EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 10
312-322
Year: 2019

NATURAL POLYMER BASED FORMULATION AND CHARACTERIZATION OF MATRIX CONTROLLED RELEASE TABLET OF LOSARTAN POTASSIUM EMPLOYING SINTERING TECHNIQUE.

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Article Received on 24/07/2019 **Article Revised on 13/08/2019** **Article Accepted on 02/09/2019**

ABSTRACT
Exploration of Sintering concept in pharmaceutical science is relatively recent. In the present investigation, controlled release (CR) matrix tablets of Losartan potassium were prepared by direct compression method using natural polymer pullulan and then sintered by employing thermal sintering technique. Various batches of matrix tablets of Losartan potassium were prepared with varying concentrations of polymer and then sintered thermally at different time periods and temperatures and were evaluated for physicochemical parameters and in-vitro dissolution studies. The sintering time and temperature markedly affects the characteristics of the tablets. From *In-vitro* drug release profile, sintered formulations exhibited sustained drug release profiles with maximum sustaining effect when compared with unsintered formulation in about 10 hrs. By using sintering technique, friability of tablets was found to decrease and hardness was found to increase with increasing sintering time.

KEYWORDS: Losartan potassium, Sintering technique, pullulan, controlled release.

INTRODUCTION
In the recent years, there has been an increasing effort to develop prolonged release dosage forms. The prolonged release dosage forms have many advantages in safety and efficacy over immediate release products in that frequency of dosing can be reduced, drug efficacy can be prolonged and the incidence of adverse effects can be decreased. These formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improves patient convenience and compliance, by incorporating the dose in a unit dosage form from which the drug is slowly released for 24 hr.[1,2]

Sintering technique is relatively recent technique in the pharmaceutical sciences. Sintering is defined as the bonding of adjacent particle surfaces in a mass of powder, or in a compact, by the application of heat. The term sintering means fusion of particles or formation of welded bonds between particles of polymer. The sintering process has been used for the production of sustained release matrix tablets for the stabilization and retardation of the drug release from dosage form. The concept of sintering was applied in the investigation of the effect of heating on the mechanical properties of the pharmaceutical powders. The formation of solid bonds within powder bed during tablet compression was also studied in terms of sintering. The changes in the hardness and disintegration time of tablets stored at elevated temperatures were described as result of sintering.[15, 32]

Losartan potassium is a potent, highly specific Angiotensin II type 1 (AT1) receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 hr. Administration of losartan potassium in a sustained release dosage form would be more desirable for antihypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration.[21,27]

The aim of this study is to investigate the effect of sintering on release characteristics of matrix tablet prepared by using natural polymer pulullan as release retardant. Pullulan is a neutral polysaccharide obtained from *Aureobasidium pullulans*. It has excellent bioadhesion and film forming properties. Its principle advantages includes it is biodegradable, blood compatible, freely soluble in water, thermo stable, non-toxic, non-immunogenic, and non-carcinogenic. Thermal stability and elastic property allow it to be used in many different ways.[45,46]

MATERIAL AND METHODS

Materials

Losartan potassium was received as a gift sample from Sunij Pharmaceuticals Hyderabad. Pullulan (Gangawal Chemicals, Mumbai) was used as procured. Pullulan was procured from Gangaval chemicals, Mumbai,Spray dried lactose was obtained from Okasa Pharma, Satara, India.Talc and magnesium stearate were purchased from LobaChemiePvt. Ltd., Mumbai, India. All other ingredients used throughout thestudy were of analytical grade and were used as procured.

Methods

FTIR spectrum of losartan potassium

The IR spectrum of losartan potassium was recorded using Fourier transforminfrared spectroscopy [ATR-FTIR] to check its purity. The spectrumwas recorded over the wave number of 4000 to 400 cm-1.[4, 34]

Differential scanningcalorimetry [DSC] of losartan potassium

DSC study was carried by using Mettler-Toledo DSC 821e instrument[Switzerland]. About 2 mg of the losartan potassium was sealed in thealuminum pan and heated at the rate of 10 °C/min, covering at temperature range of 30 °C to 200 °C under a nitrogen atmosphere, at flow rate of 40 ml/min.

Drug–polymer compatibility study

FTIR study

FTIR spectra of, pullulan and physicalmixtures of losartan potassium with polymer were recorded to study theinteraction between them. The spectra were recorded over the wavenumber of 4000 to 400 cm-1[19, 20].

DSC study

In order to assess the compatibility of losartan potassium with a polymer,thermogram of pure losartan potassium, pullulanpolymers and formulations were recorded using Mettler-Toledo DSC821e instrument [Switzerland]. About 5 mg of the physical mixturewas sealed in the aluminum pan and heated at the rate of 10°C/min, covering a temperature range of 30 °C to 200 °C under anitrogen atmosphere, at a flow rate of 40 ml/min.[35]

Preparation of controlled release matrix tablet: Controlled release matrix tablets of losartan potassium were prepared by direct compression method using varying concentrations of Pullulan. The entire excipients without talc were blended uniformly. After sufficient mixing of drug with other excipients, talc was added and further mixed for 5 minutes. The prepared powder mass was compressed with 11 mm punch on multitooling compression machine (Rimek II Karnavati Eng. Ltd. Ahmedabad) to give tablet of 300mg weight.

Sintering of matrix tablet: Prepared matrix tablets were then subjected to thermal treatment by putting them onan aluminium foil and subjected to sinteringatdifferent temperatures i. e. 60^0 and 70^0 C for differentdurations 3hrs. and 6 hrs. in a hot air oven.[19, 26]

Table 1: Formula for sintered controlled release tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Losartan potassium	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Pullulan	80	100	120	80	100	120	80	100	120	80	100	120	80	100	120
Spray dried lactose	100	80	60	100	80	60	100	80	60	100	80	60	100	80	60
Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Total	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

Note: All quantities are given in mg, formula for one tablet is shown in table.

F1 – F3 = Unsintered.

F4 - F6 = Sintered at 60^0 c for 3 hrs. , F7 – F9 = Sintered at 60^0 c for 6 hrs.

F10 – F12 = Sintered at 70^0 c for 3 hrs. , F13 – F15 = Sintered at 70^0 c for 6 hrs.

Evaluation of various batches of formulated tablets

The formulated tablets were evaluated for different parameters like thickness, hardness, friability, drug content and *in vitro* dissolution studies.

1. Hardness and thickness

The hardness [kg/cm2] of the prepared formulations was determined by using a Monsanto hardness tester and thickness was measured by micrometre screw gauge [mm] [n = 3].[33]

2. Friability

Test for tablet friability was carried out according to I.P 2007, according to which friability below 1% passes the test. Tablets from each formulation were tested for friability using Roche Friabilator (Rolex Scientific Engineers Limited). Twenty tablets were weighed initially and transferred to the friabilator. The instrument was operated at 25 rpm for 4 minutes. The tablets were reweighed and percentage loss was calculated.[33,34]

3. Weight variation test: The weight of tablet is measured to ensure that a tablet contains the proper amount of drug. Weight variation test was performed as

per IP 2007. Twenty tablets were selected randomly and weighed. Average weight of the tablet was determined. Not more than 2 tablets should deviate from the average weight of tablets and the maximum percentage of deviation allowed.[n=20][33]

Table no 2: IP standards for uniformity of weight.

Sr. No.	Average weight of tablet	Percentage deviation
1	80 mg or less	10
2	80 mg to 250 mg	7.5
3	250 or more than 250 mg	5

4. Drug content uniformity: The drug content uniformity of Losartan potassium controlled release tablets was determined. Ten tablets were taken in morter and trituted with the help of pestle. A quantity equivalent to 10 mg was taken in 100 ml (100 µg/ml) volumetric flask and to it 100 ml PBS pH 6.8 was added. From this stock solution 1 ml aliquote was taken and was diluted to 10 ml with PBS pH 6.8 (10 µg/ml). Finally the absorbance of prepared solution was measured against blank (PBS pH 6.8) at 236 nm using UV visible spectrophotometer.[11 ,33,34]

5. *In–vitro* release study

In-vitro drug release was studied, using USP II apparatus, with 900 ml of dissolution medium maintained at 37±1°C for 10hr., and at 50 rpm. 0.1 N HCl(pH 1.2) was used as a dissolution medium for the first 2 hrs.followed by pH 6.8 phosphate buffers for further 8 hrs. 0.5 ml of sample was withdrawn at predetermined time intervals, and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analyzed after appropriate dilution by using double beam UV spectrophotometer at 234 nm for 0.1 N HC1 and 236 nm forpH 6.8 phosphate buffer, and cumulative percent drug release was calculated. The study was performed in triplicate.[11, 34]

6. Kinetics of *in vitro* drug release

To study the release kinetics of *in vitro* drug release, data was treated with different kinetic equations such as Zero order (equation 1), First order (equation 2), Hixon-Crowel (equation 3), Higuchi (equation 4) and Korsmeyer-Peppas (equation 5).

- Zero order kinetics

$W = K_1 t$……(1)

- First order Kinetics

$\ln (100-W) = \ln 100 - K_2 t$……(2)

- Hixon-Crowel's Cube- Root Equation (Erosion Model)

$(100-W)^{1/3} = 100^{1/3} - k_3 t$……(3)

- Higuchi's Square Root of Time Equation (Diffusion Model)

$W = K_4 t^{1/2}$……..(4)

- KorsmeyerPeppas Equation (Diffusion/Relation Model)

$M_t / M = K_5 t^n$……(5)

Where, W is % drug release at time t and K1–K4 are release rate constants, depending on the kinetic model used. Mt/M is the fractional drug release into the dissolution medium and K5 is a constant incorporating the structural and geometric characteristics of the tablet. The term n is the diffusional constant that characterizes the drug release transport mechanism. When n = 0.5, then the drug release mechanism is Fickian diffusion. If n<0.5 the mechanism is quasi-Fickian diffusion, and 0.5<n<1.0, then it is non-Fickian or anomalous diffusion and when n = 1.0 mechanism is non Fickian case II diffusion or zero order release kinetics could be observed.[37, 38]

7. Stability studies

Optimized formulation was sealed in aluminum packaging coated internally with polyethene, and kept instability chamber maintained at a temperature of 45 °C • }2 °C and relative humidity75%}5% for 3 mo. Samples were withdrawn at 0, 30, 60 and 90d and evaluated for the hardness, drug content and *in-vitro* dissolution test.[39]

RESULTS AND DISCUSSION

FTIR study

The IR spectra of drug exhibited distinctive peaks at 757.27 (cm^{-1}) due to C-X (Chloride) Stretch. The drug exhibited distinctive peaks at 995.69 and 927.94 (cm^{-1}) due to C-H in plane and out plane bending. The peaks at 1253.81 (cm^{-1}) due to C-N Stretching, peak at 1352.15 (cm^{-1}) due to C=O stretching, at 1675.49 (cm^{-1}) due to C=C stretching and at 3429.93 (cm^{-1}) due to O-H stretching.

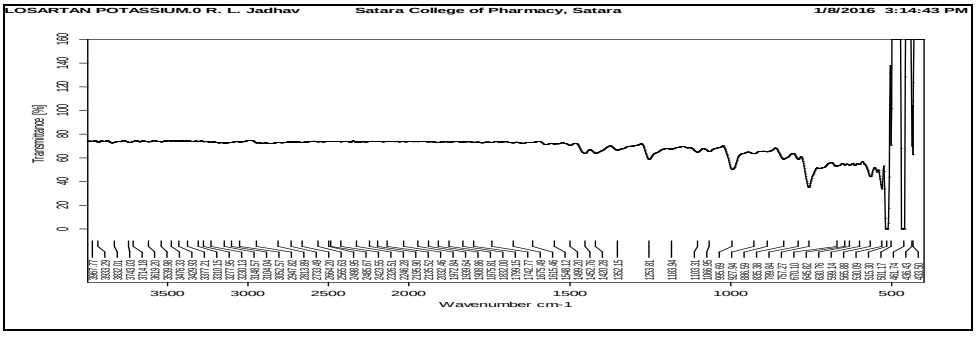

Fig.1: FTIR spectrum of Losartan potassium.

DSC study

The DSC thermogram of the drug depicted an endothermic peak 274.85^{0}C. Such an endothermic peak was also reported for standard drug material ((Aswartha U. et al., 2012). This indicated that Losartan potassium drug was in pure form.

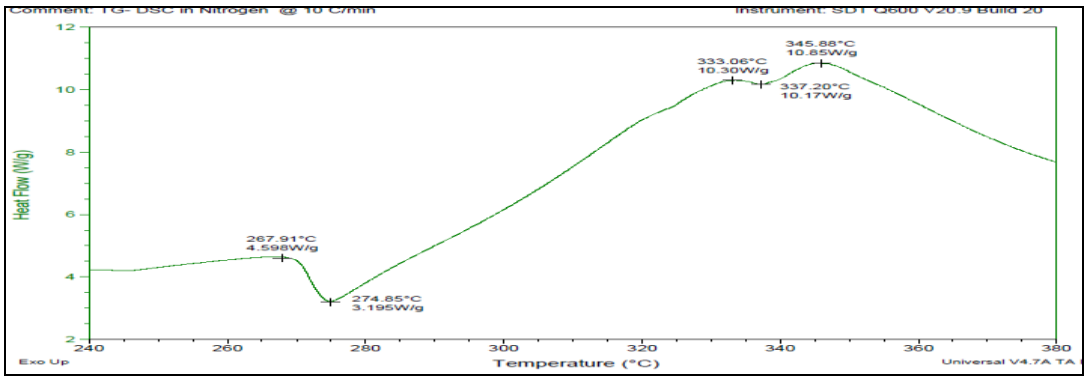

Fig. 2: DSC thermogram of Losartan potassium.

Drug–polymer compatibility study

FTIR study

The IR spectra of pure drug and formulation were found similar with each other. The main absorption bands of drug appeared in the formulation spectra in the region of O-H stretching band is located at 3417.27 (cm^{-1}). The C=C, C-N, C-O stretching bands are located at 1644.56, 1254.44, 1349.37 (cm^{-1}). The peaks due to C-H and C-X stretch were found to be located at 995.37cm^{-1},933.89cm^{-1},757.27cm^{-1} respectively. It was proved that the peaks found in pure drug and formulation is similar. Thus incorporation of drug in polymer did not change the position of its functional groups. This indicated that there was no difference between the internal structures and conformation of these samples at the molecular level. Hence FTIR study ruled out any possible interaction between drug and polymer.

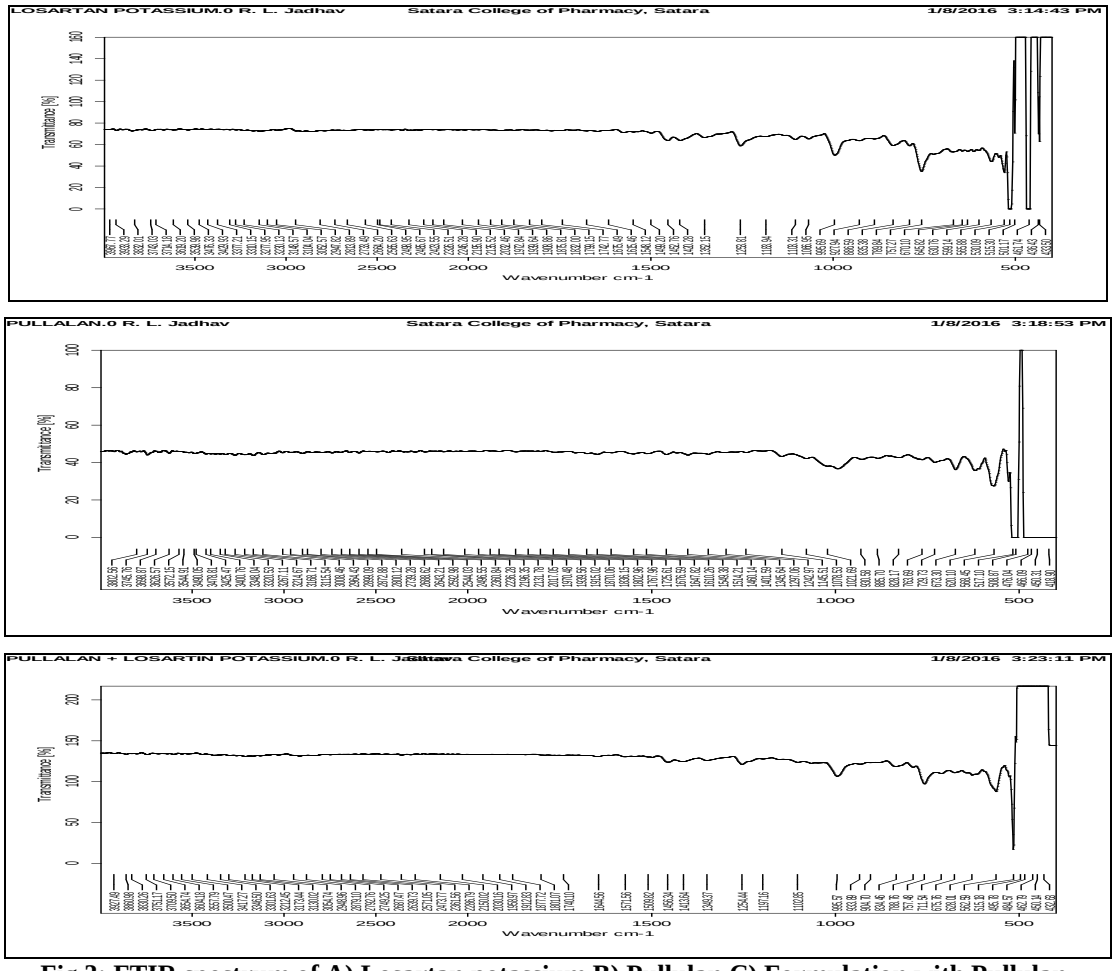

Fig 3: FTIR spectrum of A) Losartan potassium B) Pullulan C) Formulation with Pullulan.

Table no.3: Characteristic peaks of FTIR spectrum of Losartan potassium and formulation with pullulan.

Sr. no.	Standard wave Number (cm^{-1})	Observed wave number (cm^{-1})		Functional groups associated
		Losartan potassium	Losartan potassium + pullulan	
1	3400-3200	3429.93	3417.27	O–H Stretch
2	1680-1600	1675.49	1644.56	C=C Stretch
3	1350-1000	1253.81	1254.44	C-N Stretch
4	1300-1000	1352.15	1349.37	C-O Stretch
5	900-690	995.69	995.57	C-H Stretch (aromatic)
		927.94	933.89	C – H stretch (aliphatic)
6	785-540	757.27	757.48	C-X Stretch

DSC study

Pure drug exhibited an endothermic peak at 274.85^{0}C. In DSC thermogram of formulation, it showed endothermic peak at 269.32^{0}C, hence there was no any significant shifting in the endothermic peaks of drug so it indicated that there was no any interaction between drug and formulation mixture.

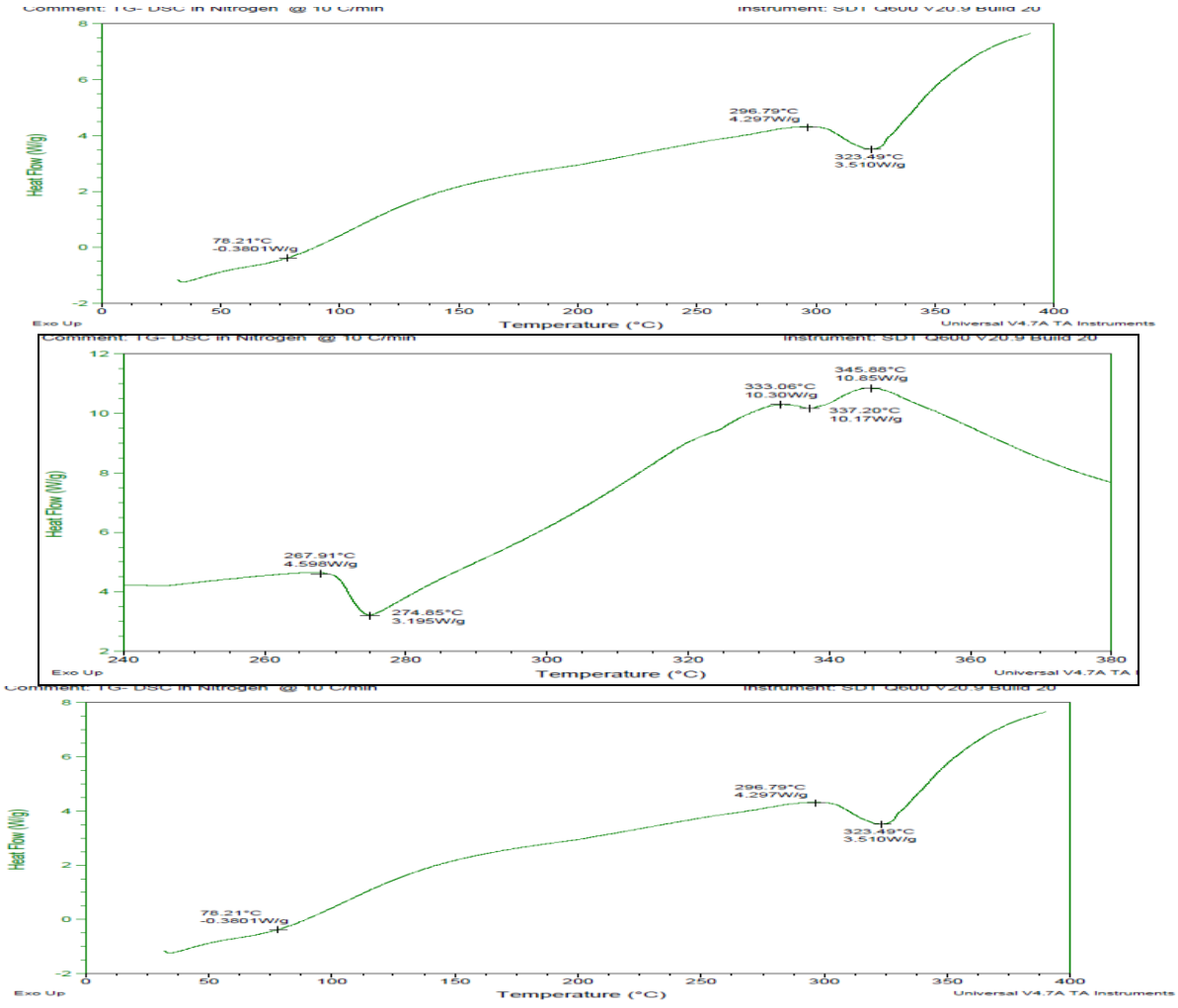

Fig. 4. DSC Thermogram of A) Losartan potassium B) Pullulan C) formulation containing Pullulan

EVALUATION OF TABLETS

1. Tablet dimensions

The thickness and diameter of tablets were found to be almost uniform in all formulations F1 to F15.Thickness of tablets ranged from 2.14±0.11 to 2.29±0.02mm and diameter of all the tablets was found to be11.056±0.0321mm. None of the formulations F1 to F15 showed a deviation. Hence, it is concluded that all formulations has uniform flow properties, uniform density, compression pressure applied was uniform and drug particles have uniform size and shape.

2. Hardness

Hardness of tablets from all batches was found to be in the range of4.133 ±0.071kg/cm^2 to 5.921±0.276 kg/cm^2. All tablets were found hard enough so that they could

easily withstand the storage conditions without getting themselves broken. A high compressibility is required to obtain sufficient strength of the final tablets. Sintering time and temperature affects on hardness of the temperature. It was observed that as the sintering time and temperature went on increasing, hardness also increased.

3. Friability

All the tablets exhibited acceptable friability as none of the tested batches showed percentage friability that exceeded 1%. As per IP, % friability below 1% is an indication of good mechanical resistance of the tablets. Thus it was proved that tablets could withstand the pressure, mechanical shocks during handling, transportation, storage and manufacturing processes. % friability of tablets was found to be decreased with increase in sintering time as wellas sintering temperature.

4. Weight variation test

After performing weight variation test it was found that all tablets were within the range of Pharmacopoeial Specifications and none of the tablets deviated from the stated specification. Hence it revealed that the all formulations passed weight variation test according to IP.

6. Drug content

The drug content for all the formulation batches (F1 to F15) were carried out as per the standard protocol and the results are shown in the table no.4. Drug content of all the formulation batches was found to be between 95.7±0.002 to 99.69±0.004. Hence, it can be concluded that all the formulations are having uniform distribution of drug in powder mass and following acceptable limits as per IP specification i.e.85 to 115 % of average content.

Table 4: Evaluation parameters of tablets.

Batches	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation		Drug content (%)
					Averge weight (mg)	Inference	
F1	2.15±0.09	11.056±0.21	4.255±0.05	0.79	303.5	Passes	99.23±0.003
F2	2.18±0.07	11.056±0.21	4.133±0.071	0.78	302.6	Passes	98.27±0.004
F3	2.14±0.11	11.056±0.21	4.355±0.076	0.79	304.2	Passes	97.63±0.002
F4	2.19±0.14	11.056±0.21	4.535±0.057	0.72	306.1	Passes	98.23±0.001
F5	2.25±0.13	11.056±0.21	4.733±0.219	0.70	299.59	Passes	97.53±0.003
F6	2.16±0.04	11.056±0.21	4.626±0.173	0.71	303.4	Passes	98.66±0.002
F7	2.28±0.02	11.056±0.21	4.622±0.210	0.64	305.6	Passes	99.31±0.002
F8	2.19±0.07	11.056±0.21	5.012±0.321	0.63	299.7	Passes	97.73±0.003
F9	2.29±0.02	11.056±0.21	5.220±0.242	0.61	302.3	Passes	96.29±0.001
F10	2.28±0.24	11.056±0.21	5.312±0.156	0.56	301.6	Passes	98.43±0.004
F11	2.27±0.017	11.056±0.21	5.502±0.209	0.54	303.5	Passes	99.20±0.002
F12	2.13±0.018	11.056±0.21	5.732±0.341	0.53	302.6	Passes	97.17±0.005
F13	2.19±0.09	11.056±0.21	5.819±0.239	0.46	304.2	Passes	99.38±0.003
F14	2.22±0.012	11.056±0.21	5.921±0.276	0.44	306.1	Passes	98.23±0.002
F15	2.20±0.032	11.056±0.21	5.917±0.173	0.43	299.59	Passes	97.40±0.001

*** mean ± SD [n = 3]**

7. *In vitro* drug release

The results of *in–vitro* dissolution study given in table 5 and 6 and , itwas observed that an increase in polymer concentration causes decrease inrelease rate.

Pullulan has powerful retardant property resulting in a matrixformation which is required for sustained release formulations. Formulation F4 was considered asoptimized formulation as it showed highest cumulative % drug release i.e. 91.84%.

Un-sintered formulations were compared with sintered formulations. The dissolution profiles of the unsintered and sintered matrix tablets at 60^0 C and 70^0 C at different time durations are presented in fig. 5, 6, and 7.

In–vitro dissolution study data shows, sintered formulations F_4, F_5 , F_6, F_7, F_8, F_9, F_{10}, $F_{11,}$ $F_{12,}$ F_{13}, F_{14} and F_{15} exhibited sustained drug release profiles with maximum sustaining effect as compared with unsintered formulations F_1, F_2, and F_3, in about 10 hours.

From the Figures 5, 6 and 7 it is cleared that the increase in sintering time and sintering temperature causes the decrease in the cumulative percentage of drug release. Hence it can be concluded that sintering temperature and duration markedly affected the drug release properties of the matrix tablets.

Table no. 5: % cumulative of drug release of F1 –F9.

TIME (Hr.)	%CDR							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	20.12 ± 0.39	9.3 ± 0.6	14.72± 0.87	20.18 ± 0.54	10.86 ± 0.65	9.38 ± 0.72	12.68 ± 0.45	14.2± 0.62
2	23.1 ± 0.79	18.46 ± 1.06	20.40± 0.58	26.82 ± 1.41	13.28 ± 0.33	10.58 ± 0.4	17.86 ± 0.81	18.9 ± 1.2
3	33.8 ± 0.36	27.64 ± 0.66	32.6 ± 1.38	35.44 ± 0.6	20.7 ± 0.63	16.80 ± 0.84	22.46 ± 0.72	27.58 ± 1.59
4	42.68 ± 0.8	36.2 ± 0.96	40.86± 0.69	47.24 ± 1.43	25.88 ± 0.5	27.32 ± 0.39	28.1 ± 0.8	34.42 ± 0.7
5	50.12 ± 1.36	48.2 ± 1.98	49.12± 1.53	55.24 ± 0.74	32.9 ± 0.92	31.86 ± 0.48	38.72 ± 0.91	38.64 ± 0.78
6	59.24 ± 0.28	53.8 ± 3.07	53.28 ± 1.71	69.14 ± 1.39	37.12 ± 1.11	35.9 ± 1.81	43.2 ± 0.66	46.34 ± 0.8
7	68.19± 1.13	59.06 ± 0.18	64.72 ± 0.62	73.82 ± 1.11	48.5 ± 1.37	48.12 ± 0.85	48.72 ± 0.18	52.52 ± 1.23
8	86.18 ± 0.15	66.6 ± 0.61	69.74 ± 1.37	78.18 ± 1.24	62.44 ± 1.56	57.52 ± 1.01	53.92 ± 1.11	58.06 ± 0.91
9	93.46 ± 0.23	74.34 ± 1	76.52 ± 1.01	86.76 ± 1.59	70.68 ± 0.73	70.86 ± 1.5	66.12 ± 1.47	67.04 ± 0.73
10	98.8 ± 0.9	89.16 ± 2.52	81.52 ± 1.17	91.84 ± 0.71	82.62 ± 1.74	77.5 ± 1.15	82.26 ± 0.63	76.5 ± 1.02

Table no. 6 % cumulative of drug release of F9 –F15.

TIME (Hr.)	%CDR						
	F9	F10	F11	F12	F13	F14	F15
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	10.7 ± 0.9	13.12 ± 0.9	9.82 ± 0.9	9.56 ± 0.9	13.46 ± 0.9	10.66 ± 0.9	8.64 ± 0.9
2	13.94 ± 0.9	17.52 ± 0.9	14.66 ± 0.9	13.04 ± 0.9	17.02 ± 0.9	12.5 ± 0.9	11.3 ± 0.9
3	22.56 ± 0.9	23.5 ± 0.9	19.44 ± 0.9	19.72 ± 0.9	23.56 ± 0.9	24.9 ± 0.9	20.3 ± 0.9
4	26.12 ± 0.9	32.38 ± 0.9	28.04 ± 0.9	24.38± 0.9	32.38 ± 0.9	28.26± 0.9	26.06± 0.9
5	34 ± 0.9	40.4 ± 0.9	34.4± 0.9	27.5± 0.9	37.5 ± 0.9	35.1 ± 0.9	32.8 ± 0.9
6	39.04 ± 0.9	46.48 ± 0.9	43.12± 0.9	37.02 ± 0.9	44.22 ± 0.9	35.72 ± 0.9	32.46 ± 0.9
7	43.54 ± 0.9	57.5 ± 0.9	46.2 ± 0.9	40.1 ± 0.9	50.64 ± 0.9	41.98 ± 0.9	38 ± 0.9
8	50.94 ± 0.9	63.6 ± 0.88	56.4 ± 0.19	43.42 ± 0.46	57.74 ±0.25	47.38 ± 0.45	44.16±0.24
9	67.1 ± 0.9	71.76± 0.9	60.88± 0.9	53.16 ± 0.9	66.64 ± 0.9	52.46 ± 0.9	50.74 ± 0.9
10	72.58 ± 0.9	78.18 ± 0.9	72.62 ± 0.9	66.86 ± 0.9	75.58 ± 0.9	68.26 ± 0.9	64.12 ± 0.9

*** mean ± SD [n = 3]**

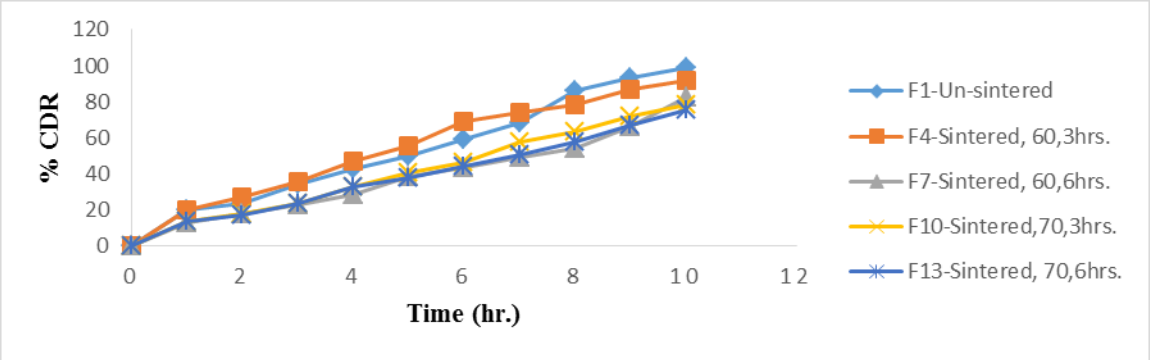

Fig 5: Comparison of in vitro drug release profile of sintered and un-sintered matrix tablet formulations of 80 mg Pulullan.

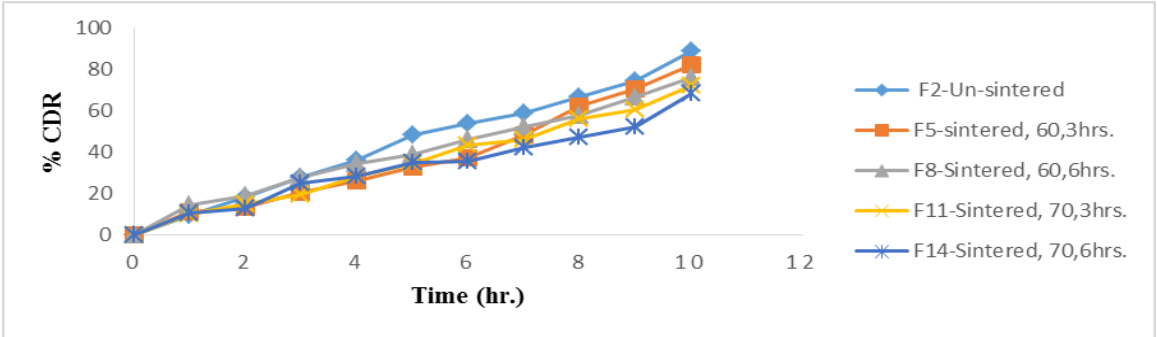

Fig. 6: Comparison of in vitro drug release profile of sintered and un-sintered matrix tablet formulations of 100 mg Pulullan.

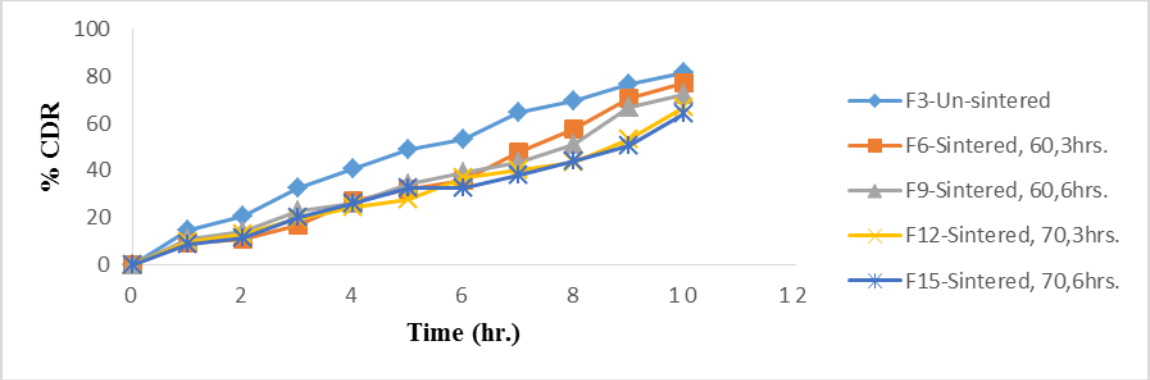

Fig. 7: Comparison of in vitro drug release profile of sintered and un-sintered matrix tablet formulations of 120 mg Pulullan.

Kinetics of *in vitro* drug release

In Table no.7, the kinetic parameters of release of losartan potassium from the matrix tablets are presented. As clearly indicated from Table no.7, the formulations did not follow first-order release patterns. The in vitro release profiles of drug from all the formulations could be best expressed by Higuchi and zero order release kinetics. The term 'n' is the diffusional constant that characterizes the drug release transport mechanism. Optimized batch F4 showed non-fickian or diffusion (0.5< n <1.0) i.e. drug transport mechanism associated with diffusion controlled release in which polymer swell in water or biological fluids.

Table 7: Study of various kinetic models.

Batch	Zero order	First order	Higuchi	Hixson-Crowell	Korsemeyer-peppas		Best fit model
	r^2	r^2	r^2	r^2	r^2	n	
F1	0.967	0.838	0.951	0.976	0951	0.869	Higuchi
F2	0.960	0.813	0.977	0.872	0.954	0.973	Higuchi
F3	0.931	0.775	0.971	0.833	0.938	0.914	Higuchi
F4	0.924	0.786	0.970	0.837	0.944	0.841	Higuchi
F5	0.983	0.887	0.952	0.943	0.962	1.041	Zero-order
F6	0.985	0.883	0.955	0.941	0.956	1.115	Zero-order
F7	0.971	0.851	0.967	0.908	0.967	0.932	Zero-order
F8	0.995	0.812	0.974	0.870	0.949	0.883	Higuchi
F9	0.971	0.845	0.962	0.907	0.956	0.936	Zero-order
F10	0.976	0.842	0.987	0.899	0.966	0.953	Higuchi
F11	0.977	0.830	0.986	0.896	0.974	1.018	Higuchi
F12	0.965	0.838	0.959	0.899	0.957	0.975	Zero-order
F13	0.971	0.836	0.980	0.894	0.957	0.912	Higuchi
F14	0.937	0.789	0.951	0.851	0.921	0.944	Higuchi
F15	0.951	0.801	0.959	0.866	0.939	1.012	Higuchi

Stability studies

Short-term stability studies of the optimized formulation indicated that there were no significant changes in physical parameters, drug content and *in-vitro* dissolution studies at the end of three months period.

Similarity factor *f2* was calculated to know similarity of dissolution profiles of optimized formulation F4 before and after stability study. The value was found to be 88.54, which indicates that dissolution profiles of optimized formulation before and after stability study was similar. Drug release profile of formulation F4 before and after stability study is as shown in figure no.8.

Table 8: Stability study data of formulation F4

Parameters	0 Month	1 Month	2 Months	3 Months
Weight Variation(mg)	306.10	306.10	306.10	306.10
Hardness(Kg/cm^2)	4.5±0.05	4.5± 0.02	4.6± 0.6	4.6± 0.03
Drug content (%)	98.23	98.18	97.51	97.12

*mean ± SD [n = 3]

Table no. 9: Results of dissolution study of optimized formulation.

Time (Hrs.)	Cumulative % drug release			
	0 Month	1 Month	2 Months	3 Months
0	0	0	0	**0**
1	20.12	20.80	19.56	**20.18**
2	23.96	25.32	26.09	**24.98**
3	33.8	34.87	35.49	**35.72**
4	42.68	49.63	48.17	**49.23**
5	50.12	55.48	54.37	**53.40**
6	59.24	67.82	69.15	**67.94**
7	68.90	74.36	73.48	**72.49**
8	86.18	76.20	74.89	**76.30**
9	93.46	85.70	83.90	**86.74**
10	**98.80**	**90.18**	**92.57**	**91.26**

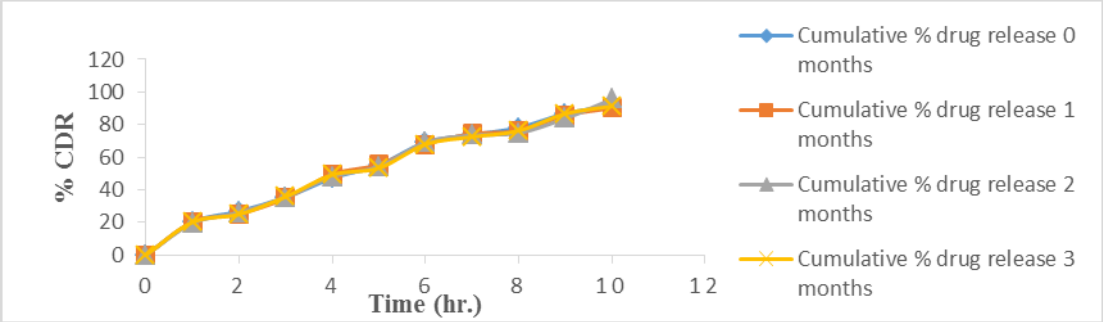

Fig. 8: Dissolution profile of optimized formulation before and after stability study.

CONCLUSION

A simple technique of sintering method was used in the present investigation. Controlled release matrix tablets of losartan potassium were prepared by using natural polymer pululan in different concentration employing thermal sintering technique.

On the basis of results obtained, it is concluded that sintering of controlled release matrix tablets increases the hardness and controls the *in-vitro* drug release of the tablets as compared to the un-sintered tablets.

From the compatibility study there is no interaction between drug and excipients. Pullulan, a novel natural polymer can be used to control the release of drug from matrix tablets. Thus, it can be concluded that sintering technique can be effectively used for the fabrication of controlled release formulations for the release rate retardation of drug from the tablets.

ACKNOWLEDGEMENT

The authors are thankful to the Sunij Pharma Pvt. Ltd., Ahmedabad, Indiafor providing me gift sample of losartan potassium and Satara College of Pharmacy, Satara for providing me necessary facilities to carry out this work.

REFERENCES

1. ChughIsha, Seth Nimrata, Rana A. C., Gupta Surabhi, Oral Sustained Release Drug Delivery System: An Overview, International Research Journal Of Pharmacy, 2012; 3(5): 57-66.
2. K. P. Sampath Kumar, DebjitBhowmik, Shweta Srivastava, Shravan Paswan And A.S. Dutta, Sustained Release Drug Delivery System Potential, The Pharma Innovation, 2012; 1(2): 48-60.
3. A. Bharathi, S. Bhagya Lakshmi, K.N.V Deepthi, Ramchandra, Formulation And Evaluation Of Sustained Release Matrix Tablet Of Losartan Potassium Using Meltgranulation Technique, International Journal Of Pharmacy Review & Research, 2015; 5(2): 95-102.
4. A. H. Beckett, J.B. Stenlake, practical pharmaceutical chemistry, CBS publishers and distributors pvt., ltd., IR, 2007; 4th ed. Part-II: 379-407.
5. A. Seetha Devi, M. Tabasum, T. Harika, V. Anusha, B. Viswanath And SanikommuBaji Reddy, Formulation And Evaluation Of Diclofenac Sodium Matrix Tablets Using Abelmoschus Esculentus Mucilage As A Polymer, International Journal Of Pharmaceutical, Chemical And Biological Sciences, 2013; 3(2): 418-423.
6. Ajaykumar Patil, Ashish Pohane, RamyaDarbar, SharanyaKoutika, AlekhyaPothanganti, Formulation And Evaluation Of Sustained Release Matrix Tablets Of Nicorandil, International Journal Of Applied Biology And Pharmaceutical Technology, 2011; 2(3): 242-246.

7. Arvind Singh Rathore, R.C. Jat, Narendra Sharma, Rahul Tiwari, An Overview: Matrix Tablet As Controlled Drug Delivery System, International Journal Of Research And Development In Pharmacy And Life Sciences, 2013; 2(4): 482-492.
8. Ashok Kumar P and Damodar Kumar S. Design and Evaluation of Controlled Release Matrix Tablets Of Acyclovir, Der Pharmacia Lettre 2013; 5(2): 347-353.
9. Asija R., Modi J., Kumawat R., Asija S., Goyal M., Formulation and Evaluation of Diclofenac sodium Sustained Release tablets using melt Granulation Technique, International Journal of Pharmacy, 2012; 3(5): 216-220.
10. Aulton M. E. Pharmaceutics The science of dosage form 2nd End. Churchill Livingstone; London, 2002; 397-439.
11. B. Dileep, B. Ramarao G. Chiranjeevi, Ramyasri, Diffusion Sustain Release Matrix Tablet Of Losartan Potassium By Selecting Different Grades Of HPMC And Guar Gum As Retarding Polymers, World Journal Of Pharmaceutical Research, 2015; 4(10): 2115-230.
12. Bhanja Satyabrata1, Ellaiah , Mohanty Chandan, K.V.R Murthy, Design And In Vitro Evaluation Of Mucoadhesive Buccal Tablets Of Perindopril Prepared By Sintering Technique, International Journal Of Pharmtech Research, 2010; 2(3): 1813-1823.
13. Bhavani Boddeda1, P.V. Kamala Kumari, K.P.R. Chowdary, Formulation And Evaluation Of Glipizide Sustained Release Tablets, International Journal Of Pharmaceutical And Biomedical Research, 2012; 3(1): 44-48.
14. Chaitali K. R., GoliRavali, Chaudhari S. P., Formulation development and in vitro evaluation of sustained release matrix tablet of Lamivudine, International Research Journal of Pharmacy, 2012; 3(12): 171-174.
15. Chandan Mohanty, Sintering Technique in Pharmaceutical Sciences: A Brief Review, International Journal of Pharmacy & Technology, 2011; 3(1): 799-806.
16. Chaudhari A., Pacharane S., Jadhav K.R., Kadam V. J. Formulation and Evaluation of Extended Released Tablets of Lamotrigine, International Journal on Pharma and Bio Sciences, 2011; 2 (1): 198-210.
17. Chien Y. W. Novel Drug Delivery Systems. 2nd Ed. New York: Marcel Dekker Inc, 1992; P. 139-160.
18. Encyclopedia of Controlled Drug Delivery, By Mathiowitz E., Vol.-2 Page No.: 583-584.
19. Flowerlet Mathew, K.R. Anoop, Shoma Jose, Asha Jose, Formulation Of Metformin Hydrochloride Matrix Tablets By Sintering Technique And Its Evaluation, International Journal Of Pharmacy &Technology, 2010; 2(2): 293-306.
20. Harekrishna Roy, Sanjay Kumar Panda , KirtiRanjanParida , Asim Kumar Biswa, Formulation And In-Vitro Evaluation Of Matrix Controlled Lamivudine Tablets, International Journal Of Pharma Research And Health Sciences, 2013; 1(1): 1-7.
21. Indian Pharmacopoeia, Government of India, Ministry of health and family welfare, controller of India: New Delhi, 2007; 662-663, 1021-1022.
22. Ishab Kumar, GaliVidyasagar , Anil Bhandari, Formulation And Evaluation Of Sintered High Density Matrix Tablets Of Metformin HCl For The Treatment Of Type-2 Diabetes Mellitus, International Journal Of Research In Pharmaceutical And Nano Sciences, 2013; 2(5): 602- 611.
23. Joshi K., Dhole S., Doltode A. Formulation and In-VitroEvaluation of Sustained Release Matrix Tablet of Dicyclomine Hydrochloride by Using Hydrophilic Polymers, International Journal of Pharmaceutical Scinces and Research, 2014; 5(4): 1331-1338.
24. Lachman L, Lieberman Ha and Kanig J. The Theory and Practice of Industrial Pharmacy. 3rd Ed., Varghese Publishing House, Mumbai, 2009; 67-71, 183-184, 293-344.
25. Loyd V. Allen, Nicholas G. Popovich And Howard C. Ansel's Pharmaceutical Dosage Forms And Drug Delivery Systems, Tablets, 231-237.
26. M. Parvathi, P. Prathyusha And J. Raveendra Reddy, Formulation And Evaluation Of Sintered Matrix Tablets Of Metformin Hydrochloride And Its Comparision Over Unsintered Matrix Tablets, International Journal Of Research In Pharmacy And Chemistry, 2013; 3(3): 521-529.
27. Martindale, A complete drug reference, 35th edition, edited by Sean C. Sweetman, page no.1191.
28. Murthy P.N. V. N., Shafiulla D., Murthy D. Formulation development and evaluation of controlled release matrix tablets of guaiphenesin and salbutamol sulphate, Der Pharmacia Lettre, 2011; 3(4): 325-334.
29. Patel Harnish, Panchal Dhrupesh R., Patel Upendra, BrahmbhattTushar, SutharMayur. Matrix Type Drug Delivery System: A Review, Journal of Pharmaceutical Science and Bio scientific Research, Nov-Dec 2011; 1(3): 143-151.
30. Patel Mubarak Husen, P Ashok Kumar, Suresh V Kulkarni, Someshwara Rao B, Design And Evaluation Of Controlled Release Matrix Tablets Of Metoclopramide Hydrochloride Using Hydrophilic Polymers, International Journal Of Current Pharmaceutical Research, 2012; 4(3): 64-69.
31. Pawar R. G., Gadhave M. V., Jadhav S. L., Gaikawad D. D. Formulation and Evaluation of Pregabaline Sustained Release Matrix Tablet, International Journal of Pharmaceutical Research and Development, 2011; 4(2): 153-159.
32. Pawatekar T. S., Ramdas B. Rode, A Review On Sintering Method In Pharmaceutical Sciences, Asian Journal Of Pharm. Tech, 2014; 4(2): 106-109.
33. Indian Pharmacopoeia, 2010; 218-20.
34. Prajapati B.G. And Patel K. R., Once-Daily Sustained-Release Matrix Tablets Of Losartan Potassium: Formulation and In Vitro Evaluation,

International Journal of Medical and Clinical Research, 2010; 1(1): 1-7.
35. Pavia, Lampman, Kriz, Vyvyan, Spectroscopy. India ed. Cengazelearning, IR, 2007; 26-92.
36. Nokhodchi A, Amire O, Jelvehgari M. Physico-mechanical and dissolution behaviors of ibuprofen crystals crystallized in the presence of various additives. DARU, 2010; 18: 74-83.
37. Anuj Patnaik N, Nagarjuna T, Thulasiramaraju TV. Sustainedrelease drug delivery system: a modern formulation approach.Int J Res Pharm Nano Sci, 2013; 2: 586-601.
38. Brahmankar DM, Jaiswal SB. 2nd ed. Biopharmaceutics andpharmacokinetics: a treatise, Vallabh Prakashan, 2009; 431-3.
39. Stability studies in an overview of ICH guidelines for drug products.Natalie Mc Clure, Matrix Pharmaceutical Inc.; 1997. Available from: http: //www.mcclurenet.com. [Last accessed on 20 Oct 2017]
40. R.C. Jat, Arvind Singh Rathore, Narendra Sharma, Rahul Tiwari, An Overview: Matrix Tablet As Controlled Drug Delivery System, International Journal Of Research And Development In Pharmacy And Life Sciences, 2013; 2(4): 482-492.
41. Remington: The Science and Practice of Pharmacy. 20th Ed. Easton, Pennsylvania: Mac Publishing Company, 2001; 903.
42. Rowe RC, Sheskey PJ and Weller PG. Handbook of Pharmaceutical Excipients London: Pharmaceutical Press, 2003. P.104, 184-185, 237-240.
43. RupavathMahendar and KavatiRamkrisha, Formulation and Evaluation of Floating matrix tablets of Stavudine using Pullulan gum, International Journal of Chemical and Pharmaceutical Sciences, 2012 June; 3(2): 80-83.
44. Sameer Shafi, Chowdary K.A., NagobaShivappa, HangargekarSachin, Formulation And Evaluation Of Sintered Matrix Tablets Of Diltiazem Hydrochloride, International Joural Of Applied Pharmaceutics, 2011; 3(3): 2011.
45. SathishUmmadi, B. Shravani, N. G. Raghavendra Rao, M. Srikanth Reddy, B. SanjeevNayak, Overview on Controlled Release Dosage Form, International Journal of Pharma Sciences, 201; 3(4): 258-269.
46. Shalin A. Modi, P. D. Gaikwad,V. H. Bankar, S. P. Pawar Sustained Release Drug Delivery System: A Review International Journal Of Pharma Research & Development, 2011; 2(12): 147-160.
47. Chatap VK, Maurya AR, Prashant K, Deshmukh, Zawar LR.Formulation and evaluation of nisoldipine sublingual tabletsusing pullulan and chitosan for rapid oromucosal absorption. APP, 2013; 1: 18-25.
48. Maurya AR, Chatap VK, Deshmukh PK, Mullurwar VK, BariSanjay B. Pullulan as a novel solubilizer for solubilityenhancement of nisoldipine. NSIJPS, 2012; 1: 374-85.