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Development and characterization of controlled release mucoadhesive tablets of captopril

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ABSTRACT

The present investigation concerns the development of mucoadhesive tablets of Captopril which were designed to prolong the gastric residence time after oral administration. Matrix tablets of Captopril were formulated using different mucoadhesive polymers such as guar gum, xanthan gum, hydroxyl propyl methyl cellulose K4M and K15M in various ratios. The tablets were evaluated for physical properties, content uniformity, swelling index, bioadhesive strength and in-vitro drug release. Swelling was increased as the concentration and viscosity of HPMC increases. Tablets formulated using guar gum and xanthan gum alone were eroded faster and dissolved completely within 5-7 hr, while tablet containing HPMC remain intact and provided slow release up to 11-12 hr. It was evident from the study that the formulation F10 containing HPMC K15M and xanthan gum (1:1) exhibited maximum bioadhesive strength of 31.59±0.05 gm and in vitro drug release was found to be 91.85 % at the end of 12 hr with non-fickian diffusion mechanism. The stability studies of optimized batch showed that there was no change in bioadhesive strength and in-vitro release when stored at different temperature condition for 60 days. It was concluded that formulation F10 shows the better bioadhesive strength and drug release.

KEYWORDS: Captopril, Gastro-retentive tablet, Mucoadhesive tablets, Swelling Index.

RESUMEN

El estudio actual trata del desarrollo de los comprimidos mucoadhesivos de captopril, que se diseñaron con el fin de prolongar el tiempo de permanencia gástrica después de la administración oral. Se formularon matrices de comprimidos de captopril mediante diferentes polímeros mucoadhesivos, tales como goma guar, goma xantana, hidroxipropilmetilcelulosa K4M y K15M, a varias concentraciones. Los comprimidos se evaluaron según sus propiedades físicas, uniformidad del contenido, índice de inflamación, fuerza de bioadhesión y liberación farmacológica in vitro. La inflamación se incrementó cuando la concentración y la viscosidad de HPMC aumentaron. Los comprimidos formulados solamente con goma guar y goma xantana se descompusieron con mayor rapidez y se disolvieron completamente en un rango de 5-7 horas, mientras que los comprimidos con HPMC permanecieron intactos y mostraron una liberación lenta de hasta 11-12 horas. Se observó que la formulación F10 con HPMC K15M y goma xantana (1:1) tenía una fuerza bioadhesiva máxima de 31,59±0,05 g y la liberación farmacológica in vitro fue del 91,85%, al final de un periodo de 12 horas con un mecanismo de difusión no de Fick. Los estudios de estabilidad de lotes optimizados mostraron que no hay cambios en la fuerza bioadhesiva y la liberación in vitro cuando se mantiene bajo condiciones de diferentes temperaturas durante 60 días. Se concluyó que la formulación F10 presenta la mejor fuerza bioadhesiva y liberación farmacológica.

PALABRAS CLAVE: Captopril, Comprimido gastro-retentivo, Comprimidos mucoadhesivos, Índice de inflamación.

INTRODUCCIÓN

One of the novel approaches for drug delivery system is Gastro-retentive delivery system (GRDS). Prolonging the gastric retention of a delivery system are desirable for achieving therapeutic benefit of drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT) or that are less soluble in GIT or are degraded by the alkaline.[1,2] GRDS are thus beneficial for such drugs by improving their bioavailability, therapeutic efficacy and by possible reduction of dose.[3] Park and Robinson et al., had first introduce the term "Bioadhesion". Bioadhesive polymers are platforms for oral controlled drug delivery method to study bioadhesion has been studied extensively in the last decade and applied to improve the performance of these drug delivery systems.[4]

Mucoadhesive controlled release dosage formulations have gained considerable attention due to their ability to adhere to the mucus layer and release the drug in a sustained manner. The relevant routes of mucoadhesive formulations have involved nasal, gastrointestinal, buccal, ocular, vaginal and rectal ways. By using these dosage forms, the intimate contact time with the mucus surface would increase, thus resulting in an increased drug retention time and drug concentration in the local sites. This would lead to an improved therapeutic effect for the local diseases.[5,6] Mucoadhesive delivery systems offer several advantages over other oral controlled release (CR) systems by virtue of prolongation of residence time of drug in GIT, and targeting and localization of the dosage form at a specific site.[7] Mucoadhesive polymers are able to interact with mucus which is secreted by the underlying tissue. More specifically, it is predicted that such polymers interact with mucus glycoprotein, called mucins, which are responsible for gel-type characteristics of the mucus. Mucoadhesive polymers can increase the contact time with the mucosal tissue and moreover, also increase directly drug permeability across epithelial barriers.[8,9]

Captopril, an antihypertensive agent, has been widely used for the treatment of hypertension and congestive heart failure. Captopril is acid stable and completely absorbed in gastric pH. It has been reported, that the duration of antihypertensive action after a single oral dose of Captopril is only 6–8 h, biological half life is 2-3 h and bioavailability in the stomach is 60- 75%. The pKa value is 4.5. Hence, as the pH increases, it becomes unstable and undergoes a degradation reaction and thus reducing its bioavailability.[10-12] Water-soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparation due to their susceptibility to ''dose dumping phenomenon.'' Attempts have been made to regulate their release process by use of mucoadhesive polymers in order to achieve a once-a-day dose treatment.[13]

The current study aims at developing and evaluating oral mucoadhesive drug delivery system of Captopril, as it may prove to be more productive than the conventional CR systems by virtue of prolongation of drug residence time in GI tract. Captopril exhibits pH dependant degradations and is more stable in acidic pH compared to neutral or alkaline pH conditions. Hence, an attempt was made to develop mucoadhesive tablets of Captopril which would increase the bioavailability of Captopril. The prepared tablets were evaluated for physical properties (thickness, weight variation, friability and hardness), swelling index, bioadhesion test, in vitro drug release and accelerated stability studies.

MATERIALS AND METHODS

Materials

Captopril BP (Macleods Pharmaceutical Ltd.), HPMC K4M and HPMC K15M (Colorcon Asia, Goa, India), Xanthan gum, guar gum and Avicel PH-102 (Signet Chemical Corp., Mumbai, India), PVP K-30, Dicalcium Phosphate (DCP), Talc I.P. and Magnesium stearate I.P. (Loba Chemie, Mumbai, India) were received as gift sample.

Preparation of Mucoadhesive Tablets

Mucoadhesive tablets of Captopril were prepared by wet granulation technique using different concentrations of HPMC K4M, HPMC K15M, Xanthan gum and Guar gum. All the ingredients were passed through sieve no 85# and were mixed uniformly. Granulation was carried out with sufficient quantity of binder solution (PVP K 30 - 5% in isopropyl alcohol). Wet mass was passed through sieve no 12# and dried at 45-55oc for 2 hr. Dried granules were sized by sieve no. 18# and add Avicel PH 102, magnesium stearate and talc. Granules obtained were compressed with 9mm flat punch (Cadmach, Ahmedabad, India). The formulations are shown table 1.[14]

Evaluation of Mucoadhesive tablets

Physical parameters

Tablets were tested for hardness, friability, weight variation and drug content. Hardness of the tablets was tested using a Monsanto hardness tester and Friability of the tablets was determined in a Roche friabilator (Model EF2, Electrolab, Mumbai, India).[15]

Swelling index

Initial weight (W1) of tablet was carried out and placed it in a beaker containing 200 ml of HCl buffer (pH 1.2). After each interval time the tablet was removed from beaker, remove excess water and blotted with filter paper to remove the

Table 1. Formulae of Captopril Mucoadhesive Tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Captopril	100	100	100	100	100	100	100	100	100	100	100
Guar gum	50	100		-	-	-	-	-	-	-	-
Xanthan gum	-	-	50	100	-	-	-	-	-	50	50
HPMC K4M	-	-	-	-	50	100	-	-	50	-	50
HPMC K15M	-	-	-	-	-	-	50	100	50	50	-
PVP K-30	20	20	20	20	20	20	20	20	20	20	20
Dicalcium Phosphate (DCP)	54	04	54	04	54	04	54	04	04	04	04
Talc	3	3	3	3	3	3	3	3	3	3	3
Mg. stearate	3	3	3	3	3	3	3	3	3	3	3

All the quantities are in mg.

excess of water 16. Then the device immediately weighed and again introduce in to the same beaker, and note down the weight (W2) and was performed up to 8 hr. The swelling index was calculated using following formula.

$$\text{Swelling index} = (W2 - W1) / W1 \quad (1)$$

In Vitro (ex vivo) evaluation of bioadhesion

Bioadhesion studies were conducted, using a modification of the assembly described earlier, with porcine gastric mucosa as the model membrane. The mucosal membrane was excised by removing the underlying connective and adipose tissue, and equilibrated at 37°C ± 1°C for 30 min in PBS before the bioadhesion evaluation study. The tablet was lowered on to the mucosa under a constant weight of 5 g for a total contact period of 1 min. Bioadhesive strength (f) was assessed in terms of the weight in grams required to detach the tablet from the membrane.[17]

Tablet bioadhesion is assessed by detachment tests measured between the tablet and a substrate to which it has been previously applied. Many of these types of tests have been described with different substrates and means of measuring the detachment forces. Though artificial substrates have been studied, typically the substrate is a mucosa. A mucosa should be chosen which is similar to that at the intended site of adherence of the tablet. The tablet and mucosa are wetted then put into contact for a given time to allow interpenetration of the polymer chains and adhesion to develop. Detachment is typically in the vertical direction and the force is measured via a balance.[18]

In vitro drug release studies

Dissolution studies of all batches were performed employing USP XXIII paddle-type dissolution test apparatus (Model TDL-08, Electrolab, Mumbai, India) using 900 ml HCl buffer (pH 1.2) as dissolution medium at 50 rpm and 37°C ± 0.5°C. A 5-mL aliquot of the sample was withdrawn periodically at suitable time intervals and the volume replaced with an equivalent amount of the dissolution medium. The samples were analyzed spectrophotometrically at 209 nm using UV Visible Spectrophotometer (Shimadzu, UV 1601). Drug release experiments were conducted in triplicates.

Stability study

Optimized batch of Captopril tablets (Formulation F10) were kept for a short term stability study in high density polyethylene sealed cover at 40 ± 2 °C / 75 ± 5% RH as per ICH Guidelines. Samples were withdrawn for Six week and 3 month of storage and evaluated for appearance, drug content, bioadhesive strength and in vitro dissolution.

RESULT AND DISCUSSION

It was desirable to deliver such drug in a gastro retentive dosage form or mucoadhesive drug delivery systems which would prolong the gastric residence time of drug delivery thereby giving sufficient time for drug delivery system to release the drug and efficient absorption of active moiety. It was suggested that mucoadhesive drug delivery system are easiest approach for technical and logical point of view among gastro retentive drug delivery system, so for present study mucoadhesive drug delivery system was chosen.[19,20]

Mucoadhesive tablets were evaluated for its physical characteristics; the results are shown in Table 2. Hardness of the tablets was found in the range of 6.57 ± 0.400 - 7.53 ± 0.451 kg/cm^2. Percentage weight loss in the friability test was found to be 0.41 % in all batches. Content uniformity of all the prepared batches is within the limit (Captopril 100 ± 3 % of the labeled content). We can conclude that all the batches of tablets prepared were of good quality with regard to hardness, friability and drug content.

Initially, tablets were formulated employing mucoadhesive polymer guar gum alone, it was observed that the tablets were eroded faster and completely dissolved in 4-5 hr.

Table 2. Formulae of Captopril Mucoadhesive Tablets.

Batch Code	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	240.3±5.12	6.83±0.289	3.033±0.11	0.57	98.56
F2	240.8±3.95	6.63±0.321	2.80±0.05	0.58	99.43
F3	239.9±4.09	6.57±0.401	2.76±0.05	0.55	97.12
F4	239.8±4.23	7.20±0.263	2.70±0.15	0.39	98.76
F5	240.2±2.89	6.77±0.250	2.66±0.05	0.41	99.96
F6	240.1±2.78	7.53±0.451	2.93±0.15	0.49	98.51
F7	240.3±2.05	6.43±0.494	2.55±0.08	0.61	99.84
F8	239.9±2.22	7.07±0.502	2.62±0.05	0.76	98.39
F9	240.0±2.10	7.10±0.458	2.53±0.052	0.67	99.78
F10	239.8±2.39	6.60±0.173	2.81±0.076	0.48	97.01
F11	240.5±2.11	6.70±0.200	2.76±0.115	0.39	98.45

Each reading is an average of three determinations (Avg.± S.D)

So, tablets were prepared using xanthan gum and HPMC mucoadhesive polymers. It was found that the tablets were intact over a period of 12 hr; this may be due to the high gel forming nature of HPMC and Xanthan gum.

In Vitro (ex vivo) evaluation of bioadhesion

Many research articles have been published presenting with slightly different theories and mechanisms of mucoadhesion. The reason for this disagreement is may be not so surprising because there have been so many different in vivo and in vitro methods utilized to measure mucoadhesive properties of polymers, resulting in inconsistent results.

The mucoadhesive property of Captopril tablets, alone or combination of xanthan gum and HPMC K15M grade polymer were determined with modified balance. Results are shown in Table 3. Several studies have demonstrated that the bioadhesiveness of tablets depends on the rate of swelling and initial contact time.

It was observed that polymer mixtures showed higher adhesion and higher water uptake. The highest adhesion force i.e. highest strength of the mucoadhesive bond (31.59±0.05 gm) was proposed by F10 containing HPMC K15M and Xanthan gum (1:1) in combination with total polymer concentration is 40%. The mixture Xanthan gum:HPMC K15M 1:1 showed good in vitro mucoadhesion compared to mixture HPMC K4M : HPMC K15M and xanthan gum : HPMC K4M.

It was concluded that as the concentration of polymer increases, mucoadhesive strength increases and viscosity of polymer also affect the mucoadhesive strength.

The ex vivo bioadhesion results illustrate the positive effect of contact time and contact force on work of adhesion. This

Table 3. In-vitro Mucoadhesive strength for all formulated batches

Batch code	Mucoadhesive strength (g)[a]
F1	07.22±0.035
F2	09.24±0.070
F3	14.15±0.115
F4	18.74±0.065
F5	16.42±0.114
F6	20.15±0.110
F7	21.57±0.030
F8	27.52±0.100
F9	29.38±0.100
F10	31.59±0.050
F11	29.96±0.293

[a]Each reading is an average of three determinations (Avg.± S.D)

is predicted by the diffusion theory of Mucoadhesion, which requires interpenetration and entanglement of the polymer chains with mucus chains. The bond strength increases as the degree of interpenetration increases with contact time and contact force.

Swelling Study

Swelling study was performed for all the batches up to 8 hr. The results of swelling index are shown in Fig. 1. The batches contains HPMC K15M (F8) had more swelling because of its higher viscosity as compared to batches contains HPMC K4M (F6). In the present study, the higher swelling index was found for tablets of batch F10 containing HPMC K15M having 15,000 cps viscosity. We can also conclude that the viscosity of the polymer had major influence on swelling process, matrix integrity, as well as adhesion capability. Hence, it can be concluded

Figure 1. Water uptake study of mucoadhesive tablets at different time interval.

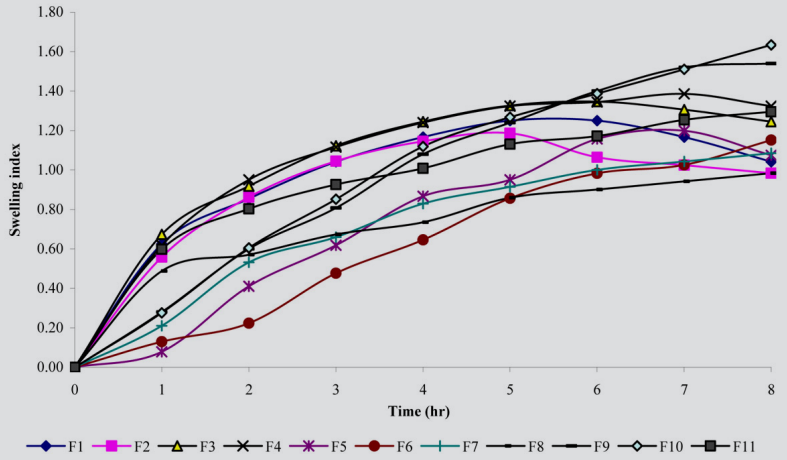


Figure 2. Drug Release profile of Captopril mucoadhesive tablets (Batches F1 to F8).

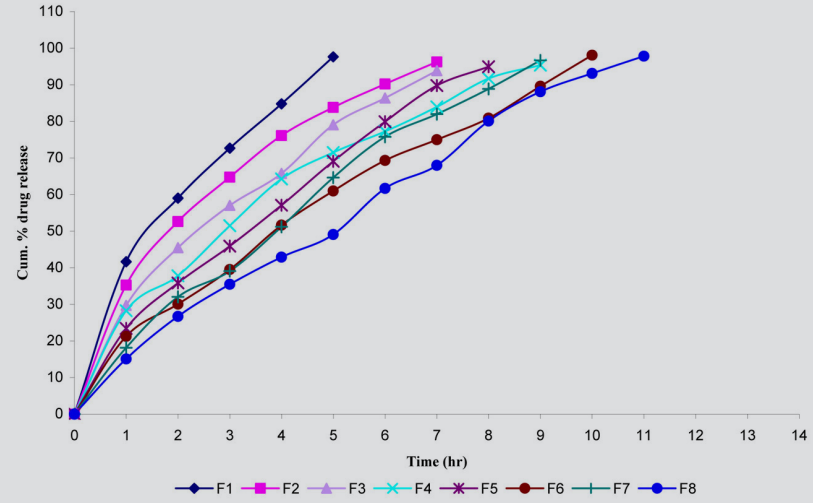
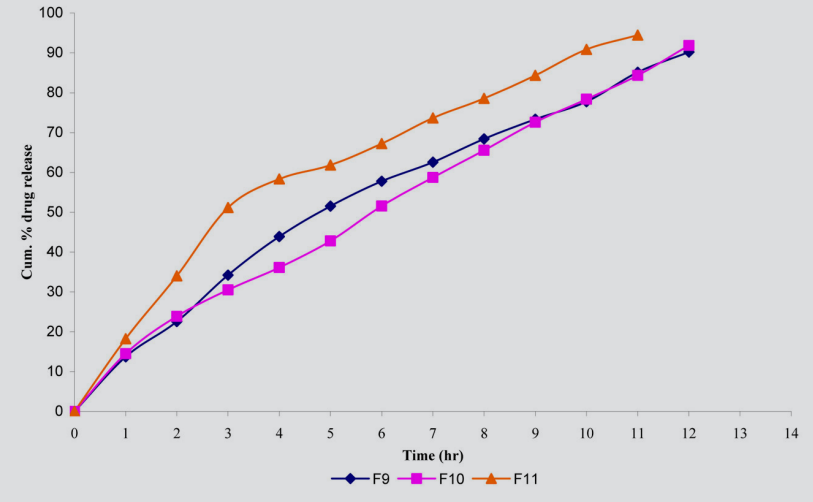


Figure 3. Drug Release profile of Captopril mucoadhesive tablets (Batches F9 to F11).



from the results that linear relationship exists between swelling process and bioadhesion of polymer.

It was also observed that the maximum swelling was attained in 7 hr, after words polymer slowly started erosion in the medium. The high initial uptake of water may be due to the faster hydration rate of HPMC K15M. It was also observed that the swelling rate increased with an increase in HPMC content of the tablets.

In-vitro Dissolution Study

The In-vitro drug release profiles of Captopril are shown in Fig. 2 and 3. The In-vitro release study showed satisfactory sustained release of Captopril from all medicated formulae. Xanthan gum and HPMC are hydrophilic swellable polymer matrices; they are able to form a viscous gel layer; which controls the drug release via diffusion through the gel and erosion of the gel barrier.

It was observed that as there was a reduction in the amount of the polymer to the half ensures faster release. This may be attributed due to the reduction of the strength of the gel layer, which enhances drug diffusion and water uptake through the matrix. It was concluded from the results that as there was increases in polymer concentration of HPMC the release of drug might be slower. This is also supported by Xu and Sunada who reported that HPMC content was predominant controlling factor.[21]

The cumulative % release of batch F1 and F2 were found to be 97.61% in 5hrs and 96.22% in 7 hrs respectively. The cumulative % release of batch F3 and F4 were found to be 93.34% in 7 hrs and 94.32 % in 9 hrs respectively.

The cumulative % release of batch F5 and F6 were found to be 94.89% in 8 hr and 98.07 % in 9 hr, respectively. It was observed that the release is less as compared to Xanthan gum polymer. This may be because it's a high viscosity.

Table 4. Diffusion coefficient (n) and r values of various formulation of Captopril.

Formulation	Parameters	
	n	R^2
F1	0.5241	0.9987
F2	0.5188	0.9965
F3	0.5923	0.9984
F4	0.5787	0.9920
F5	0.6929	0.9958
F6	0.682	0.9938
F7	0.7719	0.995
F8	0.789	0.9962
F9	0.7713	0.9986
F10	0.7456	0.9981
F11	0.645	0.9691

R^2:Regression coefficient; n: Release exponent.

The cumulative % release of batch F7 and F8 were found to be 96.65% in 9 hr and 97.79 % in 11 hr, respectively.

While using blends of polymers in different batches like Batch F9 (HPMC K4M and HPMC K15M in 1:1 ratio), Batch F10 (Xanthan gum and HPMC K15M in 1:1 ratio), and Batch F11 (Xanthan gum and HPMC K4M in 1:1 ratio), the cumulative % release of batch F9, F10 and F11 were found to be 90.20% in 12 hr, 91.85% in 12 hr and 97.79 % in 11 hr, respectively.

Finally, it was concluded from dissolution profile of different batches that the drug release rate was decreased as the concentration of polymer increases and also affect the type of polymer used. This can probably be attributed to the different diffusion and swelling behaviors of the polymer. With the increasing macromolecular weight, the degree of entanglement of the polymer chains increases. Thus the mobility of the macromolecule in the fully swollen systems decreases.

It was also conclude that the release rate was decreased when the viscosity and/or concentration of the polymer was increased. The linear relationship was found between the viscosity of the polymer and release rate of drug from the drug delivery system.

Analysis of the drug release data

Method of Bamba and Puisieusx was adopted for study of kinetics of drug release for the most appropriate model. The dissolution data of all batches were fitted to zero-order, first-order, Higuchi, Hixson-Crowell, Korsemeyer and Peppas, and Weibull models.[22]. The results of regression coefficient were used for the selection of the most appropriate model. The release profile of the best batch F10 fitted best to Korsemeyer and Peppas (R^2 = 0.9981), showing the least residual sum of square as compared to Higuchi (R^2 = 0.9811) and zero-order equation (R^2 = 0.9975) model. This superiority is however statistically insignificant among these three models as shown by the goodness of regression coefficient. Thus, it may be concluded that the drug release from hydrophilic matrix of Captopril tablets is best explained by Korsemeyer and Peppas model. The n-values obtained between 0.5188 to 0.789 for fitting the drug release data to the Peppas-korsmeyer equation, indicated that the drug release mechanism from these tablets was non-fickian diffusion controlled.

Stability studies

The results stability studies are shown in table 5, it revealed that there was no significant change in appearance, and mucoadhesive strength for optimized batch F10. However, there was slight variation in In-vitro release of optimized batch (F10), when it was stored at room temperature and at 40 ± 2 ^oC/ 75 ± 5% RH for three months. It was concluded that tablets are stable after stability studies.

CONCLUSION

The current study indicates that the hydrophilic matrix tablets of captopril, prepared using hydrophilic polymer like Xanthan Gum, HPMC K4M and HPMC K15M. The tablets exhibited good mucoadhesive properties in an in vitro test. Captopril release from these mucoadhesive tablets was slow and extended over longer periods of time. The Batch F10 mixture HPMC K15 M: Xanthan Gum (50:50) Showed good mucoadhesion.

It may be concluded that mucoadhesive tablet of Captopril prepared using mucoadhesive polymer by wet granulation method seems to be the promising formulation, providing controlled delivery of Captopril, with imporved

Table 5. Stability study of optimized batch F10.

Formulation	Parameters		
	Hardness (kg/cm^2)	Mucoadhesive strength (g)	Drug release (%)
After 6 week	6.50±0.173	31.585±0.041	89.86
After 12 week	6.50±0.5	31.55±0.049	89.15

bioavailability of drugs such as Captopril that undergo degradation in higher pH when administered orally.

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