

# Sustained release matrix tablet of 100 mg losartan potassium: Formulation development and *in vitro* characterization

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Sustained release matrix tablets of 100 mg losartan potassium HCl were fabricated with two release retarding polymers namely HPMC K100 M and affinisol by direct compression method. Nine trial formulations were prepared by varying content of these polymers, each from 50 mg to 100 mg; keeping the total weight of the tablet 310 mg. The best formulation was selected based on *in vitro* drug release profile for 12 hours conducted in Type II dissolution apparatus at 50 rpm and water as dissolution medium. Pre-compression parameters such as bulk density, tap density, Carr's index and Hausner ratio were evaluated for the selected tablet. The tablets were subjected to thickness, weight variation test, drug content, hardness and friability. Drug release kinetics, surface morphology and accelerated stability study were investigated for that selected formulation. Formulation F4 with the composition of 75 mg HPMC K100M and 100 mg affinisol was selected as the best formulation that extended the drug release up to 12 hours. Pre-compression parameters and other tableting properties were within the Pharmacopoeia limit. Release kinetics analysis proved non-fickian zero-order drug release and that was further confirmed by surface morphology of the tablets before and after dissolution study visualized by SEM. The developed formulation was found to be stable for one month stored at 60 °C.

**Keywords:** Hypertension. Losartan potassium. Sustained-release matrix tablet. HPMC. Affinisol. Formulation development.

## INTRODUCTION

The design of any dosage form (either solid or liquid) must be developed inherently within the characteristics of physiological GI, pharmacokinetics, pharmacodynamics and formulation in order to achieve a maximum therapeutic efficacy irrespective of its drug release mode (immediate, sustained or controlled release)(Gupta, Ray, 2012). Drug released over a prolonged period at a predetermined rate by a sustained or controlled-release formulation gives certain advantages over an immediate release formulation that requires frequent drug administration. The objective of the developing a sustained release formulation is to

decrease dosing frequency, ensure consistent drug release at a specific target region, maintain a constant level of drug in plasma and thereby improving patient compliance (Zalte, Saudagar, 2013). Adverse effects or toxic effects due to excess amount of drugs in the body from immediate release dosage form can be reduced by a properly designed sustained release dosage form (Isha *et al.*, 2012).

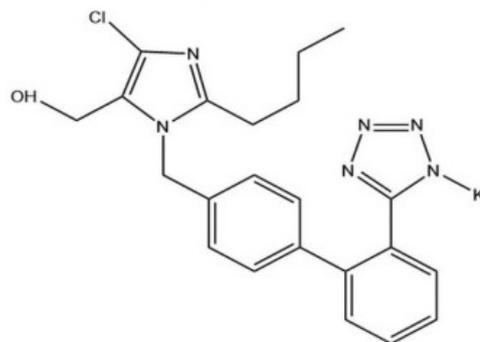
Hypertension - or elevated blood pressure - is a serious medical condition that significantly increases the risk of many complicated diseases like heart attack, stroke, kidney failure and blindness (Mancia *et al.*, 2007). It is one of the leading causes of premature death worldwide. Prevalence of hypertension is increasing very fast in India (Mahmood, Ahmad, Kashyap, 2019). As per World Health Organization's (WHO) recent reports, approximately 207 million persons (men 112 million, women 95 million) suffer with hypertension in India

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(Gupta, Ram, 2019; Nadar, 2019). It is estimated that 11% of women and 15% men aged 15–49 years have hypertension in India (Prenissl *et al.*, 2019). According to one study, one in five young adults in India has high blood pressure (Ramakrishnan *et al.*, 2019). Primarily, hypertension can only be controlled with the vast range of antihypertensive drugs. However, it depends on judicious selection of an appropriate medication containing single or a combination of few antihypertensive agents with suitable dose regimens depending on the patient's health profile (Gupta, 2019).

Losartan potassium (LSR) (Figure 1) is an antagonist with oral activity angiotensin-II used for treatment of high blood pressure due to a blockage of AT<sub>1</sub> receptor primarily (Kim *et al.*, 2019). It is a highly preferred antihypertensive drug prescribed by medical practitioners (Toto *et al.*, 1998). The drug is highly soluble in water; however its oral bioavailability is 33%. This has been attributed to its insufficient absorption from the lower gastrointestinal tract and a plasma elimination half-life of 1.5 to 2.5 hours (Lo *et al.*, 1995; Samyuktha *et al.*, 2013). Due to its low half-lives, it would be more desirable to administer losartan potassium in a sustained release dosage form to maintain the plasma level of the drug for 8-12 hours or more and reduce its drug administration frequency (Michelson, 1991; Nokhodchi *et al.*, 2012). There are few reports of formulation development of LSR sustained-release tablets (Shanmugam *et al.*, 2011; Velmurugan, Srinivas, 2013; Tallapaneni *et al.*, 2012; Gollapudi *et al.*, 2011). Shanmugam and co-workers reported sustained release matrix tablet formulation of losartan potassium with semisynthetic hydrophobic and hydrophilic polymer as well as natural polymer that extended the drug release until 10 hours (Shanmugam *et al.*, 2011). A different approach namely mucoadhesive buccal tablets were developed by Velmurugan and Srinivas (2013) with carbopol 940P, pectin, sodium CMC, Sodium alginate, HPMC K4M, HPMC K15M and HPMC K100M in alone and in combination. In another study, non-conventional excipients like chitosan and trisodium citrate were used as cross-linking agent in combination with HPMC K100M, carbopol 934P, and xanthan gum as release retarding polymers to achieve sustained drug release profile of losartan potassium for

24 hours (Tallapaneni *et al.*, 2012). Gollapudi *et al.* (2011) explored various release retarding polymers like Eudragit RLPO, RSPO and ethyl cellulose, alone and in various combinations, for development of sustained release tablet preparation of losartan potassium by direct compression method. However, these studies were limited to *in vitro* data only; the studies were not furthered explored for *in vivo* evaluation. Losartan potassium is commercially available as 25 mg, 50 mg and 100 mg immediate-release tablets. So far, there is no sustained-release product of LSR in the Indian market. So, the aim of this study was to prepare and characterize LSR sustained release matrix tablet using Affinisol and HPMC K 100M by direct compression method.



**FIGURE 1** - Molecular structure of losartan potassium.

## METHODOLOGY

### Materials

Losartan potassium was received from the Alkem Pharmaceutical Pvt. Limited, India as a gift sample. Hydroxy Propyl methylcellulose (HPMC K 100M) and Affinisol (HPMC AS126G) were gift samples received from the Colorcon Asia Pvt Limited, India. Talc, magnesium stearate and lactose were purchased from Loba Chemie Pvt. Ltd., India. The analytical grade of all other chemical/ reagents were used.

### Pre-formulation studies

At preformulation studies, various tests such as organoleptic properties of the drug, melting point

(purity), infra-red (IR) identification test, ultraviolet-visible (UV) –spectrophotometric scan for absorption maxima ( $\lambda$  max) and drug-excipient interaction were carried out. Drug-excipient compatibility study was performed by differential scanning calorimeter (DSC) (DSC400, Perkin Elmer, and USA) and Fourier transform IR (FTIR) (FTIR-8400S, Shimadzu, Japan) to ensure that LSR does not react or undergoes any kind of degradation during storage of the developed tablets. LSR and excipient alone and their 1:1 mixture were analysed for DSC and FTIR studies.

For DSC, 2 mg sample was taken in a pan and the other pan was kept empty as a reference. The samples were run at a temperature range of 30 °C to 300 °C. The increase in temperature of the instrument was recorded as 10 °C/min whereas the flow of nitrogen was maintained at 60 mL/min. The developed data was acquired using Pyris (Perkin-Elmer, USA) (Azharuddin *et al.*, 2011). For FTIR study, the sample was dispersed well into dry potassium bromide in a mortar pestle. A disk of the mixture was prepared with a pressure of 1000 psig. The disk was placed in the holder and it was scanned at 4mm/s at a resolution of 2cm<sup>-1</sup> over a wave number region of 400 to 4000cm<sup>-1</sup>. The characteristic peaks at particular wave number (cm<sup>-1</sup>) were recorded and checked for characteristic functional groups present in the molecular structure of the drug molecule (Sinha *et al.*, 2010).

### UV-Spectrophotometric Method

Standard stock solution of LSR was prepared by dissolving 50 mg of LSR in 50 mL of water which gave

a concentration of 1000 µg/mL. The secondary stock solution of 100 µg/mL was prepared by taking 10 mL from standard stock solution and diluted up to 100 mL with water. Volumes of 0.1 mL, 0.2 mL, 0.4 mL, 0.6 mL, 0.8 mL, 1 mL, 1.5 mL and 2.0 mL were pipetted out into separate 10 mL volumetric flasks and final volume was made up to 10 mL with water to produce concentrations of 1, 2, 4, 6, 8, 10, 15 and 20 µg/mL, respectively. All the samples were prepared in triplicate and the absorbances of respective concentrations were measured at 234 nm ( $\lambda_{max}$ ) using water as blank. The standard curve was constructed with absorbance (Y-axis) against concentration (X-axis) followed by estimation of the coefficient of correlation using Microsoft excel. The overlay spectrum containing all the calibration samples was also obtained.

### Preparation of sustained-release matrix tablet

The composition of the various trial formulations prepared using varying amount of HPMC K100M and Affinisol as a release retarding polymers, in the range of 50 to 100 mg for each, along with a fixed amount of talc and magnesium stearate as listed in Table I. Lactose was used as filler. The matrix tablet formulation was prepared by direct compression method. The drug, polymer and excipient were precisely weighed and completely mixed in a polybag according to the specified formula. The final weight of the individual tablet was adjusted to 310 mg. The powder mixture was compressed on the single punch compression machine (Amar Enterprises, Ambala Cantt, India; Model No.: AE-347-IV) with 9.5mm round concave punches.

**TABLE I** - Composition of 100mg losartan potassium sustained r release matrix tablet

Sr. No	Ingredients	Trial formulations (each composition in mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	HPMC K100M	100	100	100	75	75	75	50	50	50
2	Affinisol	100	75	50	100	75	50	100	75	50
3	Losartan potassium	100	100	100	100	100	100	100	100	100

**TABLE I** - Composition of 100mg losartan potassium sustained r release matrix tablet

Sr. No	Ingredients	Trial formulations (each composition in mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
4	Talc	3	3	3	3	3	3	3	3	3
5	Magnesium stearate	3	3	3	3	3	3	3	3	3
6	Lactose	4	29	54	29	54	79	54	79	104
7	Total weight (mg)	310	310	310	310	310	310	310	310	310

### **In vitro drug release study**

*In vitro* drug release studies of the formulations were carried out using USP type 1 (Basket) dissolution apparatus at 100 rpm. A volume of 900 ml distilled water maintained  $37 \text{ }^\circ\text{C} \pm 0.5 \text{ }^\circ\text{C}$  was used as the dissolution medium. The study was conducted for 12 hours and at a specific time interval, an aliquot (1ml) was removed, replacing the equivalent amount of distilled water. The drug content was determined by UV spectrophotometer (SHIMAZDU UV-1800 spectrophotometer) at 234nm. Every time the apparatus was run with 6 tablets from each batch of the formulation.

### **Release kinetics**

To study the mechanism of drug release from the prepared matrix tablets, the release data were fitted to the following equations:

Zero-order equation:  $Q_t = Q_0 + k_0 t$

where  $Q_t$  is the amount of drug release in time  $t$ ,  $Q_0$  is the initial amount of drug in the solution and  $k_0$  is the zero-order release rate constant.

First-order equation:  $\ln Q_t = \ln Q_0 + k_1 t$

where  $Q_t$  is the amount of drug released in time  $t$ ,  $Q_0$  is the initial amount of drug in the solution and  $k_1$  is the first-order release rate constant.

Higuchi's equation:  $Q = k_H t^{1/2}$

where  $Q$  is the amount of drug release at time  $t$  and  $k_H$  is the Higuchi diffusion rate constant.

Koresmeyer *et al.* (1983) equation:  $M_t/M_\infty = Kt^n$

where  $M_t$  is the amount of drug released at time  $t$ ,  $M_\infty$  is the amount of drug released after infinite time and  $K$  is a kinetic constant incorporating structural and geometric characteristics of the tablet and  $n$  is the diffusional exponent indicative of the drug release mechanism.

### **Characterization of matrix tablet**

#### *Micromeritic properties of powder*

Evaluation of pre-compression parameter, which involves bulk density, tapped density, compressibility index and angle of repose, is very important before compression (Mandal, Pal, 2008a; Patel, 2019). All these parameters were evaluated with a pre-defined method as mentioned below:

#### *Bulk density*

A pre-seived mixture of drug and excipient was accurately weighed and poured into a 100 ml graduated cylinder. The volume occupied by the mixture was noted. Bulk density was calculated as gm/ml as in equation 1 given below:

Bulk density = Mass of powder/Volume of packing

*Equation 1*

### Tapped Density

Tapped density was determined by placing a 100 ml of a graduated cylinder on bulk density apparatus, containing a known mass of pre-sieved drug and excipients. The tapped volume was evaluated in a constant volume by tapping the powder. It is expressed by gm/ml as in equation 2 given below:

$$\text{Tapped Density} = \frac{\text{Mass of powder}}{\text{Tapped volume of Packing}} \quad \text{Equation 2}$$

### Carr's Index

Carr's Index (CI) is used to determine the powder blend flowability before compression. The bulk density and the tapped density of a freely-flowing powder would be of close value, so the Carr's index would be small. A Carr's index (Equation 3) higher than 25 indicates a low flowability, and lower than 15 is an indication of good flowability.

$$\text{CI} = \frac{\text{Tapped density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100 \quad \text{Equation 3}$$

### Angle of repose

The angle of repose was determined using the funnel with a vibration-free base. The cone forming technique was used. The funnel height was fixed to 2cm from the base for a symmetrical powder cone to be closely built at the basal tip of the funnel. The height of the cone powder (h) and cone radius (r) formed were measured and from the following equation (Equation 4) the angle of repose ( $\theta$ ) was calculated.

$$\theta = \tan^{-1} (h/r) \quad \text{Equation 4}$$

### Weight variation

Weight variation test was used to ensure that the appropriate quantity of drug is included in each tablet. The tablets were sampled randomly and the individual weight of 20 tablets was taken in an analytical balance to

determine the weight variation of each batch. The weight variation percentage is calculated with the equation 5 given below (Indian Pharmacopoeia, 1996).

$$\% \text{ of weight variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Equation 5

### Thickness and diameter

The thickness of 10 tablets was measured individually with the Vernier calliper from randomly sampled tablets. Diameter variation: diameters were checked for 10 tablets per batch using the digital Vernier calliper and the mean  $\pm$  SD value was calculated (Indian Pharmacopoeia, 1996).

### Hardness

Tablet requires some resistance to mechanical handling shocks in the fabrication, packaging and transport process. Hardness is generally measured by the crushing strength of a tablet and can be defined as the force needed in a diametrically compressed tablet. The hardness test was conducted using the Monsanto type hardness tester (Amar Enterprises, India). The tablet was placed between two anvils; strength was applied to the anvil and the crushing force causing the breakdown of the tablet was recorded. The hardness test was repeated on six tablets and the mean value was recorded (Indian Pharmacopoeia, 1996).

### Friability

The friction and shock effects, which often cause chip, cap or break, were evaluated by a friability test. It generally reflects a lack of cohesion in powder mass within a tablet. There were 10 tablets placed into the Roche friabilator and 100 revolutions (at 25rpm) were operated. The tablets, which lose less than 1.0% of their weight generally is considered to be acceptable, were then dedusted and reweighed. Friability was calculated from equation 6 given below (Indian Pharmacopoeia, 1996):

$$\% \text{ Friability} = \frac{W_0 - W}{W_0} \times 100 \quad \text{Equation 6}$$

Where,  $W_0$  is the initial weight of the tablet and  $W$  is the weight of tablet after friability test

### Drug content

20 Tablets were taken and crushed to powder with mortar and pestle. Exact amount of powder equivalent to 100 mg losartan potassium was taken in a 100 ml volumetric flask and diluted with water up to the mark. After sonication for 15 min, the solution was filtered through 0.45  $\mu\text{m}$  filter paper. The total amount of drug within the tablets was analyzed after appropriate dilution of the test solution by using the developed UV method mentioned earlier.

### Surface morphology

Surface morphology of the developed tablet was studied before and after drug release study. During dissolution study, samples were taken in the different time intervals (1, 2, 4, 8 and 18 hours) and blotted to remove excess water. Then they were dried in an oven at 60°C for 1 hour, gold coated and observed under scanning electron microscope (Jeol, JSM-6390LV) at various magnifications (50–1000 $\times$ ) with direct data capture of the images.

### Stress testing

Due to non-availability of accelerated stability chamber and time constraint, the selected formulation was subjected to only 1-month stability study at 60 °C. Tablets were kept open inside a digital drying oven (Research Equipment, RG-10012, Ambala, India) and the temperature was maintained throughout the study period. Physical appearance of the tablet, drug content and drug release were studied.

### Statistical tests

All the experiments were repeated three times except six times for in vitro dissolution studies and data were expressed as the mean value  $\pm$  SD. Statistical data were analyzed and  $p$  value less than 0.5 was considered to be significant. To compare between two dissolution profiles,  $f_2$  value (similarity factor) was calculated as per the following equation:

$$f_2 = 50 \times \log \{ [1 + (1/n) \sum (R_t - T_t)^2]^{-0.5} \times 100 \} \quad \text{Equation 7}$$

Where,  $R_t$  and  $T_t$  are drug release of dissolution samples at time  $t$  for reference and test sample.

## RESULTS AND DISCUSSION

### Preformulation studies

Testing of organoleptic evaluation revealed that the supplied LSR was odorless white crystalline powder. Obtained FT-IR spectrum of LSR (Figure 2) matched exactly with that of the reference library (LabSolutions IR, Shimadzu). The peaks obtained at 3624  $\text{cm}^{-1}$  represents N–H stretching, 3180.4  $\text{cm}^{-1}$  for OH stretching, 3035.75  $\text{cm}^{-1}$  for C–H stretching aromatic, 2953.78  $\text{cm}^{-1}$  for C–H stretching aliphatic, 1577.66  $\text{cm}^{-1}$  for C=C, 1462.91  $\text{cm}^{-1}$  for C=C Stretching and 791.72 for C–Cl Stretching. These characteristic peaks were present in the FTIR spectrum when LSR were mixed with all the excipients of the formulation and stored at 40 °C for two weeks (Figure 2). No change or the shift of the characteristics was observed which confirms drug-excipient compatibility for the proposed formulation. It was further proved by DSC studies. The obtained melting point of the drug (273.35 °C) did not change significantly rather than peak height and sharpness when the drug was mixed with the proposed excipients of the formulation (Figure 3).

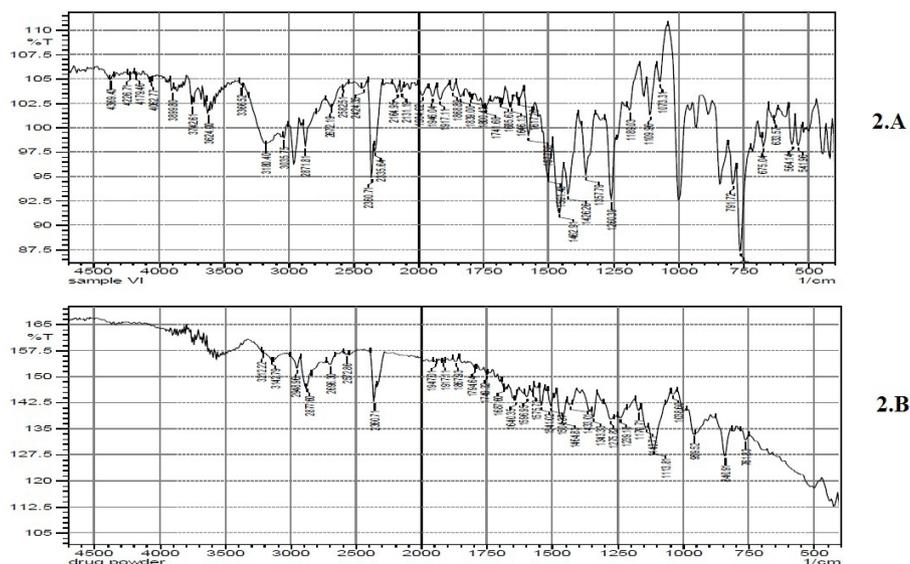


FIGURE 2 - FT-IR spectrum of losartan potassium.

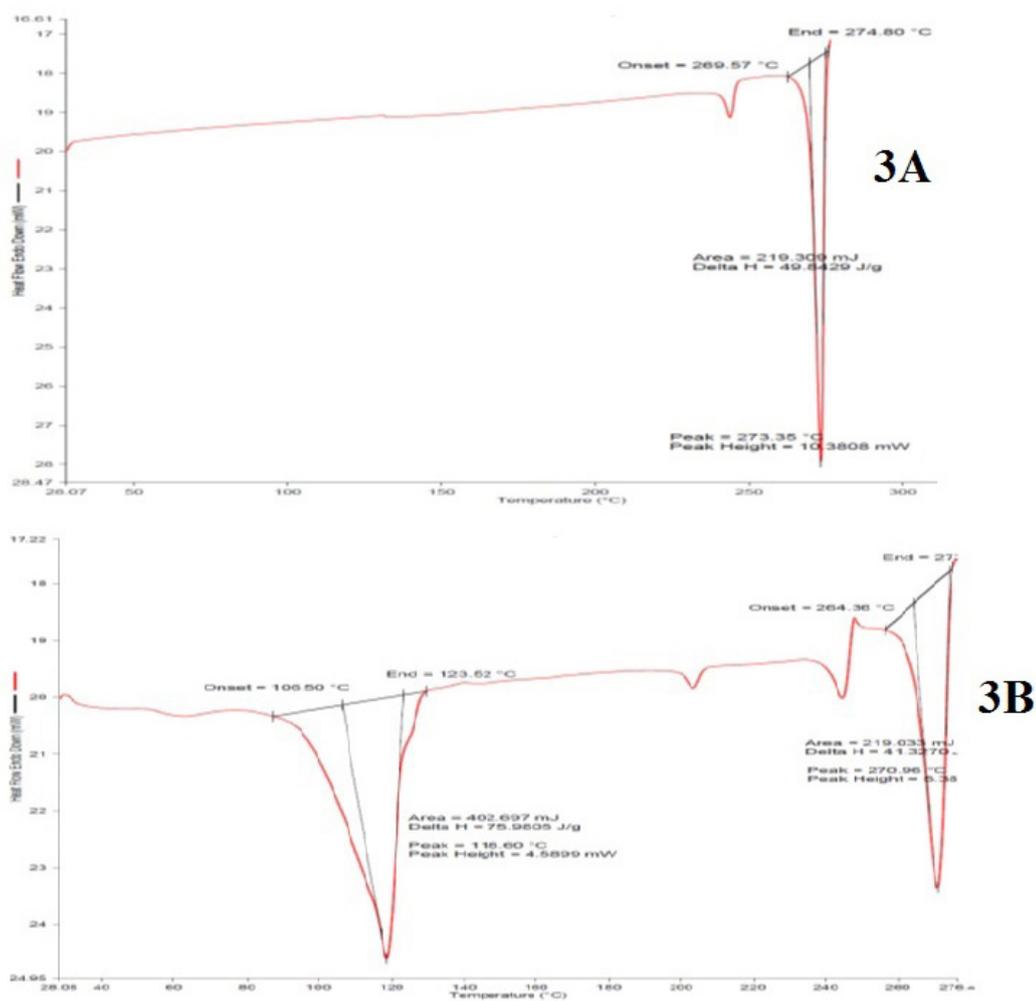


FIGURE 3 - FT-IR spectrum of losartan potassium with all excipients of LSR tablet formulation.

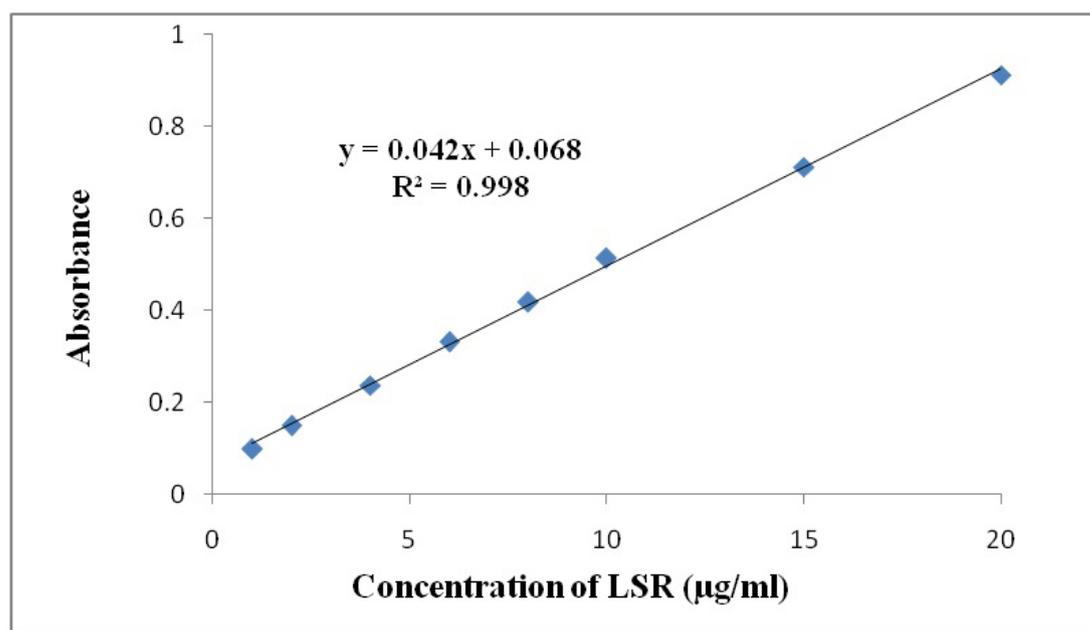
## Formulation development

Losartan potassium is very common and preferred medication for hypertension and is also indicated in the patient with type 2 diabetes for decreased renal disease progression, microalbuminuria (>30mg/24hours) or proteinuria (>900mg/24hours) (Lozano *et al.*, 2001). The pharmaceutical technologists have found always challenging to develop oral sustained release matrix tablets for water-soluble extremely soluble drugs that maintain constant release rates for an extended period of time. In this regard, selection of a release retarding polymer, either alone or a combination, should be the most important part. For the present work, HPMC K 100M was preferred over HPMC K15M and HPMC K15 M due to its higher viscosity and proven track record with respect to the development of sustained-release matrix tablet for a highly water-soluble drug like losartan (Sung *et al.*, 1996). However, in present work, HPMC K100M was not sufficient enough to get the desired drug release profile in a given set of limitations, mainly the non availability of higher capacity tablet punch size at our disposal. So, we selected affinisol

(HPMC AS126G), in combination with HPMC K100M for the formulation development. Chemically, affinisol is hypromellose acetate succinate (HPMCAS), acts as hydrophilic polymer. HPMC AS126G grade of affinisol has a unique solubility profile which is soluble at higher pH (above pH7), however its aqueous solubility decreases below pH 7, mainly in acidic pH. That's why we selected affinisol (HPMC AS126G) in combination of HPMC K100M to optimize the drug release rate for the developed formulation. HPMC HME grade of affinisol has been used previously to enhance the solubility of poorly soluble drug by solid dispersion technique (spray drying and hot-melt extrusion) (Huang *et al.*, 2016; O'Donnell *et al.*, 2013). However, as per our knowledge, the use of the same for preparation of sustained-release tablet has not been reported elsewhere.

## UV spectrophotometric method

Experimentally,  $\lambda_{\max}$  of losartan potassium was found to be 234 nm in distilled water. Figure 4 shows the standard curve in the range of 1 to 20  $\mu\text{g/ml}$ , it resulted an equation  $y = 0.042x + 0.068$  and  $R^2$  value 0.998.



**FIGURE 4** - DSC thermogram of losartan potassium showing drug melting point at 273.35 °C.

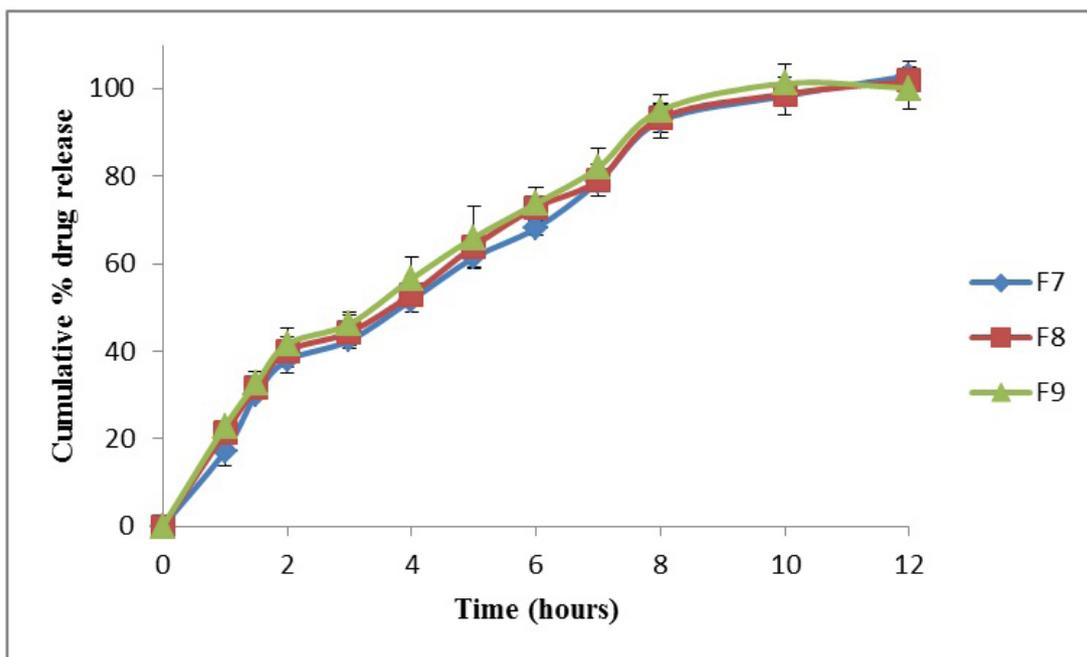
**In vitro dissolution studies**

Dissolution samples were analyzed by the developed analytical method (UV) for the estimation of the drug release. Results of drug release of all the trial formulations are presented in Table II. Complete drug release of losartan potassium occurred within 12 hours for formulation F4 to F9. Quantity of HPMC K100M and affinisol in the formulations considerably affected the losartan potassium release for all the formulations. Accordingly, F1 to F3 resulted incomplete drug release due to the higher amount of both the polymers used in those formulations. Keeping the amount of HPMC K100M constant at the lowest level (50 mg), drug release slightly decreased ( $p > 0.05$ ) on increasing the amount of affinisol 50 mg to 100 mg (Figure 5; comparison

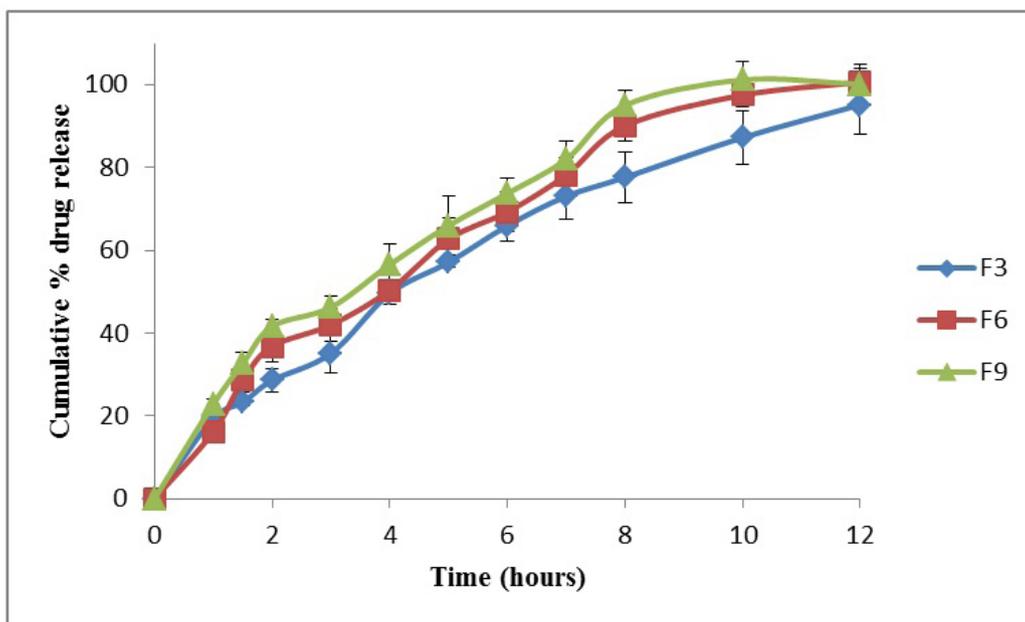
among F9, F8 & F7). Similarly, drug release decreased on increasing amount of HPMC K100M from 50 mg to 100 mg while keeping the amount of affinisol constant at the lowest level (Figure 6; comparison among F3, F6 & F9). These results confirm release retarding properties of both the polymers i.e HPMC K100M and affinisol, however the effect of HPMC K100M was more prominent than affinisol. This was further confirmed when the amount of both the polymers increased at an equal amount from 50 mg to 100 mg (Figure 7; Comparison among F9, F5 and F1). Among all the trial formulations, formulation F4 resulted desired release profile: Not more than 30% drug release in 2 hours, at least 50% drug release in 6 hours and 100% drug release in 12 hours. Accordingly, Formulation F4 was selected for further investigation.

**TABLE II** - Mean ( $\pm$  SD) drug release of all the trial formulations (F1 to F9) of LSR 100 mg Tablet

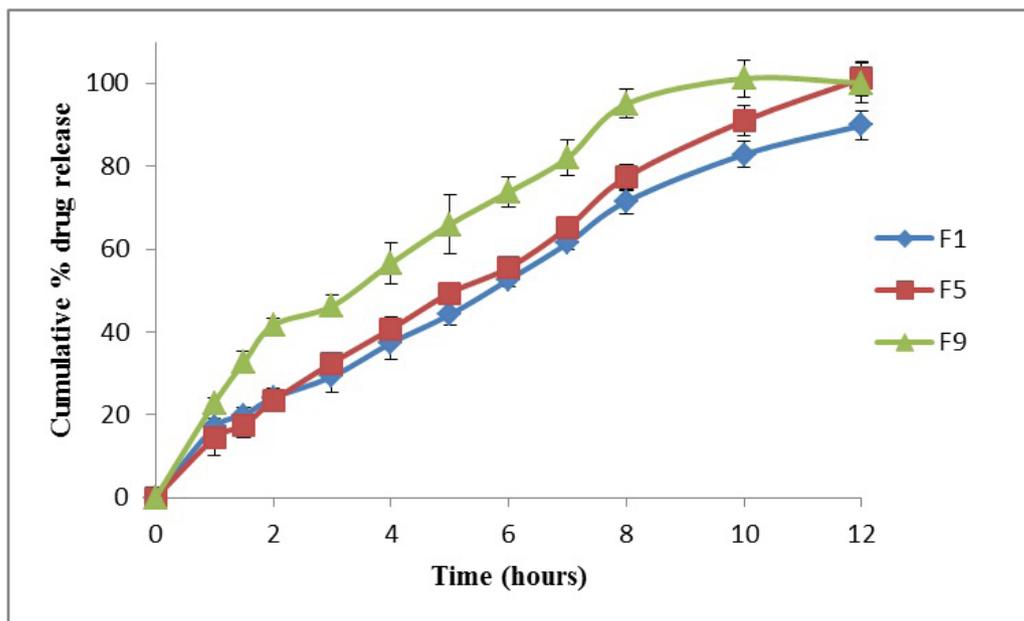
Time (hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	16.98 $\pm$ 2.21	17.65 $\pm$ 1.60	19.41 $\pm$ 1.55	12.59 $\pm$ 1.18	14.31 $\pm$ 4.16	16.10 $\pm$ 2.53	17.17 $\pm$ 3.52	21.34 $\pm$ 2.53	22.82 $\pm$ 1.27
1	19.85 $\pm$ 2.02	21.85 $\pm$ 1.96	23.25 $\pm$ 0.75	15.90 $\pm$ 1.11	17.46 $\pm$ 2.92	28.66 $\pm$ 3.06	30.12 $\pm$ 1.08	31.71 $\pm$ 1.65	32.60 $\pm$ 2.65
1.5	24.08 $\pm$ 2.45	26.87 $\pm$ 2.67	28.55 $\pm$ 2.81	19.28 $\pm$ 1.61	23.38 $\pm$ 2.13	36.79 $\pm$ 3.75	37.87 $\pm$ 1.46	40.01 $\pm$ 5.13	41.60 $\pm$ 1.52
2	29.22 $\pm$ 3.74	32.96 $\pm$ 3.34	35.11 $\pm$ 4.64	28.97 $\pm$ 2.54	32.50 $\pm$ 2.48	41.95 $\pm$ 4.09	42.45 $\pm$ 1.11	44.34 $\pm$ 3.88	46.22 $\pm$ 2.58
3	37.30 $\pm$ 3.91	48.42 $\pm$ 0.99	49.56 $\pm$ 1.07	37.34 $\pm$ 5.27	40.67 $\pm$ 2.98	50.37 $\pm$ 3.58	51.72 $\pm$ 0.90	53.05 $\pm$ 3.98	56.53 $\pm$ 4.92
4	44.15 $\pm$ 2.46	53.10 $\pm$ 1.48	57.08 $\pm$ 1.06	47.30 $\pm$ 9.38	49.38 $\pm$ 2.09	62.66 $\pm$ 5.05	61.37 $\pm$ 2.02	63.97 $\pm$ 2.33	65.94 $\pm$ 7.22
5	52.61 $\pm$ 1.79	63.14 $\pm$ 1.43	65.91 $\pm$ 3.69	53.97 $\pm$ 7.59	55.48 $\pm$ 1.91	69.28 $\pm$ 4.73	68.11 $\pm$ 1.79	72.85 $\pm$ 4.46	73.74 $\pm$ 3.79
6	61.35 $\pm$ 1.55	69.45 $\pm$ 1.52	73.01 $\pm$ 5.49	60.47 $\pm$ 4.10	65.17 $\pm$ 2.22	78.17 $\pm$ 4.33	78.69 $\pm$ 1.90	79.08 $\pm$ 3.75	81.98 $\pm$ 4.32
8	71.45 $\pm$ 2.85	75.51 $\pm$ 2.64	77.60 $\pm$ 6.13	74.30 $\pm$ 3.58	77.36 $\pm$ 3.12	90.04 $\pm$ 3.56	92.59 $\pm$ 3.77	93.27 $\pm$ 3.27	95.01 $\pm$ 3.45
10	82.82 $\pm$ 3.04	85.64 $\pm$ 3.06	87.21 $\pm$ 6.38	86.18 $\pm$ 4.97	90.93 $\pm$ 3.55	97.47 $\pm$ 2.84	98.32 $\pm$ 4.21	98.75 $\pm$ 2.33	101.15 $\pm$ 4.56
12	89.85 $\pm$ 3.55	93.89 $\pm$ 3.92	95.12 $\pm$ 7.05	99.70 $\pm$ 4.01	101.14 $\pm$ 4.22	100.58 $\pm$ 3.24	102.93 $\pm$ 3.34	101.76 $\pm$ 2.54	100.10 $\pm$ 4.72



**FIGURE 5** - DSC thermogram of losartan potassium with all excipients of LSR tablet formulation.



**FIGURE 6** - Standard curve of losartan potassium developed by UV spectrophometric method.



**FIGURE 7** - Comparative in-vitro drug release study of formulations F7, F8 and F9.

### Evaluation of pre-compression parameters

All the formulations were prepared by direct compression method. However, precompression parameters were evaluated for only selected formulation i.e formulation F4. LSR, HPMC K100M, affinisol and lactose were mixed in a mortar for 10 minutes. These resulted spontaneous granules formation due to the characteristic property of affinisol. The mixture was further lubricated with talc and magnesium stearate

for 2 minutes only. Powder was examined for angle of repose, LBD, TBD, compressibility index and total porosity and results are shown in Table III. The result of the angle of repose ( $<30$ ) indicates that powder had good flow property. This is further established by its Carr's index (11.72) and Hausner's ratio (1.13) values. For a powder mass to comply with good flow property, its Carr's index and Hausner's ratio should lie within a range of 11 to 15 and 1.12 to 1.18, respectively (India Pharmacopoeia, 1996).

**TABLE III** - Results of pre-compression parameters of selected formulation F4

Bulk Density	Tapped Density	Hausner's Ratio	Carr's Index	Angle of Repose
0.414gm/cc	0.469gm/cc	1.13	11.72	26.5°

### Tablet characteristics and drug content:

Various evaluation tests such as thickness, hardness, friability and drug content were conducted for the formulation F4 (Table IV). The results were within the

limits recommended by Indian pharmacopoeia and as per industrial requirements (Indian Pharmacopoeia, 1996). The pharmacopoeia limit for a percentage deviation of tablets greater than 250mg for a weight variation test is  $\pm 5\%$ . The average variation in the proportion of all tablets

was observed in the above limit and therefore the tablets were given weight uniformity according to the official requirement. With respect to friability, conventional compressed tablet with a weight loss of less than 1% is

usually acceptable. The friability of the tablet formulations in this study was below 1%, indicating that it is within the limit prescribed. Drug content of the optimized formulation (F4) was recorded to be  $97.80 \pm 0.57\%$ .

**TABLE IV** - Physical properties of losartan potassium 100mg SR Tablet

Weight variation	Thickness ( $\pm$ SD)	Diameter ( $\pm$ SD)	Friability	Hardness ( $\pm$ SD)	Drug Content ( $\pm$ SD)
0.37 $\pm 0.04\%$	4.45 $\pm 0.02$ mm	9.93 $\pm 0.01$ mm	0.48%	8.87 $\pm 0.95$ Kg/cm <sup>2</sup>	97.80 $\pm 0.57\%$

### Drug release kinetics

Table V summarizes  $R^2$  values and other related parameters of different mathematical models applied in order to confirm drug release kinetics. Based on the criteria of best fitting method, optimized formulation was found zero-order release kinetics (highest  $R^2$  value, Table V). It does not follow first-order or Higuchi release kinetics. Drug release occurs due to the process of diffusion. However, it follows non-fickian diffusion as evidenced by  $n$  value of Korsmeyer- Peppas model. In case of Korsmeyer- Peppas model,  $n$  is the release exponent which indicates the drug release mechanism (Korsmeyer *et al.*, 1983). Most of the times, drug release mechanism from a delivery device composed of hydrophilic polymeric excipients can be described by diffusion (Fickian diffusion). However, during the process of diffusion, the polymer network undergoes relaxation, which can influence the overall drug release rate. The present formulation is composed of both hydrophilic (HPMC K100M) and hydrophobic (affinisol below pH 7) polymers. That's why drug release follows non-Fickian diffusion where uniform swelling and dissolution of the hydrophilic polymer is inhibited by the hydrophobic polymer present in the matrix. This is proved by its  $n$  value which is 0.692 ( $>0.5$ ). For a delivery system with fixed geometry, the value of  $n$  is found to be 0.5 in case of Fickian diffusion and above 0.5, but below 1.0 in case of non-Fickian diffusion (Mandal, Pal, 2008a). Apart from those two

mechanisms, the third type of diffusion mechanism named as Case II diffusion is also frequently observed where the value of  $n$  is exactly 1.0 (42). Proposed drug release mechanism is further justified by surface morphology study by SEM.

**TABLE V** - Summary of mathematical modeling of release profile from the optimized formulation

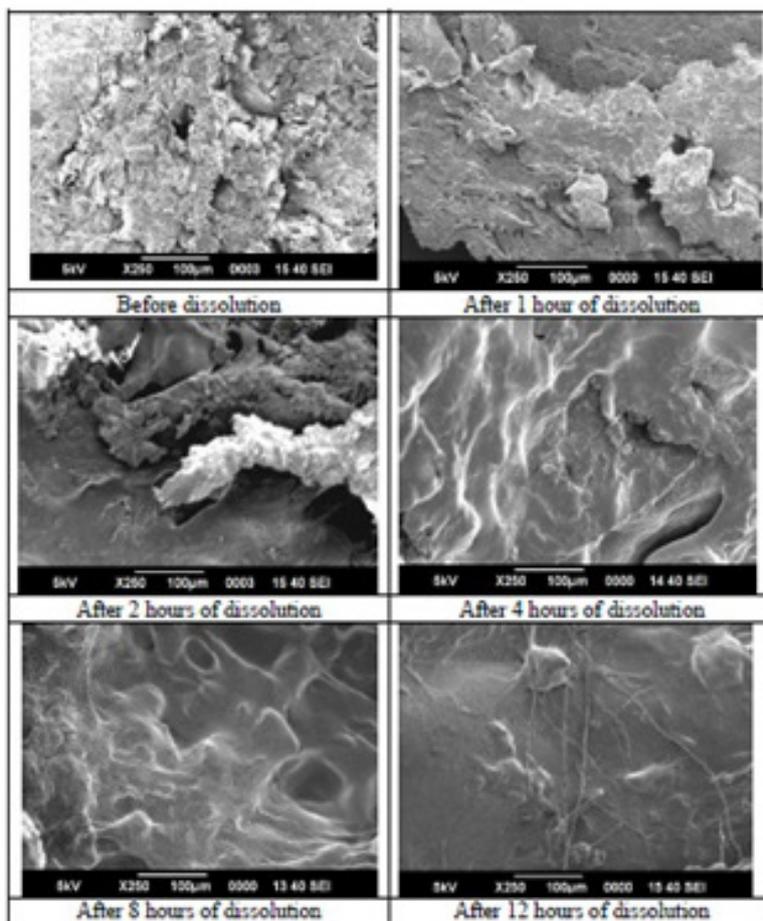
Model	Parameters
Zero order	$K_0 = 7.9366$ , $R^2 = 0.9892$
First order	$K_1 = 0.3488$ , $R^2 = 0.8512$
Higuchi	$K_H = 29.7670$ , $R^2 = 0.9879$
Korsmeyer Peppas	$K_{KP} = 0.1749$ , $n = 0.692$ , $R^2 = 0.9860$

### Scanning electron microscopy (SEM)

SEM figures (Figure 8) depicted the non-porous nature of tablet's outer surface. As the dissolution study progressed, the degree of porosity decreased and it was converted into a smooth non-porous structure. This behaviour is completely opposite to the property of hydrophilic polymers undergoing dissolution in water. Hydrophilic polymers undergo swelling as welling dissolution (Mandal, Pal, 2008b). Swelling increases diffusional path length while dissolution increases porosity (Mandal *et al.*, 2007). Combination

of these regulates overall drug release from the matrix of hydrophilic polymers (Mandal *et al.*, 2007). But, in present formulation, a hydrophobic polymer (affinisol) was added and it influenced the process of swelling and

dissolution of hydrophilic polymer HPMC K100M. This resulted in a smooth non-porous surface and drug release occurred through non-Fickian diffusion as evidenced by analysis of drug release kinetics.



**FIGURE 8-** Comparative in-vitro drug release study of formulations F3, F6 and F9.

### Stress testing

Developed tablet formulation was found to be stable for one month at 60 °C. Content of LSR decreased from 97.80% to 96.65%. As the samples were kept open (without

any packing), moisture exposure caused some of the tablets to stick together. With respect to drug release, there were not any significant changes on drug release up to 12 hours. It resulted similarity factor of 53 when compared it with that of 0 months tablet samples (Table VI).

**TABLE VI** - Similarity factor (f2) results of tablets after stability study

Time	$R_t$	$T_t$	$(R_t - T_t)$	$(R_t - T_t)^2$
30	12.59	6.95	5.64	31.8096
60	15.9	14.73	1.17	1.3689
90	19.28	19.09	0.19	0.0361
120	28.97	22.74	6.23	38.8129
240	47.3	38.04	9.26	85.7476
360	60.47	53.58	6.89	47.4721
480	74.3	64.89	9.41	88.5481
600	86.18	86.86	0.68	0.4624
sum $(R_t - T_t)$				39.47
sum $(R_t - T_t)^2$				294.2577
sum $R_t$				344.99
<b>Similarity factor f2</b>				<b>53</b>
<b>Difference factor f1</b>				<b>11</b>

$R_t$ : Drug release of stability samples at time t,  $T_t$ : Drug release of stability samples at time t

## CONCLUSION

A sustained-release matrix tablet of 100 mg losartan potassium was successfully developed by the direct compression method. Formulation F4 with the composition of 75 mg HPMC K100M and 100 mg affinisol was selected as the best formulation that extended the drug release up to 12 hours. Pre-compression parameters and other tableting properties were within the pharmacopoeial limits. The drug release followed zero-order kinetics in agreement with the surface morphology studied by scanning electron microscopy. The formulation was stable for 1 month at 60 C. However, it needs further investigation with respect to stability of the formulation at accelerated stability conditions (40 C and 75% RH) for six months and at real-time storage conditions for at least one year. Formulation also should be studied by an

appropriate *in vivo* model to support these encouraging *in vitro* outcomes.

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## CONFLICT OF INTEREST

Authors declare that there is no conflict of interest regarding publication of this article.

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