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# DESIGN, FORMULATE AND EVALUATION OF SUSTAIN RELEASE FLOATING MATRIX TABLETS OF LOSARTAN POTASSIUM

**Haritha N*, Tarachandhra Sekar C, Umasankar K**

Department of Pharmaceutics,
Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati-517506, Andhra Pradesh, India.

**ABSTRACT**

An orally administered sustained release matrix tablets of Losartan potassium using hydrophilic polymers hydroxypropyl methylcellulose (HPMC) with different grads like HPMC K4M, HPMC E10M and HPMC K100M and to optimize using a 3(2) full factorial design, the drug delivery system encounters a wide range of highly variable conditions, such as pH, agitation intensity, and composition of the gastrointestinal fluids as it passes down the G.I tract. Losartan potassium is an angiotensin II receptor antagonist readily absorbed from the GIT that produce more predictable and increased bioavailability of drug. Gastroprotective dosage forms are drug delivery systems which remain in the stomach for an extended period and allow both spatial and time control of drug liberation. These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), and effervescent components, The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach multiple unit floating pills that generate carbon dioxide when ingested, floating mini capsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC). The Formulation of floating tablets of Losartan Potassium with HPMC K4M, HPMC E10M and HPMC K100M and floating systems based on ion exchange resin technology.

**KEY WORDS**: Losartan Potassium, Floating Matrix Tablet, Sustain Release.

## INTRODUCTION

The oral route currently represents the most predominant and preferable route of drug delivery. Unlike majority of parenteral dosage forms [1], it allows ease of administration by the patient and it's the natural, and therefore a highly convenient way for substances to be introduced into the human body. Oral drug delivery systems have progressed from conventional immediate release to site-specific delivery over a period of time. Every patient would always like to have an ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action [2].

### Types of floating drug delivery systems (FDDS)

Floating properties based on the mechanism of buoyancy are divided into:

**1. Non effervescent systems** with inherent low density or low density due to swelling;

**2. Effervescent systems** with low density due to gas generation and entrapment.

Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastrointestinal tract and aid in enhancing the absorption and also for the drugs having specific site of absorption in the upper part of the small intestine. It should stay in the stomach, maintain its structural integrity, and release drug constantly from the dosage form [3]. The success of HBS capsule as a better system is best exemplified.

### Objective

To design, formulate and evaluation of sustain release floating matrix tablets of losartan potassium.

Corresponding Author:- **Haritha N** E-mail: harithanagalappagari@gmail.com

## MATERIALS AND METHODS

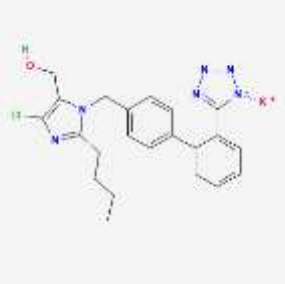
### DRUG PROFILE

Nonproprietary name: **Losartan potassium**

*Chemical name* ***(2-butyl-4-chloro-1-{[2'-(1H-tetrazo5yl) biphenyl-4yi] methyl-1H- imidazol-5-yl)methanol***

Molecular formula: $C_{22}H_{23}ClN_6O$

Molecular weight : 422.91 g/mol



**Physicochemical Profile**

Description: White to off White crystalline powder

Melting point:172 - 174 °c

Solubility: It is soluble in water.

**Formulation Development**

**Preparation of Floating Matrix Tablets of Losartan Potassium**

**Technology Applied**: Direct compression.

The key ingredients included in the formulations are:

- Hydrophilic Polymers : HPMC K4M, HPMC E10M and HPMC K100M to modify the pattern of drug release from matrix.
- Effervescent agent: Sodium bicarbonate
- Filler: Micro Crystalline Cellulose
- Anti-adherent: Talc
- Lubricant: Magnesium Stearate

Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed geometrically, to this required quantity of Losartan Potassium was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and powdered with pestle [4]. The powder is passed through sieve no 40 and mixed with the drug blend which is also passed through sieve no. 40 (#). The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. The mixture equivalent to 400mg was compressed into tablets with 10 mm round concave punches at a hardness of 6 kg/cm$^2$ [5].

**Evaluation of Floating Matrix Tablets of Losartan Potassium** [6]

- Weight variation, Thickness, Hardness, Friability, Floating time, Floating lag time
- Drug content
- *In vitro* drug release

This type of analysis of release behavior is valuable is to the formulator for comparative purposes (Hariharan et al., 1997b). The Release exponent can be obtained from the slope and the Constant ($K_k$) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t [7].

**Higuchi Model** [8]

$$Q_t = K_H t^{1/2}$$

Where $Q_t$ = the amount of drug released at time t and $K_H$ = the Higuchi release rate.

This is the most widely used model to describe drug release from pharmaceutical matrices. Therefore, a plot of amount of drug released versus the square root of time should be linear if drug release from the matrix is diffusion controlled. Alternatively, the drug release rate is proportional to the reciprocal of the square root of time [9]. An important advantage of the above equations is its simplicity [10].

## RESULTS AND DISCUSSION

### Calibration Curves of Losartan Potassium

An UV- Spectrophotometric method was used for estimation of Losartan Potassium. A solution of Losartan Potassium (10µg/ml) was scanned in the wavelength range of 200-300 nm and found to have maximum absorption (λmax) at 256 nm. The standard plot of Losartan Potassium was prepared in 0.1 N HCl (pH 1.2). The standard graph showed good linear ity with $R^2$ value 0.9942.

### Drug-Excipient Compatibility Studies

### Fourier Transform Infrared (FTIR) Spectroscopy

Potential chemical interaction between drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibility of chemical interaction between drug and polymer FTIR spectra of pure Losartan Potassium and optimized formulations were analyzed over the range 400–4000 $cm^{-1}$. The IR spectrum of pure Losartan Potassium showed strong absorption bands at wave numbers of 3434 $cm^{-1}$, 2956 $cm^{-1}$, 1577 $cm^{-1}$, 1460 $cm^{-1}$ and 997 $cm^{-1}$ attributable to Cyclic amines, C-H stretching, C=O stretching, O-H bending and Chlorine respectively. FTIR spectra of the optimised formulations displayed all the characteristic bands of both drug and excipients, without any significant spectral shift. This suggested that there was no potential chemical interaction between the components of the formulations.

### Differential Scanning Calorimetry (DSC)

The thermal properties of the drug and the mixture of drug and excipients are of important interest since this can help to assess the interaction among different components of the formulations. The DSC curve of

Losartan Potassium showed a single endothermic peak at 176.11°C corresponding to its melting point (MP 172–174°C). The DSC curves of optimised formulations showed the sharp endothermic peak of the drug at 179.17°C (FS4), 174.69°C (FS8), 180.17°C (FS12), 175.81°C (FM5), 176.92°C (FM10), 174.93°C (FM15), 177.57°C (FH6), 178.46°C (FH8) and 175.84°C (FH12). In optimized formulations, endothermic peak of drug was well preserved with slight changes in terms of broadening or shifting towards the lower or higher temperature. It has been reported that the quantity of material used, especially in drug–excipient mixtures, affects the peak shape and enthalpy. Thus, these minor changes in the melting endotherm of drug could be due to the mixing of drug and excipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility. Thus, it was concluded that Losartan Potassium is compatible with all the excipients used in the formulation.

**Evaluation of Physical Parameters Floating Tablets of Losartan Potassium**

All the prepared formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeias limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

**Floating Properties of Losartan potassium Floating Tablets**

All the formulations were tested for floating properties like floating lag time and total floating time. The results of the tests were tabulated. All the batches showed good *in vitro* buoyancy.

***In – Vitro* Drug Release Data and Profiles**

The dissolution conditions used for studying the drug release from the matrix tablets of LOSARTAN POTASSIUM were:

**Apparatus:** USP Type 2 (paddle)
**Agitation speed (rpm):** 50
**Medium:** 0.1N HCl (pH 1.2), 900ml
**Temperature:** 37.0 ± 0.5 C
**Time:** 0.5, 1, 2, 3, 4, 6, 8, 10, and 12hr
**Wavelength:** 256nm

**RESULTS AND DISCUSSION**

**Table 1. Composition of floating matrix tablets of Losartan Potassium**

| Ingredients (Weight in mg) | Formulations | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F 9 | F10 | F11 | F12 |
| Losartan Potassium | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| (HPMC) Methocel K4M | 63 | 75 | 88 | 100 | - | - | - | - | - | - | - | - |
| (HPMC) Methocel E10M | - | - | - | - | 63 | 75 | 88 | 100 | - | - | - | - |
| (HPMC) Methocel K100M | - | - | - | - | - | - | - | - | 63 | 75 | 88 | 100 |
| Sodium bicarbonate | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 | 27 |
| Micro Crystalline cellulose (Avicel pH 102) | 150 | 138 | 125 | 113 | 150 | 138 | 125 | 113 | 150 | 138 | 125 | 113 |
| Purified Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium Stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

**Table 2. Absorbance of Losartan Potassium against different concentrations at $\lambda_{max}$ (256nm)**

| Concentration (mcg/ml) | Absorbance |
|---|---|
| 0 | 0 |
| 10 | 0.245 |
| 20 | 0.493 |
| 30 | 0.78 |
| 40 | 0.941 |

**Table 3. Physical properties of powder blends of tablet formulations**

| Formulation | CI | Angle of repose | Hausner ratio |
|---|---|---|---|
| F1 | 12.3 | $26.8^o$ | 1.14 |
| F2 | 15.9 | $27.5^o$ | 1.18 |
| F3 | 12.8 | $28.0^o$ | 1.13 |
| F4 | 15.7 | $29.4^o$ | 1.18 |
| F5 | 12.4 | $28.5^o$ | 1.14 |

| | | | |
|---|---|---|---|
| F6 | 11.2 | 29.4$^o$ | 1.13 |
| F7 | 13.6 | 28.4$^o$ | 1.02 |
| F8 | 12.5 | 26.9$^o$ | 1.16 |
| F9 | 14.6 | 27.5$^o$ | 1.15 |
| F10 | 12.6 | 27.1$^o$ | 1.17 |
| F11 | 12.5 | 28.6$^o$ | 1.18 |
| F12 | 11.3 | 29.8$^o$ | 1.14 |

**Table 4. Physical parameters of floating matrix tablets of Losartan Potassium**

| Formulation code | Weight variation (mg) | Hardness (kg/cm$^2$) | Thickness (mm) | Friability (%) | Assay (%) |
|---|---|---|---|---|---|
| F1 | 298.38±3.84 | 6.5±0.3 | 4.84±0.05 | 0.32 | 98.23 |
| F2 | 301.52±2.87 | 6.6±0.5 | 4.76±0.06 | 0.19 | 99.65 |
| F3 | 299.23±2.73 | 6.8±0.4 | 4.86±0.03 | 0.26 | 99.12 |
| F4 | 302.6±2.13 | 6±0.5 | 4.76±0.04 | 0.33 | 98.44 |
| F5 | 300.19±3.48 | 7±0.2 | 4.63±0.06 | 0.29 | 99.23 |
| F6 | 301.71±2.3 | 6.8±0.4 | 4.65 ±0.06 | 0.22 | 98.63 |
| F7 | 297.2±1.19 | 6.8±0.5 | 4.68±0.05 | 0.37 | 99.65 |
| F8 | 299.46±2.27 | 5.9±0.2 | 4.55±0.25 | 0.23 | 98.65 |
| F9 | 300.67±3.84 | 6.8±0.5 | 4.506±0.04 | 0.29 | 98.45 |
| F10 | 298.38±3.84 | 6.5±0.3 | 4.62±0.07 | 0.37 | 99.64 |
| F11 | 300.52±2.87 | 6.8±0.5 | 4.78±0.02 | 0.41 | 98.12 |
| F12 | 298.23±2.73 | 6.7±0.2 | 4.60±0.04 | 0.24 | 99.72 |

**Table 5. Floating properties of floating matrix tablets**

| Formulation Code | Floating Lag time (sec) | Total floating time (hrs) |
|---|---|---|
| F1 | 95 | >12 |
| F2 | 103 | >12 |
| F3 | 87 | >12 |
| F4 | 97 | >12 |
| F5 | 89 | >12 |
| F6 | 99 | >12 |
| F7 | 101 | >12 |
| F8 | 98 | >12 |
| F9 | 94 | >12 |
| F10 | 79 | >12 |
| F11 | 84 | >12 |
| F12 | 89 | >12 |

**Table 6. Cumulative percentage drug release of formulations with HPMC K4M**

| Time (hrs) | Cumulative % drug released | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| 0 | 0 | 0 | 0 | 0 |
| 0.5 | 23.72 | 17.43 | 12.09 | 18.85 |
| 1 | 35.16 | 25.38 | 17.78 | 26.32 |
| 2 | 50.08 | 35.08 | 26.21 | 29.16 |
| 3 | 67.58 | 51.93 | 28.45 | 34.15 |
| 4 | 77.73 | 62.15 | 33.43 | 36.99 |
| 6 | 83.83 | 73.88 | 54.07 | 44.82 |
| 8 | 90.87 | 81.09 | 60.47 | 51.93 |
| 10 | 99.96 | 87.04 | 72.92 | 56.91 |
| 12 | | 96.02 | 78.12 | 64.74 |

**Table 7. Cumulative percentage drug release of formulations with HPMC E10M**

| Time (hrs) | Cumulative % drug released | | | |
|---|---|---|---|---|
| | **F5** | **F6** | **F7** | **F8** |
| 0 | 0 | 0 | 0 | 0 |
| 0.5 | 21.75 | 19.47 | 12.07 | 18.49 |
| 1 | 30.94 | 28.16 | 18.48 | 24.84 |
| 2 | 38.98 | 37.48 | 24.17 | 29.16 |
| 3 | 52.6 | 49.32 | 28.45 | 34.86 |
| 4 | 60.68 | 56.8 | 40.53 | 36.92 |
| 6 | 72.85 | 64.6 | 54.05 | 39.84 |
| 8 | 88.41 | 78.72 | 62.6 | 49.09 |
| 10 | 96.14 | 85.13 | 71.49 | 54.78 |
| 12 | | 92.28 | 76.82 | 62.6 |

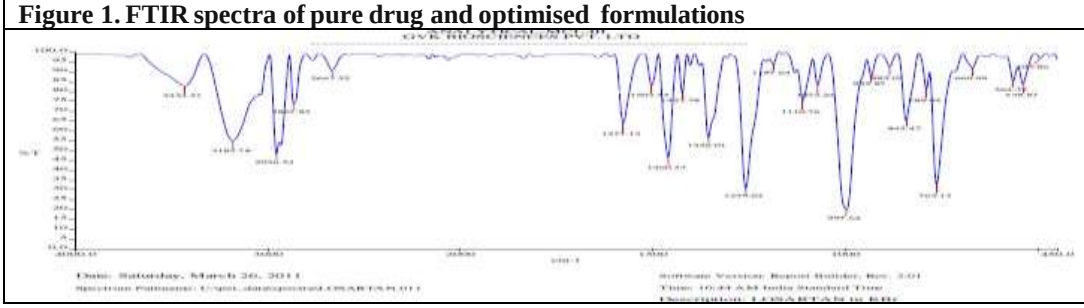
**Table 8. Cumulative percentage drug release of formulations with HPMC K100M**

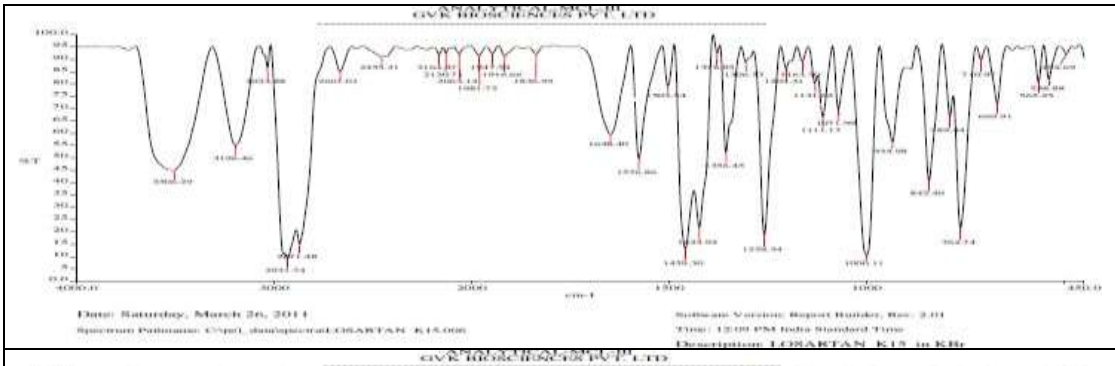
| Time (hrs) | Cumulative % drug released | | | |
|---|---|---|---|---|
| | **F9** | **F10** | **F11** | **F12** |
| 0 | 0 | 0 | 0 | 0 |
| 0.5 | 24.67 | 16.43 | 12.09 | 11.74 |
| 1 | 30.32 | 27.89 | 19.92 | 18.49 |
| 2 | 41.7 | 37.68 | 27.35 | 25.21 |
| 3 | 49.3 | 40.86 | 34.14 | 32.86 |
| 4 | 58.17 | 47.03 | 40.26 | 38.99 |
| 6 | 68.27 | 57.66 | 54.78 | 43.39 |
| 8 | 77.2 | 63.59 | 64.03 | 48.37 |
| 10 | 88.9 | 71.19 | 71.267 | 54.78 |
| 12 | 97.33 | 85.54 | 77.47 | 61.18 |

**Table 9. Regression coefficient ($R^2$) values of floating matrix tablets for different kinetic models**

| Formulation | Zero-order | First-order | Higuchi model | Korsmeyer Peppas | |
|---|---|---|---|---|---|
| | | | | $R^2$ | N |
| **F1** | 0.8341 | 0.4187 | 0.975 | 0.6021 | 0.354 |
| **F2** | **0.8966** | **0.4875** | **0.9886** | **0.5516** | **0.41** |
| **F3** | 0.9677 | 0.5741 | 0.9733 | 0.4216 | 0.413 |
| **F4** | 0.8865 | 0.4161 | 0.9827 | 0.2377 | 0.218 |
| **F5** | 0.9282 | 0.465 | 0.997 | 0.563 | 0.37 |
| **F6** | **0.9105** | **0.4563** | **0.9972** | **0.5122** | **0.357** |
| **F7** | 0.9592 | 0.5653 | 0.9834 | 0.431 | 0.4163 |
| **F8** | 0.8742 | 0.4099 | 0.9745 | 0.213 | 0.206 |
| **F9** | **0.914** | **0.4317** | **0.9972** | **0.5072** | **0.319** |
| **F10** | 0.9107 | 0.4531 | 0.989 | 0.4248 | 0.3257 |
| **F11** | 0.9502 | 0.539 | 0.9938 | 0.4422 | 0.4065 |
| **F12** | 0.8986 | 0.4885 | 0.9938 | 0.3205 | 0.322 |

**Figure 1. FTIR spectra of pure drug and optimised formulations**





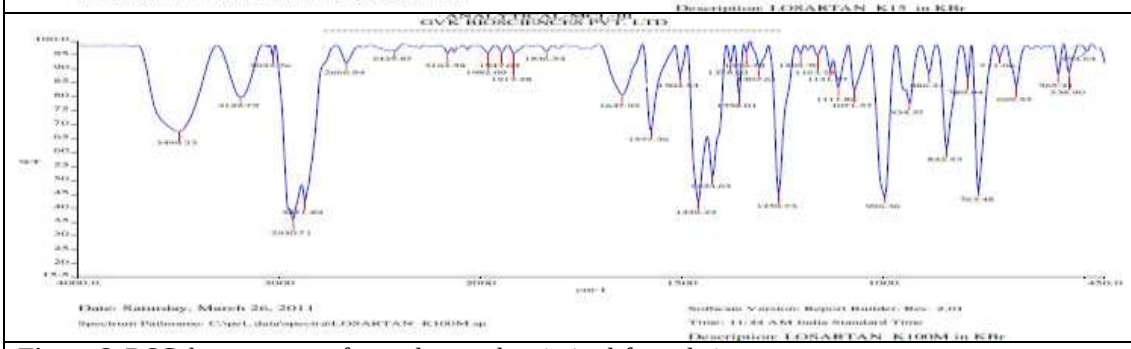


**Figure 2.** DSC thermograms of pure drug and optimised formulations

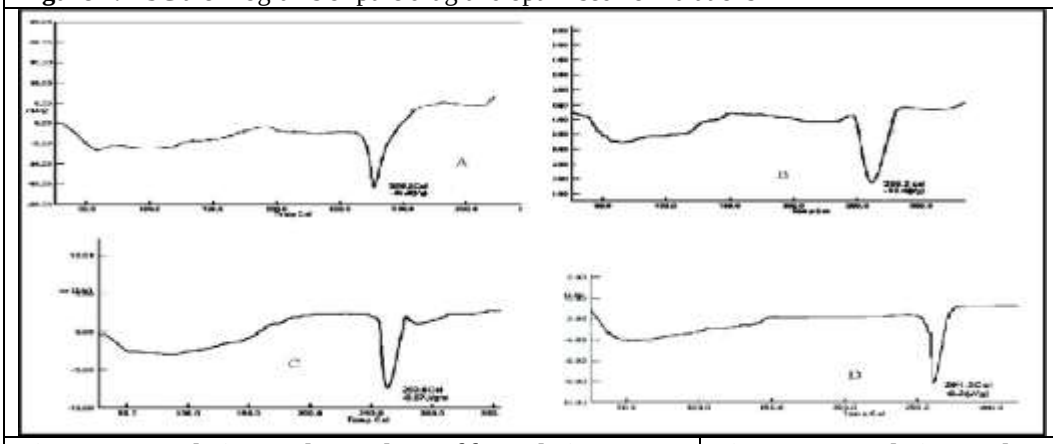


**Figure 3. Cumulative % drug release of formulations containing HPMC E10M**

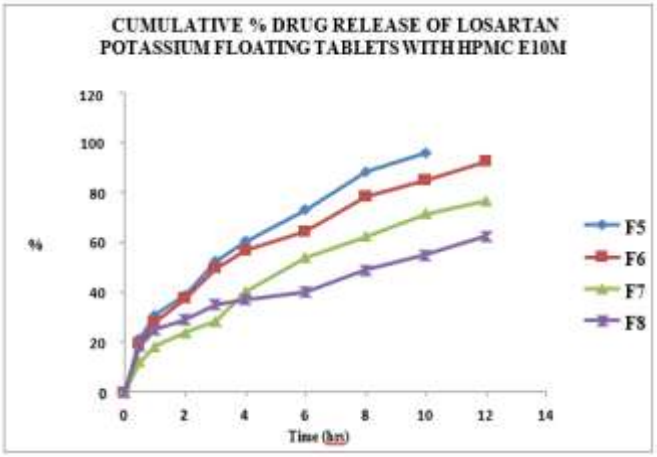
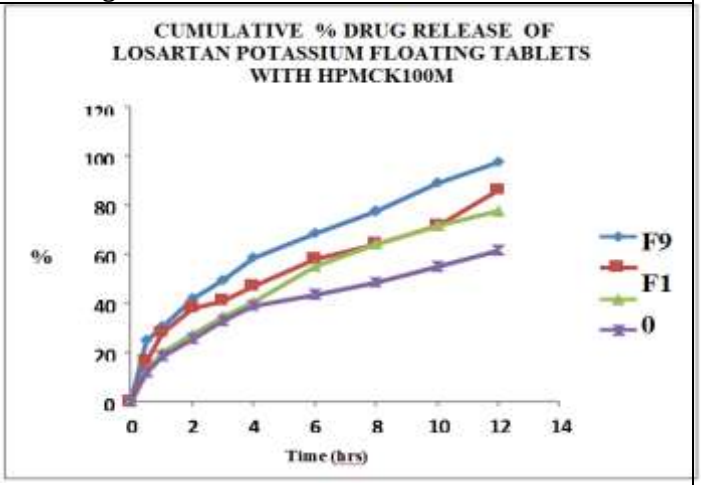



**Figure 4. Cumulative % drug release of formulations containing HPMC K100M**



**Cumulative % drug release of formulations containing HPMC K4M**

From the above figure it can be observed that the polymer HPMC K4M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F2, F3 and F4 was 96.02, 78.12 and 64.74 in 12 h respectively. Formulation F1 was unable to sustain the drug release desired period of time (total drug was released within 10 hr). Formulations F3 and F4 were failed to release the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. All these four formulations floated for 12 h. The release profiles from all these formulations were followed diffusion-controlled release complying with higher correlation coefficient values of Higuchi and Peppa's equations. The cumulative percent drug release from various formulations and release coefficients values of the various models for respective formulations were represented in tables 15 and 1 respectively. Formulation F2 was considered as best formulation among all the four formulations as it showed good buoyancy properties (floating lag time: 103 sec & floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

**Release profiles of formulations containing HPMC E10M**

It is evident that the polymer HPMC K15M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug released from formulations F6, F7and F8 was 92.28, 76.82 and 62.6 in 12 h respectively. Formulation F5 was unable to sustain the drug release desired period of time (total drug was released within 10 hr). Formulations F7 and F8 were failed to release the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. All these four formulations floated for 12 h. The release profile from all these formulations were followed diffusion-controlled release complying with higher correlation coefficient values of Higuchi and Peppas equations. The cumulative percent drug release from various formulations and release coefficients values of the various models for respective formulations were represented in tables 18 and 20 respectively. Formulation F6 was considered as best formulation among all the four formulations as it showed good buoyancy properties (floating lag time: 99 sec & floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

**Release profiles of formulations containing HPMC K100M**

From the above figure it is evident that the polymer HPMC K100M has sustaining effect on the release of drug from the floating matrix tablet. The percent of drug release from formulations F9, F10, F11 and F12 was 97.33, 85.54, 77.47 and 61.18 in 12 h, respectively. Formulations F10, F11 and F12 were failed to release the drug within the desired time. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer. All these four formulations floated for 12 h. The release profile from all these formulations were followed diffusion-controlled release complying with higher correlation coefficient values of Higuchi and Peppas equations. The cumulative percent drug release from various formulations and release coefficients values of the various models for respective formulations were represented in tables 19 and 20 respectively. Formulation F9 was considered as best formulation among all the four formulations as it showed good buoyancy properties (floating lag time: 94 sec & floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

**Mathematical Modeling of Dissolution Profiles**

The release from all the formulation was followed diffusion-controlled release followed by zero order which was confirmed by higher correlation coefficient values for Higuchi and release exponent values of Korsmeyer Peppas equations. All the formulations (both single unit and multiple unit tablets) followed Higuchi profiles with $R^2$ values more than 0.9, followed by Zero order which account for the diffusion-controlled release from the formulations.

**CONCLUSION**

Systematic studies were conducted for the preparation of floating formulations of Losartan Potassium. FTIR and DSC studies showed no incompatibility between drug, polymer and various excipients used in the formulations. Sustained release floating matrix tablets of Losartan Potassium were successfully prepared with hydrophilic polymers like HPMC K4M, HPMC E10M and HPMC K100M by simple direct compression method. Formulated tablets gave satisfactory results for various evaluation parameters like tablet dimensions, hardness, weight variation, friability, content uniformity, *in vitro* buoyancy properties and *in vitro* drug release. The tablet formulations F2, F6 and F9 gave better controlled drug release and floating properties in comparison to the other formulations. The drugs release from the optimised tablets was sufficiently sustained and fickian transport of drugs from tablets was confirmed as the release exponent value was less than 0.5.

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