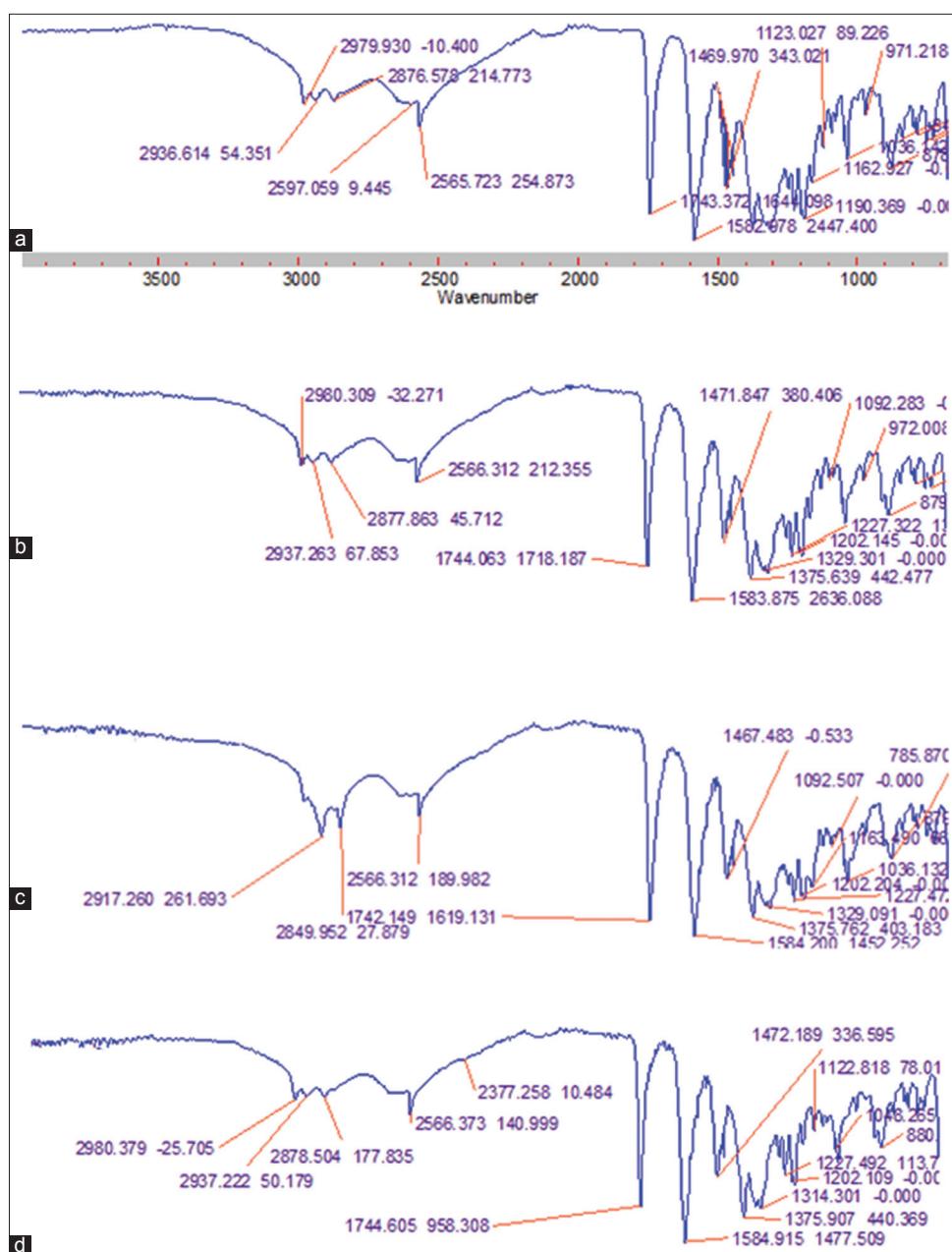


Figure 5: Infrared spectra of captopril (a), captopril: Almond gum (1:1) (b), captopril: Gelucire (1:1) (c), and captopril: HPMC (1:1) (d)

at the end of 8 h itself. Now in the formulation, F3 gelucire (43/01) is included keeping the almond gum quantity same as in F2 and also the ethyl cellulose proportion is also reduced (compared to the EC amount in F2). This formulation F3 has exhibited a slower release than compared to F2 confirming the efficacy of combined presence of almond gum and gelucire in more effectively controlling the release of captopril F2. In the case of F1 where the amount of almond gum the release was incomplete and very slow. Moreover, in the case of F2 formulation when almond gum quantity is reduced the release is very fast. Moreover, it is observed that in F3 there is slow but complete release of the drug spread over the 12 h. Now to crosscheck the influence of added gelucire, in F4, the amount of gelucire is increased keeping the almond gum quantity constant, and EC is completely removed. It is

observed that release is very highly retarded which suggests the contribution of gelucire in retarding the drug release. The theoretical release profile required for captopril is calculated based on its pharmacokinetic parameters. The drug should be released at the rate of 8.66 mg/h from the sustained dose. Of the various formulations, F3 formulation exhibited a release which is close to the theoretical release and the release is also found to be fairly linear. In formulations F5 and F6 both gelucire and almond gum are removed and these 2 formulations exhibited relatively faster release, and nearly 90% of the drug is released in about 6 h itself. The findings of the drug release study thus suggest the utility of almond gum and gelucire in controlling the release of water soluble drug captopril from matrix tablets. The details of drug release are given in Table 3 and shown in Figure 2.

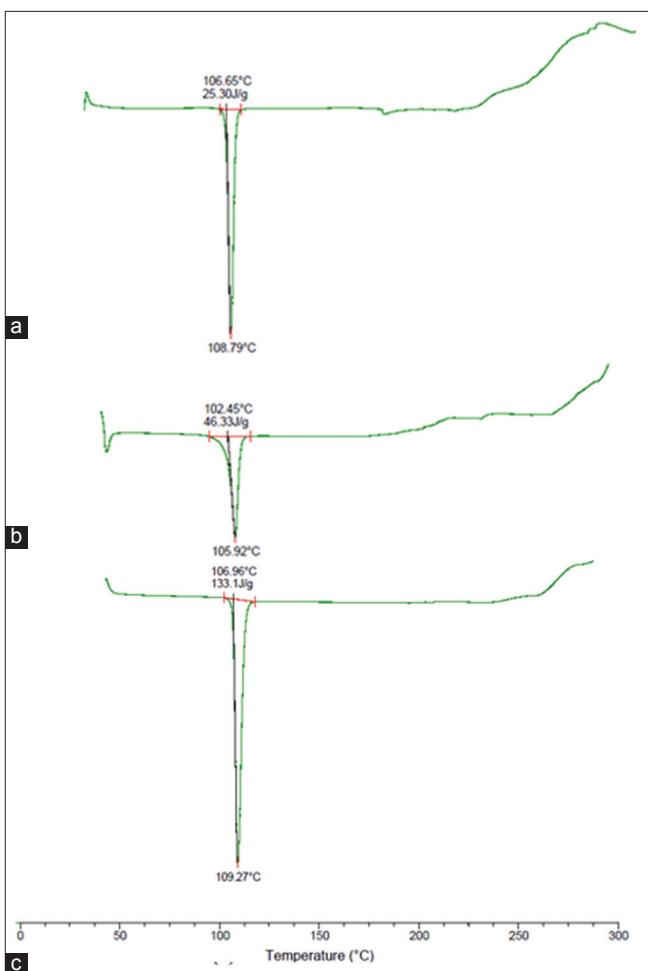


Figure 6: Differential scanning calorimetry thermograms of captoril (a), captoril: Gelucire (1:1) (b), and captoril: Almond gum (1:1) (c)

Table 8: Drug release profile comparison of various matrix tablets of captoril by employing difference and similarity factors

Products compared	Difference factor (f1)	Similarity factor (f2)
F1 and F2	37.03	29.26
F1 and F3	17.79	49.04
F3 and F4	29.72	38.95
F3 and F6	41.31	21.29
F5 and F6	6.58	59.95

In our investigation, we tested the usefulness of almond gum and gelucire in the formulation to control the release of captoril. Hence, we compared the drug release profiles for the formulations F1-F6 and calculated the F1 (difference factor) and F2 (similarity factor) values. Moore and Flanner proposed a model independent mathematical approach to compare the dissolution profile using two factors difference and similarity factors, f1 and f2, respectively.^[10] The various calculated values are shown in Table 8. It can be seen that there is a significant difference in the F1 and F2 formulations,

this is because the amount of almond gum in F1 is double that of in F2 which resulted in higher retarding effect. But as per the values (f1 and f2) obtained for the two formulations F1 and F3, there appears to be no significant difference between them. However, it should be noticed that in the case of F3 formulation the release is slow and spread over 12 h and complete drug release was obtained whereas, in case of F1, the release was very slow and incomplete (only 76% released) at the end of 12 h. Thus, the combined effect of hydrophilic and hydrophobic polymers may be advantageous in achieving the desired release spread over 12 h. Furthermore, this retarding effect of gelucire is confirmed by the significant difference observed between F3 and F4 formulations. In formulations F5 and F6 in which both gelucire and almond gum are absent, the release profiles are similar as reflected in the f1 and f2 values.

A statistical analysis is performed to compare the drug release profiles of various matrix tablets. Analysis of variance (ANOVA) was performed using two factors completely randomized design by employing MSTAT C statistical analysis software. The results of ANOVA analysis for products are shown in Table 9.

From the results shown in Table 9, it may be concluded that (1) the differences in the mean values among the treatment groups are greater than would be expected by chance, (2) the calculated F value (as shown in Table 9) is greater than tabulated F value (at 0.01 level of probability), and (3) there is a statistically significant difference ($P = 0.01$).

According to the results of ANOVA, the percent drug released was found to be significantly different at each time level ($P < 0.01$) and among the drug products ($P < 0.01$), implying time with drug product interaction was significant (at $P < 0.01$), i.e., that the drug release profiles were not parallel. This interaction indicated that the mean difference of percent released between two drug products was not constant at any two points of time considered. The results of ANOVA also showed that the drug products were significantly different in terms of percent drug released at each time point ($P < 0.01$).

Design of multi-unit forms

Initially, captoril loaded calcium alginate microspheres were prepared by ion gelation technique.^[11,12] All the microspheres were found to be spherical and free flowing. However, the drug content is found to be very low. This low drug content is probably because of high water solubility of the drug which is lost into the manufacturing medium (calcium chloride solution) during the preparation of the microspheres. Hence, in the next stage, wax embedded drug as a core is employed to be dispersed in the sodium alginate mixture before it is added to the calcium chloride solution. The idea is if the highly water soluble drug is embedded in a wax matrix, its loss subsequently can be greatly reduced. With the encouraging results that were obtained with the matrix tablets

Table 9: ANOVA of the drug release data

Source	Degree of freedom	Sum of squares	Mean of square	F value**	P
Time (A)	5	43783.294	8756.659	13503.358	0
Percent drug released (B)	8	74382.684	9297.836	14337.8888	0
Interaction (AB)	40	2491.569	62.289	96.0542	0
Error	108	70.036	0.648		0
Total	161	120727.584			

**Highly significant difference at 0.01 level of probability, ANOVA: Analysis of variance

where gelucire (43/01) was used, we employed this lipophilic gelucire and also BW as the lipoidal carriers to disperse the drug in them. The resulting microspheres are found to be having satisfactory drug content close to the theoretical drug content. The details of drug content of the wax embedded microspheres are given in Table 4.

Although the drug content of such microspheres is satisfactory, the drug release could be sustained only for about 3 h. Hence, these wax embedded captoril microspheres are then microencapsulated with ethylcellulose as a coat by employing emulsion solvent evaporation technique.

Characterization of microcapsules

The microcapsules prepared were found to be discrete, spherical, and free flowing. The sizes could be separated, and a more uniform size range of microcapsules could readily be obtained. The size analysis of different batches of microcapsules showed that generally the size ranged from 750 to 850 μ . It was observed that when the microcapsules were prepared employing a higher proportion of coating polymer - it resulted in microcapsules of higher size. This could be because of the higher amount of polymer - resulted in a more viscous dispersion and a bigger seed microcapsule being formed in the liquid manufacturing medium (liquid paraffin) into which the polymer solution and core mixture is slowly added as a thin stream. The details of different microcapsules prepared are given in Table 5. The drug contents of different batches of microcapsules found to be uniform. It is found that there is no major drug loss during the preparation of microcapsules and the drug content present in different microcapsules is close to 90% of the theoretical quantity calculated. The encapsulation efficiency is also found to be satisfactory. The drug content and encapsulation efficiency are calculated from the following equations:

$$\text{Actual drug content (\%)} (M_{act}) = (a/b) \times 100$$

$$\text{Encapsulation efficiency} = (M_{act}/M_{the}) \times 100$$

Where,

a = the drug content determined in the microcapsules

b = the weight of the microcapsules

M_{act} = the actual drug content

M_{the} = theoretical drug content.

Initially, when the drug release was studied from the alginate microspheres, the release could not be sustained for more than 3 h. The SEM photographs of microspheres shown in Figure 3 indicate that the alginate microspheres are nearly spherical and existed as discrete individual units but surface appears to be slightly rough in nature and porous. This could be the reason for the rapid release of the drug from these alginate pellets. However, when the calcium alginate pellets were subsequently microencapsulated the SEM pictures showed that the resulting microcapsules were surrounded by a smooth continuous coating and the pores of the pellets are now completely blocked. This could be the reason why there is observed a slow release from the microcapsules.

The drug release from the various microcapsules is found to be slow and sustained, but more than 90% of the drug is released in about 9 h only [Figure 4]. Although slow release could be obtained from the multi-unit forms such as these microcapsules, the release is less retarded than compared to the single unit matrix dosage forms. This could be because in the tablet formulations, the drug is more intimately dispersed in the network of the hydrophilic and hydrophobic polymers and so the diffusion of the drug from the matrix tablets is better controlled.

However, some interesting observations could be made in case of the microcapsules. The drug release depended on the nature of core and the percent coat (core; coat ratio) material employed. In the case of MC1 and MC2 where the core comprised dispersion of captoril in gelucire (43/01), the drug release is slower than MC3 and MC4 in which the core consisted of the BW dispersed drug. Also as the percent of coat material increased from 10% to 20%, the release is found to be slower.

The kinetics of drug release from the single unit and multi-unit forms is evaluated by different models, and the details of the release rate kinetics are shown in Tables 3 and 6.

FTIR studies

FTIR studies were conducted to confirm if there is any chemical interaction of captoril molecules with the excipients used in this research to formulate the matrix tablets. The FTIR spectrum for pure sample of captoril is shown in Figure 5a. The FTIR spectrum of pure drug captoril

exhibits characteristic absorption peaks at 2936 cm^{-1} (CH stretching), 2979 cm^{-1} (CH stretching), 2597 cm^{-1} , 2565 cm^{-1} (S-H stretching), 1743 cm^{-1} (C=O stretching), 1582 cm^{-1} , 1190 cm^{-1} , 1162 cm^{-1} , 1036 cm^{-1} , 878 cm^{-1} , and 675 cm^{-1} .^[13]

In the structure of captopril, the functional groups such as hydroxy (-OH), thiol (SH), and carbonyl (C=O) groups may have a possibility chemically interact with excipients. To study any possible interactions, the FTIR studies of physical mixture of captopril with excipients were conducted. The physical mixtures of captopril with the excipients (almond gum, gelucire, and hydroxypropyl methylcellulose [HPMC]) were prepared by triturating, and FTIR spectra were recorded. The corresponding spectra are shown as b, c, and d, respectively, in Figure 5. The FTIR spectrum for physical mixtures exhibited all the absorption peaks of captopril including peaks for thiol group (2565 cm^{-1}) and carbonyl group (1743 cm^{-1}). This reveals that there is no interaction between the excipients and captopril.

DSC

The thermograms of captopril and the dispersions are shown in Figure 6. The endotherm of pure drug captopril showed a sharp peak between 106°C and 109°C which is due to its melting point.^[14] In the mixtures of the drug with gelucire and almond gum also the endothermic peak of captopril is seen at 109°C and additionally the melting peak of gelucire is also seen at around 43°C . Thus as the melting peak of captopril is retained and did not undergo any significant displacement, it is concluded from the DSC study that the two major polymers investigated did not show any interactions with the drug captopril.

Stability testing

The results of the stability testing are given in Table 7. There are no visible physical changes observed in the tablets. The friability, hardness of the tablets remained same as before the stability testing study. The drug release from the tablets is also evaluated, and there is no change in the percent released at various time points and the release rate constant values also did not vary. Thus, the tablet formulations are found to be stable and retained their slow release characteristics. However, in case of microcapsules prepared by employing gelucire embedded captopril (MC 2), there is observed some softening of the microcapsules. The microcapsules did not retain their original integrity and were found to be losing their discrete nature. This could be because of the melting of gelucire during stability testing. However, the drug contents were found to be same as before the stability study. However, MC4 microcapsules (made of employing BW embedded drug as core) did not show any such characteristic, and they are found to be stable with respect to drug content and the drug release.

CONCLUSIONS

This study was taken up to design single and multi-unit SR dosage forms of captopril. Single unit matrix tablets of captopril were developed by employing hydrophobic gelucire (43/01) and hydrophilic almond gum. The release of the drug could be controlled by varying the amount of gelucire or almond gum in the formulations. Microcapsules (multi-unit dosage forms) of captopril are also developed. Initially, calcium alginate microspheres were prepared and evaluated. But as the drug loading efficiency and drug release are not satisfactory, these microspheres are then microencapsulated with ethylcellulose as coating polymer employing emulsification solvent evaporation technique. Entrapping the drug in a lipophilic material such as gelucire or BW and preparing the calcium alginate microspheres which are subsequently microencapsulated is a promising new approach to obtain the SR of highly water soluble drugs such as captopril. Although the multi-unit forms such as microcapsules are expected to give slower and more controlled release, in our study the single unit matrix tablet of captopril (a highly water-soluble drug) is found to be showing more SR characteristic than the microcapsules.

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