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RESEARCH ARTICLE

Formulation and evaluation of controlled-release effervescent floating bioadhesive tablets of losartan potassium

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Formulation and evaluation of controlled-release effervescent floating bioadhesive tablets of losartan potassium

Summary

The purpose of the present study was to develop a gastroretentive controlled-release drug delivery system for losartan potassium with swelling, floating and biodhesive properties. Various release retarding polymers like Hydroxypropyl methylcellulose (HPMC) K4M, HPMC K15M, Carbopol (CP) 971P and Sodium carboxymethyl cellulose (SCMC) in combinations were tried and optimized to get the release profile for 12 h. Sodium bicarbonate ($NaHCO_3$) and citric acid were used for producing effervescent base for buoyancy of tablets. Tablets were evaluated for swelling study, buoyancy behavior, adhesion period and in-vitro drug release. The in vitro drug release of optimized formulation (F10) followed Higuchi kinetics and the drug release mechanism was found to be of non-Fickian type. Analyses of data revealed that tablets containing SCMC (14% w/w), CP 971P (10%, w/w) and $NaHCO_3$: citric acid (16%, w/w) (formulation F10) were promising systems exhibiting excellent floating properties, extended adhesion periods and sustained drug release characteristics. Formulation F10 was stored at 40°C/75% relative humidity (RH) for 3 months according to international conference on harmonization (ICH) guidelines. No significant change was observed in physical appearance, thickness, friability, drug content, floatability or in vitro dissolution pattern after storage.

Key Words: *Adhesion period, Controlled-release, Effervescent Tablets, Gastroretentive, Losartan potassium, Swelling study*

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Kontrollü Salımlı, Yüzen, Biyoadezif, Efervesan Losartan Potasyum Tablet Formülasyonu ve Değerlendirilmesi

Özet

Bu çalışmanın amacı, losartan potasyum için şişme, yüzme ve biyoadezif özellik taşıyan, gastroretentif kontrollü salım yapan ilaç taşıyıcı sistem geliştirmektir. Hidroksipropil metilselüloz (HPMC) K4M, HPMC K15M, Karbopol (CP) 971P ve Sodyum karboksimetil selüloz (SCMC) gibi salımı geciktiren çeşitli polimerler kombine edilmiş ve salım profili 12 saat olacak şekilde ayarlanmıştır. Sodyum bikarbonat ($NaHCO_3$) ve sitrik asit, tabletlerin yüzmesi için efervesan özellik oluşturmak üzere kullanılmıştır. Tabletler; şişme oranı, yüzme özelliği ve adezyon süresi ölçümü ile in vitro ilaç salım çalışması yapılarak değerlendirilmiştir. Optimize edilen formülasyonun (F10) in vitro ilaç salımı, Higuchi kinetiğine uyum göstermektedir ve salım mekanizması non-Fickian tiptedir. SCMC (%14 a/a), CP 971P (%10, a/a) ve $NaHCO_3$:sitrik asit (%16 a/a) içeren tabletler (F10 formülasyonu), mükemmel yüzme özelliği, uzun adezyon süresi ve uzatılmış ilaç salım karakteri göstererek umut verici olmuşlardır. Stabilite çalışması için F10 formülasyonu, International Conference on Harmonisation (ICH) klavuzuna göre, 3 ay süresince 40°C/%75 bağıl nem (RH) ortamında saklanmıştır. Fiziksel görünüş, kalınlık, ufalanabilirlik, miktar tayini, yüzme veya in vitro dissolüsyon özellikleri açısından önemli bir değişiklik gözlenmemiştir.

Anahtar Kelimeler: *Efervesan tabletler, Gastroretentif, Kontrollü salım, Losartan potasyum, Şişme çalışması, Adezyon süresi.*

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INTRODUCTION

It is a fact that drug molecules confronting no difficulties in their solubility and/or absorption problems along the gastrointestinal (GI) tract are sound candidates for sustained-release formulations. However, a significant obstacle may rise up if there is a narrow absorption window for drug in the GI tract and/or if a stability problem exists in GI fluids. Placement of a drug delivery system in a specific region of the GI tract frequently improves absorption of those drugs which may involve these kinds of problems [1]. These problems encouraged the development of gastro retentive drug delivery systems (GRDDSs). The advantage provided by the GRDDSs include: continuous and sustained delivery of drugs to the small intestinal absorption window, better and extended therapeutic effect and therefore reducing the frequency of drug administration, provide more efficient treatment of local stomach disorders, and reducing together lower-tract inactivation of the drug and drug effects on the lower intestinal flora [2]. GRDDSs, however, are not suitable for drugs candidates that may cause gastric lesions. Also, the drug substances that are unstable in the strong acidic environment of the stomach are not the suitable candidates to be incorporated in such systems. In addition, these systems do not offer significant advantages over the conventional dosage form of drugs, which are absorbed throughout the gastrointestinal tract [3].

Various approaches for gastro retention include: floating systems, high density systems, mucoadhesive systems and swelling systems [4]. Compressed hydrophilic matrices are commonly used as oral drug delivery systems. Drug release from hydrophilic matrix tablets is controlled by the formation of a hydrated viscous layer around the tablet which acts as a barrier to drug release by opposing penetration of water into tablet and also movement of dissolved solutes out of the matrix tablet. Water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the gel layer, whereas poorly water-soluble drugs are released predominantly by erosion mechanisms. The overall drug release process is influenced not only by drug solubility but also by the physical and mechanical properties of the gel barrier that forms around the tablet [5].

Losartan is the first orally acting anti-hypertensive agent that acts by specifically blocking the actions of angiotensin II at the AT_1-subtype receptor. Following oral administration, losartan is rapidly absorbed, and then approximately 14% of a losartan dosage is metabolized into active carboxylic acid metabolite (E3174) by CYP2C9; the systemic bioavailability of losartan is 25-35%. The mean terminal $t_{1/2}$ of losartan is short relative to the E3174: 2.1 h vs 6.3 h. The systemic availability of losartan potassium is about one-third that of intravenous losartan. The low bioavailability may be due to combination of incomplete absorption and first-pass metabolism [2]. Accordingly, the GRDDS was designed to prolong gastric residence time and provide for enhanced bioavailability of losartan relative to an equal dose of an immediate-release formulation.

MATERIALS AND METHODS

Materials

Losartan potassium was obtained as a gift sample from Zim laboratory, India. HPMC K4M, HPMC K15M and microcrystalline cellulose (MCC) were gifted by Glenmark Pharmaceuticals, India. CP 971P received as a gratis sample from Colorcon Asia Pvt. Ltd., India. SCMC was taken from SD Fine Chemicals Ltd., Mumbai, India. All other solvents and reagent were purchased from Loba Chemie, India, and were of analytical grade and were used as such.

Methods

Preparation of tablets

Losartan potassium, HPMC K4M, HPMC K15, CP 971P, SCMC (2500 CPs), $NaHCO_3$ and citric acid were passed through Sieve no.18, separately. The drug was then mixed with the polymers and other ingredients. Finally, magnesium stearate was uniformly mixed with the above blend and then directly compressed in a single punch tablet compression machine (Chamunda Pharma Machienary Pvt. Ltd., India) with 8 mm flat punch.

Table 1. The composition of the losartan potassium tablets

Batch (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	50	50	50	50	50	50	50	50	50	50	50	50
Carbopol 971P	—	2.5	05	7.5	—	2.5	05	7.5	—	2.5	05	7.5
HPMP K4M	40	37.5	35	32.5	—	—	—	—	—	—	—	—
HPMC K15M	—	—	—	—	40	37.5	35	32.5	—	—	—	—
Sodium CMC	—	—	—	—	—	—	—	—	40	37.5	35	32.5
NaHCO3	30	30	30	30	30	30	30	30	30	30	30	30
Citric acid	10	10	10	10	10	10	10	10	10	10	10	10
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	—
Mg. Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	—
MCC	65	65	65	65	65	65	65	65	65	65	65	65
Tablet weight	200	200	200	200	200	200	200	200	200	200	200	200

EVALUATION OF THE PREPARED TABLETS

The thickness, diameter, hardness and friability of the tablets were determined using digital vernier calipers, Monsanto hardness tester and friabilator, respectively. Weight variation test and content uniformity test were carried out according procedure stated in the United State pharmacopoeia (USP) [6].

Tablet floating behaviour

The floating property of the tablets was studied using USP type II dissolution apparatus [4]. The study was performed using 900ml of 0.1N HCl at 37 ±0.5°C at a rotational speed of 50 rpm. The time taken for tablet to emerge on surface of medium and the duration of time by which the tablet constantly remain on surface of medium was noted [7]. The measurements were carried out for each series of tablets (n = 3).

Swelling studies

The swelling of the polymers can be measured by their ability to absorb water and swell. The swelling property of the formulations was determined by using USP dissolution apparatus II [8]. Medium used was 0.1N HCl, 900 ml, maintained at 37 ±0.5°C throughout the study. At hourly intervals, the previously weighed tablets were removed, gently wiped with a tissue to remove surface water, and reweighed [9]. The degree of swelling was calculated using the following equation [10].

Swelling Index (S.I.) = $\{(W_t - Wo) / Wo\} \times 100$

Where, S.I. = swelling index

Wt = weight of tablet at time t

Wo = weight of tablet before immersion

Bioadhesion study

The ex vivo mucoadhesion time was performed (n = 3) after application of the tablet on freshly cut goat gastric mucous membrane, which is obtained from local slaughter house. Goat's fresh gastric mucosa was pasted on the glass slide using a cyanoacrylate adhesive, and the mucoadhesive core side (MA layer) of tablet was wetted with a drop of pH 1.2 acid buffer and adhered to goat's gastric mucosa by applying a light force with fingertip for 30 s. The glass slide was then placed in a beaker, which was filled with 200 ml of the pH 1.2 acid buffer and kept at 37°C ±0.5°C. After 2 min, a slow stirring rate (50 rpm) was applied to simulate the gastric environment, and the tablet mucoadhesion was monitored for 12 h [11, 12]. The time for the tablet to detach from goat's gastric mucosa was recorded as the mucoadhesion time.

Dissolution studies

The in vitro drug release was determined by USP apparatus-II Paddle dissolution apparatus

(Electrolab Tablet Dissolution tester – USP, Model No. TDT – 06P). The release of losartan potassium from matrix tablets was performed at 37 ±0.5°C using a standard dissolution apparatus [2]. The rotation speed was 50 rpm, and the dissolution medium was 900 ml 0.1N HCl. Aliquots (5 ml) of solution were taken at specific time intervals and the volume was made up to the original value by adding fresh dissolution medium. The amounts of losartan potassium released in the dissolution medium were determined spectrophotometrically at 254 nm [2] (Model No. V-630, Jasco 2000 series). Results are given as the mean values of six determinations. The cumulative % drug release at different time intervals was calculated using PCP DISSO – V3 software (Poona College of Pharmacy, Pune, India).

Kinetic modeling of drug release profiles

To describe the kinetics of drug release from the formulations, mathematical models zero-order, first order, Higuchi, Hixon-crowell, Korsmeyer-Peppas were used [13]. The model with the highest correlation coefficient was considered to be the best fitting one.

Physical stability studies

The tablets were stored at 40°C/75% RH for 3 months [14]. Physical stability studies were conducted according to ICH guidelines [15]. The optimized formulation, F10 was enclosed in polyethylene bottle and loaded in a desiccator containing a saturated solution of sodium chloride (75% RH). The desiccator was kept in an oven at 40°C for 3 months [16]. At specified time intervals, the tablets were examined for any statistical difference in their hardness values, thickness, friability, matrix integrity, dissolution studies, adhesion retention periods and floating characteristics.

RESULTS AND DISCUSSION

Physicochemical characteristics of tablets

The incorporation of MCC in the designed systems was suggested to impart superior flow and enhance powder compaction in direct compression.

Moreover, it was proved [17] that MCC is capable of swelling in contact with aqueous fluids as simulated gastric fluid leading to an increase in the water uptake capacity, porosity of the matrix and consequently would enhance floating abilities.

Gambhire et al. [18], studied the influence of the tablet hardness on: (i) The floating lag time and (ii) Drug release profile and concluded that tablet hardness had no (or little) effect on the drug release profile but was a determining factor with regard to buoyancy of the tablets. Increasing the hardness (>5–6 $kg.cm^{-2}$) would possibly lead to prolongation of the floating lag time by affecting the rate of the tablet penetration by the dissolution medium. Based on these conclusions, the hardness of the floating tablets was adjusted, in the current work, to 4-5 $kg.cm^{-2}$. The physicochemical properties of the tablets are summarized in table 2. The thickness of all tablet batches ranged from 2.98 ±0.04 to 3.16 ±0.05 mm. All the tablet formulations showed acceptable physicochemical properties and complied with the pharmacopoeial specifications for weight variation, drug content and friability. The weight of the tablets ranged from 195.26 ±05.56 to 205.06 ±07.62 mg. All the prepared formulations meet the USP [6] requirements for weight variation tolerance. Drug uniformity results were found to be good among different batches; the percentage of drug content ranged from 96.69 ±0.34 to 101.91 ±0.09%. The percentage friability for all formulations was less than 1%, indicating good mechanical resistance.

Dissolution studies

The graph of cumulative drug release (%) v/s time (h) was plotted for each formulation and depicted as figure 1.

Effect of different concentrations of polymers on *in vitro* release of losartan potassium was studied. All formulations led to sustained release of losartan potassium. Initially, tablets containing 40 mg of HPMC K4M (F1) and SCMC (F9) could not retain its physical integrity for desired period (12 h) of time. As the concentration of CP 971P increases in remaining batches containing HPMC K4M (F2, F3 and F4) and sodium CMC (F10, F11 and F12), it retains integrity up to desired period of time (12 h). Further, formulation (F1, F5 and F9) provided burst drug release. In case of F1, F5 and F9 burst drug release after 2 h was 30.24

Table 2. Physicochemical properties of the prepared losartan potassium tablets

Formulation code	Tablet weight (mg)	Thickness (mm)	Tablet Hardness (kg.cm-2)	Tablet friability (%)	Drug content (%)	Adhesion retention period (h)	Floating lag time (min)	Total floating duration (h)
F1	202.45 ±05.85	3.16 ±0.05	4.6 ±0.2	0.59 ±0.030	97.46 ±0.25	06.32 ±0.1	3.8 ±0.9	08.8 ±0.7
F2	205.06 ±07.62	3.01 ±0.09	4.9 ±0.3	0.64 ±0.015	96.69 ±0.34	07.39 ±0.5	4.1 ±0.3	>12
F3	204.21 ±05.23	3.15 ±0.07	5.1 ±0.2	0.56 ±0.021	101.32 ±0.14	09.29 ±0.8	4.7 ±0.8	>12
F4	198.14 ±05.68	3.12 ±0.04	4.5 ±0.3	0.63 ±0.012	103.87 ±0.24	10.02 ±0.4	4.8 ±1.1	>12
F5	195.85 ±03.56	3.09 ±0.05	4.9 ±0.1	0.52 ±0.014	98.58 ±0.28	07.15 ±0.7	4.1 ±0.8	>12
F6	197.26 ±04.63	2.99 ±0.08	4.7 ±0.4	0.46 ±0.028	99.82 ±0.55	08.65 ±0.9	4.8 ±0.5	>12
F7	207.71 ±06.98	3.12 ±0.06	4.6 ±0.4	0.34 ±0.015	97.98 ±0.34	09.76 ±0.6	5.1 ±0.6	>12
F8	199.43 ±04.03	3.06 ±0.05	4.2 ±0.2	0.48 ±0.023	100.58 ±0.84	10.34 ±0.9	5.5 ±0.8	>12
F9	196.54 ±09.39	3.11 ±0.03	4.8 ±0.3	0.63 ±0.027	99.04 ±0.53	07.76 ±0.6	2.5 ±0.5	07.04 ±0.5
F10	195.26 ±05.56	2.98 ±0.04	4.7 ±0.2	0.39 ±0.042	97.84 ±0.25	08.25 ±0.9	2.8 ±0.5	>12
F11	203.65 ±07.19	3.07 ±0.07	4.8 ±0.1	0.67 ±0.023	104.91 ±0.09	08.38 ±0.5	3.8 ±1.1	>12
F12	201.54 ±05.43	3.10 ±0.13	4.9 ±0.4	0.61 ±0.074	102.75 ±0.64	08.46 ±0.3	4.1 ±1.3	>12

±2.55, 22.98 ±1.46 and 48.84 ±3.23%, respectively. Therefore, amount of CP 971P was increased to 2.5 (F2, F6 and F10), 5.0 (F3, F7 and F11) and 7.5 (F4, F8 and F21) mg/tablet. As the concentration of CP 971P increased, initial burst drug release as well as drug release in the latter hours decreased as compared to the formulations without CP 971P. This is substantiated that CP 971P which has a pK_a of 6.0, remains unionized in the acidic environment of dissolution medium. Hence, CP 971P acting as a physical barrier to drug release. It was observed that the concentration of HPMC and CP 971P sustained the release of a drug for longer period of time. This might be due to swelling of the tablet due to CP 971P and HPMC leading to an increase in the dimension of the tablet with an increase in the diffusion pathways and thus a reduction in dissolution rate. In case of F2, F3 and F4 formulations, burst drug release after 2 h was found to be 13.21 ±3.94, 12.24 ±4.24 and 10.43 ±3.92%, respectively. In case of formulation F2, F3 and F4, cumulative drug release at the end of 12 h was found to be 85.02 ±2.98 and 73.84 ±1.16 and 59.43 ±1.65%, respectively.

Formulation F6, F7 and F8 containing HPMC K15 with CP 971P showed similar pattern of drug release as that of the formulation F2, F3 and F4 containing HPMC K4M with CP 971P. In case of F6, F7 and F8 formulations, burst drug release after 2 h was found to be 14.24 ±2.55, 11.35 ±1.24 and 10.43 ±2.63%, respectively. In case of formulation F6, F7 and F8, cumulative drug release at the end of 12 h was found to be 76.24 ±3.55 and 62.09 ±3.37 and 47.98 ±4.57%, respectively.

Comparing release of formulations F1, F5 and F9 containing HPMC K4M, HPMC K15M and SCMC, respectively; F1 and F5 showed similar pattern of drug release with F1 releasing more drug at the end of the 12 h than F5. This was attributed to the fact that, viscosity of the HPMC K15M is more than that of the HPMC K4M causing the drug to release slowly. Formulation F9 releases the entire drug in 9 h with tablet being dispersed in the dissolution medium unable to maintain its physical integrity, presumably due to faster hydration and erosion of SCMC compared with HPMC. SCMC is a hydrophilic polymer, which swelled during dissolution, forming a gel layer. The loosely bound polymer molecules were easily eroded, allowing release of drug at a faster rate. The cumulative drug release at the end of 12 h of formulation F1, F5 and F9 was found to be 96.54 ±4.57, 84.24 ±2.24 and 100 ±3.25%, respectively.

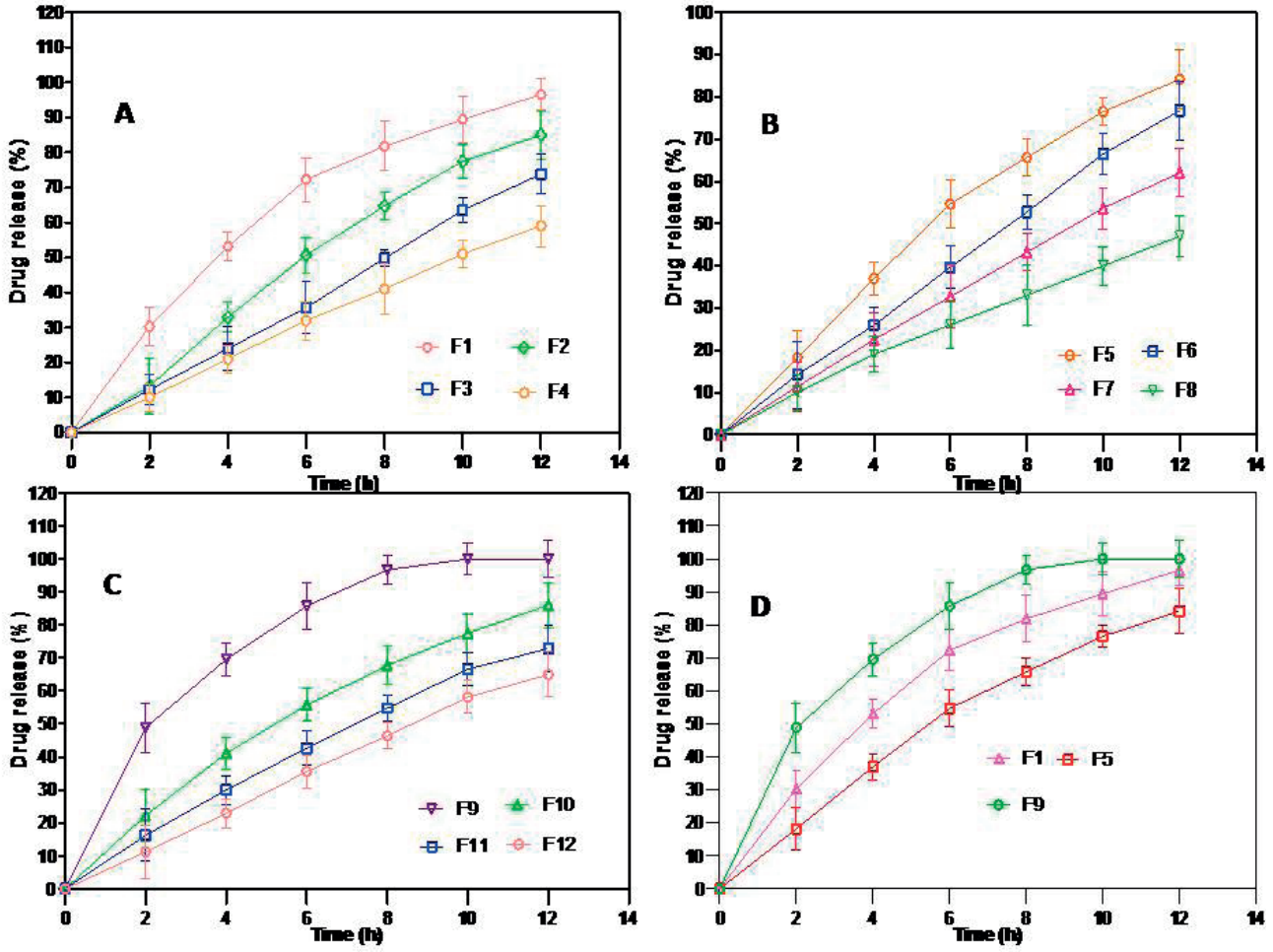

Figure 1. (A) *in vitro* dissolution studies of formulations F1- F4
(B) *in vitro* dissolution studies of formulations F5- F8
(C) *in vitro* dissolution studies of formulations F9- F12
(D) Comparative *in vitro* dissolution studies of formulations F1, F5 and F9

Swelling indices

As can be seen in figure 2, it can be concluded that the matrices hydration volume increases at the beginning, attains a maximum and then declines. Formulation F12 containing combination of CP with SCMC showed the highest SI throughout the study period. This may be related to the high affinity of SCMC containing matrices to the test medium. The maximum SI of this formulation (2.56 ±0.15) was achieved after 6 h. On the other hand formulation F9 with SCMC alone showed intermediate SI with maximum swelling (1.87 ±0.16) in 6 h. This was attributed to the fact that CP 971P is synthetic high molecular weight cross linked polymer of acrylic acid. These carbomers readily hydrate, absorb water with good degree of swelling. At high water content, the polymer chain relaxation takes place, thereby increasing the hydrodynamic volume of polymer compact. As polymer chain becomes more hydrated and gel becomes more diluted, the disentanglement concentration may be reached, i.e. the critical polymer concentration below which the polymer chain disentangle and detached from a gelled matrix. These events result in swelling. This effect of CP on swelling indices had been seen in other formulations too where it was used in combination with HPMC.

Comparing the swelling indices of formulations F1, F5 and F9 containing HPMC K4M, HPMC K15M and SCMC, respectively; formulation F1 showed rapid hydration in initial 6 h and achieved maximum swelling (1.45 ±0.1), followed by decline. The tablet was unable to maintain physical integrity for the period of 12 h, and fragments of tablet were seen in

the dissolution medium after 8 h. Formulation F5 showed continuous increased in the SI and achieved maximum swelling (1.66 ±0.13) in 12 h. This could be related to the lower affinity of HPMC K15M containing matrices to the test medium. HPMC does not swell at an appreciable level and hence HPMC containing formulations had lower SI as compared to formulation containing CP. Due to higher affinity of SCMC to the dissolution medium, formulation F9 showed rapid hydration with maximum swelling (1.87 ±0.15) achieved after 6 h followed by erosion and break down of tablet. On the other hand formulations containing combination of CP and HPMC (F2, F3, F4, F6, F7, F8) showed good swelling indices with maximum SI (1.96 ±0.17) shown by formulation F4. Non-ionic polymer HPMC and anionic polymer CP produces synergistic increase in viscosity, this was due to strong hydrogen bonding between the carboxylic group and the hydroxyl group of the HPMC leading to stronger cross- linking between two polymers. But as the concentration of CP lowered, the formulation was unable to withstand in dissolution medium till 12 h, and hence swelling was followed by sharp erosion.

Floating lag time and duration

As shown in table 2, the different polymer ratios have a marked effect on the floating lag time of the formulations prepared with a constant $NaHCO_3$: Citric acid ratio. The tablets with low-viscosity grade HPMC K4M exhibited short floating lag time and floated for longer duration as compared with formulations containing high viscosity grade HPMC K15M. This indicated that the molecular weight

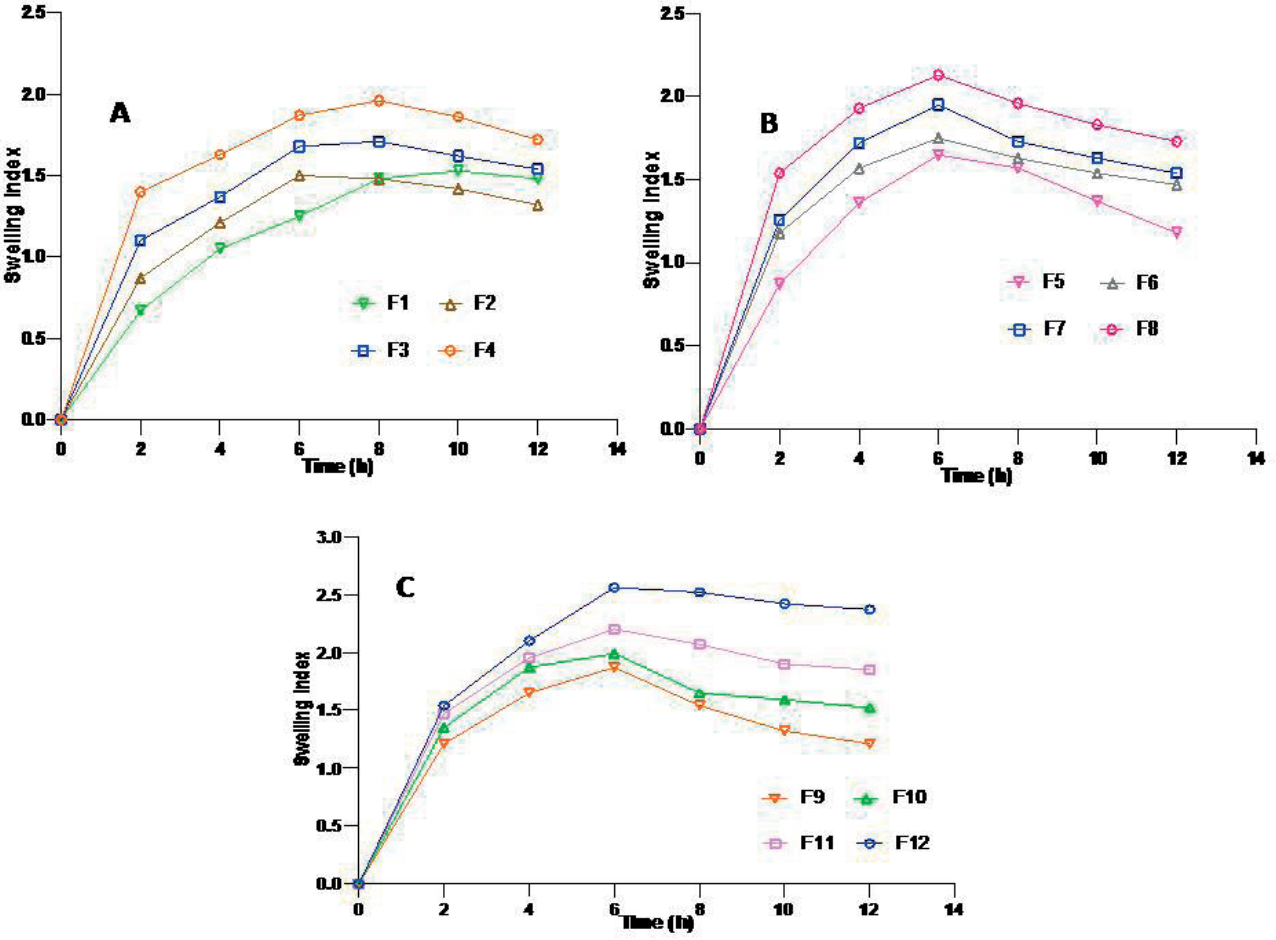

Figure 2. (A) Swelling profiles showing the swelling indices against time (h) of formulations F1- F4
(B) Swelling profiles showing the swelling indices against time (h) of formulations F5- F8
(C) Swelling profiles showing the swelling indices against time (h) of formulations F9- F12

distribution or viscosity of the gel-forming polymer HPMC influenced the *in vitro* buoyancy. Reduction in HPMC level in the formulations prolonged the floating lag time and shortened the total floating time. With reference to buoyancy studies results it can be concluded that the batch containing HPMC K4M polymers showed good floating lag time (FLT) and total floating time (TFT) when compared to batch containing HPMC 15KM and SCMC polymers. This could be explained with regard to the rate of the test medium penetration into these matrices and consequently the time required for gel formation. The pH of the stomach is elevated under fed condition (~3.5), therefore citric acid was incorporated in the formulation to provide an acidic medium for $NaHCO_3$.

It can be concluded that formulation F10 containing combination of sodium bicarbonate (30 mg) and citric acid (10mg) with SCMC (37.5 mg) and CP (2.5mg) was found to achieve optimum *in vitro* buoyancy and floatability of more than 12 h.

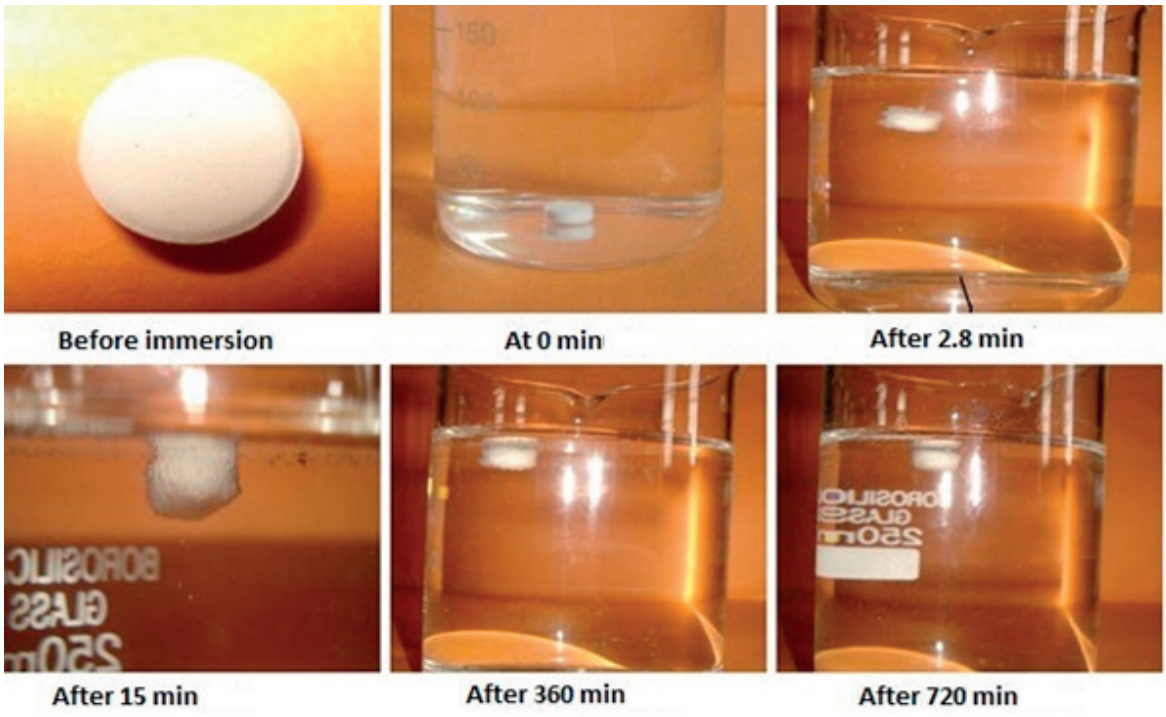

Figure 3. Photographs taken during *in vitro* buoyancy study of formulation F10 in 250 ml 0.1 N HCl at different time intervals.

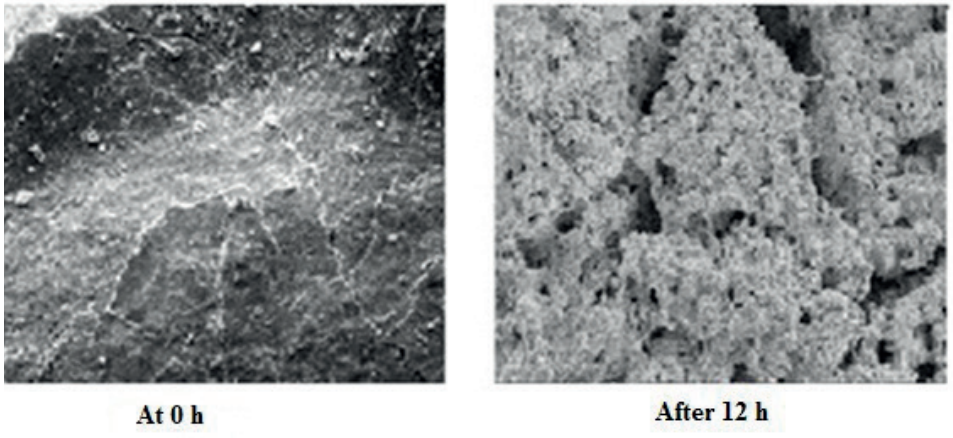

Figure 4. Scanning electron microscopy photograph taken during the dissolution studies at 0 and 12 h

Mucoadhesion studies

The maximum mucoadhesion duration (10.34 ±0.9 h) was observed in formulation containing CP 971P and HPMC K15M (Table 4) in a concentration of 7.5 mg and 32.5 mg (Formulation F4), respectively. Formulation F1 showed the lowest mucoadhesion while formulations (F2 and F3) containing CP and HPMC K4M show considerable mucoadhesion duration. HPMC and CP combination showed good mucoadhesion on account of their hydrogen bonding properties. This property of both polymers is closely associated with mucoadhesion because polymer swells readily when come in contact with hydrated mucus membrane, which in turn increases diffusion and interpenetration of polymer. The same thing applies for the increase in mucoadhesive duration for the formulations (F6-F8) containing combination of CP and HPMC K15M to that of the formulation F5 which only contain HPMC K15M.

Formulation (F5) containing HPMC K15M shows higher mucoadhesion time (07.15 ±0.7 h) compared to formulation F1 (06.32 ±0.1 h) containing HPMC K4M due to higher viscosity of HPMC K15 M. In order to increase the mucoadhesive time of low viscosity polymer containing HPMC K4M was combined with CP 971P having good mucoadhesive property. This combination results in good mucoadhesive properties as seen in F2 to F4. From the above results it was found that polymers having high molecular weight and high viscosity exhibited higher adhesion. HPMC K15M and CP 971P were found to be having good mucoadhesive property. HPMC and CP possess hydroxyl and carboxyl groups, respectively required for mucoadhesion. This correlation however, is not applicable to the blend of SCMC and CP 971P, but with this blend, an increase in CP 971P content of formulation did not lead to synergistic increase in the adhesion time.

Kinetic Evaluation of Release Data

On application of different release kinetics model mentioned earlier, it was found that maximum formulation batches has shown better fitting with Korsmeyer-Peppas model. Korsmeyer-Peppas equation gave higher values for the correlation coefficient for maximum formulations, as compared to other release kinetics model. Thus, fitting of drug release data into Korsmeyer-Peppas equation indicates, the possible mechanism of drug release is by diffusion and erosion through tablets (non-Fickian).

Table 3. Mathematical modeling and release kinetics of losartan potassium from the prepared tablets

Formula code	Zero-order plots	First order plots	Higuchi's plots	Korsmeyer–Peppas plots		
	Correlation coefficient (R2)	Correlation coefficient (R2)	Correlation coefficient (R2)	Correlation coefficient (R2)	Diffusional exponent (n)	Order of release
F1	0.9755	0.9086	0.9954	0.9914	0.7888	Non-Fickian
F2	0.9972	0.9442	0.9928	0.9973	1.0826	Case II transport
F3	0.9991	0.9536	0.9867	0.9993	1.0301	Case II transport
F4	0.9990	0.9698	0.9873	0.9939	0.8980	Non-Fickian
F5	0.9960	0.9630	0.9911	0.9948	0.8582	Non-Fickian
F6	0.9989	0.9761	0.9836	0.9947	0.8504	Non-Fickian
F7	0.9991	0.9521	0.9920	0.9990	0.9303	Non-Fickian
F8	0.9959	0.9445	0.9939	0.9983	0.8975	Non-Fickian
F9	0.9732	0.9199	0.9959	0.9943	0.5388	Non-Fickian
F10	0.9944	0.9495	0.9986	0.9979	0.7614	Non-Fickian
F11	0.9991	0.9612	0.9912	0.9993	0.8513	Non-Fickian
F12	0.9998	0.9505	0.9903	0.9998	1.0412	Case II transport

Stability studies

The results of stability study of optimized formulation F10 revealed that there was no significant change in tablets color, thickness, hardness, friability, drug content, mucoadhesion duration, total floating duration and *in vitro* drug release with slightly decrease in hardness on storage. So, the formulation was found to be stable for the tested period under accelerated stability conditions.

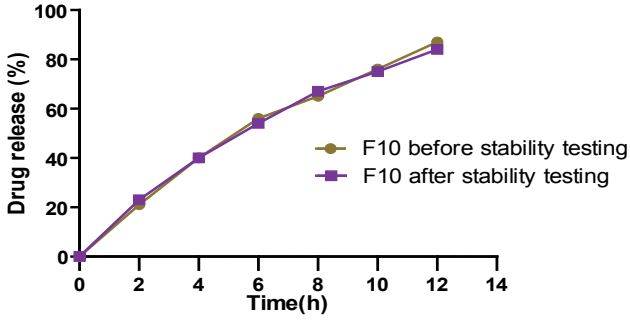

Figure 5. Release profile of formulation F10 after stability testing

Table 4. Stability testing of optimized formulation F10

Formulation	Tablet weight (mg)	Tablet Hardness ($kg.cm^{-2}$)	Thickness (mm)	Tablet friability (%)	Drug content (%)	Adhesion retention period (h)	Floating lag time (min)	Total floating duration (h)
F10 (Before stability Testing)	195.26 ±05.56	4.7 ±0.2	2.98 ±0.04	0.39 ±0.042	97.84 ±0.25	08.25 ±0.9	2.8 ±0.5	>12
F10 (After stability Testing at 40°C/75% RH for 3 months)	197.32 ±04.38	4.6 ±0.2	3.10. ±0.06	0.36 ±0.056	96.30 ±0.31	08.10 ±1.0	3.1 ±0.6	>12

CONCLUSION

The mucoadhesive drug delivery system has potential to be an effective sustained release system over a long period of time for losartan potassium. The type and level of polymer used are important factors that can affect the drug release and also the physico-chemical properties of these mucoadhesive tablets. Formulation F10 shows better retention period (8.25 ±0.9 h), *in vitro* release (87.32%), floating lag time (2.8 ±0.5 min) and total floating duration (≥12 h). Therefore F10 formulation was found to be the best formulations to achieve the aim of this study.

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