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FORMULATION DEVELOPMENT AND EVALUATION OF SINTERED MATRIX TABLET OF LOSARTAN POTASSIUM

Ravindra B. Saudagar[1*] and Pratik V. Bidwe[2]

[1*]Department of Pharmaceutical Chemistry, KCT's R. G. Sapkal College of Pharmacy, Anjaneri, Nashik- 422213, Maharashtra, India.
[2]Department of Quality Assurance and Techniques, KCT's R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India.

***Corresponding Author: Ravindra B. Saudagar**
Department of Pharmaceutical Chemistry, KCT's R. G. Sapkal College of Pharmacy, Anjaneri.

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ABSTRACT
Exploration of sintering concept in pharmaceutical science is relatively recent. The objective of this study is to investigate the release characteristics of matrix tablet consisting of a hydrophobic polymer and Losartan potassium for sustain release formulation using sintering technique. Losartan potassium is a Angiotensin receptor II blocker commonly used to treat high blood pressure and it is an ideal candidate for designing sustaining drug formulation due to its frequent dosing and short biological half-life (about 1.5 to 2.5hrs; active metabolite: 3 to 9 hrs.). The tablets were compressed by direct compression method and formulation were sintered at 75^0 C temperatures and various time points. Sintering i.e. application of heat, causes the bonding of adjacent particle surfaces in a mass of powder or in a compact leading to the retardation of drug release. The sintered tablets were characterized by their physical parameters and in-vitro dissolution tests. FT-IR and differential scanning calorimetry studies ruled out the occurrence of drug interaction after sintering condition. It can be concluded that as sintering time increases drug retardation also increase.

KEYWORDS: Sintering, Eudragit RL 100, sintered matrix tablet, Thermal sintering.

INTRODUCTION
The oral route is most common and advantageous route of administration for many drugs. Sustain release formulation in many case provide further advantageous including improved therapeutic effect, increased patience compliance and reduced dosing frequency.[1] An ideal controlled drug delivery system is the one, which delivers the drugs at predetermined rate, locally or systematically, for specific period of time.[2] In SR matrix tablets the drug is released at predetermined rate and it depends on required therapeutic concentration and drugs pharmacokinetic parameters. Incorporating a drug within the insoluble matrix provides a conventional mean to controlled release. Losartan potassium is a Angiotensin receptor II blocker commonly used to treat high blood pressure It is reported to have Half-life of (about 1.5 to 2.5hrs; active metabolite: 3 to 9 hrs.). Losartan potassium is administered as conventional tablet, containing 50 mg two times a day hence sustain release formulation of Losartan potassium is desirable. Since Losartan potassium requires frequent dosing to maintain therapeutic concentration, it was chosen as a candidate.

Sintering is defined as the bonding of adjacent particles surfaces in a mass of powder or in a compact by the application of heat.[3] Conventional sintering involves the heating of compact at a temperature below the melting point of the solid constitute in a controlled environment under atmospheric pressure.[4] The sintering process has been used for the fabrication of controlled-release matrix tablets and for the stabilization of the drug permeability of film coatings derived from various pharmaceutical lattices.[5]

MATERIALS AND METHODS
Losartan potassium was obtains as a gift sample from IPCA Laboratories Mumbai. Eudragit RL 100 was procured from Modern Scientific Nashik. Magnesium stearate is procured from Pure Chem Lab, Hyderabad. Talc and Microcrystalline cellulose were procured from Research-Lab Fine Chem. Industry- Mumbai.

Preparation of Matrix Tablet
Losartan potassium was mixed according to the formula given in table 1 with excipients (except lubricant) by geometric mixing in polyethylene bag for 10 min. Then lubricant was added and mixed for an additional 5 min

and then final blend was directly compressed using 9 mm stainless steel punch using rotary press (Karnavati Minitab, India). Compression force for all the tablets was adjusted to get tablets of hardness 4-4.2 kg/cm^2.

Sintering of Matrix Tablets

The prepared matrix tablets were sintered by Thermal treatment or Heat treatment method.

Thermal treatment

The prepared tablets were placed on aluminum foil and subjected to heating at a temperature 75^0 C for 1, 4 and 8 hours in hot air oven.

Table 1: Composition of different formulations (All values are expressed in mg).

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan Potassium	50	50	50	50	50	50	50	50	50
EUDRAGIT RL 100	25	75	125	25	75	125	25	75	125
Microcrystalline cellulose	172.5	122.5	72.5	172.5	122.5	72.5	172.5	122.5	72.5
Talc	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Magnesium stearate	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
Total	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Evaluation of Sintered and Unsintered matrix Tablets

The Sintered and Unsintered matrix tablets were subjected to various evaluation parameters such as hardness, thickness, weight variation, friability and drug content.

Dissolution Study

In vitro drug release studies of the prepared matrix tablets were conducted for a period of 12 hours by using an USP Type II (Paddle) Dissolution apparatus (Electrolab TDT 08L, India) at 37± 0.5° C. The agitation speed was 50 rpm. The dissolution study was carried out in 900 ml 0.1 N hydrochloric acid at 37±0.5 ºC for first 2 hours and then in 900 ml of phosphate buffer (pH 6.8) up to 10hours. 5 ml of the sample was withdrawn at regular intervals and the same volume of fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered through a whatmmam filter no.1 and the drug content in each sample was analysed with UV spectrophotometer. The amount of drug present in the samples were calculated with the help of calibration curve constructed from reference standard.

Differential Scanning calorimetry

The powdered samples (3 mg) were hermetically sealed in aluminum pans and heated at a constant rate of 10^o C/min, over a temperature range of 30-300^{o}C with nitrogen flow rate of 30 ml/min. Thermograms of the samples were obtained using differential scanning calorimeter (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale.

Dissolution Kinetic study

The dissolution data were analyzed on the basis of zero order (cumulative amount of drug release vs. time), first order rate (Log cumulative amount of drug remaining vs. time), Hguchi system (cumulative amount of drug released vs. root of time) and Korsmeyer's and Peppas (log cumulative amount released vs. log time). Interpretation of diffusion release mechanisms from polymeric film is given in Table 2.

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.5 < n > 1.0	Anomalous transport
1.0	Case-II transport
Higher than 1.0	Super Case-II transport

Stability studies

Stability study of optimized tablet formulation was carried out to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of reproducible tablet formulation was assessed at 40±2 ^{0}c/ 75±5% RH as per ICH Guidelines in the stability chamber tempo instrument pvt ltd. TI-710. Tablets equivalent to 8 mg of Losartan potassium were filled and were with packed with aluminum strips and stored for 3 months. Samples were analyzed at 0, 30, 60, & 90 days for physical appearance, drug content, and in vitro dissolution profile.

RESULT AND DISCUSSION

Drug Polymer compatibility study

Infra- red spectra of physical mixture showed matching peaks with the drug spectra. The characteristic peaks of drug were also present in the spectra of all drug- polymer combinations. A spectrum of physical mixture is shown in figure 1.

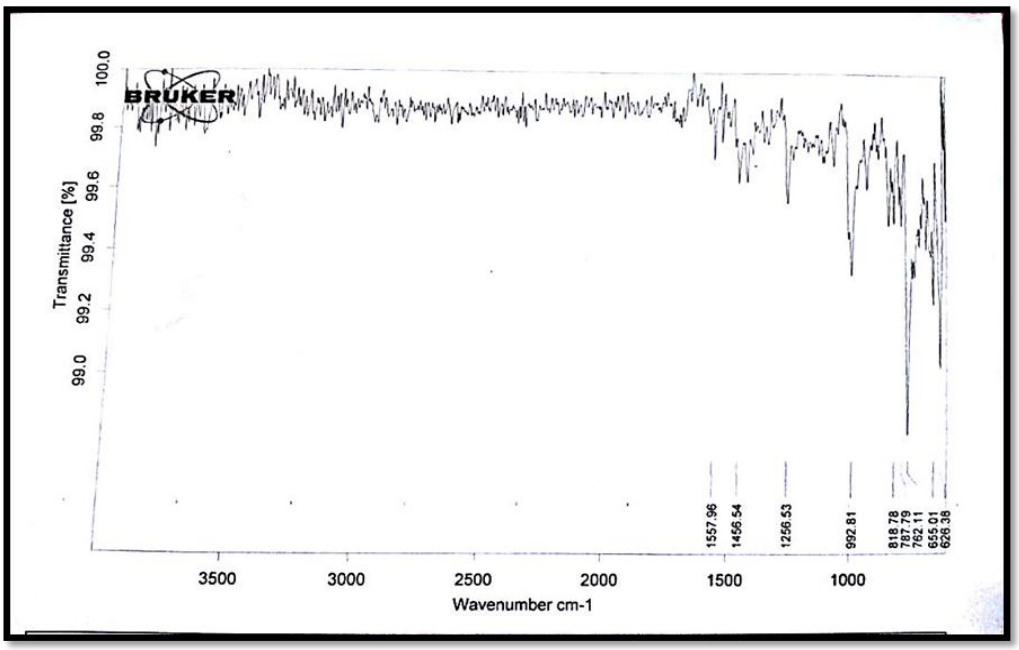

Figure 1: FTIR spectrum of physical mixture of Losartan Potassium and Eudragit RL 100.

Table 3: Interpretation of FT-IR for Compatibility studies.

Sr. No.	Functional Group	Pure drug	Physical mixture
1.	C=C Aromatic Stretch	Yes	Yes
2.	C-O Stretch of alcohol	Yes	Yes
3	C-H Aromatic	Yes	Yes
4	C-H Bending of -CH_3	Yes	Yes

Evaluation of Unsintered Matrix Tablet

Table 4: Evaluation of Unsintered Matrix Tablet.

Formulation Code	Average Weight (mg) Mean ± S.D	Hardness ($kg/cm^{2)}$ Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean± S.D	Drug content (%) Mean± S.D
F1	246.95±3.67	3.98±0.13	3.59±0.013	0.47±0.01	96.9±0.10
F2	248.7±3.06	4.02±0.13	3.59±0.017	0.44±0.015	97.18±0.014
F3	248.1±2.95	4.04±0.16	3.59±0.014	0.43±0.015	`97.82±0.10
F4	247.95±3.66	3.94±0.11	3.58±0.029	0.52±0.012	96.84±0.17
F5	248.1±2.98	4±0.15	3.59±0.021	0.44±0.015	97.12±0.09
F6	247.95±3.81	3.98±0.19	3.59±0.070	0.45±0.017	97.93±0.092
F7	248.2±3.76	3.96±0.20	3.60±0.071	0.46±0.015	97.07±0.09
F8	248.2±2.97	4.04±0.11	3.60±0.025	0.42±0.025	97.30±0.19
F9	248.3±3.06	4.08±0.16	3.61±0.018	0.41±0.16	98.10±0.10

In-Vitro dissolution study of unsintered matrix tablet

The prepared unsintered matrix tablets were subjected to dissolution test to assess in-vitro release of all tablet formulations. All Unsintered matrix tablets shows 100% drug release in 6-7 hours as shown in table.

Table 5: In-Vitro dissolution study of Unsintered Matrix Tablet

Time (Hrs.)	Cumulative Drug Release (%)(Mean± S.D)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	13.02± 0.015	10.77± 0.022	8.67± 0.015	13.09± 0.2	10.71± 0.01	8.52± 0.014	13.05± 0.01	12.86± 0.022	8.48± 0.014
2	29.97± 0.22	26.63± 0.05	21.97± 0.031	30.06± 0.22	26.69± 0.015	22.31± 0.01	30.03± 0.015	29.70± 0.05	20.58± 0.01
3	48.65± 0.014	46.39± 0.02	41.40± 0.05	49.52± 0.015	46.33± 0.14	41.70± 0.25	49.59± 0.031	48.46± 0.070	41.13± 0.015
4	69.28± 0.15	66.13± 0.014	61.33± 0.014	69.86± 0.014	66.07± 0.015	61.63± 0.15	69.75± 0.014	69.14± 0.015	64.18± 0.021
5	87.12± 0.011	85.47± 0.15	80.96± 0.016	87.40± 0.1	85.39± 0.023	81.29± 0.015	87.32± 0.025	86.95± 0.025	80.63± 0.022
6	104.13± 0.015	102.39± 0.015	92.29± 0.03	104.40± 0.016	102.31± 0.022	92.62± 0.022	104.30± 0.015	102.92± 0.014	91.95± 0.015
7			102.64± 0.021			100.44± 0.01			100.53± 0.05

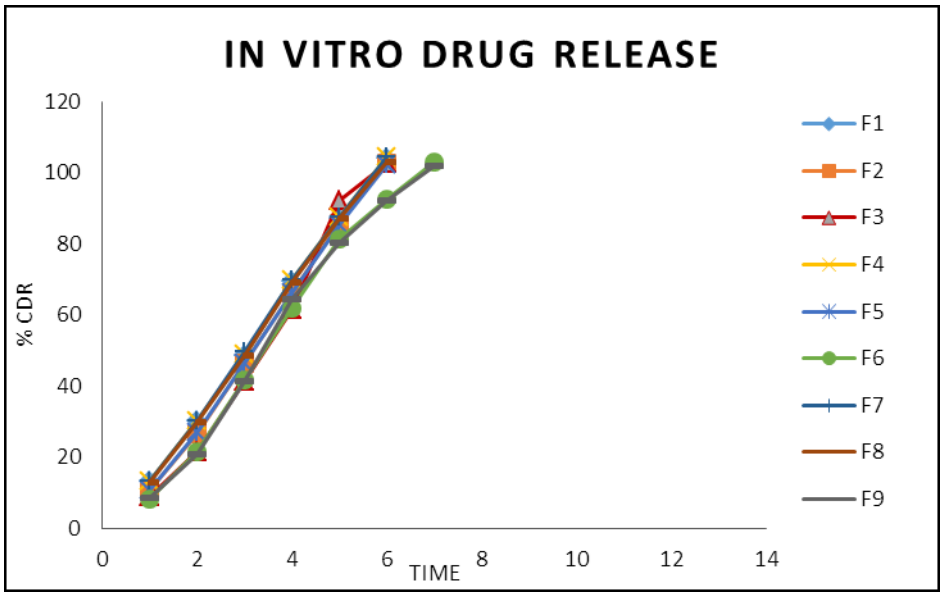

Figure 2: In-vitro dissolution study of Unsintered Matrix Tablets.

Evaluation of sintered Matrix Tablet

Table 6: Evaluation of Sintered Matrix tablet.

Formulation Code	Average Weight (mg) Mean ± S.D	Hardness ($kg/cm^{2)}$ Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean± S.D	Drug content (%) Mean± S.D
F1	246.95±3.67	4.14±0.1	3.59±0.013	0.44±0.02	96.9±0.10
F2	248.7±3.06	4.16±0.13	3.59±0.017	0.42±0.015	97.18±0.014
F3	248.1±2.95	4.19±0.16	3.59±0.014	0.39±0.017	97.82±0.10
F4	247.95±3.66	3.27±0.11	3.58±0.029	0.47±0.012	96.84±0.17
F5	248.1±2.98	4.38±0.15	3.59±0.021	0.40±0.014	97.12±0.09
F6	247.95±3.81	4.54±0.19	3.59±0.070	0.36±0.02	97.93±0.092
F7	248.2±3.76	4.38±0.20	3.60±0.071	0.40±0.025	97.07±0.09
F8	248.2±2.97	5.24±0.11	3.60±0.025	0.33±0.012	97.30±0.19
F9	248.3±3.06	5.6±0.16	3.61±0.018	0.27±0.021	98.10±0.10

In-Vitro dissolution study of Sintered Matrix Tablet

Table 7: In-Vitro dissolution study of Sintered Matrix Tablet.

Time (Hrs.)	Cumulative Drug Release (%)(Mean± S.D)								
	F1	F12	F3	F4	F5	F6	F7	F8	F9
1	3.91± 0.070	3.46± 0.016	2.47± 0.15	2.27± 0.070	2.16± 0.015	2.02± 0.012	2.14± 0.070	1.80± 0.069	1.01± 0.015
2	6.89± 0.029	6.47± 0.021	5.35± 0.026	5.19± 0.031	5.08± 0.014	5.08± 0.02	5.08± 0.02	4.00± 0.025	3.58± 0.014
3	13.57± 0.10	13.06± 0.02	11.11± 0.022	11.07± 0.021	10.99± 0.021	10.95± 0.015	10.95± 0.015	9.99± 0.017	8.96± 0.02
4	22.96± 0.02	22.30± 0.15	19.27± 0.80	19.02± 0.02	18.97± 0.016	18.80± 0.015	18.94± 0.01	17.89± 0.02	15.94± 0.021
5	46.58± 0.015	46.04± 0.025	42.31± 0.025	40.25± 0.067	39.93± 0.024	39.62± 0.014	39.91± 0.017	24.95± 0.015	27.48± 0.024
6	62.57± 0.025	61.80± 0.015	60.56± 0.015	59.56± 0.016	59.34± 0.15	58.55± 0.080	59.33± 0.023	40.78± 0.021	37.67± 0.070
7	71.59± 0.016	70.99± 0.017	70.56± 0.021	70.23± 0.02	70.23± 0.070	69.98± 0.01	70.05± 0.21	51.75± 0.071	49.69± 0.015
8	84.24± 0.063	83.26± 0.069	82.86± 0.026	82.46± 0.010	82.27± 0.014	81.96± 0.016	87.29± 0.01	60.89± 0.25	58.34± 0.05
9	94.65± 0.12	93.75± 0.017	93.37± 0.026	93.28± 0.15	92.97± 0.02	90.91± 0.22	92.98± 0.02	68.71± 0.15	67.07± 0.015
10	102.97± 0.031	102.46± 0.15	101.88± 0.15	101.37± 0.015	100.89± 0.070	96.11± 0.086	100.91± 0.015	79.14± 0.014	77.45± 0.017
11						102.60± 0.012		88.61± 0.16	86.96± 0.014
12								97.07± 0.015	94.72± 0.015

From the above in- vitro study data it can conclude that, sintered matrix formulations i.e. batches F1 to F9, from which F9 batch show significant retardation of drug release i.e. 94.72% up to 12 hrs shown in Table 7. The result behind retardation of drug release was the increase in time of sintering and polymer concentration.

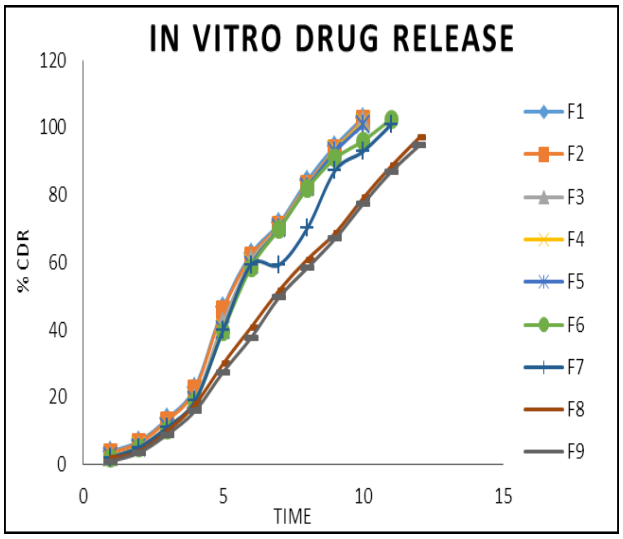

Figure 3: Cumulative Drug Release of Formulations (F1-F9).

Table 8: Comparative Dissolution of Unsintered matrix tablet (f9) and Optimized sintered matrix tablet (f9).

Time (hrs)	% Drug release (± S.D.)	
	Unsintered matrix tablet (F9)	Sintered matrix tablet (F9)
1	8.48 ±0.014	1.01±0.015
2	20.58 ±0.01	3.58±0.016
3	41.13 ±0.015	8.96±0.02
4	64.18 ±0.021	15.94±0.021
5	80.63 ±0.022	27.67±0.024
6	91.95 ±0.015	37.67±0.070
7	100.53 ±0.05	49.69±0.015
8		58.34±0.05
9		67.07±0.015
10		77.45±0.017
11		86.96±0.014
12		94.72±0.015

From the comparative in-vitro study data it is concluded that, in-vitro comparison is done between unsintered matrix tablet (F9) and sintered matrix tablet (F9) and this shows that unsintered matrix tablet shows 100.53%drug release in 7 hrs. And sintered matrix tablet shows 94.72% drug release in 12 hrs. This is shown in figure 4.

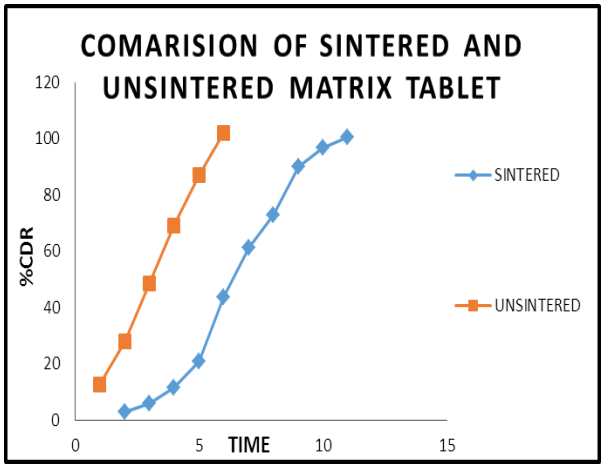

Figure 4: In-vitro comparative study of unsintered matrix tablet (F9) and Optimized sintered matrix tablet (F9).

Differential Scanning calorimetry

DSC spectra of Losartan potassium and sintered tablet are as shown in figure 5 and 6. The DSC Thermogram of Losartan potassium exhibited an endothermic peak at 264.22^0 C and in the physical mixture of polymer and drug after sintering shows endothermic peak at 263.24^0 C. This indicates that during sintering, drug did not undergo degradation.

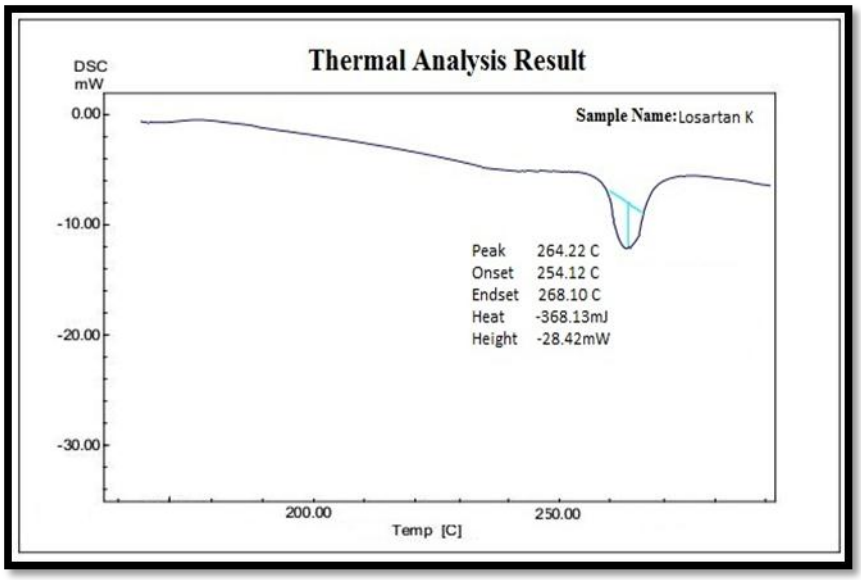

Figure 5: DSC Thermogram of Losartan potassium.

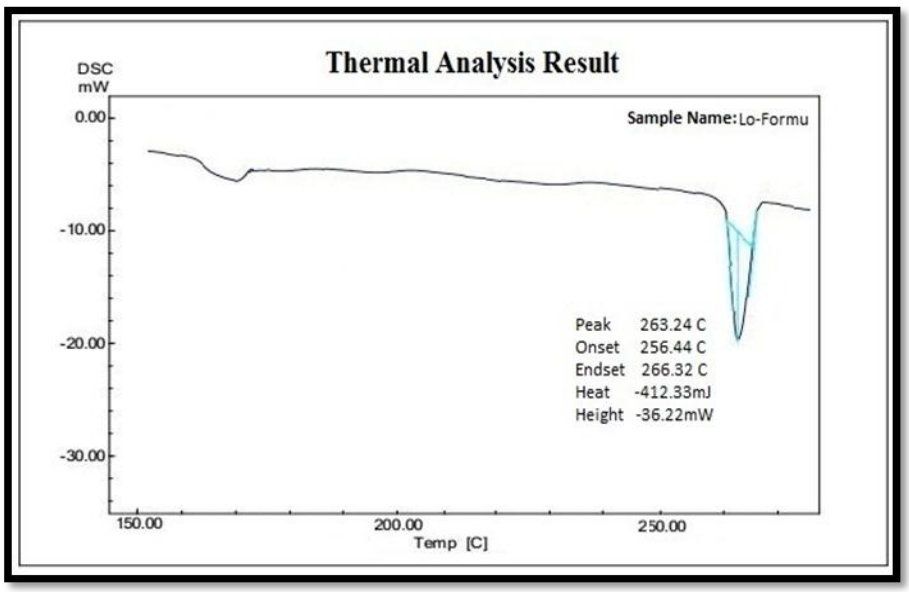

Figure 8.13: DSC Thermogram of sintered tablet.

Dissolution kinetic study

To analyze the mechanism of drug release from the tablet, data obtained from the drug release studies was subjected to different mathematical models (Zero order, First order, Matrix (Higuchi) and Korsmeyer's Peppas). The correlation coefficient (r^2) was used as an indicator for the best fitting for each of the models. Table 9 shows the Kinetics treatment for the optimized formulations.

Table 9: Model fitting of Optimize Batch of Losartan Potassium Sintered Matrix Tablet.

Code	Zero order	1st order	Higuchi	Peppas	
				R^2	n-Value
F9	0.9911	0.8512	0.6749	0.9914	0.6275

CONCLUSION

From the In vitro dissolution study it was concluded that sintered matrix tablet shows sustain release up to 12hrs when compared with the unsintered matrix tablet which shows 100 percent drug release in 7 hours. On sintering, as the sintering time increased the release of active ingredients from the polymeric matrix decreased. By using sintering technique, Friability of tablets was found to decrease with increasing sintering time and hardness was increased. The F9 batch shows highest hardness as compared to unsintered matrix tablet and shows less friability as compared to unsintered matrix tablet. From the DSC analysis it can be concluded that drug did not degraded during sintering. Stability studies indicated that prepared sintered matrix tablets did not show any significant change in physical appearance, % drug content and dissolution rate. It can be concluded that sintering technique is good for formulation of controlled release dosage form.

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