# Formulation and evaluation of losartan potassium matrix tablet by using natural gum

**Toraskar S. D.* and M. G. Maniyar.**

SVERI's college of pharmacy, Pandharpur, 413304, (affiliated to Solapur University), Maharashtra, India.

**ABSTRACT:**

Matrix tablet of losartan potassium was prepared by using hibiscus obtained resin and were evaluated as rate controlling matrix materials. Losartan potassium is an class antihypertensive drug and belongs to angiotensin receptor blockers. It is administered orally but has limitation of short half life so selected. Hibiscus resin was studied for solubility, physical characterization and various chemical test were found to be soluble. It showed solubility in methanol, ethanol, lukewarm and cold water while it was insoluble in acetone. The hibiscus resin is prepared by using solvent acetone. It showed ash value 87.25%, pH 2.5±0.22,viscocity 46±0.10 cps. The physiochemical tests having foam test is positive. Losartan potassium tablets were prepared direct compression method by using hibiscus resin. The FTIR study revealed that compatibility of resin and drug. Losartan potassium matrix tablets showed slow and controlled release of losartan potassium over 8 hours. It follows non-fickian type drug kinetic model. Good linear relationships were observed between percent polymer and release rate in each case. Losartan potassium matrix tablet exhibited the optimized formulation of 92% release after 8 hr.

***Keywords:*** Losartan potassium, antihypertensive drug, hibiscus resin.

## INTRODUCTION

## MICROSPHERES

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm) are also referred as microparticles. Microspheres are manufactured from various natural and synthetic materials. Polyethylene and polystyrene microspheres are two most common types of polymer microspheres. Polystyrene microspheres are typically used in biomedical applications due to their ability to facilitate procedures such as cell sorting and immuno precipitation. Lower melting temperature enables polyethylene microspheres to create porous structures in ceramics and other materials. High sphericity of polyethylene microspheres, as well as availability of coloured and fluorescent microspheres, makes them highly desirable for flow visualization and fluid flow analysis, microscopy techniques, health sciences, process troubleshooting and numerous research applications. Charged polyethylene microspheres are also used in electronic paper digital displays.[1]

Oral ingestion has long been the most convenient and most commonly employed route of drug delivery. Indeed for sustained release systems, oral route of administration has received most of the attention with respect to research on physiological and drug constraints as well as design and testing of product .The design of oral sustained release delivery systems is subject to several intercalated variables of considerable importance.[3]

Matrix tablets are considered to be the commercially feasible sustained action dosage form that involves the least processing variables, utilize the conventional facilities and accommodate large doses of drug. There remains an interest in developing novel formulations that allow for sustained drug release using readily available, inexpensive excipients by matrix based formulations.[4]

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology. In fact, a matrix is defined as a well –mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and

osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.[5]

The matrix tablet of losratan potassium were prepared by using natural binder having hibiscus.The hibiscus resin is prepared by using fresh leaves of hibiscus, the resin was isolated and then evaluated by solubilty test, ash value viscocity and pH were evaluated. Then the microspheres were prepared and evaluated. Then losartan potassium microspheres were used as a granule in tablet. Then the matrix was prepared by using the formula having table no.2.

## MATERIALS AND METHODS

### Materials

The losartan potassium was purchased from Yarrow chem products co. Mumbai.Fresh leaves of hibiscus were collected from Gopalpur Village (Pandharpur, India).Solvents i.e. methanol and acetone, were obtained from Loba chem. Pvt. Ltd, Mumbai. Sodium alginate (molecular weight = 216.121) and calcium chloride was obtained from Loba chem Pvt. Ltd, Mumbai.All the materials uses one of analytical grade.

### Methods

### Isolation of mucilage

The fresh leaves of hibiscus *rosasinensis* Linn were collected, washed with water to remove dirt and debris and then dried. The powdered leaves were soaked in water for 5-6 h, boiled for 30 min and kept aside for 1 h for complete release of the mucilage in to the water. The material was squeezed from an eight fold muslin cloth bag to remove the marc from the solution. Acetone was added to the filtrate to precipitate the mucilage in a quantity of three times the volume of the total filtrate. The mucilage was separated, dried in oven at a temperature < 50°C collected, dried, powdered and passed through a sieve no.80 and stored for further use in desiccators.

### Solubility determination of hibiscus mucilage

The solubility test of hibiscus mucilage was performed in various aqueous and organic solvents. This was in order to determine appropriate solvents for the mucilage as required for the preparation of the hydrogel beads and analytical studies described in the next sections. Dried samples of known quantity were added to 1 ml of solvent taken in a glass test tube and mixed properly. The test tubes were kept at temperatures between 8 and 40°C and observed for a duration of 72 h. The complete dissolution of the sample was considered as being soluble or otherwise phasing out /separation of the sample from solvent was considered as being insoluble.( Table 1).

**Table 1: Solubility tests of hibiscus resin in various solvents:**

| Sr. No. | Solvents | Solubility behaviour |
|---|---|---|
| 1 | Cold water | Sparingly soluble in cold water |
| 2 | Lukewarm water | Forms a colloidal viscous suspension |
| 3 | Ethanol | soluble |
| 4 | Methanol | soluble |
| 5 | Acetone | Insoluble |
| 6 | Chloroform | Insoluble |
| 7 | Benzene | Insoluble |
| 8 | Ether | Insoluble |
| 9 | Cyclohexane | Insoluble |
| 10 | Ethyl acetate | Insoluble |
| 11 | Toulene | Insoluble |

## Physical characterization of hibiscus mucilage

The hibiscus mucilage was accessed for its physical characteristics including appearance, colour, percentage yield, weight loss on drying, swelling index, density, pH and viscosity, according to the method.(Table 2).

**Table 2: Physical characterization of hibiscus resin:**

| Sr. No. | Physical properties | Observation |
|---|---|---|
| 1 | Appearance | Dark greenish powder |
| 2 | Percent yield | 6.5 ± 1.22 |
| 3 | Weight loss on drying | 1.89 ± 0.115 |
| 4 | Swelling index (%) | 32.0 ± 0.11 |
| 5 | Density of liquid (1.0%, w/v) | 1.021 ± 0.0025 |
| 6 | pH | 2.5 ± 0.22 |
| 7 | Viscosity | 46± 0.10 cps |

## Phytochemical identification tests

Isolated mucilage samples were subjected to some phytochemical tests for identification. The tests performed were to determine the presence of alkaloids (Wagners test), carbohydrates (Molisch test), starch (Iodine test), saponins (Foam test), tannins (Alkaline reagent test), steroids and terpenoids (Salwoski's test), flavonoids (Alkaline reagent test).

**Table 3: Physiochemical identification of hibiscus resin:**

| Sr. No. | Tests | Observation |
|---|---|---|
| 1 | Iodine test | Negative |
| 2 | Wagner's test | Negative |
| 3 | Salkowski test for steroids and terpenoids | Negative |
| 4 | Molisch test for saponins | Positive |
| 5 | Alkaline reagent test for tannins | Negative |
| 6 | Alkaline reagent for flavonoids | Negative |
| 7 | Foam test for saponins | Positive |

## Preparation of single cross-linked hibiscus-alginate beads

Single cross-linked beads encapsulating losartan potassium were prepared by the simple ionotropic gelation technique involving the crosslinking of sodium alginate and hibiscus mucilage by the mediation of calcium ions. Blend of polymeric solution was prepared in100 ml volume using distilled water containing combination of sodium alginate and hibiscus mucilage. The water-soluble drug Losartan potassium (1% w/v) was added to the above polymeric solution with constant stirring for1hr using a magnetic stirrer. The resultant solution was sonicated for 30min and then was dropped into the calcium chloride solution (2% w/v) using (0.6 mm×25 mm) 23G needles and a syringe from a height of 5cm. The microspheres were obtained and excess of calcium chloride was removed by washing with distilled water and air dried overnight at 30°C according to a previously reported method. Ten different formulations using design expert software with varying ratios of sodium alginate and hibiscus[6].

**Table 4: Formulation chart of Losartan potassium microspheres**:

| Sr. No. | Factor 1 | Factor 2 | Factor 3 | Factor 4 |
|---|---|---|---|---|
| | Losartan potassium (mg) | A: Hibiscus (gm) | B: Sodium Alginate (gm) | C: Calcium Chloride (gm) |
| 1 | 50 | 1 | 2 | 1 |
| 2 | 50 | 1 | 4 | 2 |
| 3 | 50 | 1 | 2 | 2 |
| 4 | 50 | 2 | 2 | 2 |
| 5 | 50 | 1 | 3 | 3 |
| 6 | 50 | 2 | 4 | 2 |
| 7 | 50 | 2 | 3 | 1 |
| 8 | 50 | 1 | 3 | 1 |

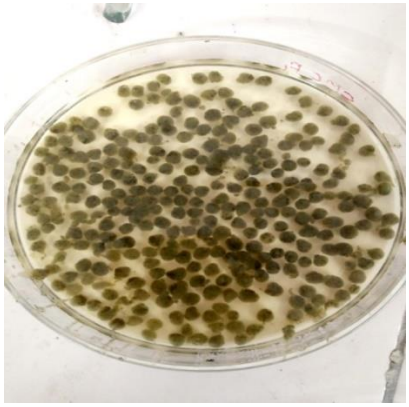

**Fig. 4. Losartan potassium microspheres in dried state**

**Fig.5 Losartan potassium microspheres in swelling state**

**(Used as a granule in tablet formulation)**

## Preparation of hibiscus mucilage matrix tablets:

The composition with respect to drug-polymer ratio was selected.

- As a control formulation to be used in the drug release studies, matrix tablets of losartan potassium were prepared by direct compression technique using magnesium stearate, talc and microcrystalline cellulose.
- The ingredients of the tablet, the drug loaded losartan microspheres is to be taken as granules in tablet.
- The other ingredients magnesium stearate and microcrystalline cellulose were sieved using sieve no.80.

These sieved ingredients are to compressed into a 9mm round, standard concave punches in the range of 4-5kg/cm$^2$.

**Table 5: Formulation chart of Sustained Release Matrix tablet of Losartan potassium:**

| Sr. No. | Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Losartan potassium (≅50 mg) microspheres | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| 2 | Microcrystalline cellulose | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| 3 | Magnesium stearate | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 |
| 4 | Talc | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 | 12.5 |

All quantities expressed in mg.

**Fig.6 Losartan potassium matrix tablet by using natural gum hibiscus**

## EVALUATION

### Evaluation for microspheres

**1. % Drug Entrapment Efficiency:** [7]

Microspheres (50 mg) were crushed in a glass mortar and pestle, and the powdered microspheres were suspended in 50 ml phosphate buffer (pH 7.2). The resulting mixture was shaken by the magnetic stirrer for 24 h. The solution was filtered, and the filtrate was analysed for the drug content. The drug entrapment efficiency was calculated using the following formula:

$$\%\ \text{Drug entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

**2. % Percentage yield**: [8]

Percentage practical yield is calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production. Practical yield was calculated as the weight of LP microspheres recovered from each batch in relation to the sum of starting material. The percentage yield of prepared LP microspheres was determined by using the formula:

$$\%\ \text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

**3. Scanning Electron Microscopy:** [9]

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry LP microspheres were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of LP microspheres were taken by random scanning of the stub.

**4. % Swelling study:** [10]

The single cross-linked bead formulation with maximum drug entrapment efficiency and the dual cross linked beads prepared there of were selected for the swelling study. Swelling tests of the beads were performed by soaking the dried beads in three different aqueous media representing stomach, intestine and colon environments. Towards this end, three different buffers were prepared with different pH values, comprising of 0.1NHCl buffer (pH 1.2) and two alkaline phosphate buffers (pH 6.8 and 7.4). Three separate aliquots (100mg each) of the beads were placed in a volume of 10ml of each of the mentioned buffers at 37 ± 1°C separately and incubated for predetermined time intervals (30, 60, 120min). The swelled beads were removed at the end of each time period and dried using blotting paper and then they were weighed again. The swelling ratio was determined using the following equation:

$$\%\ \text{Swelling index} = \frac{\text{Weight of swollen beads} - \text{Weight of dry beads}}{\text{Weight of dry beads}} \times 100$$

**Evaluation for tablet:**

**Pre-compression study:**

**Bulk density and Tap density**: [11]

Both loose bulk density (LED) and tapped density (TBD) were determined. Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. Bulk density is calculated by using a formula:

$$\text{Bulk density} = \frac{\text{Weight of sample in gm}}{\text{Volume occupied by sample in ml}}$$

The final volume was recorded and the tap density was calculated by the following equation:

$$\text{Tapped density} = \frac{\text{Weight of sample in gm}}{\text{Volume occupied by sample in ml}}$$

**Carr's index and Hausner's Ratio:** [12]

**Carr's index:**

A simple test has been developed to evaluate the friability of a powder by containing the poured (fluff) density and tapped density of a powder and the rate at which it packed down. A useful empirical guide is given by Carr's index.

$$\%\ \text{Compressibility index} = \frac{\text{Bulk density} - \text{Tapped density}}{\text{Tapped density}}$$

**Hausner's Ratio:** [12]

Hausner found that the ratio tapped density /bulk density was related to inter particle friction as such, could be used to predict powder flow properties.

$$\text{Hausner's ratio} = \frac{\text{Bulk density}}{\text{Tapped density}}$$

**Post-compression study**: [12]

All prepared matrix tablets were evaluated for following official and unofficial parameters.

**Appearanc**e:

The tablets were identified by checking the difference in colour.

**Thickness:**

Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using screw guaze on 3 randomly selected samples.

**Hardness:**

Hardness of the all tablet formulations were determined by Monsanto hardness tester. For each formulation the hardness of 5 tablets was determined, the average was calculated and presented with standard deviation is expressed in kg/cm.

**Friability**:

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure.

Twenty tablets were weighed accurately and placed in the plastic chamber that resolves at 25rpm for 4 mins dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and the percentage loss in tablet weight was determined.

**Table 6: Evaluation parametrs of tablet formulations:**

| Form. code | Thickness S.D. (mm) (n=5) | Hardness ± S.D. (Kg/cm$^2$) | Friability % | Average weight Variation ± S.D. (n=20) | Drug content ± S.D. (%) (n=2) |
|---|---|---|---|---|---|
| F1 | 2.91±0.041 | 5.2±0.22 | 0.39 | 188.75±2.45 | 95.1±0.41 |
| F2 | 2.96±0.031 | 5.4±025 | 0.32 | 190.55±2.81 | 95.4±0.71 |
| F3 | 2.81±0.035 | 5.1±0.25 | 0.21 | 192.55±3.67 | 95.5±0.13 |
| F4 | 2.81±0.023 | 4.4±0.069 | 0.23 | 195.43±3.71 | 98.1±3.11 |
| F5 | 2.88±0.071 | 4.4±0.023 | 0.26 | 198.14±3.88 | 105.3±3.40 |
| F6 | 3.00±0.027 | 5.3±0.27 | 0.25 | 189.85±2.74 | 96.9±1.56 |
| F7 | 3.01±0.042 | 4.3±0.27 | 0.17 | 196.85±3.12 | 97.9±0.71 |
| F8 | 2.96±0.056 | 4.6±0.22 | 0.17 | 199±2.63 | 99.4±0.57 |

**Drug content:** [13]

For determination of drug content at least five tablets from each formulation were weighed individually, crushed and diluted to 100 ml with sufficient amount of phosphate buffer of pH 6.8 (USP 2000). Then aliquot of the filtrate was diluted suitably and analysed spectrophotometrically at 205 nm against blank. Drug content was calculated using standard curve. All parameters of post compressional studies of the prepared matrix tablet.

**In vitro drug release studies of Losartan potassium matrix tablet**: [14]

In vitro drug release studies from the prepared matrix tablets were conducted using USP type II apparatus at 37°C at 50rpm. Dissolution mediums used were 900mL of 0.1N HCl and phosphate buffer of pH 6.8. The release rates from matrix tablets were conducted in HCl solution (pH 1.2) for 2h and changed to phosphate buffer (pH 6.8) for further time periods. The samples were withdrawn at desired time periods from dissolution media and the same were replaced with fresh dissolution media of respective pH. The samples were analysed by UV-Visible Spectrophotometer (Lab India 3000+). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time curve.

**Table 7 Dissolution data of sustained release matrix**

| Time (Hr) | Cum % Release F1 | Cum % Release F2 | Cum % Release F3 | Cum % Release F4 | Cum % Release F5 | Cum % Release F6 | Cum % Release F7 | Cum % Release F8 |
|---|---|---|---|---|---|---|---|---|
| 1 | 21.72 | 1.03 | 60.20 | 1.03 | 1.03 | 1.03 | 1.03 | 21.72 |
| 2 | 26.92 | 6.21 | 62.03 | 11.38 | 11.38 | 11.38 | 11.38 | 32.09 |
| 4 | 58.04 | 37.28 | 67.78 | 32.11 | 42.25 | 63.18 | 32.11 | 52.87 |
| 6 | 78.87 | 63.24 | 75.31 | 52.88 | 63.25 | 84.02 | 52.88 | 63.27 |
| 8 | 99.75 | 84.07 | 81.39 | 73.70 | 94.44 | 90.10 | 94.40 | 94.55 |

## RESULT AND DISCUSSION

**Post compressional study of tablet:**

Tablets were evaluated for thickness, % friability,hardness, weight variation and drug content. All the values found were within pharmacoepial limit. (Tabe no. 7)

Compatibility study:

**IR Study:**

The IR showing the percentage transmission (T %) verses wave number shown in fig.7. It displays the IR spectra of Losartan potassium using Microcrystalline cellulose. The spectra were recorded over the wave number range of 4000 to 500 cm-1.Infrared spectrum of Losartan potassium was determined on fourier transform infrared spectrophotometer using KBr dispersion method. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using Parkin elmerPharmaspec-1 FTIR spectrophotometer.

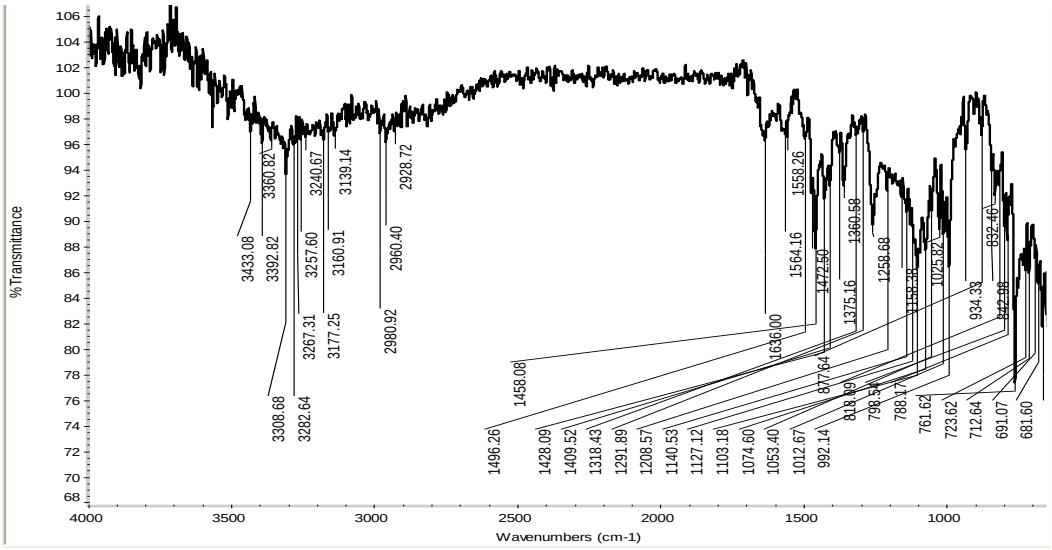


**Fig.7 IR of pure drug Losartan potassium**

IR spectra of losartan potassium and physical mixture was evaluated.

**7. *In vitro* drug release studies:**

The sustained released matrix tablet of Losartan potassium prepared by using USP Type-II (paddle). All the formulations F1, F2 (MCC) showed % DR 99.75±0.502, 84.07.34±1.60. F3, F4 (Hibiscus gum) showed 81.39±1.958, 73.70±0.778 and the formulations F5, F6 showed 94.44±2.234, 90.10±0.289 and formulations F7, F8 showed 94.40±1.895, 94.55±1.605 % respectively. The more appreciating drug release was observed with the formulations F1, F3, F8. The F1 and F8 had more sustaining effect as compared to the formulation F1 while the formulation F3 and retarding effect on the release than F7. In a very low concentration 1% w/w, F8 showed a very high sustaining effect up to 24 hours in comparison to F3 and F4 formulation having drug release up to 12 hours. From results it was concluded that, for drugs having high dose the Hibiscus gum was better polymer to sustain a drug release and to minimize a drug concentration.

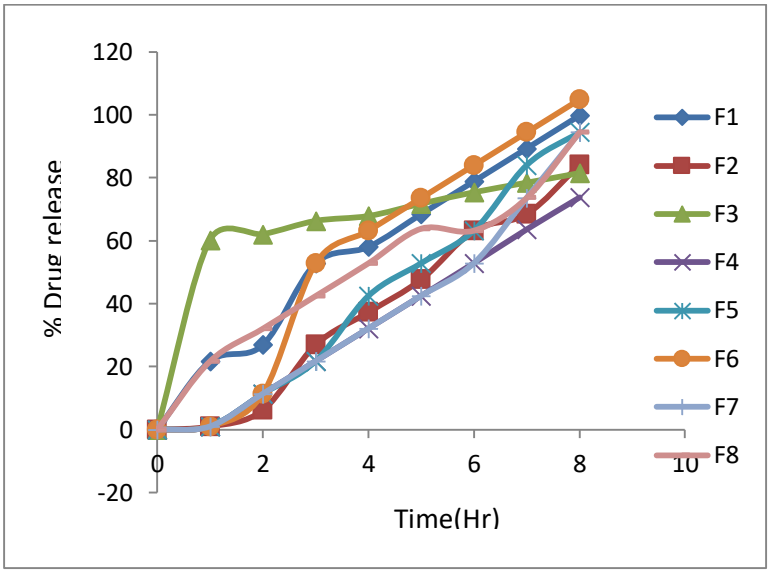


**Fig.*8 In vitro* dissolution study for F1-F8 formulation**

## 8. Drug release kinetics:

The curve fitting results of the release rate profile of the designed formulations gave an idea on the mechanism of the drug release. When the release data were analysed as per peppas equation, the release exponent 'n' was in the range of 41.96 with optimizes matrix formulations indicating non-fickian (Anamolous) diffusion as the release mechanism from all the matrix tablets. Plots of percent release from these tablets diffusion controlled. This value indicates a coupling that the diffusion and erosion mechanism (Anamolous diffusion) and indicates that the drug release was controlled by more than one process. Comparative study F1, F3, F7 was done. Formulations F1, F3, F7 showed highest linearity with r2 value of 0.978, 0.902 0.9304 which was best fitted to Higuchi, zero order and Korsmeyer peppas model.

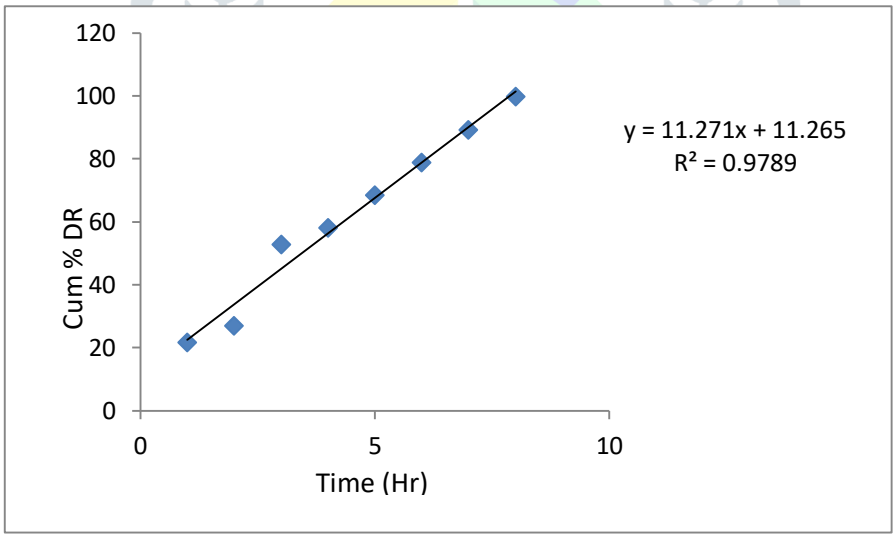


**Fig.9 Zero order plot of Losartan potassium matrix tablet F1**

**Table 8 Drug release Kinetics for losartan potassium matrix tablet formulation F1**

| Sr.No | Time (Hr) | Square root of time | Log time | Cum % DR | % DR remaining | Log Cum %DR | log cum %DR remaining |
|---|---|---|---|---|---|---|---|
| 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 1 | 1 | 0 | 21.72 | 78.28 | 1.337 | 1.894 |
| 3 | 2 | 1.414 | 0.301 | 26.92 | 73.08 | 1.430 | 1.864 |
| 4 | 3 | 1.732 | 0.477 | 52.81 | 47.19 | 1.723 | 1.674 |
| 5 | 4 | 2.000 | 0.602 | 58.04 | 41.96 | 1.764 | 1.623 |
| 6 | 5 | 2.236 | 0.699 | 68.45 | 31.55 | 1.835 | 1.499 |
| 7 | 6 | 2.449 | 0.778 | 78.87 | 21.13 | 1.897 | 1.325 |
| 8 | 7 | 2.646 | 0.845 | 89.31 | 10.69 | 1.951 | 1.029 |
| 9 | 8 | 2.828 | 0.903 | 99.75 | 0.25 | 1.999 | -0.602 |

## 9. SEM Studies:

The scanning electron microscopy of Losartan potassium microspheres can be done.

The scanning electron microscopy can be done with a magnification of ×100, × 500.

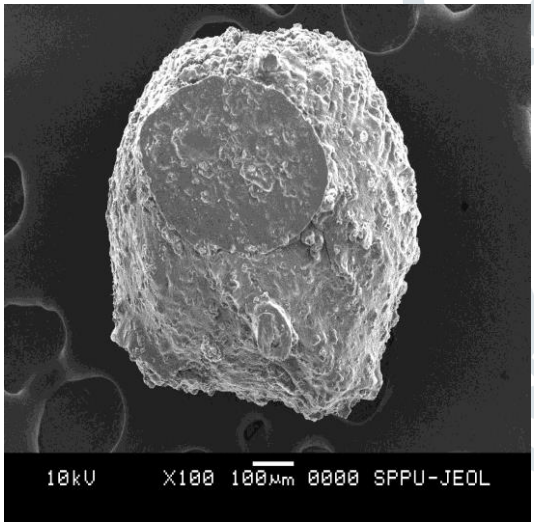


**Fig.10 A**

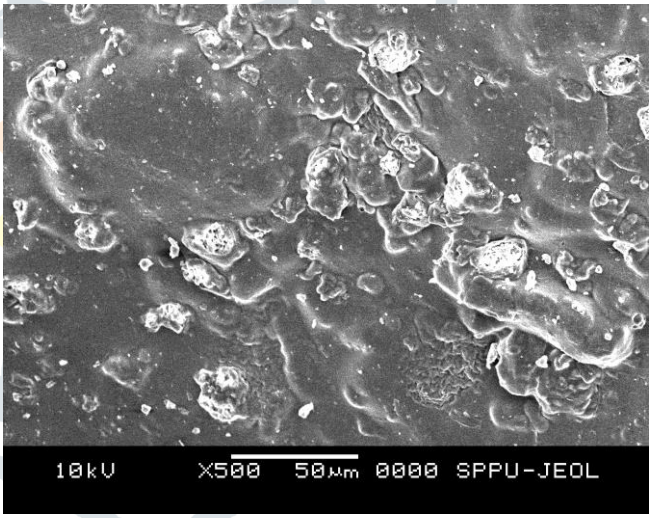


**Fig.10 B**

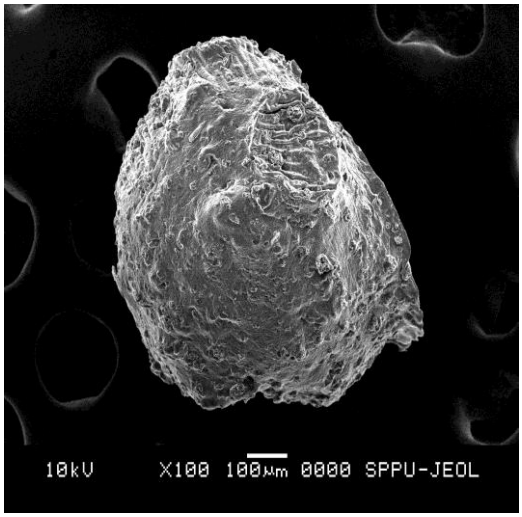


**Fig.10 C**

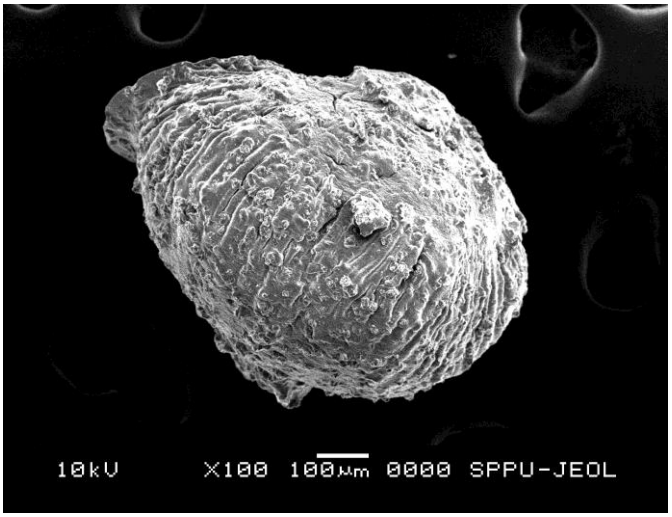


**Fig.10 D**

Fig. 10 A - SEM Studies of losartan potassium microspheres × 100 magnification

Fig. 10 B – SEM Studies of losartan potassium microspheres × 500 magnification

Fig. 10 C – SEM Studies of losartan potassium microspheres × 1000 magnification

Fig. 10 D – SEM Studies of losartan potassium microspheres × 100 magnification

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