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# FORMULATION AND EVALUATION OF SUSTAINED RELEASE FORMULATIONS OF LOSARTAN POTASSIUM BY MELT GRANULATION TECHNIQUE

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**Abstract:**

*Losartan potassium is an anti hypertensive. It is used in the treatment of hypertension. However oral bioavailability is poor (about 38%) which is due to first-pass hepatic metabolism. After oral administration, the terminal half-life is between 1.5 -2 h, and it is hygroscopic and light sensitive. Hence, it is considered as a suitable candidate for the Sustained release formulations by melt granulation method. Melt granulation can protect the drug from moisture and light and at the same time, it may also impart sustained release properties to the granulation. Thus reducing the frequency of administration and enhancing the patient compliance and maximizing the drug utility with minimum dose. To prepare the sustained release granules of Losartan potassium using different hydrophobic waxes like stearic acid, glyceryl monostearate and hydrogenated castor oil in different drug-wax ratios (1:1, 1:2, 1:3) and also in varying combinations (1:1:1), by melt granulation method and to evaluate the effect of concentration of hydrophobic polymer on the release rate of the water soluble drug, Losartan potassium. To evaluate the prepared granules for various pre-compression parameters such as angle of repose, bulk density, tapped density, compressibility index, particle size distribution, moisture absorbance and Hausner's ratio etc. To evaluate the sustained release capsules for weight variation, drug content uniformity, in vitro drug release, and drug-excipient interactions (IR spectroscopy).*

***Keywords****: Losartan potassium, Melt granulation method, Sustained release formulations.*

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## 1.INTRODUCTION:

**The goal in designing sustained or controlled delivery system is to[1-5]:**

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of novel drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery system. There are several reasons for the attractiveness of these dosage forms. It is generally recognized that for many disease states, a substantial number of therapeutically effective compounds already exists. The effectiveness of these drugs however is often limited by side effects or the necessity to administer the compound in a clinical setting. The major goal set in designing sustained or controlled delivery is to:

- Reduce the frequency of dosing.
- Increase effectiveness of the drug by localization atthe site of action.
- Reducing the dose required.
- Providing the uniform drug delivery.

In the past, many of the terms used to refer therapeutic systems of controlled and sustained release have been used in an inconsistent and confusing manner. Sustained release, sustained action, prolonged action, controlled release (drug release with zero order kinetics) and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effects by continuously releasing medication over an extended period of time after administration of a single dose.

**Sustained Release Preparation[6]**

These preparations may provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time usually 8-12 hrs. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak and valley effect which are characteristics of the conventional intermittent dosage regimen. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action.

**Controlled Release Preparations[7]**

Although this term has been interchanged widely with sustained release preparation in the past, recently it has become customary to restrict the latter term to formulations where the mechanism of prolonged action is dependent on one or more of the environmental factors in the GI tract such as pH, enzymes concentration, gastric motility etc. On the other hand, the term controlled release dosage form usually applies to preparations that are designed for all routes of administration and where the mechanism of prolonged action is inherent and determined totally by the delivery system itself. Consequently, this category offers the current state of the art products where the drug release profile is controlled accurately, following zero order kinetics and often can be targeted to a special body site or a particular organ.

**Advantages of Sustained Release Products[8]**

1. Decreased local and systemic side effects:
   - Reduced gastrointestinal irritation.
2. Better drug utilization:
   - Minimum drug accumulation on chronic dosing.
3. Improved efficiency in the treatment:
   - More uniform blood concentration.
   - Reduction in fluctuation in drug level and hence more uniform pharmacological response.
4. Improved patient compliance:
   - Less frequent dosing.
   - Reduced night-time dosing.
5. Economy
   - Although the initial unit cost of sustained release products is usually greater than that of the conventional dosage form because of the special nature of these products, the average cost of treatment over an extended time period may be less.

**DESIGN AND FORMULATION OF ORAL SUATAINED RELEASE DRUG DELIVERY[9-12]**

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form

would encounter during its transit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood level time profile similar to that after intravenous constant rate infusion.

**Sustained (zero-order) drug release has been attempted to be achieved with various classes of sustained drug delivery system**

1. Diffusion sustained system.
   i) Reservoir type.
   ii) Matrix type

2. Dissolution sustained system.
   i) Reservoir type.
   ii) Matrix type

3. Methods using Ion-exchange.
4. Methods using osmotic pressure.
5. pH independent formulations.
6. Altered density formulations.

**Techniques for Melt Granulation[12-15]**

**A) Spray congealing**

Spray congealing is a melt technique of high versatility. In addition to manufacture multiparticulate delivery system, it can be applied to process the raw meltable materials into particles of defined size and viscosity values for the melt agglomeration process. Processing of meltable materials by spray congealing involves spraying a hot melt of wax, fatty acid, or glycerides into an air chamber below the melting point of the meltable materials or at cryogenic temperature. Spray-congealed particles (10 to 3000 μm in diameter) are obtained upon cooling. The congealed particles are strong and nonporous as there is an absence of solvent evaporation. Ideally, the meltable materials should have defined melting points or narrow melting ranges. Viscosity modifier, either meltable or non-meltable at the processing temperature, may be incorporated into the meltable matrix to change the consistency of the molten droplets.

**B) Tumbling Melt Granulation**

A newer melt agglomeration technique, i.e., tumbling melt granulation, for preparing spherical beads has been reported. A powdered mixture of meltable and non-meltable materials is fed onto the seeds in a fluid-bed granulator. The mixture adheres onto the seeds with the binding forces of a melting solid to form the spherical beads. In preparing the spherical beads, both viscosity and particle size of the meltable materials should be kept at an optimum value. The particle size of a meltable material should be 1/6 or lower than the diameter of theseeds.

High-viscosity meltable materials should not be employed to avoid agglomeration of seeds and producing beads of low sphericity. Both particle size and viscosity of the meltable materials play a significant role in the melt agglomeration process. The control of the melt agglomeration process is best initiated by using meltable materials of controlled properties.

For the melt pelletization and melt granulation processes, it is desirable that meltable materials have a high viscosity to improve the mechanical strength of the agglomerates, but a reduced particle size to prevent uncontrollable agglomerate growth. In tumbling melt granulation, small meltable particles with sufficient viscous binding forces are obligatory to produce spherical beads.

## 2.MATERIALS & METHODS:

### 2.1.MATERIALS USED

Losartan Potassium, Hydrogenated Castor Oil, Glyceryl Monosterate, Stearic acid.

### 2.2. METHODS USED[15-20]

**Preparation of Losartan Potassium Granules[15-20]:**

Melt granulation method was employed to prepare sustained release granules of Losartan potassium with different hydrophobic waxes like: stearic acid, glceryl monostearate and hydrogenated castor oil in the ratios of 1:1, 1:2, 1:3. Also, combination of glyceryl monostearate and stearic acid, hydrogenated castor oil and stearic acid, glyceryl monostearate and hydrogenated castor oil with Losartan potassium, in a ratio of 1:1:1. The dose of Losartan potassium (50 mg) was kept same in every formulation.

**Procedure:**

1. Losartan potassium and all the hydrophobic waxes were individually weighed.
2. The required quantity of hydrophobic wax was then transferred into a china dish.
3. Then, the china dish, containing the wax was placed in a water bath and heated to $75^0$ C temperature.

4. Accurately weighed quantity of Losartan potassium was added to the molten wax in china dish.
5. Molten mixture was cooled to room temperature, till it got solidified.
6. The solidified mass, was then passed through sieve no. 10 and the drug loaded granules were formed.

**EVALUATION OF LOSARTAN POTASSIUM CAPSULES[20-22]**

**Weight Variation:** 20 Capsules of each formulation were weighed using an electronic balance and the test was performed as per I.P.

**Uniformity of Drug Content:** 10 mg of granules were added to 50 ml of distilled water, heated to 70-80º C and allowed to cool to room temperature. The liquid was solidified and the drug solution was filtered to Whatman filter paper, the Losartan potassium content was determined by measuring the absorbance at 267 nm after appropriate dilution with distilled water. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

***In-vitro* Drug Release Study**

*In vitro* dissolution of Losartan potassium was studied in USP- type I (rotating basket) apparatus at 50 rpm. 900 ml of pH 6.8 phosphate buffer was placed in the dissolution vessel. A sample of granules containing 50 mg of Losartan potassium was filled manually into a capsule, and placed in a cylindrical basket. The temperature of dissolution medium was maintained at $37\pm0.5^0$ C, throughout the experiment. One capsule was used in each test. Samples of the dissolution medium (5 ml) were withdrawn at each time interval and were replaced with equal volume of drug free dissolution medium. The withdrawn samples were filtered through whatman filter paper and were analyzed for drug release by measuring the absorbance at 235 nm.

**Stability testing**

Accelerated stability studies on promising formulation (F4) were carried out by storing 10 capsules in amber colored rubber stopped vials at elevated temperature of 40 ± 2º C/ 75 ± 5% RH (Stability chamber) over a period of 90 days (3 months). At interval of one month, the tablets were visually examined for any physical changes and any changes in drug content.

**Drug – Carrier interaction studies:**

While developing a new formulation, it is necessary to check the drug compatibility with the carrier or excipient used and that the drug has not undergone any degradation when it passes through the various processes. Suitable evidential experiments are conducted to justify and prove the intactness of the drug in the formulations. Various methods, available for characterizing the products are: TLC, IR spectra, X-ray diffraction, scanning electron microscopy, diffuse reflectance spectroscopy and differential scanning calorimetry.

**FTIR Studies:**

Infrared spectroscopy is one of most powerful analytical technique when it comes to the determination of presence of various functional groups involved in making up the molecule. It provides very well accountable spectral data regarding any change in the functional group characteristics of a drug molecule occurring while in the processing of formulation.

**DSC- Studies**:

The compatibility studies were done by individually subjecting the drug and excepient alone to the DSC and further subjecting the mixture of drug and excepient initial and the sample stored at acceleratory stability condition 40º C / 75 % RH for a period of 2weeks and the overlay of the thermogram was observed for any change in the drug peaks.

## 3.RESULTS:

**Table-1-Composition of different formulations**

| Formulation code | Composition | Ratio |
|---|---|---|
| **F1** | Drug: Stearic Acid | 1:1 |
| **F2** | Drug: Stearic Acid | 1:2 |
| **F3** | Drug: Stearic Acid | 1:3 |
| **F4** | Drug: Glyceryl Monosterate | 1:1 |
| **F5** | Drug: Glyceryl Monosterate | 1:2 |
| **F6** | Drug: Glyceryl Monosterate | 1:3 |
| **F7** | Drug: Hydrogenated Castor oil | 1:1 |
| **F8** | Drug: Hydrogenated Castor oil | 1:2 |
| **F9** | Drug: Hydrogenated Castor oil | 1:3 |
| **F10** | Drug: GMS: Stearic acid | 1:1:1 |
| **F11** | Drug: Stearic acid: HCO | 1:1:1 |
| **F12** | Drug: GMS: HCO | 1:1:1 |

**Table 2: Pre-compression parameters of different formulations**

| Formulation Code | Angle of repose | Bulk density (g/ml) | Tapped Density (g/ml) | Carr's Index ( % ) | Hausner's Ratio | Moisture absorption capacity (%) |
|---|---|---|---|---|---|---|
| F1 | 21.56 | 0.43 | 0.49 | 12.24 | 1.13 | 3.10 |
| F2 | 22.01 | 0.39 | 0.45 | 13.33 | 1.15 | 2.34 |
| F3 | 24.61 | 0.38 | 0.44 | 13.63 | 1.15 | 3.33 |
| F4 | 21.15 | 0.40 | 0.45 | 11.11 | 1.12 | 2.21 |
| F5 | 23.99 | 0.48 | 0.55 | 12.72 | 1.14 | 3.56 |
| F6 | 21.95 | 0.45 | 0.53 | 15.04 | 1.17 | 2.89 |
| F7 | 22.21 | 0.41 | 0.47 | 12.76 | 1.14 | 2.48 |
| F8 | 23.35 | 0.40 | 0.46 | 13.04 | 1.15 | 2.63 |
| F9 | 24.98 | 0.43 | 0.51 | 15.68 | 1.17 | 2.94 |
| F10 | 22.17 | 0.44 | 0.52 | 15.38 | 1.18 | 3.11 |
| F11 | 24.86 | 0.46 | 0.55 | 16.36 | 1.18 | 3.26 |
| F12 | 23.51 | 0.42 | 0.50 | 16.00 | 1.18 | 2.16 |

**Table-3- Percentage drug content of Losartan potassium-based formulations**

| Sl.no | Formulation Code | Drug Content (%) | | Weight of granules equivalent to 50 mg Losartan potassium | Weight variation |
|---|---|---|---|---|---|
| | | Theoretical | Practical | | |
| 1 | F1 | 50 | 51.65±0.72 | 96.80 | Within I.P limits (± 7.5 %) |
| 2 | F2 | 33.3 | 34.03±0.47 | 146.92 | |
| 3 | F3 | 25 | 23.32±0.35 | 214.40 | |
| 4 | F4 | 50 | 48.50±0.17 | 104.05 | |
| 5 | F5 | 33.3 | 33.9±0.56 | 151.10 | |
| 6 | F6 | 25 | 22.57±1.01 | 221.53 | |
| 7 | F7 | 50 | 47.62±0.71 | 104.99 | |
| 8 | F8 | 33.3 | 32.25±0.68 | 155.03 | |
| 9 | F9 | 25 | 23.62±0.45 | 211.68 | |
| 10 | F10 | 33.3 | 34.06±0.81 | 146.79 | |
| 11 | F11 | 33.3 | 32.76±0.38 | 152.62 | |
| 12 | F12 | 33.3 | 32.53±0.41 | 153.70 | |

**Table-4-Correlation coefficient ($R^2$) values of different batches of Losartan potassium granules.**

| Formulation code | Zero Order | First Order | Higuchi's | Peppa's |
|---|---|---|---|---|
| **F1** | 0.988 | 0.721 | 0.949 | 0.982 |
| **F2** | 0.996 | 0.886 | 0.966 | 0.987 |
| **F3** | 0.989 | 0.964 | 0.975 | 0.973 |
| **F4** | 0.992 | 0.828 | 0.984 | 0.989 |
| **F5** | 0.997 | 0.914 | 0.968 | 0.976 |
| **F6** | 0.992 | 0.970 | 0.967 | 0.974 |
| **F7** | 0.989 | 0.798 | 0.943 | 0.958 |
| **F8** | 0.995 | 0.902 | 0.961 | 0.984 |
| **F9** | 0.994 | 0.951 | 0.959 | 0.957 |
| **F10** | 0.996 | 0.985 | 0.955 | 0.950 |
| **F11** | 0.993 | 0.979 | 0.952 | 0.949 |
| **F12** | 0.994 | 0.977 | 0.954 | 0.951 |

**Table 5: Dissolution parameters of granules Losartan potassium**

| Formulation code | Dissolution parameters | | | | | |
|---|---|---|---|---|---|---|
| | n | $K_0$ (mg/lit/hr) | $K_1$ ($hr^{-1}$) | $T_{50\%}$ (hr) | $T_{75\%}$ (hr) | $T_{90\%}$ (hr) |
| **F1** | 0.800 | 8.832 | 0.306 | 5.24 | 7.54 | 9.30 |
| **F2** | 0.787 | 7.508 | 0.218 | 6.12 | 9.0 | 11.12 |
| **F3** | 0.731 | 6.805 | 0.168 | 5.48 | 9.10 | > 12 h |
| **F4** | 0.799 | 7.928 | 0.310 | 5.24 | 8.0 | 10.24 |
| **F5** | 0.683 | 6.783 | 0.184 | 6.06 | 8.43 | 11.54 |
| **F6** | 0.659 | 6.201 | 0.142 | 6.12 | 10.06 | > 12 h |
| **F7** | 0.650 | 6.565 | 0.184 | 6.24 | 10.24 | 11.42 |
| **F8** | 0.73 | 6.486 | 0.154 | 6.36 | 10.30 | > 12 h |
| **F9** | 0.651 | 6.098 | 0.134 | 6.48 | 10.48 | > 12 h |
| **F10** | 0.571 | 5.755 | 0.122 | 6.36 | 10.30 | > 12 h |
| **F11** | 0.632 | 6.040 | 0.133 | 6.48 | 10.36 | > 12 h |
| **F12** | 0.631 | 5.389 | 0.133 | 7.36 | 11.54 | > 12 h |

**Table 6: Drug content data of promising formulation (F12)**

| Sl.no | Trial no | 1st day (%) | 30 th day (%) | 60 th day (%) | 90 th day (%) |
|---|---|---|---|---|---|
| 1 | I | 48.36 | 48.30 | 48.22 | 48.19 |
| 2 | II | 48.69 | 48.65 | 48.58 | 48.24 |
| 3 | III | 48.45 | 48.42 | 48.32 | 48.13 |
| 4 | Mean | 48.50 | 48.45 | 48.37 | 48.18 |
| 5 | S.D | ±0.17 | ±0.18 | ±0.18 | ±0.05 |

**Table 7: Statistical analysis of drug content data for the promising formulation (F12)**

| Sl.no | Trial no | 1st day (%) A | 90th day (%) B | A-B |
|---|---|---|---|---|
| 1 | I | 48.36 | 48.19 | 0.17 |
| 2 | II | 48.69 | 48.24 | 0.45 |
| 3 | III | 48.45 | 48.13 | 0.32 |
| 4 | Mean | 48.50 | 48.18 | 0.32 |
| 5 | S.D | ±0.17 | ±0.05 | ±0.10 |

**Table 8: IR spectrum data of Losartan potassium and the promising formulation (F12)**

| Formulation Code | -CH Aromatic Stretching | -CH Aliphatic stretching | -OH (1°) Stretching deformation | -OH Stretching | C-Cl Stretching | C-N (2°) Stretching |
|---|---|---|---|---|---|---|
| Pure Drug ($cm_{-1}$) | 2929.38 | 2870.74 | 1259.93 | 3209.61 | 762.73 | 1358.17 |
| F12 ($cm^{-1}$) | 2917.57 | 2850.52 | 1258.10 | 3240.50 | 763.07 | 1358.30 |

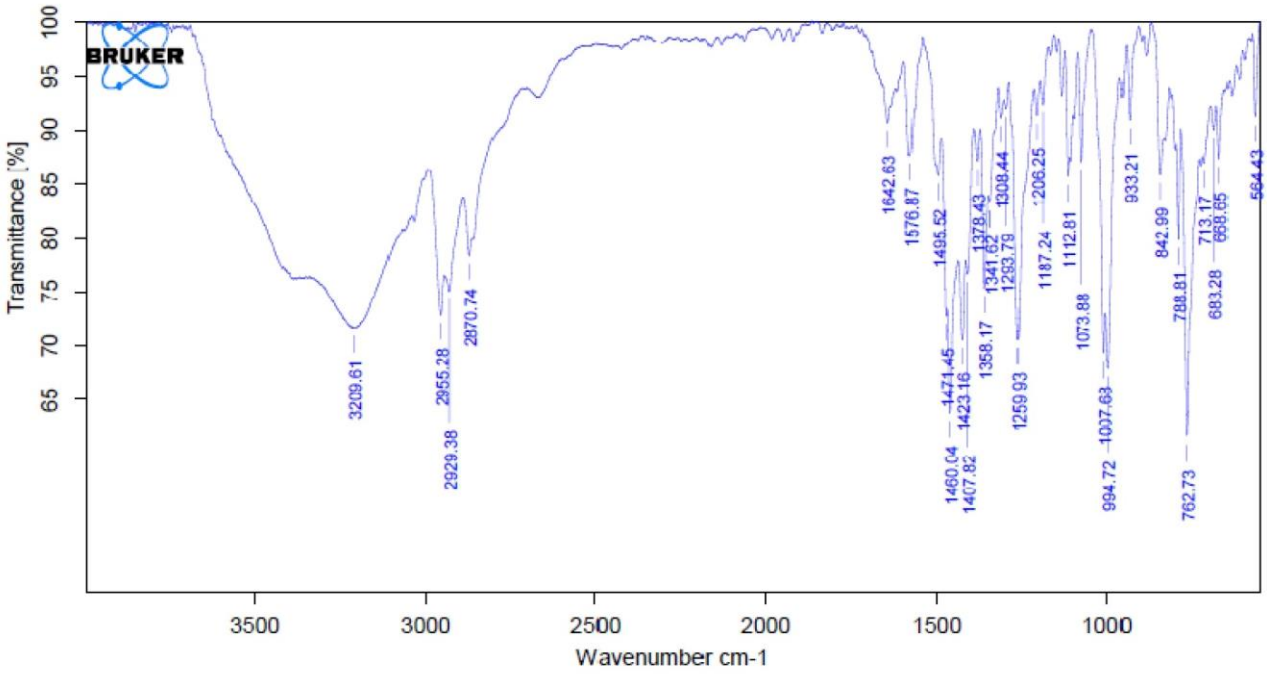


**Figure 1: IR Spectrum of Losartan potassium (Pure drug)**

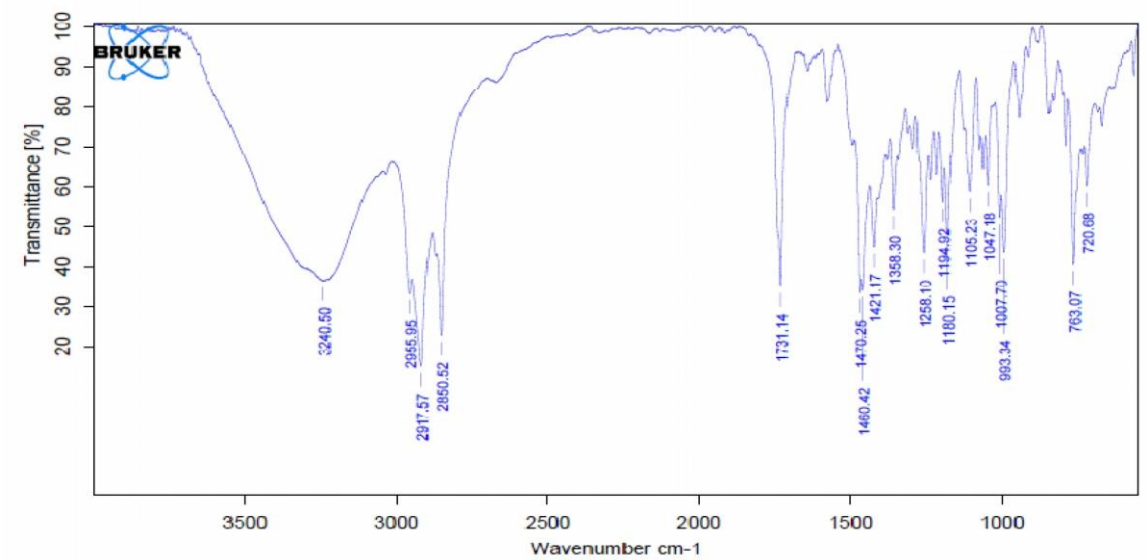


**Figure 2: IR Spectrum of the promising Formulation (F12)**

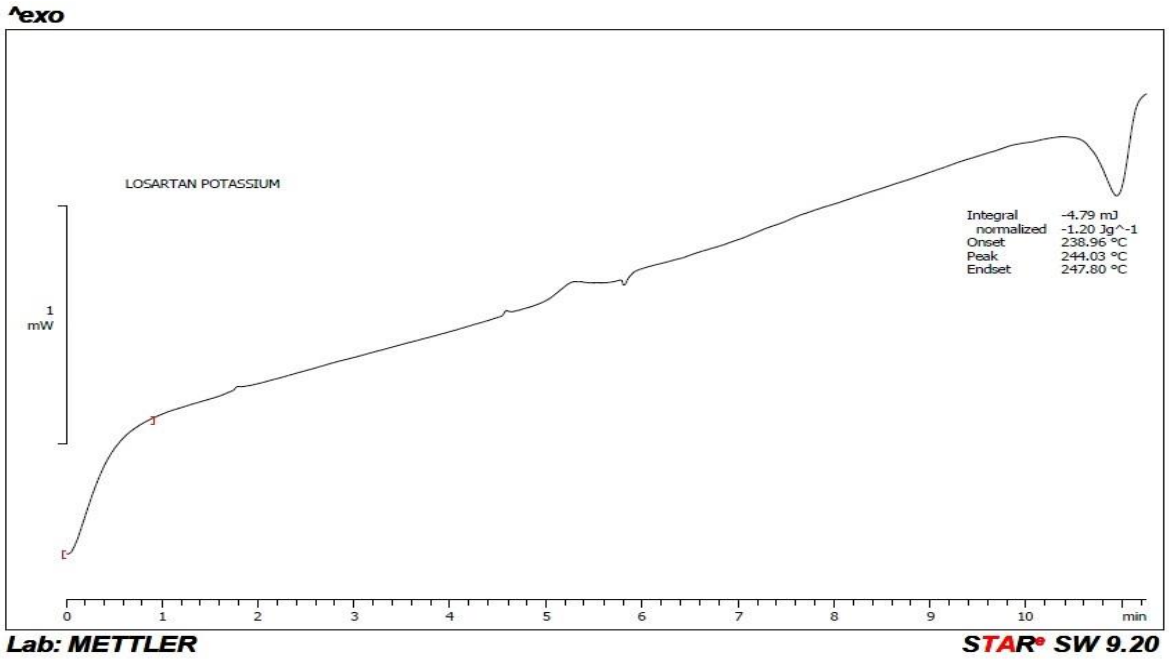


**Figure 3: DSC thermogram of Losartan potassium (pure drug)**

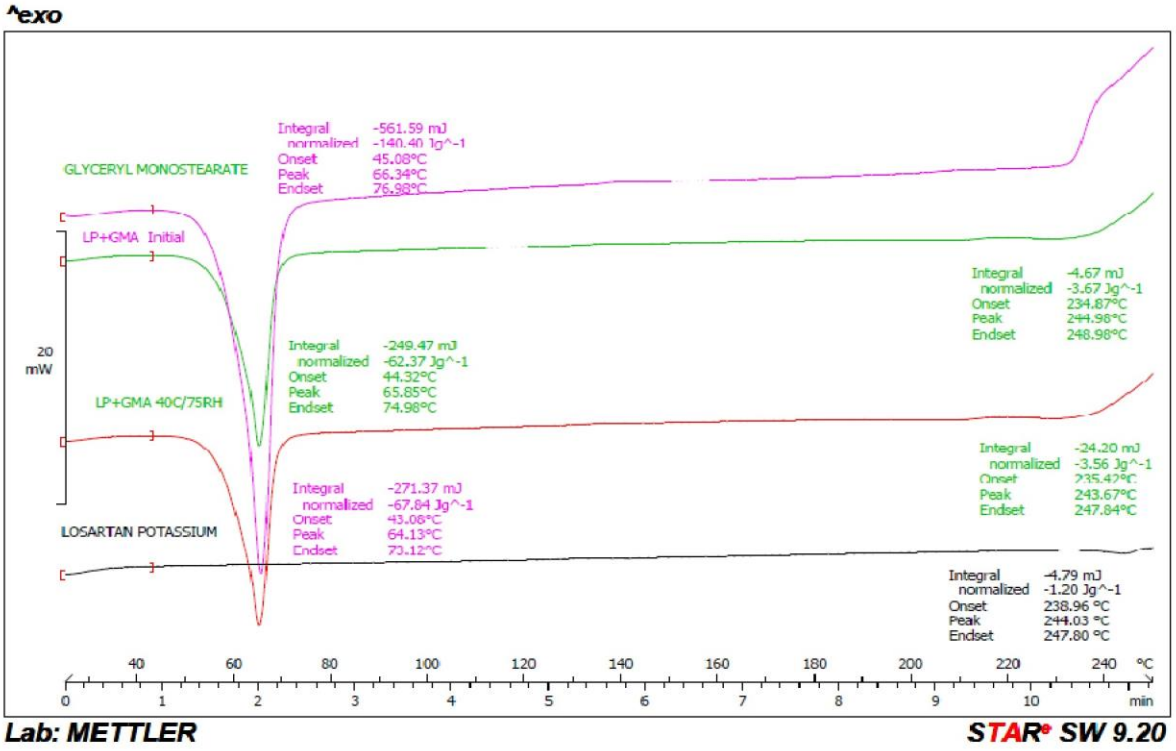


**Figure 4: DSC thermogram of promising formulation (F12)**

## 4.SUMMARY:

Sustained release granules of Losartan potassium using hydrophobic waxes like stearic acid, glyceryl monostearate and hydrogenated castor oil can be prepared by melt granulation method. The granules were found to possess excellent free flowing properties with angle of repose values in the range of 21.15 to 24.98. From the studies, it was found that all the pre-compression parameters were within the acceptable range. The drug content was uniform in all the granule formulations. The low values of SD indicate uniform distribution of drug in the granules. The increase in the size of granules decreases the release of drug, because of higher surface area offered to the dissolution medium. The drug: wax ratio were found to influence the release of drug from the formulations; as thewax content increases, the release rate of drug decreased. The formulation F12 with a LSP-glyceryl monostearate and Hydrogenated Castor Oil ratio of 1:1:1 was found to be promising, and released 75.74 % drug (following zero-order kinetics), in 12 hrs. Formulation F12 were found to release the drug by anomalous (non-Fickian) transport, since the 'n' value for peppa's plot were found to be 0.631. Short–term accelerated stability studies on the promising formulation (F12), had shown nosignificant change in drug content (t=3.12), when stored at 40±2° C /75±5 % RH for 3 months. FTIR and DSC studies indicated that the drug is compatible with the excipients. Melt granulation is a suitable method for the preparation of sustained release formulations of hygroscopic, light sensitive and water soluble drug like losartan potassium. This method does not require the use of organic solvents or aqueous solvents and drying step is not necessary, thus the process is less consuming in terms of time and energy compared to other methods.

## 5.CONCLUSION:

Sustained release granules were successfully formulated. Promising formulation (F12) had shown slow and extended release of drug upto 12 hrs (75.74 %), following zero order kinetics. Short–term accelerated stability studies on the promising formulation (F12), had shown no significant change in drug content (t= 3.12), when stored at 40 ± 2° C temperature /75 ± 5 % RH for 3 months. FTIR and DSC studies, on the promising formulation (F12) indicated that, there were no drug- excipient interactions.

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