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Current Drug Delivery, **2014**, *11*, 371-379

A Gastroretentive Drug Delivery System of Lisinopril Imbibed on Isabgol-Husk

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Abstract: The gastroretentive drug delivery system is site-specific and allows the drug to remain in the stomach for a prolonged period of time so that it can be released in a controlled manner in gastrointestinal tract. The present study was carried out to develop a gastroretentive drug delivery system using isabgol as an excipient to prolong the residence time of the model drug lisinopril in the stomach. The gastroretentive ability of isabgol was increased by addition of $NaHCO_3$ as a gas-generating agent while its mucoadhesive property was enhanced by incorporation of HPMC-K_4M. The drug, $NaHCO_3$ and HPMC-K_4M were imbibed on isabgol-husk as per entrapment efficiency of the isabgol-husk. After drying, the product was filled in a hard gelatin capsule and evaluated for its buoyancy, mucoadhesive properties, swelling index and *in vitro* drug release. The lisinopril released through isabgol was delayed by 12 hours when compared to a preparation available on the market which released the complete drug in 0.5 hours. The drug release study of lisinopril from the formulation follows first order kinetics using a diffusion controlled mechanism. The results from the present study revealed that isabgol can be used as a potential excipient for the formulation of gastroretentive drug delivery systems in the near future.

Keywords: Detachment force, Gastroretentive drug delivery, Lisinopril, Mucoadhesive, Swelling power.

INTRODUCTION

Research in the area of novel drug delivery systems is gaining popularity due to the considerable therapeutic advantages with several drugs. Furthermore, many approaches to prolong the gastric residence time (GRT) including floating drug delivery, polymeric bioadhesive and high-density systems are often being used extensively [1]. Recently, various drug delivery systems have been developed [2-4] mainly for the oral route as it is natural, safe and convenient. These systems can prolong the GRT by improving solubility and bioavailability of the drug and consequently reducing the waste. These controlled release drug delivery systems are known as gastroretentive drug delivery (GRDD) systems, and are most effective in the delivery of insoluble or sparingly soluble drugs. Gastroretentive approach is most feasible for achieving a prolonged drug delivery system that can manage the GRT of a drug in the gastrointestinal tract (GIT) [5]. GRDD is a site-specific approach in which the delivery system remains in the stomach for a prolonged period and the drug is released in a controlled manner at specific absorption sites in the GIT. A further advantage is that it assists in improving the oral sustained drug delivery that has an absorption window in a particular region of the GIT. Gastroretentive approaches provide significant prolongation in GRT of the drugs due to their stability in the gastric region for several hours. GRDD including multi-unit and floating systems are most superior as well as convenient than any other drug delivery systems due to their unique property of enhancing bioavailability and evading first-pass biotransformation, while reducing dose frequency, fluctuations of drug concentration and counter-activity of the body [6].

The drug lisinopril, a lysine derivative of enalaprilat chemically known as (*2S*)-1-[(*2S*)-6-amino-2-{[(*1S*)-1-carboxy-3-phenylpropyl]amino}hexanoyl]pyrrolidine-2-carboxylic acid, is a long acting and third most popular angiotensin-converting enzyme (ACE)-inhibitor (after captopril and enalapril) which is mostly used in hypertension, congestive heart failure and renal diseases [7]. Lisinopril has a narrow absorption window with only 25% of the drug being absorbed in the GIT. The half-life of its accumulation is 12 hours in multiple dosing and it is well tolerated by patients with heart failure [8, 9]. Isabgol, obtained from the *Plantago ovata* seeds, is hygroscopic and mucilaginous in nature, and is generally used to treat diarrhea and constipation. Isabgol-husk has been recognized as a suitable carrier for the sustained release or as a gastroretentive carrier for many drugs due to its swellable and floatable nature [10].

Although, excellent progress has been made in the field of drug delivery systems, many important drugs still have limited prolonged and sustained release due to their narrow absorption window and limited GRTs. Therefore, in the present study, isabgol is used as an excipient for the drug lisinopril to investigate a new formulation for gastroretentive drug delivery system and to prolong the residence time of lisinopril in the stomach. The general schematic approach of the present study is given in (Fig. **1**), which illustrates how

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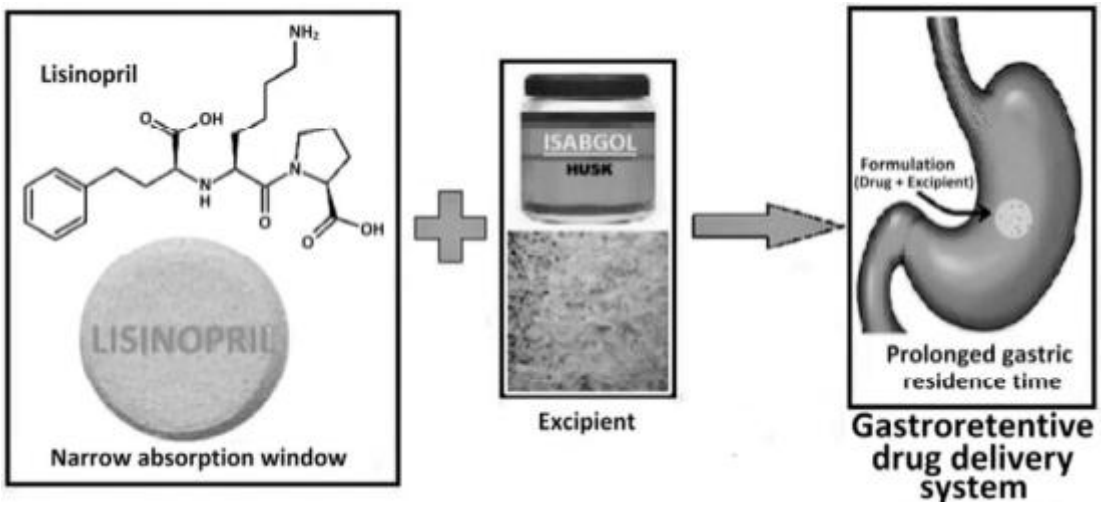


Fig. (1). General scheme for GDDS of lisinopril imbibed on isabgol-husk.

isabgol-husk can improve the properties of lisinopril which has a narrow absorption window.

MATERIALS AND METHOD

Chemical and Reagents

Lisinopril was obtained as a generous gift sample from Ranbaxy Laboratories Ltd. Gurgaon. Hydroxy propylmethyl cellulose (HPMC-K_4M) was purchased from Jubilant Organosys Ltd. Noida. Isabgol-husk was obtained from Dabur Research Foundation Lab. Ghaziabad. Sodium bicarbonate and hydrochloric acid were supplied by Loba Chemie Pvt. Ltd. Mumbai.

Pre-formulation Studies

Physicochemical Properties of Isabgol

Physicochemical properties of isabgol that include; swelling ability and water carrying capacity were determined according to the standards given in IP-1996 & BP-1993 [11, 12]. The influence of different parameters such as electrolyte concentration, *p*H of the medium and presence of drug and polymer on swelling index of isabgol were determined by taking 1 g of isabgol in 100 ml of water in different test conditions according to standard procedures. The water carrying capacity of 1 g husk was observed as incomplete wetting, complete wetting, mucilage formation and sticky mucilage with 1, 2, 3 and 4 ml of water, respectively. The results of influence of acid, alkali and HPMC-K_4M on swelling power are provided in Table **1**.

To calculate the loss on drying, glass-stopper shallow weighing bottles were dried and weighed. A mass of 0.5 g of isabgol-husk was filled in each bottle. The samples were distributed evenly as practicable by gentle sideway shaking to a depth not exceeding 10 mm. Loaded bottles were then placed in the drying chamber and the stoppers were removed. After drying, the bottles were closed immediately and allowed to cool at room temperature in a desiccator. The mass of the dried material in the bottles was determined. To calculate the swelling index, 1 g of isabgol was placed in a 25 ml round-glass-stopper cylinder, graduated over a height of about 120 to 130 mm in 0.5 ml divisions. The cylinder was closed after adding 25 ml of water and vigorously shaken at 10 minutes intervals for 1 hour and then allowed to stand for a further 3 hours. The volume occupied by the isabgol-husk was measured, including any adhering mucilage. The swelling index was calculated from the mean of the three tests.

Table 1. Influence of Acid (HCl), Alkali ($NaHCO_3$) and HPMC-K_4M Concentration on Swelling Power.

S. No.	Normality of HCl sol^n.	Swelling Power (ml)	$NaHCO_3$ Conc. % (w/v)	Swelling Power (ml)	HPMC-K_4M Conc. % (w/v)	Swelling Power (ml)
1	0.05	53.0±3.2	1.0	56.0±2.5	1.0	53.5±2.2
2	0.10	52.0±2.0	2.5	57.0±3.5	2.0	52.1±3.5
3	0.25	48.0±3.5	5.0	63.0±3.0	3.0	49.8±1.8
4	0.50	30.0±1.8	7.5	66.0±3.5	4.0	46.5±3.0
5	1.00	13.0±2.5	10.0	70.0±3.5	5.0	44.3±2.5
6	-	-	-	-	10.0	40.4±2.4

Swelling powers represent the means±S.E.M. for three independent experiments each performed in triplicates.

Physicochemical Properties of HPMC-K_4M

The effect of contact time and concentration of HPMC-K_4M on adhesion strength of HPMC-K_4M was determined according to the method published by Marvola and coworkers [13]. Adhesion of HPMC-K_4M on glass surface was recorded by keeping one drop on the center of the fixed block, and then, the second block was placed onto it and pressed with some pressure (100 g). After keeping it for fixed time intervals of 5, 10, 15, 20, and 30 minutes, the weights were added to the pan. The weights required to pull the block or to make it slide down from the base block representing the adhesion strength. 1%, 2%, 3%, 4% 5% and 10% solutions of HPMC-K_4M were subjected to the same procedure to study the effect of the concentration on adhesion strength.

Compatibility Studies of Drug with Excipient

Compatibility between lisinopril and the excipient proposed to be taken in the formulation was carried out by taking DSC curves of all the ingredients alone and in combination by using universal V4 IDTA DSC instrument (Fig. **2**).

Analytical Profile of Lisinopril

The standard curve of lisinopril was prepared using Systronics 2201 double beams UV spectrophotometer. Lisinopril (100 mg) was dissolved in 100 ml 0.1 N HCl to make a 1000 _g/ml solution (A). A 10 ml volume of A was diluted with 100 ml 0.1 N HCl to make 100_g/ml solution (B). A 30 ml volume of B was diluted with 100 ml 0.1 N HCl to make a stock solution of 30 _g/ml (C). Aliquots of C were pipette and diluted with 10 ml 0.1 N HCl to obtain the desired concentration of lisinopril ranging from 3-30 _g/ml (Fig. **3**).

Preparation and Evaluation of Lisinopril Gastroretentive Capsules

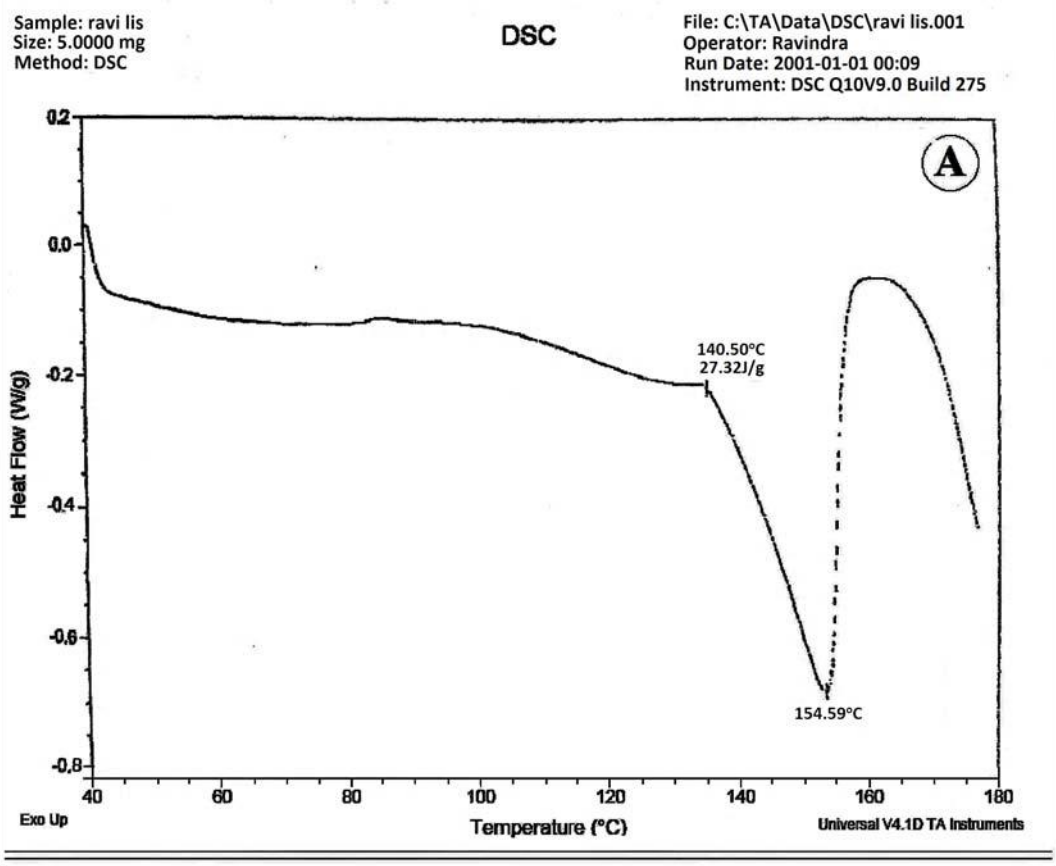
Eleven formulations, one containing 10 mg lisinopril, five containing sodium bicarbonate 1, 2.5, 5, 7.5 and 10 mg with lisinopril 10 mg in each, and five containing HPMC-K_4M 1, 2, 3, 4 and 5 mg with lisinopril 10 mg and sodium bicarbonate 7.5 mg in each, were prepared and subjected to imbibe on isabgol-husk using appropriate quantities of water. Varying quantities of isabgol-husk were taken according to its loading capacity (Table **2**). The products were dried in a desiccator overnight. The formulations were manually filled in empty hard gelatin capsule shells of size 1. Care was taken to fill the contents completely to maintain the uniformity of content and weight. The amount of lisinopril (10 mg) and total amount of product filled in the capsule were kept constant throughout the study. The prepared capsules were analysed for drug content, buoyancy percentage, dissolution and mucoadhesive properties.

Drug Content Determination

The content of lisinopril in each capsule was estimated by measuring the absorbance of a diluted sample in 0.1 N HCl. Ten capsules of the lisinopril (10 mg/GR capsule) were powered separately using a pestle and mortar and transferred into a conical flask. To this, 100 ml of 0.1 N HCl was added and the drug was extracted by filtering above drug solution. The absorbance of the diluted sample was measured at 205 nm in UV-VIS spectrometer using 0.1 N HCl as blank. The concentration of the drug in solution was estimated from the standard curve of lisinopril at 205 nm and found to be within the range from 9.62 to 0.22 mg.

Table 2. Different Gastroretentive Formulations.

S. No.	Formulation Code	Ingredients (mg)			
		Lisinopril	$NaHCO_3$	HPMC-K_4M	Isabgol
1.	F-1	10	-	-	51.50
2.	F-2	10	1.0	-	57.50
3.	F-3	10	2.5	-	64.00
4.	F-4	10	5.0	-	76.50
5.	F-5	10	7.5	-	89.00
6.	F-6	10	10	-	101.50
7.	F-7	10	7.5	1	114.00
8.	F-8	10	7.5	2	139.00
9.	F-9	10	7.5	3	164.00
10.	F-10	10	7.5	4	189.00
11.	F-11	10	7.5	5	214.00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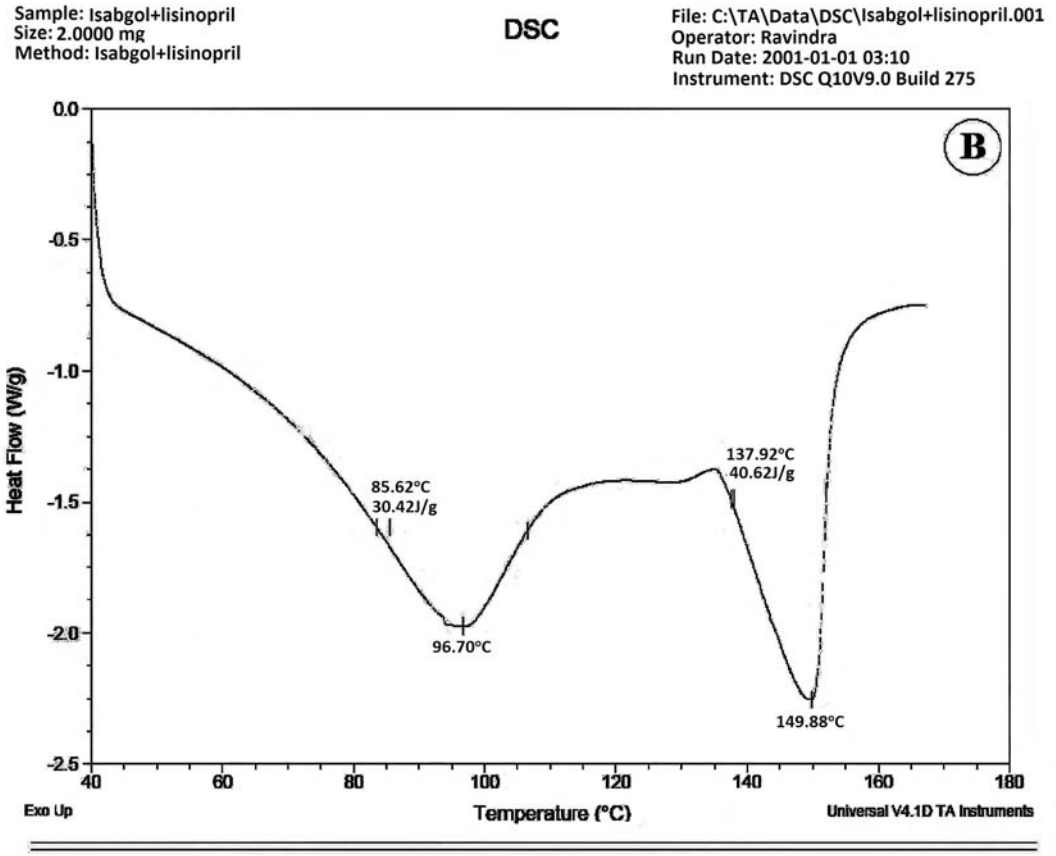
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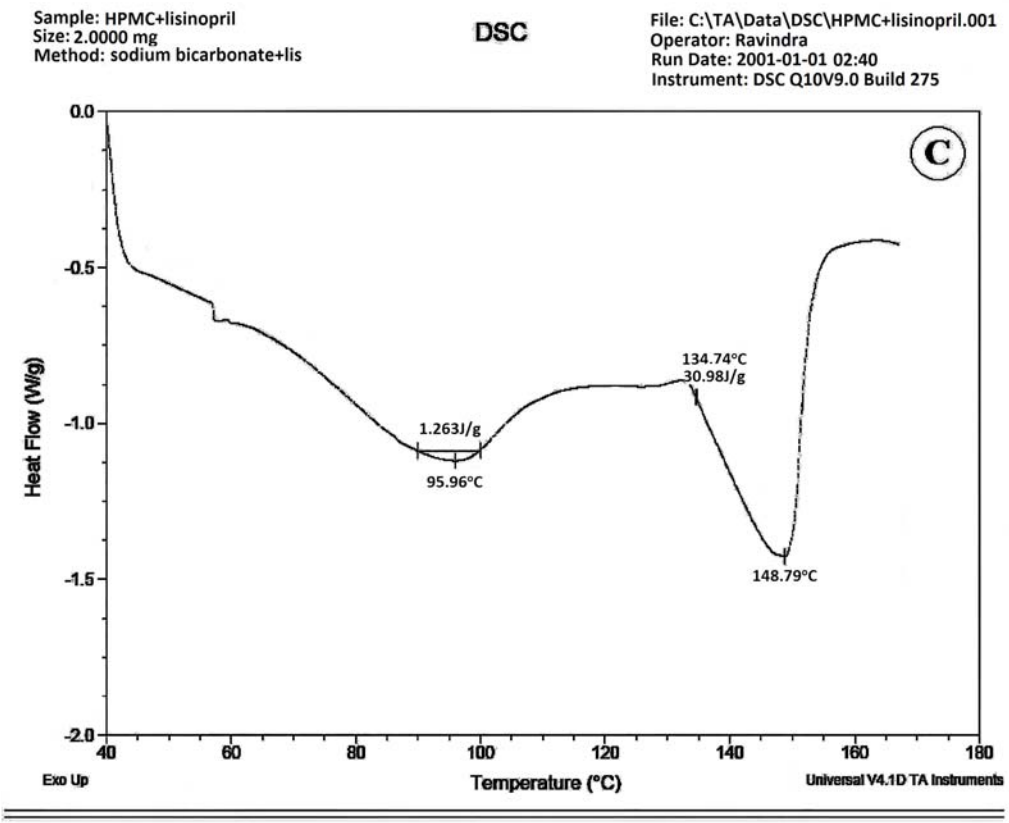

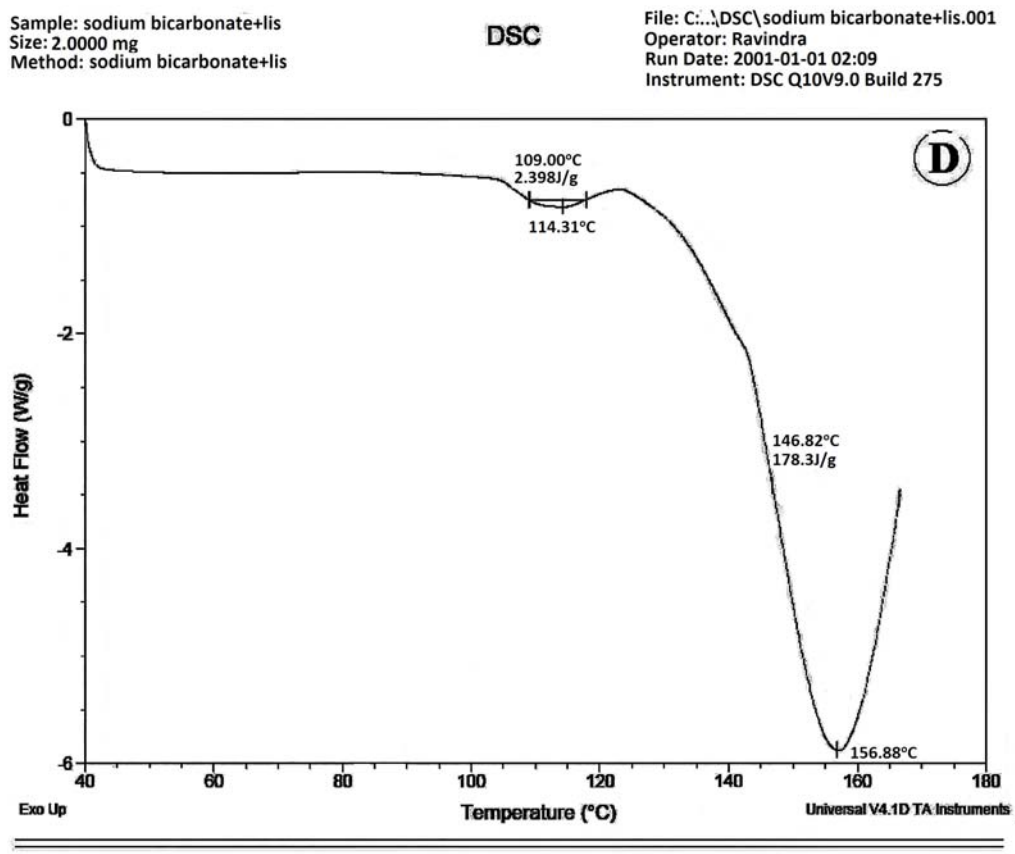

Fig. (2). DSC curves for lisinopril. **A**: pure drug; **B**: with isabgol-husk; **C**: with HPMC-K_4M; **D**: with $NaHCO_3$.

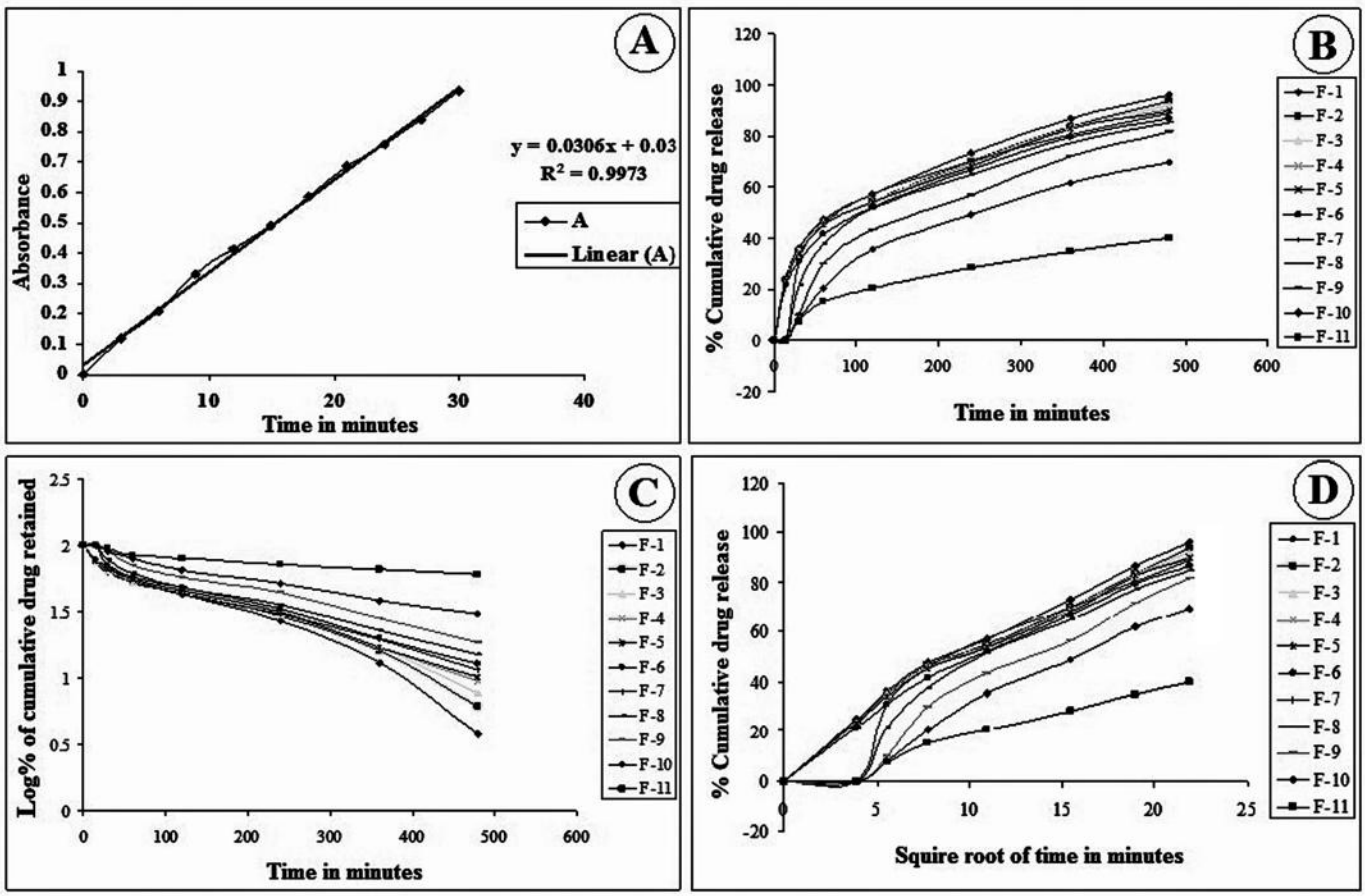

Fig. (3). A: Standard curve of lisinopril in 0.1 N HCl; **B**: *In vitro* release profile of lisinopril from imbibed isabgol-husk with different drug-$NaHCO_3$ and polymer ratios; **C**: Graph for Log % of cumulative drug retained *vs*. time; **D**: Higuchi plot of lisinopril release from the imbibed isabgol-husk containing various drug-$NaHCO_3$ and HPMC-K_4M ratios.

Table 3. Measurement of Buoyancy of Different Formulations.

S. No.	Formulation	Floating Parameter		
		Lag Time (min)	Total Time (h)	% Buoyancy
1	F-1	2.10	>8	60.40
2	F-2	1.55	>8	76.19
3	F-3	1.30	>8	78.26
4	F-4	1.05	>8	90.42
5	F-5	0.45	>8	97.82
6	F-6	0.30	>8	98.90
7	F-7	0.50	>8	85.27
8	F-8	1.00	>8	82.24
9	F-9	1.10	>8	71.13
10	F-10	1.45	>8	65.57
11	F-11	1.55	>8	50.25

Buoyancy Studies

The capsule contents (5 capsules) were spread over the surface of a USP XXIV dissolution apparatus (type II), filled with 900 ml of 0.1 N HCl. The medium was agitated with a paddle rotating at 100 rpm for 12 hours [14]. The floating and settled portions of capsule contents were recovered separately. The contents were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the contents that remain floating to the total mass of the contents (Table **3**).

Dissolution Studies

The release rate of lisinopril from gastroretentive capsule was determined using the dissolution testing apparatus USP-II. The dissolution test was performed using 900 ml 0.1 N HCl, at 37±0.5°C and 100 rpm. A sample (10 ml) of the solution was drawn from the dissolution apparatus at hourly intervals for 8 hours, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper No. 1 and the absorbance of these solutions were measured at 205 nm (Fig. **3**; Table **4**).

Data Analysis

To analyze the *in vitro* release data, various kinetic models were used to describe the release kinetics [15]. Zero order equation ($C = K_0t$, where K_0 = zero order rate constant, t = time), in which the drug release rate is independent of the conc.; First order ($\log C = \log C_0 - Kt/2.303$, where C_0 = drug's initial conc., K= first order constant), in which release rate is conc. dependent and Higuchi ($Q = Kt_{1/2}$, where K = constant reflecting the design variables of the system), in which the release of drug from insoluble matrix as a square root of time dependent process based on Fickian diffusion Equation.

Mucoadhesive Testing

The mucoadhesive strength test for the different formulations was performed using the wash-out test [16]. The artificial cellofen membrane was attached to the glass block. The glass block was kept in disintegration vessel of USP disintegration apparatus. The time required to wash the formulation completely from the cellofen membrane was considered as washout time. Mean share stress force and detachment force were also measured to determine the mucoadhesiveness (Table **5**).

Statistical Analysis

Results are expressed as means ± standard errors of the mean (S.E.M.) for n=3. Statistical analyses were made using Student's t-test and data were considered as significant at $p< 0.05$.

RESULTS AND DISCUSSION

The swelling property of isabgol-husk was explored to prepare a gastroretentive dosage form, using lisinopril as a model drug. The gastro-retentive ability of isabgol was further increased by addition of sodium bicarbonate as a gas-generating agent and it was made mucoadhesive by incorporation of HPMC-K_4M to prevent washing away of the formulation due to movements within the stomach. The mucoadhessive strength of HPMC-K_4M increased with increasing concentration and time of contact which showed a linear relationship. The swelling power was observed as 55 ml with loss of drying by 11.3% and swelling index by 21.4 ml whereas the Pharmacopoeia limit for swelling power, loss of drying and swelling index is _ 40 ml, _ 12 % and _ 10 ml, respectively.

The influence of various parameters such as the concentration of electrolytes, *p*H, and HPMC-K_4M were investi-

Table 4. Kinetic Equation Parameters of the Formulations.

Formulation	R^2 Value		
	Zero Order	First Order	Higuchi
F-1	0.8484	0.9666	0.9783
F-2	0.8508	0.9718	0.9774
F-3	0.8457	0.9780	0.9761
F-4	0.8411	0.9805	0.9748
F-5	0.8435	0.9816	0.9757
F-6	0.8565	0.9820	0.9831
F-7	0.8048	0.9716	0.9250
F-8	0.8582	0.9721	0.9549
F-9	0.9103	0.9876	0.9692
F-10	0.9301	0.9846	0.9755
F-11	0.9170	0.9428	0.9750

Table 5. Mucoadhesiveness of Different Formulations.

S. No.	Formulation	Time Required to Complete Wash (h)	Mucoadhesive Force Measurement	
			Mean Shear Stress (g)	Detachment Force (g)
1	F-1	0.32±0.2	20.5±2.1	45.0±2.5
2	F-2	0.27±0.5	19.0±2.5	43.5±2.7
3	F-3	0.25±0.2	18.7±2.7	42.0±1.6
4	F-4	0.24±0.6	18.5±3.3	41.6±1.5
5	F-5	0.24±0.7	17.8±2.5	40.3±3.5
6	F-6	0.24±0.5	15.0±1.8	37.5±2.7
7	F-7	0.50±0.5	45.8±3.7	70.5±2.5
8	F-8	1.55±0.1	50.3±4.5	98.7±3.3
9	F-9	3.10±0.8	59.8±3.6	128.9±4.5
10	F-10	3.25±0.3	64.7±4.5	136.5±4.5
11	F-11	3.33±0.5	70.6±4.5	140.2±3.8

Data points represent the means±S.E.M. for three independent experiments each performed in triplicates.

gated. There was negligible influence of these parameters found on the swelling power of isabgol-husk. The swelling power was decreased with increase in the concentration of electrolytes and increase in the normality of acid solution which might be due to the shrinkage of isabgol-husk owing to an increase in the osmotic pressure in the former case and increase in *p*H in the later. With increase in the concentration of sodium bicarbonate, the swelling power of isabgol increased probably due to the increase in density and the alkali nature of the medium. The addition of sodium bicarbonate also increased the floating time of isabgol-husk in 0.1 N HCl due to the formation of carbon dioxide gas. There was no significant change observed in the loading capacity of isabgol with incorporation of sodium bicarbonate whereas incorporation of HPMC-K_4M decreased the loading capacity of lisinopril in isabgol.

Differential scanning calorimetry (DSC) of the resulting products revealed that there was no change in the peak temperature of the optimized formulation when compared to that of pure lisinopril, which showed a peak at 154.50 °C compared to 149.88, 148.79 and 156.88 °C with isabgol, HPMC-K_4M and $NaHCO_3$, respectively. These results indicate that there is no chemical interaction between the constituents of the formulation i.e. drug and excipient.

In vitro release studies reveled that release of lisinopril through isabgol was delayed by about 12 hours while the marketed preparation showed almost 100% drug release in 0.5 hours. There was an initial lag time of about 0.25 hours before the release of drug, which was influenced by the addition of HPMC-K_4M. The release of lisinopril showed a first order, diffusion controlled kinetics which was evident through the R^2 values of percent cumulative drug retained versus time and Higuchi's plot. The release pattern of new formulations was found to follow the Higuchi kinetics, and confirms the release mechanism by diffusion [17]. Varying the concentration of sodium bicarbonate had no effect on the release rate of the drug whereas increasing the concentration of HPMC-K_4M decreased the release rate of drug which could have been due to the increase in the viscosity of the medium surrounding the formulation.

Sodium bicarbonate (a gas-generating agent) was used in the study as it could react with gastric HCl by inducing carbon dioxide generation in the presence of 0.1 N HCl. The gas is trapped by the polymer HPMC-K_4M gel which decreases the tablet density, and when the density falls below 1, the tablet starts to float [18]. To prevent washing of the preparation, it was made mucoadhesive by incorporation of HPMC-K_4M. The gastroretention was thus achieved by the combination of flotation, swelling and mucoadhesion. The absorption windows of most drugs are thought to be located in the proximal small intestine, which gives narrow absorption. Hence, there is a need to develop the gastroretentive drug delivery systems for such drugs by formulating them with some suitable excipients that can improve their absorption and GRTs in the stomach [19]. In this study, lisinopril was used as a model drug as it has a narrow absorption window and is absorbed from the upper part of GIT. As a result, its oral bioavailability is ~25% only. The prolongation of GRT increases its bioavailability, reduces its oral dose, decreases the dosing frequency and thus increases patient compliance.

CONCLUSION

The present study concludes that isabgol can be used as an ideal excipient for the formulation of gastroretentive drug delivery system. Its gastroretentive ability can further be increased by incorporating a gas-generating chemical like $NaHCO_3$. The swelling power of isabgol decreases with increase in normality of the acid solution and the concentration of HPMC-K_4M, but increases with an increase in the concentration of sodium bicarbonate. Addition of a mucoadhesive polymer significantly decreases the drug release rate through

it [20, 21]. Release of lisinopril from the formulation follows first order kinetics following a diffusion controlled mechanism. The swelling ability of isabgol-husk can be increased by adjusting various parameters such as temperature, *p*H and the concentration of the polymers. The bioavailability of drugs having narrow absorption windows can be increased and their dosing frequency can be decreased with the help of incorporating them in isabgol-husk.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This work was financially supported by UGC, New Delhi [Grant No. F.4-2/2006(BSR)/13-321/2010(BSR) and F.4-2/2006 (BSR)/13-460/2011(BSR)].

PATIENT CONSENT

Declared none.

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Received: August 03, 2013 **Revised: August 16, 2013** **Accepted: October 05, 2013**