PHARMACIA
Vol. -2 , Issue - 1, Year - June 2013
ISSN 0976-9692

FORMULATION AND EVALUATION OF GASTRORETENTIVE MUCOADHESIVE FILMS OF CAPTOPRIL

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Abstract:

Gastroretentive mucoadhesive drug delivery system mucoadhesive films of captopril were formulated by using polymers like EC, HPMC and Carbopol 934 and plasticizer like glycerine for treatment of hypertension. Currently hypertension has become a common problem in all over the world, due to effectiveness and intensive use of captopril as a drug of choice in the treatment of hypertension and congestive heart failure, development of oral controlled release dosage form of captopril has been an interested topic of research for a long period of time. Difficulties encountered with this drug are its half life is 2-3 hrs; stability in acidic media, absorption window is in upper part of GIT, 20–30% protein binding, 60-70% bioavailability, less dose and its freely water solubility give the direction to formulate a gastroretentive mucoadhesive drug delivery system of this drug . Prepared gastroretentive mucoadhesive films were evaluated for various parameters such as Film thickness, Surface pH of films, Folding endurance, Percent swelling, Moisture content, Moisture uptake, Tensile strength, Elongation at break, Mucoadhesion studies, Determination of Drug content and In vitro drug release studies. The release rate of the gastroretentive mucoadhesive films of captopril was found to obey korsmeyer peppas kinetics.After analysis of different evaluation parameters and drug release kinetics, formulation code F8 was selected as a promising formulation for delivery of captopril as a mucoadhesive Gastroretentive film with best mucoadhesive strength and 99.06% drug release at 24th hour.

Key-words : Captopril, Gastroretentive mucoadhesive films, Hypertension and Bioavailability.

Introduction:

Oral delivery of drugs is the most preferred administration route due to ease of administration. Drug bioavailability of pharmaceutical oral dosage forms is influenced by various factors. One important factor is the gastric residence time of these dosage forms [1]. Indeed, gastric retention has received significant interest in the past few decades as most of the conventional oral delivery systems have shown some limitations related to fast gastric emptying time. A gastroretentive dosage form can overcome this problem and is particularly useful for drugs that are primarily absorbed in the stomach, duodenum and upper jejunum segments. [2]

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulations. However, this approach is associated with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility. Furthermore, the relatively brief gastric emptying time in humans, normally averages 2-3 h. therefore, control and placement of a drug delivery system in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem. These considerations have led to the development of a unique oral controlled release dosage form with gastroretentive properties. [3]

Hypertension is defined as a sustained diastolic blood pressure greater than 90mmHg accompanied by an elevated systolic blood pressure more than 140mmHg.[4]

About 90-95% of cases are termed primary hypertension. The remaining 5-10% cases (secondary) are caused by other conditions that affect the kidneys, arteries, heart or endocrine systems. [5]

Captopril is an angiotensin converting enzyme inhibitor used for the treatment of hypertension, congestive heart failure and some other diseases [6]. Its gastroretentive mucoadhesive formulation may be a better alternative; this mode of administration would best achieve the known pharmacokinetic and pharmacodynamic

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advantages by using gastroretentive mucoadhesive film. It is suitable for the drug captopril which is absorbed in the proximal part of the gastrointestinal tract,It provides good bioavailability and reduces hepatic first pass effect by prolonging gastric retention of drug. It also improves patient compliance; reduce fluctuation in steady state plasma drug concentration levels and therefore better control of disease condition. [7]

Mucoadhesion is a more specific term than bioadhesion. Most mucosal surfaces such as in the gut or nose are covered by a layer of mucus. Adhesion of a matter to the layer is hence called mucoadhesion. Mucoadhesive agents are usually polymers containing hydrogen bonding groups that can be used in wet formulations or in dry powders for drug delivery purposes. The subsequent formation of Van der Waal's, hydrogen and, in the case of a positively charged polymer, electrostatic bonds between the mucins and the hydrated polymer promotes prolonged adhesion.[8]

The mucoadhesive films were prepared by using Carbopol-934, Hydroxypropyl methylcellulose (HPMC), and Ethyl cellulose (EC). Slowly dissolving polymers are suitable for sustaining the release may be good for long-term therapy in controlled alleviation of clinical manifestation. Ethyl cellulose, Hydroxypropyl methylcellulose and Carbopol-934 provide a potentially useful means of delivering drugs because they are stable, both physically and chemically amenable to preparation in large batches, non-antigenic, metabolize within the body and capable of accommodating a wide variety of drug molecules in a relatively non-specific fashion.[9]

Therefore main objective of the present work was to develop gastroretentive mucoadhesive films of captopril to study the formulation variables affecting the release of drug.

Materials And Methods:

Materials:

The Captopril was obtained as a gift sample from Wockhardt Ltd., Aurangabad. Ethyl cellulose (EC), Hydroxyl propyl methyl cellulose (HPMC) and Carbopol-934 and Glycerin were purchased from CDH (P) Ltd., New Delhi.

Preparation of mucoadhesive oral films: [5]

The mucoadhesive films were prepared by a solvent casting technique from plasticizer-containing polymeric solution. The Polymer solution was prepared by dissolving Ethyl cellulose, HPMC and Carbopol-934 in different concentration. Finally dispersing or dissolving of weighed quantity of drug to form thick viscous formulation in different ratio of methanol and water as solvent. Different concentrations of plasticizer were added. The polymeric solution was left overnight at room temperature to obtain clear and bubble-free solution. The prepared viscous formulation was poured on glass mould, covered with inverted funnel to control the rapid evaporation of solvent and allowed for drying at room temperature for 2 hrs and followed to evaporate the solvent in hot air oven for 24 hrs at 60^0C. After complete drying, gently remove the film for further studies. Compositions were showed in Table no 1.

INGREDIENTS	FORMULATION CODE & QUANTITY							
	F1	F2	F3	F4	F5	F6	F7	F8
Drug (mg)	75	75	75	75	75	75	75	75
Ethyl Cellulose (%)	1.2	0.72	0.72	1.2	_	0.48	0.72	0.72
HPMC (%)	0.72	1.2	0.72	_	1.2	0.72	0.72	0.72
Carbopol (%)	_	_	_	0.48	0.48	0.24	0.24	0.36
Plasticizer (%)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Table: 1 Different Concentration of polymers used in formulation of gastroretentive mucoadhesive films of captopril.

Characterisation of Film:

Film thickness: [10]

Three films of each formulation were taken and the film thickness was measured using Micrometer Screw Gauge (Mitutoyo-25DS) at three different places and the mean value was calculated. Results showed in Table no 2.

PARAMETERS	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Film thickness(mm)*	0.544± 0.026	0.546± 0.020	0.421± 0.006	0.430± 0.042	0.464± 0.009	0.433± 0.039	0.460± 0.028	0.485± 0.024
Surface pH*	6.78± 0.026	6.73± 0.041	6.69± 0.083	6.22±0 .165	6.34± 0.109	6.47± 0.190	6.68± 0.10	6.52± 0.088
Folding endurance*	158.81± 5.267	205.42 ±8.894	219.66 ±9.234	235.96 ±6.342	240.17 ±2.456	256.89 ±3.867	245.75 ±2.564	247.62±3 .452
Swelling index (%)*	18.38± 1.024	26.46± 1.385	23.36± 1.011	28.42± 0.321	46.23± 0.486	35.56± 1.342	30.02± 0.348	37.69±0. 486
%Moisture content*	1.15± 0.045	1.68± 0.086	1.26± 0.025	1.98± 0.096	2.38± 0.168	2.24± 0.149	2.18± 0.098	2.35± 0.083
%Moisture uptake	2.69± 0.094	3.44± 0.112	2.98± 0.097	3.52± 0.086	4.82± 0.124	4.42± 0.187	4.37± 0.238	4.65± 0.246
Mucoadhesive Strength (g)	20.32± 0.462	28.89± 0.254	22.34± 0.186	38.21± 0.642	47.19± 1.082	42.56± 0.642	41.62± 0.436	43.26± 0.384
Mucoadhesion Force (N)	1.99± 0.089	2.83± 0.102	2.19± 0.068	3.74± 0.096	4.62± 0.132	4.17± 0.148	4.08± 0.084	4.24± 0.068
Mucoadhesion Time (h)	12	24	12	24	24	24	upto 24	24
% Drug content	91.55± 0.586	93.21± 1.218	93.94± 0.826	97.04± 0.146	92.41± 0.235	94.25± 0.727	95.85± 0.209	96.56± 0.148
Tensile strength	3.26± 0.483	5.67± 0.215	3.98± 0.654	4.65± 0.784	6.86± 0.658	5.46± 0.985	5.30± 0.846	5.79± 0.762
% Elongation	19.45± 0.243	26.59± 0.198	21.86± 0.236	23.06± 0.169	32.82± 0.153	24.68± 0.142	23.52± 0.132	27.45± 0.087

(MEAN ± SD)

Table: 2 Evaluation parameters of prepared mucoadhesive films

Surface pH of Films: [11]

For determination of surface pH, three films of each formulation were allowed to swell for 2 h on the surface of an agar plate. The surface pH was measured by using pH meter. Electrode of pH meter placed on the surface of the swollen patch allowing it to equilibrate for 1 m. A mean of three readings were recorded. Results showed in Table no 2.

Folding Endurance:

Three films of each formulation of size (2.5×2.5 cm) were cut by using sharp blade. Folding endurance was determined by repeatedly folding the film at the same place till it broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean value of three evaluation procedure results and standard deviation showed in Table no 2.

Percent Swelling:

After determination of the original film weight and diameter, the samples were allowed to swell on the surface of agar plate kept in an incubator maintained at 37± 0.2ºC. Weight of the films (n=3) was determined at different time intervals (1-5 h). The percent swelling, % S was calculated using the following equation:

Percent swelling (% S) = (Xt–Xo/Xo) ×100,

Where Xt is the weight of the swollen film after time t, Xo is the initial film weight at zero time.

Moisture content:

The prepared films weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 h. The films are weighed again after a specified interval until they showed a constant weight. The percent moisture content was calculated by using following formula:

% Moisture content = [Initial weight – Final weight / Final weight] x 100

Moisture uptake:

Weighed films were kept in a desiccators at room temperature for 24 h.These were then taken out and exposed to 84% relative humidity using saturated solution of potassium chloride in a desiccators until a constant weight is achieved % moisture uptake is calculated as given below [12] :

% Moisture uptake = [Final weight – Initial weight/ Initial weight] x 100

In vitro Mucoadhesion study: [13], [14]

Mucoadhesive strength of the films was measured on a modified two-arm physical balance. The fresh goat gastric mucosa was used as biological membrane for the studies. Goat gastric mucosa was obtained from the local slaughter house and stored in buffer media, 0.1N HCl solution at 4^0C from the time of collection and used within 3 hrs of procurement. The membrane was washed with distilled water and then with 0.1N HCl buffer. The gastric mucosa of goat was cut into pieces and washed with 0.1N HCl buffer. A piece of goat gastric mucosa was tied to the glass vial, which was filled with 0.1N HCl buffer. The glass vial was tightly fitted into a glass beaker (filled with 0.1N HCl buffer), so that it just touches the mucosal surface. The gastroretentive mucoadhesive film was stuck to lower side of a rubber stopper. The two side of the balance were made equal before the study, by keeping a 5 g weight on the right side and weight was removed from the right-hand pan, which lowered the pan along with the film over the mucosa. The balance was kept in the position for 5 m as contact time. Mucoadhesive strength was assessed in terms of weight (g) required to detach the film from the membrane.

Mucoadhesive strength was measured as force of adhesion in Newton's by using following formula-

Force of adhesion (N) = Mucoadhesive strength / 100 X 9.81

Mucoadhesion time study: [15]

The time taken for detachment of film from goat stomach mucosa was measured in 0.1N hydrochloric acid (pH 1.2). This was evaluated by an in vitro adhesion testing method, by using in vitro dissolution apparatus.

A piece of goat stomach mucosa, (3 cm diameter) was attached inside, 0.1N HCl buffer containing beaker of dissolution apparatus assembly with cyanoacrylate glue and film was attached by applying pressure for 5 m. Suitable rotation speed of dissolution apparatus assembly was maintained at 37 ± 0.5 ^{0}C and observes the time of detachment of mucoadhesive film from mucous membrane.

Tensile strength:

To determine tensile strength, polymeric film was sandwiched separately by corked linear iron plates. One end of the film was sandwiched separately by corked linear iron plates. One end of the film kept fixed with the help of an iron screen and other end was connected to a freely movable thread over a pulley. The weights were added gradually to the pan attached with the hanging end of the thread. A pointer on the thread was used to measure the elongation of the film. The weight just sufficient to break the film was noted. The tensile strength was calculated by using the following equation-

Tensile strength (Kg/mm2) = Force at break (Kg)/ Initial cross sectional area of the sample (mm2)

Elongation at break:

It would be defined as the ratio of the length of film/patch in normal position to stress condition. Here, stress conditions would be stated as stretching the film/patch to the point till it breaks down and measuring the largest length of the intact patch before breaking. Percnt Elongation at break was calculated by using the following equation - **[16], [17]** :

% Elongation at break = Increase in length/ Original length × 100

Determination of drug content:

Accurately cited 2.2 cm diameter of the film was taken and dissolved in 100 ml of 0.1 N HCl solution in 100 ml volumetric flask and kept for 24 hours with occasional shaking. Then whole solution was sonicated. After sonication and subsequent filtration, suitable dilutions were made with 0.1 N HCl solution. The prepared solutions were analyzed by using UV–Visible spectrophotometer at 212 nm. Results showed in Table no 2.

In vitro drug release studies:

Dissolution studies were carried out for all the formulations, employing USP dissolution apparatus I (Basket method) at 37± 0.5ºC, rotated at constant speed of 50 rpm using 900 ml of 0.1N HCl as the dissolution medium. A sample of Captopril film was used in each test. An aliquot of the sample was periodically withdrawn at suitable time interval and the volumes were replaced with fresh dissolution medium. The sample was analyzed spectrophotometrically at 212 nm **[5]**.

Time (Hrs)	Formulation code							
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	12.56	18.69	16.58	28.60	27.52	15.28	13.89	14.67
2	22.82	31.53	28.46	43.36	42.63	30.80	21.40	23.52
4	33.64	49.85	44.85	69.40	71.87	46.62	33.38	31.93
6	44.85	65.48	58.68	78.68	84.43	57.89	41.45	43.21
8	51.2	82.21	68.27	85.42	91.26	71.71	49.86	50.78
10	57.98	96.64	84.7	94.68	98.59	78.38	56.29	58.36
12	65.45	-----	98.96	-----	-----	86.75	62.06	64.18
18	82.89	-----	-----	-----	-----	98.13	79.96	81.64
24	99.27	-----	-----	-----	-----	-----	98.59	99.06

Table: 3 Cumulative % drug releases of prepared gastroretentive mucoadhesive films

Formulation code	Equation of the line	Correlation coefficient (r^2)
F_1	Y = 3.890X + 13.99	R^2 = 0.948
F_2	Y = 9.232X + 8.312	R^2 = 0.981
F_3	Y = 7.715X + 8.589	R^2 = 0.981
F_4	Y = 8.637X + 18.91	R^2 = 0.880
F_5	Y = 9.307X + 18.25	R^2 = 0.889
F_6	Y = 5.387X + 17.43	R^2 = 0.893
F_7	Y = 3.810X + 13.29	R^2 = 0.957
F_8	Y = 3.840X + 14.09	R^2 = 0.952

Table: 4 Zero order kinetic treatment of dissolution data of captopril mucoadhesive films.

Formulation code	Equation of the line	Correlation coefficient (r^2)
F_1	Y = - 0.073X + 2.157	R^2 = 0.823
F_2	Y = - 0.128X + 2.107	R^2 = 0.882
F_3	Y = - 0.079X + 2.031	R^2 = 0.972
F_4	Y = - 0.117X + 1.992	R^2 = 0.979
F_5	Y = - 0.168X + 2.079	R^2 = 0.947
F_6	Y = - 0.089X + 2.081	R^2 = 0.955
F_7	Y = - 0.063X + 2.122	R^2 = 0.838
F_8	Y = - 0.069X + 2.141	R^2 = 0.827

Table: 5 First order kinetic treatment of dissolution data of captopril mucoadhesive films.

Formulation code	Equation of the line	Correlation coefficient (r^2)
F_1	Y = 20.64X - 5.495	R^2 = 0.992
F_2	Y = 30.98X - 7.683	R^2 = 0.976
F_3	Y = 28.52X - 8.122	R = 0.973
F_4	Y = 30.79X + 0.627	R^2 = 0.988
F_5	Y = 32.97X - 1.067	R^2 = 0.985
F_6	Y = 25.10X + 3.399	R^2 = 0.987
F_7	Y = 20.09X – 5.474	R^2 = 0.990
F_8	Y = 20.31X - 4.989	R^2 = 0.992

Table: 6 Higuchi's square root kinetic treatment of dissolution data of captopril mucoadhesive films

Formulation code	Equation of the line	Correlation coefficient (r^2)
F_1	Y = 0.631X + 1.136	R^2 = 0.994
F_2	Y = 0.705X + 1.275	R^2 = 0.999
F_3	Y = 0.698X + 1.227	R^2 = 0.997
F_4	Y = 0.522X + 1.477	R^2 = 0.981
F_5	Y = 0.567X + 1.461	R^2 = 0.977
F_6	Y = 0.638X + 1.250	R^2 = 0.976
F_7	Y = 0.607X + 1.146	R^2 = 0.999
F_8	Y = 0.592X + 1.171	R^2 = 0.998

Table: 7 Korsmeyer equation kinetic treatments of dissolution data of captopril mucoadhesive films

Result And Discussion:

Gastroretentive mucoadhesive films of captopril were prepared by solvent casting technique by using different types of polymers such as EC, HPMC, and Corbopol, and glycerine as plasticizer. Optimizations of solvent system, plasticizer concentration as well as polymer concentration were done. It was found that the polymer concentration is a major factor affecting the drug release and mucoadhesion strength of the mucoadhesive gastroretentive films. Prepared gastroretentive mucoadhesive films of captopril was smooth, flexible and good in appearance. The evaluation studies of all the formulations were performed by standard methods.

Surface pH, Thickness, Folding endurance, Percent swelling, Moisture content, Moisture uptake, Tensile strength, Elongation at break, Mucoadhesion studies, Determination of Drug content, and In vitro drug release studies, of the formulation were found to be satisfactory result.

After analysis of different evaluation parameters and drug release kinetics, formulation code F8 having (Carbopol- 0.36%, HPMC- 0.72%, EC- 0.72%) was selected as best promising formulation for delivery of captopril as a mucoadhesive gastroretentive film with best mucoadhesive strength and 99.06% drug release at 24th hour.

To establish the order and mechanism of drug release, dissolution data of all the formulations were fitted to four different kinetic models named as zero order model, first order model, higuchi model and koresmeyer peppas model **[16]**. The model for best fit was predicted from the regression value r2. The value which was closer to 1 was selected as the best fit model for the drug release **[17]**. The in vitro drug release was found to follow Korsmeyer-Peppas kinetics as correlation coefficient r^2 =0.999 which was closer to 1.

The aim of this study was to formulate the gastroretentive mucoadhesive films of captopril by using different polymers and plasticizer which may deliver the drug in well controlled manner and provides good bioavailability by prolonging gastric retention of drug. It also improves patient compliance; reduce fluctuation in steady state plasma drug concentration levels and therefore better control of disease condition. Because of the Maximum utilization of drug it enables reduction in total dose administered, health care costs through improved therapy and frequency of dosing as well as shorter treatment period. It is also considerable that by developing such sort of promising formulations may open the doors for these kinds of drugs having

bioavailability problems and are not able to give efficient bioavailability which is a soul criteria for the development of perfect and efficient drug delivery system.

Acknowledgements:

The author is deeply thankful to Wockhardt Ltd., Aurangabad, India for providing gift sample of captopril.

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