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Formulation Development of Losartan Potassium Immediate Release Tablets and Process Optimization using SeDeM Expert System

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ABSTRACT

The present research work aims to develop drug product using SeDeM technique, this technique employed in preformulation studies which reveals direct compression suitability of active pharmaceutical ingredient (API) and excipient in formulation, study also aims to mask the poor flow property of drug substance using SeDeM expert system and prepare robust composition for direct compression. 12 test of SeDeM technique was applied on Losartan potassium and other commonly used excipients, obtained radius values were considered to check suitability and deficiencies of excipients and drug, % corrective excipient is identified and incorporated in formula, F1 to F3 composition derived based on SeDeM outcome, Set of SeDeM test were performed on all 3 blends, optimized composition derived based on IPP value, Tablets compressed using direct compression method, and comparative evaluation done using marketed product. RP value for Losartan potassium found 3.44 which shows poor flow property. Microcrystalline cellulose, Lactose SD, and maize starch RE value estimated 5.66, 7.41, and 5.49 respectively. Lubricated blend of composition F2 found average radius value IPP is 6.68, compressed tablet shown good physical properties, while f1 and f2 values found to be 6 and 68 respectively. Formulation found pharmaceutical equivalent with marketed product and stable as well. Hence SeDeM system can be employed as cost effective, quicker technique for prediction of material behavior in terms of flow.

INTRODUCTION

Losartan potassium is a competitive AT1 angiotensin II receptor antagonist. Angiotensin II helps to maintain constant blood pressure despite fluctuations in a person's state of hydration, sodium intake and other physiological variables. Angiotensin II also performs the regulatory tasks of inhibiting excretion of sodium by the kidneys, inhibiting norephedrin reuptake and stimulating aldosterone biosynthesis. By inhibiting angiotensin II binding to AT1 receptors, losartan disrupts the vasoconstriction mediated by AT1 receptors. Blocking vasoconstriction by angiotensin II has been found to be beneficial to patients with hypertension (Lifshitz *et al*., 2004). In preset study losartan potassium immediate release tablet was formulated by using direct compression method. As per the literature it was observed that Losartan potassium API having very poor flow (Lifshitz *et al*., 2004). All the effort was to make this API suitable by direct compression, as in the industries maximum time wet granulation process is used to formulate Losartan potassium tablet, in direct compression case its recommended to employ excipient which has good flow or which are directly compressible grade qualitatively, to incorporate such excipient quantitatively is always a task for the formulator. While developing the formulation it's important to be cautious and specific to select concentration of excipient (mg per tablet) so that they should not become toxic to patient and this can be achieve by accessing inactive ingredient database of USFDA. This gives us information about highest possible level of use (Safe level) of particular excipient as per dosage form and route of administration as well. Qualitative and quantitative formulas mentioned in patent as well as in literature are protected by intellectual property right and restricted to use option remain is to perform trial and error approach. In the current development SeDeM expert system is

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introduced which shows the suitability of API & excipient for direct compression process also it reveals the % concentration of excipient or polymer to be incorporated in the formulation so that poor flow characteristic of API will get masked. This optimization tool is well reported in literature as well as in scientific books (Pilar *et al*., 2006). SeDeM Method used while preformulation studies emphases always on the physical properties of drug substances related to its suitability in the direct compression process. For the present study different excipient is used to correct the API's poor flow and make it suitable for direct compression using SeDeM Method. SeDeM can be termed as Secure Development Method, ICH-Q8 provides a basis for the SeDeM expert system. It is used for an evaluation of critical quality attributes which is a part of Quality by Design which has an impact on the final product. This system provides prediction of flow and a physical profile of drug and excipients intended to be used (Khan *et al*., 2013). SeDeM expert system may be coined as time saving as this technique may reduce no of trials. Due to the ability of prediction for deficient part this technique may serve as economic and choice of technique compared to other time consuming conventional trial and error approach or software based prediction models.

MATERIALS AND METHOD

Losartan potassium, Avicel PH 101, Lasctose SD, Maize Starch, Sodium Starch Glycolate and Magnesium Stearate obtained from Wockhardt Pharmaceuticals Ltd Aurangabad, India. All the materials were of pharmaceutical grade.

Preformulation studies

API confirmation using UV spectrometry

UV spectrometry was performed in order to confirm the received active pharmaceutical ingredient. The ultraviolet absorption spectrum of Losartan potassium was obtained using Shimadzu 1700-PC UV visible spectrophotometer and 1 cm quartz cells, over a wavelength range of 400 to 200 nm in 0.1N HCl solution. The wavelength maxima (λ max) was shown by using UV Probe software. A stock solution was prepared by weighing 10 mg of Losartan Potassium in 100 mL of volumetric flask and dissolved in Distilled Water to obtain a concentration 0.1 mg/mL or 100 µg/mL (stock) (Bonfilio, 2010).

API confirmation using FT-IR analysis

The IR absorbance spectrum of drug was recorded using IR 200 spectrometer (Thermo Electron Corporation) over a range of 400 to 4000 cm^{-1}. The drug sample was directly placed in the sample cell in IR chamber and spectrum was recorded. The obtained graph was analyzed for different functional group using IR solution software version 1.40 (Hemalatha *et al*., 2011).

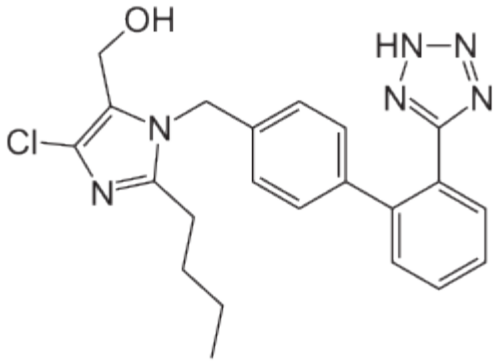

Fig. 1A: Structure of Losartan potassium.

Evaluation of material as per SeDeM expert system

Powder material including excipient and drug Losartan potassium was evaluated for different parameters according to the SeDeM expert system to determine their suitability for direct compression. Some of them were determined experimentally according to the established procedure and some were calculated from experimental values as per Table 1 (Suñé Negre *et al*., 2011).

Table 1: Parameters of SeDeM expert system along with limits & factors.

Incidence Factor	Parameter (Symbol)	Unit	Equation	Limit Value	Conversion factor applied
Dimensions	Bulk Density (Da)	gm/ml	Da = P/Va	0–1	10v
	Tapped Density (Dc)	gm/ml	Dc = P/Vc	0–1	10v
Compressibility	Interparticle porosity (Ie)	-	Ie = DC − Da/Dc × Da	0–1.2	10v/1.2
	Carr index (Icd)	%	IC = (Dc − Da/Dc)	0–50	10-(v/5)
	Cohesion index (IC)	N	Experimental	0–200	v/20
Powder Flow	Hausner Ration (IH)	-	IH = Dc/Da	3–0	10-(10v/3)
	Angle of repose (α)	-	$A = \tan^{-1}h/r$	50–0	10-(v/5)
	Flowability (t^n)	S	Experimental	20–0	10-(v/2)
Stability	Loss on Drying (% LOD)	%	Experimental	10–0	10-v
	Hygroscopicity (% H)	%	Experimental	20–0	10-(v/2)
Lubricity	Particles <50 m (% Pf)	%	Experimental	50–0	10-(v/5)
	Homogeneity index (IΘ)	-	Eq. (1)	0–0.02	500v

Determination of basic parameters

The basic parameters of the SeDeM expert system shown in Table 1 are given as below (Suñé Negre *et al*., 2011).

1) Bulk density (Da)

Bulk density was calculated in accordance with the method described in Section 2.9.15 of European Pharmacopoeia.

The total volume in bulk density measurements included particle volume, inter-particle void volume and internal pore volume.

2) Tapped density (Dc)

Dc was calculated in accordance with the method described in Section 2.9.15 of European Pharmacopoeia. It was determined by applying a controlled packing force to the sample and included the interstitial volume and pore volume in its calculations. Graduated cylinder was employed for density measurements and the volume taken was the value obtained after 2500 strokes using a settling apparatus.

3) Inter-particle porosity (Ie)

The inter-particle porosity of the drug powder was calculated by the following equation

$$Ie = Dc - Da/Dc \times Da.$$

4) Carr index (IC%)

It was computed from Da and Dc using the following equation

$$IC = (Dc - Da/Dc) \times 100.$$

5) Cohesion index (Icd)

The cohesion index was determined by directly compressing the drug powder under study using an eccentric press. The hardness (N) of the obtained tablets was determined andthe mean hardness was calculated.

6) Hausner ratio (IH)

This was calculated from Da and Dc using the following expression IH = Dc/Da.

7) Angle of repose (α)

It is the three dimensional angle formed by cone like pile of the material during the determination. The angle of the cone formed was calculated after the product was passed through a funnel with the following dimensions: funnel height 9.5 cm, upper diameter of spout 7.2 cm, internal diameter at the bottom, narrow end of spout 1.8 cm. The funnel was placed on a support at 20 cm from table surface, centered over a millimeter-grid sheet on which two intersecting lines were drawn, crossing at the Centre. The narrow end of the funnel spout was plugged and the funnel was filled with the product under study until it was flushed with the top end of the spout when smoothed with a spatula. Thereafter, the plug was removed and the powder was allowed to fall onto the millimeter sheet. The radius of the cone base was measured with a slide caliper and the mean value (r) was calculated. Additionally, the cone height (h) was measured and the angle tangent value (α) of the cone was calculated employing the following equation: tan α = h/r.

8) Flowability (tn)

The flow rate described herein as flowability was determined in accordance with the method described in Section 2.9.16-2 of European Pharmacopoeia as the time for a fixed amount of powder to flow through a glass tunnel with 0.85 cm orifice diameter. It was expressed in seconds and tenths of a second per 100 grams of sample, with the mean value of three determinations always being taken.

9) Loss on drying (% HR)

This is determined by the loss on-drying test carried out in accordance with General method 2.2.32 in European Pharmacopoeia. Excipient was dried in a convection oven at 105°C ± 2°C until a constant weight is obtained.

10) Hygroscopicity (% H)

The hygroscopicity of a powder is its equilibrium moisture content after being exposed to air humidity under given conditions. It was determined by calculating the increase in sample weight after being kept in a humidifier at ambient relative humidity of 76% ± 2% and a temperature of 22°C ± 2°C for 24 h.

11) Percentage of particles measuring < 50 μ (% Pf)

Particle size was determined by means of the sieve test in accordance with the General method 2.9.12 of European Pharmacopoeia (14) and was expressed as the % of particles that pass through a 0.05 mm sieve (ASTM#270), when vibrated for 10 min at speed 10 using a sieve vibrator.

12) Homogeneity index (Iθ)

The method for determination of Iθ was based on General method 2.9.12 of European Pharmacopoeia for determining particle size by means of the sieve test (Singh and Kumar 2012; Shahi and Tadwee 2017). The grain size of a 100 g sample was determined by submitting a sieve stack to vibration for 10 min at the speed 10 using a sieve vibrator. Sieve sizes used were: 0.355, 0.212, 0.100 and 0.05 mm. (ASTM#45, #70, #140 #270 respectively). The percentage of product retained in each sieve and the quantity that passes through the 0.05 mm sieve were calculated. The percentage of fine particles (<50 μ) determined previously in a separate operation was considered. The following equation was then applied to the data obtained:

$$I\theta = \frac{F_m}{100 + (d_m - d_{m-1})\,F_{m-1} + (d_{m+1} - d_m)\,F_{m+1} + (d_m - d_{m-2})\,F_{m-2} + \ldots\ldots + (d_m - d_{m-n})\,F_{m-n} + (d_{m+n} - d_m)\,F_{m+n}}$$

Where Iθ = relative homogeneity index; F_m = percentage of particles in the majority range; F_{m-1} = percentage of particles in the range immediately below the majority range; F_{m+1} = percentage of particles in the range immediately above the majority range; n = order number of the fraction under study, within a series, with respect to the majority fraction; d_m = the mean diameter of particles in the majority fraction; d_{m-1} = the mean diameter of particles in the fraction of the range immediately below the majority range; d_{m+1} = mean diameter of the particles in the fraction of the range immediately above the majority range (Tadwee *et al*., 2017).

Conversion of experimental values (V) to radius value of sedem diagram

The numerical values for different parameters of the material obtained by experimental determination were converted into a radius value 'r' of the SeDeM expert system diagram. For the conversion of experimental value of each parameter, specific factors were applied[4] as listed in Table 1 (Suñé Negre *et al*., 2011).

Graphical presentation of SeDeM diagram

SeDeM diagram was drawn on the basis of 12 parameters. Results obtained from the experimental determination of various parameters were converted and presented as a SeDeM diagram (Díaz *et al*., 2009) as shown in Figure 1b (Suñé Negre *et al*., 2011).

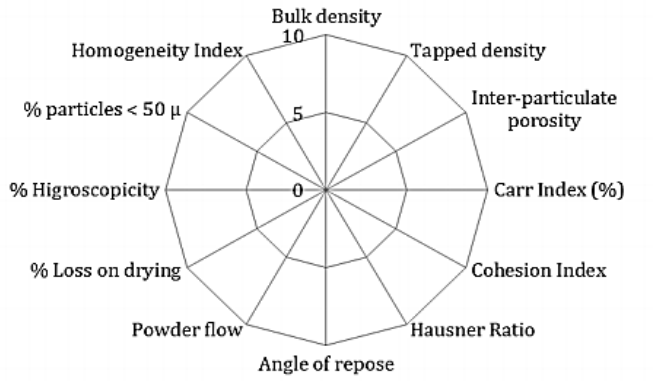

Figure 1b: SeDeM diagram.

Calculation of acceptance values

For determination of suitability of the material for direct compression the following indices are calculated on the basis of the SeDeM system as below (Suñé Negre *et al*., 2011).

1) Parameter index

$$I.P. = No.\ P \geqslant 5\ No.\ Pt \qquad (1)$$

Where No. P ⩾ 5 = Parameters with values equal to or more than 5; No. Pt = Total number of parameters.

Acceptability limit corresponds to a score of 5.

2) Parameter profile index

I.P.P. = Average of r value of all parameters

The acceptable limit corresponds to a score of 5.

3) Good compressibility index

$$I.G.C. = I.P.P. \times f \qquad (2)$$

Where f = Reliability factor (0.952).

Application of SeDeM method to determine the amount of excipient required for the direct compression process for deficient API (Suñé Negre *et al*., 2011)

Determination of amount of excipient required to correct the deficiency of poor flow API can be obtained using equation (3), this equation can be applied to 5 parameters, (Dimension, compressibility, flowability).

This equation allows calculation of the amount of excipient required to compress the API on the basis of the SeDeM radius considering 5 (min) for each parameter of incidence which allows correct compression

$$CP = 100 - [(RE - R)/(RE - RP) \times 100] \qquad (3)$$

Where CP = % Corrective Excipient; RE = mean-incidence radius value (compressibility) of the corrective excipient; R = mean-incidence radius value to be obtained in the blend; RP = mean-incidence radius value (compressibility) of the API to be corrected.

In this calculations unknown values were replaced by the calculated ones required for each substance in order to obtain R = 5 (5 is the minimum value considered necessary to achieve satisfactory compression). For example, if a deficient compressibility parameter for an API requires correction, Equation (3) is applied by replacing the terms RE and RP with the values calculated for each substance with the purpose to obtain a R = 5, thus obtaining the optimal excipient to design a first drug formulation and the maximum amount required for a comprehensive understanding of the proposed formula. From this first formulation, research can get underway for the final optimization of the formulation, taking into consideration the biopharmaceutical characteristics required in the final tablet (disintegration, dissolution, etc.) (Suñé Negre *et al*., 2011).

Formula composition

Based on the radius values obtained on API & excipient as well as % corrective excipient requirement formulation F1 to F3 derived & presented in Table 2.

Table 2: Formulation composition.

Sr. No	Name of Ingredient	F1	F2	F3
1	Losartan Potassium	25	25	25
2	Microcrystalline cellulose (Avicel pH 101)	70	-	-
3	Lactose SD	-	40	-
4	Maize Starch	2*	32*	72
5	Sodium Starch Glycolate	2	2	2
6	Magnesium Stearate	1	1	1
	Total Tablet weight	100	100	100

* In order to maintain tablet weight 100 mg maize starch used as filler (Rowe 2009) as maize starch was having average radius value 5.46 which is close to standard radius value 5.

Preparation of lubricated blend

Formulation wise all ingredient in the composition were dispensed as per the batch size of 5000 tablets, API potency calculated as per below formula and respective compensation was considered while dispensing for batch manufacturing (g/batch).

$$API\ Potency = Assay\ on\ anhydrous\ basis \times (100 - water)/100$$

Losartan potassium, Microcrystalline cellulose, Lactose SD, Sodium Starch glycolate were sifted through ASTM#40 and loaded in double cone blender having capacity 2 Liter and blended for 10 min for 20 rpm, further Magnesium stearate sifted through

ASTM#60 and loaded in blender and blended for 5 min at 20 rpm.

Blend evaluation using SeDeM

Obtained blend were subjected to 12 test of SeDeM as per Table 1, result obtained were calculated for radius values, on the basis of radius values SeDeM diagram was plotted, acceptance values were calculated using equations (1), (2) & (3) composition whose blend yielding higher IPP value (mean r of all parameters) was considered as optimized batch for further evaluation (Suñé Negre *et al*., 2011; Tadwee *et al*., 2017).

Tablet compression & evaluation

Optimized blend was compressed using 6.5 mm round beveled edges punch having plain surface on both sides. Compressed tablets were subjected to in process quality control (IPQC) tests (DT, thickness, hardness, and weight variation).

Physical properties of coated and uncoated tablets were evaluated as per the procedures reported in official Pharmacopoeias, as under.

a) Tablet weight

Weight was calculated after measuring 20 tablets individually using a digital balance (Sartorius). Average weight of 20 tablets were reported in Table 7.

b) Thickness & diameter

The thickness and diameter of 10 tablets from each formulation was measured using a Vernier caliper (Digimatic) and their average thickness and diameter reported in Table 7.

c) Hardness test

Crushing strength of 10 tablets one after another of optimized formulation, was determined using a tablet hardness tester (Dr. Schleuniger) & mean values were calculated and reported in Table 7.

d) Friability test

Friability was determined according to official monograph using single drum friabilator (Electrolab). Final % friability is reported in Table 7.

e) Disintegration test (DT)

Disintegration test performed as per USP apparatus (Electrolab) on 6 tablets, DT is reported in Table 8.

Tablet coating & evaluation

In order to protect from moisture and other environmental factor, compressed tablets were coated using Opadry Clear® Coating ready-mix manually in rolling coating pan, 5% w/w coating solution prepared, tablet were coated up to 2% weight gain (2 mg), and curing done at 45°C bed temp for 15 min. Coated tablets were subjected to routine IPQC test as per Table 7.

Assay

Losartan potassium content of tablets was determined as per the official method described in Pharmacopoeia. Absorbance of the sample solution and standard solution was measured at Mode: LC, Detector: UV 250 nm, Column: 3.9-mm × 15-cm; 5-µm packing L7, Flow rate: 1.0 mL/min. Injection volume: 10 µL. The drug content was calculated by a comparison of absorbance of two solutions. All determinations were made in triplicate and their average was calculated. Injection volume was 10 µL (USP-NF 37).

Dissolution

As per the OGD recommendation of USP monograph for dissolution of losartan potassium tablet, dissolution studies were carried out using water as dissolution medium, apparatus 2, 50 rpm, aliquots were withdrawn at 5, 10, 15, 30, 45 and 60 min. % drug release were estimated using UV spectrometry. f1& f2 value were calculated and shown in Table 7 (USP-NF 37).

Stability study

Optimized formulation were exposed at room temperature, 40°C/75% Relative Humidity, and 30°C/65% Relative Humidity for 6 months. The tablets were withdrawn for analysis of following parameters & results reported in Table 10 (ICH Guidelines Q1A (R2) 2003).

1. Average weight
2. Hardness
3. Disintegration time (D. T.)
4. Moisture content
5. Assay.

RESULT & DISCUSSION

Preformulation studies

API Confirmation through UV

UV spectra of Losartan potassium exhibited wavelength maxima at wavelength 205 nm, which complies with the reported literature value 205 nm (Bonfilio, 2010), with this we may confirm that received chemical is losartan potassium.

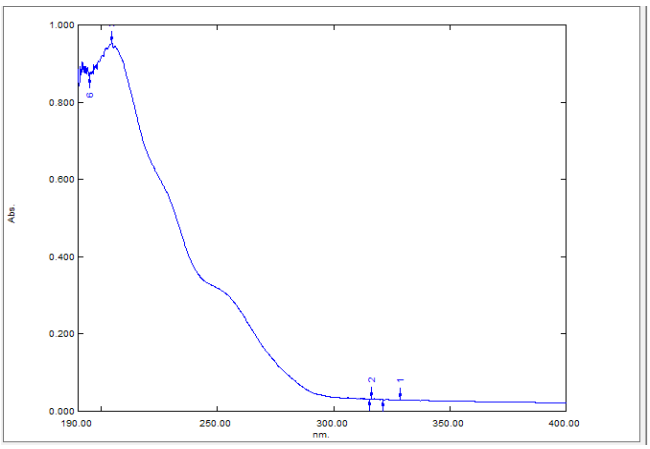

Fig. 2: UV spectrum of losartan potassium.

API confirmation through IR

FTIR interpretation revealed that the observed frequency with respect to vibration/stretch matches with the structure of losartan potassium. Hence this may be considered that obtained drug is losartan potassium.

Table 3: FT-IR interpretation for losartan potassium.

Sr no	Observed frequency	Type of vibration	Frequency
1	2954.95 cm^{-1}	C-H stretch	3000–2850 cm^{-1}
2	1577.77 cm^{-1}	NH	1640–1550 cm^{-1}
3	1259.55 cm^{-1}	C-N	1350–1000 cm^{-1}
4	765.74 cm^{-1}	C-Cl	785–540 cm^{-1}
5	1460.11 cm^{-1}	CH_2 bend	1465 cm^{-1}
6	3650 cm^{-1}	OH	3650–3600 cm^{-1}

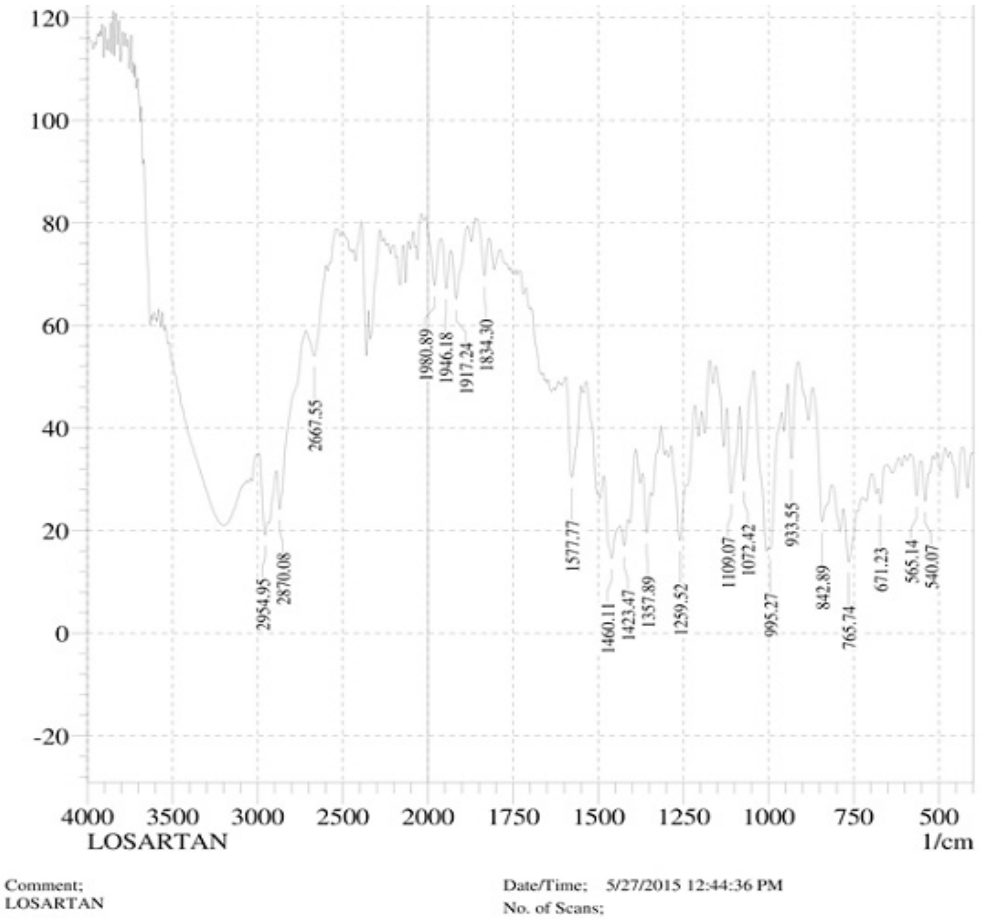

Fig. 3: IR spectrum of losartan potassium.

Table 4: Radius parameters, mean incidence and parametric index for API & excipients.

	PARAMETERS (Radius values)												FACTOR					INDEX		
Excipient	Da	Dc	Ie	IC	Icd	IH	(a)	t"	% HR	% H	% Pf	(IQ)	Dimension	Compressibility	Flow ability/ Powder flow	Lubricity/ Stability	Lubricity/ Dosage	IP	IPP	IGC
Losartan	5.95	8.13	3.76	5.36	1.22	8.17	1.54	2.0	9.05	3.0	7.2	1.8	7.04	3.44	3.90	6.02	4.5	0.5	4.77	4.54
Microcrystalline cellulose	3.57	4.76	5.86	5.0	6.12	8.33	2.55	1.0	9.33	8.75	9.8	4.5	4.17	5.66	3.96	9.04	7.15	0.58	5.80	5.52
Lactose SD	4.90	8.11	6.73	7.91	7.6	6.725	4.59	7.5	9.2	8.1	10	7.32	6.51	7.41	6.27	8.65	8.66	0.83	7.39	7.04
Maize Starch	5.55	6.98	3.07	4.09	9.31	4.15	8.75	4.0	8.82	1.25	4.6	5.0	6.27	5.49	5.63	5.04	4.80	0.50	5.46	5.20

Excipients evaluation using SeDeM method

Each SeDeM treated excipients were calculated for radius value of 12 test, IP, IPP and IGC value. Result obtained are showed in Table 4.

Determination of amount of corrective excipient required

As per the outcome of SeDeM radius values and graphs required amount of excipient is calculated using equation no 3. Result obtained is shown in Table 5.

Blend evaluation using SeDeM diagram

All 3 formulation blend was further processed through SeDeM parameters in order to finalized optimized formulation, values reported in Table 6.

Table 5: Amount of excipient required to be mixed with API in order to obtain compressibility factor equal to 5.

Excipient	Microcrystalline Cellulose	Lactose SD	Maize Starch
RE	5.66	7.41	5.49
RP (API)	3.44	3.44	3.44
R	5	5	5
% Excipient (CP)	70.27	39.29	76.09

Table 6: Radius parameters, mean incidence and parametric index for ready to compress blend.

Formulation	PARAMETERS (Radius values)												FACTOR				INDEX		
	Da	Dc	Ie	IC	Icd	IH	(a)	t”	% HR	% H	% Pf	(IQ)	Dimension	Compressibility	Flow ability/ Powder flow	Lubricity/ Stability	Lubricity/ Dosage	IP	IPP	IGC
F1	4.15	5.10	3.98	3.92	7.8	8.78	2.27	5.50	7.80	7.25	4.25	7.5	4.63	5.23	5.51	7.52	5.87	0.58	5.69	5.42
F2	3.85	4.95	4.82	4.44	5.85	8.57	5.55	7.00	8.05	8.05	9.5	9.5	4.40	5.14	7.04	8.05	9.50	0.67	6.68	6.36
F3	5.56	6.58	2.32	3.10	6.62	9.08	3.48	4.50	8.25	5.37	7.5	5.5	6.07	4.01	5.68	6.81	6.50	0.67	5.66	5.38

SeDeM diagrams

A) Losartan potassium

See Figure 4.

B) Microcrystalline cellulose

See Figure 5.

C) Lactose SD

See Figure 6.

D) Maize starch

See Figure 7.

E) Flow masking of Losartan with Lactose SD

See Figure 8.

F) SeDeM diagram of F1 formulation

See Figure 9.

G) SeDeM diagram of F2 formulation

See Figure 10.

H) SeDeM diagram of F3 formulation

See Figure 11.

In process quality control (IPQC) results

See Table 7.

Determination of assay and dissolution

Results obtained after evaluation of Losartan potassium formulation for assay and dissolution test was tabulated in Tables 8 & 9.

Stability study

Stability studies of the optimized losartan potassium tablet (formulation F2) was carried out at various atmospheric conditions like room temperature, 40°C/75% RH, 30°C/65% RH and 25°C/60% RH. Even after the period of six month exposure at various atmospheric conditions different stability parameters like average weight, hardness, dissolution time, moisture content, and drug content (assay) were satisfactory (Table 7). Thus, these results confirmed that the optimized losartan potassium tablet (formulation F2) was stable enough.

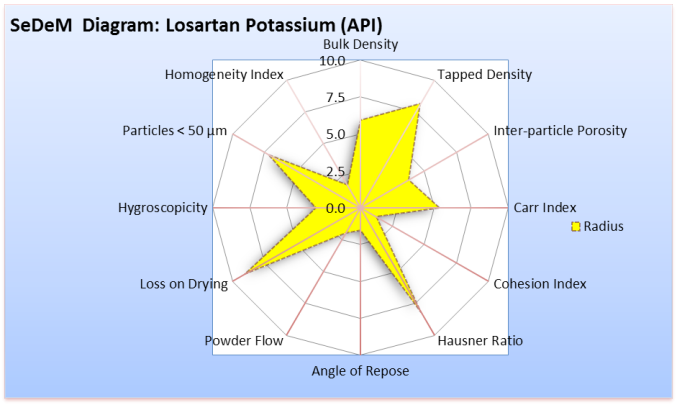

Fig. 4: SeDeM diagram of losartan potassium (API).

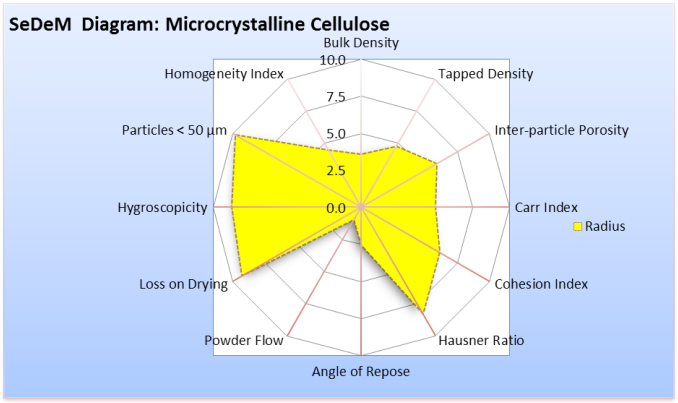

Fig. 5: SeDeM diagram of microcrystalline cellulose.

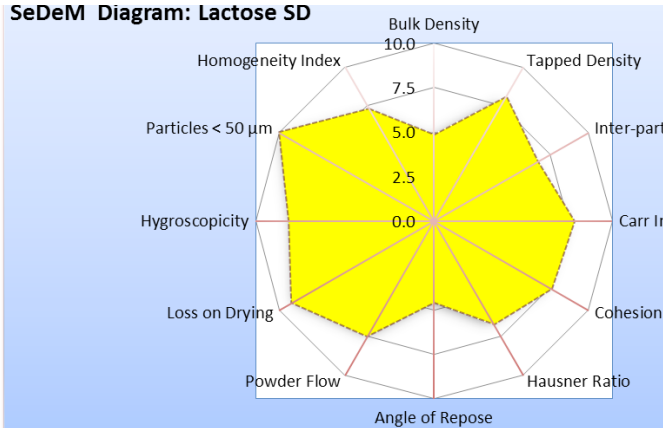

Fig. 6: SeDeM diagram of lactose SD.

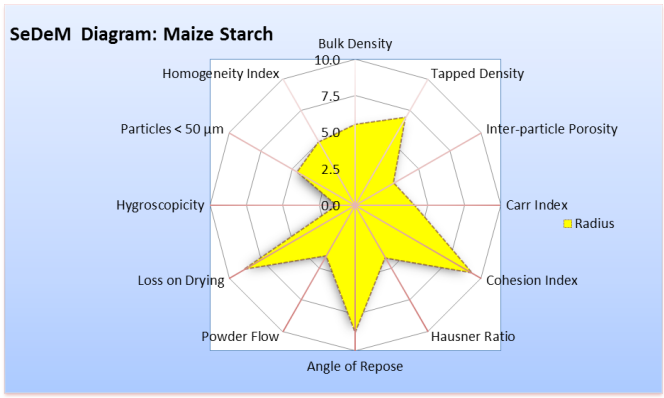

Fig. 7: SeDeM diagram of maize starch.

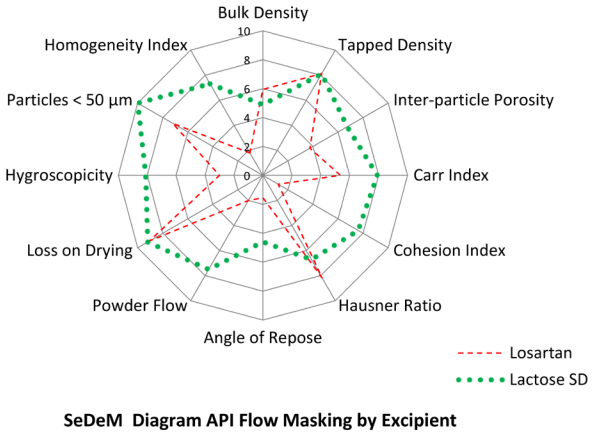

Fig. 8: Representation of API flow masking using SeDeM diagram.

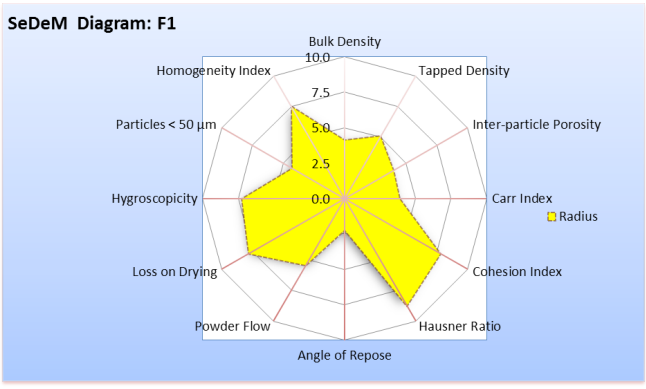

Fig. 9: SeDeM diagram of F1 formulation.

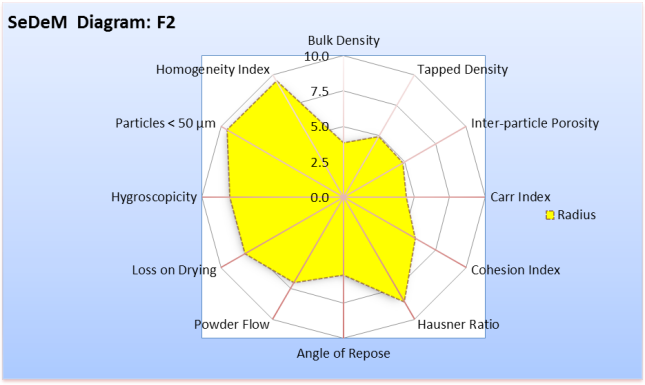

Fig. 10: SeDeM diagram of F2 formulation.

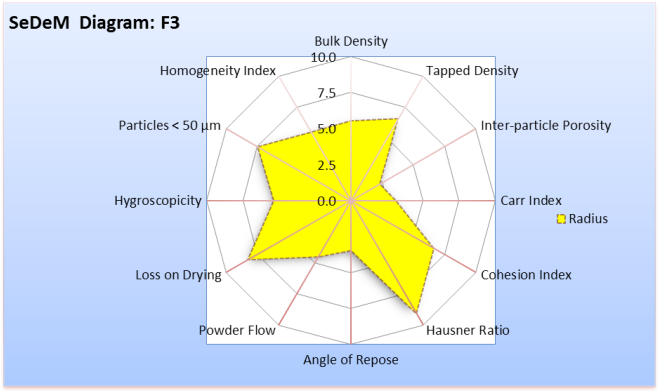

Fig. 11: SeDeM diagram of F3 formulation.

Table 7: IPQC evaluation of coated and uncoated tablet of f1 composition and comparative evaluation using marketed product.

Sr. No	Test	USP monograph Limit	Losacar Tablet (Marketed Sample) Mfg. By: Zydus	F2 (Uncoated tablet)	F2 (Coated tablet)
1	Description	NA	White round film coated tablet im-printed with Z25 at one side and plain surface on other side	White round uncoated tablet having plain surface on both side	White round film coated tablet having plain surface on both side
2	Tablet weight (n = 20)	±10% (90–110 mg)	99 mg	99.5 mg	101.9
3	Thickness (n = 10)	NA	2.92 mm	2.95 mm	3.03
4	Diameter (n = 10)	NA	6.51	6.50	6.53
5	Disintegration Time (in water at 37°C) (n = 6)	NMT 15 min	6 min 30 sec	5 min	7 min
6	Friability (20 tablet)	NMT 1%	0.3%	0.25%	0.1%
7	Hardness (n = 10)	NA	5.1 kp	4.5 kp	5.5 kp

Table 8: Comparative assay and dissolution values of optimized formulation with marketed products.

Sr. No	Test	Limits	Reference Sample (Losacar)	F2
1	Assay	95–105	100.2	98.5
2	Dissolution Condition; Media: Water (deareated), Volume: 900ml, Apparatus: USP Type II (Paddle), RPM: 50, Unit = 6 (as per OGD & USP recommendation)	NLT 75% (Q) of the labeled amount of losartan potassium is dissolved in 30 min		
		Time	% drug dissolved	
		5	25	21
		10	40	34
		15	65	59
		30	89	95
		45	99	97
		60	99	97
3	Difference factor (F1)	NMT 15 = 6		
4	Similarity factor (F2)	NLT 50 = 68		

Table 9: Multimedia dissolution of marketed product and optimized formulation.

Time point	Dissolution in pH 1.2		Dissolution in pH 4.5		Dissolution in pH 6.8	
Condition: Volume: 900ml, Apparatus: USP Type II (Paddle), RPM: 50, Unit = 6						
Time	Losacar	F2	Losacar	F2	Losacar	F2
5	5	6	10	12	30	35
10	7	12	16	18	41	49
15	12	18	22	21	58	61
30	16	21	35	29	69	78
45	22	28	45	38	88	95
60	35	36	55	49	98	99

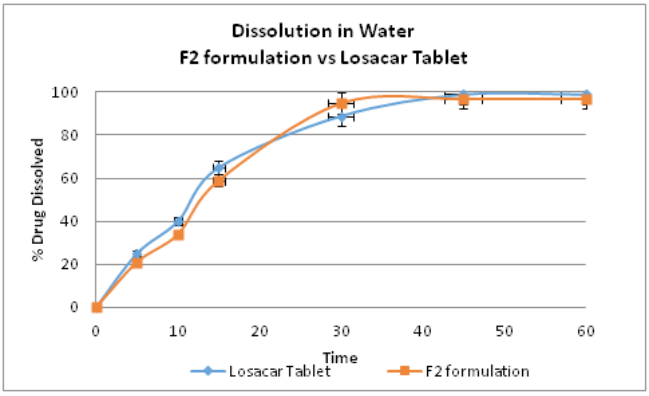

Fig. 12: Dissolution study in water and comparison with marketed product.

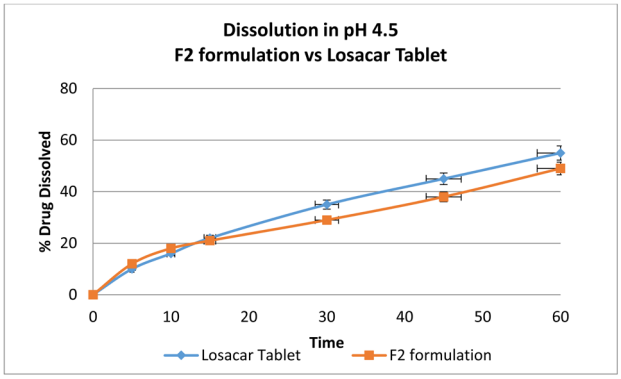

Fig. 14: Dissolution study in pH 4.5 and comparison with marketed product.

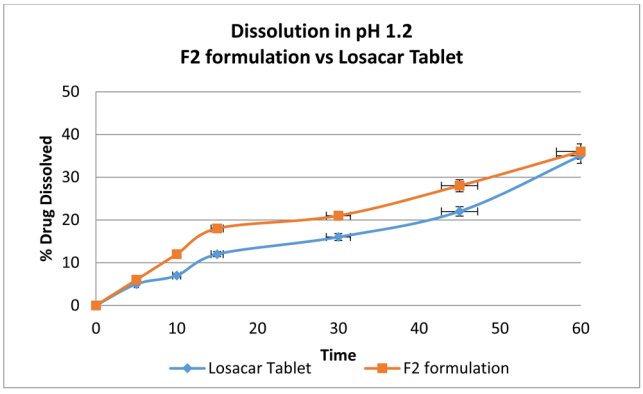

Fig. 13: Dissolution study in pH 1.2 and comparison with marketed product.

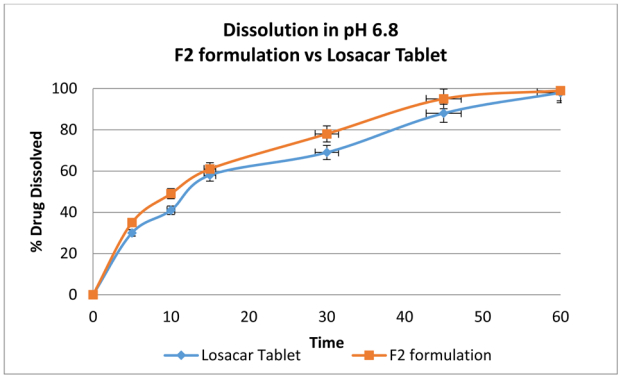

Fig. 15: Dissolution study in pH 6.8 and comparison with marketed product.

Table 10: Stability result of optimized formulation F2.

Condition	Avg. wt (mg) (N = 20)	Hardness (Kp) (N = 10)	DT (Min) (N = 6)	Moisture Content (LOD %w/w)	Assay (%)
Room Temp. (25°C/60% RH)	102.2	5.8	7	1.85	99.5
40°C/75% RH-1M	103.5	6.1	8	2.20	100.1
40°C/75% RH-6M	101.9	6.5	8	2.47	100.3
30°C/65% RH-1M	102.5	5.5	7	2.15	99.8
25°C/60% RH-6M	102.4	5.8	7	1.79	100.9

CONCLUSION

As per the outcome of preformulation studies the API is having average radius (r) <5 (less than five) this value implies that Losartan API is not suitable for direct compression. It has been concluded from the study that the SeDeM expert system can be successfully applied for the prediction of suitability of material for direct compression. It gives accurate predictions about material behavior and response of the material was same as predicted by the SeDeM expert system. It provides information about shortcoming of the material to be processed by direct compression which can be rectified at a preformulation level to get a robust formulation that can be easily scaled up for commercial manufacturing. The SeDeM expert system also reduces the number of trials at a preformulation level to get produced by direct compression especially in the case of a high drug load. By developing a database of the excipients commonly used in pharmaceutical formulation, the material of the desired characteristics can be selected with particular characteristics. Application of SeDeM expert system in the formulation masked flow of API and lactose was choice of excipient for selecting in direct compression process. SeDeM may become very economical and time saving tool. In conclusion, it could be determined that formulation F2 was the optimized product, which possessed satisfactory results in SeDeM parameters and parameters for finished products. There are very low variations observed in all the physical and chemical tests performed. It was observed that the optimized losartan potassium tablets were pharmaceutically equivalent with the marketed product. Even after the period of one month exposure at various atmospheric conditions, formulation found stable at various stability test. Dissolution found good in water and pH 6.8 compare to other dissolution medias with low variation.. IR formulation with losartan potassium drug has been developed using SeDeM technique, using this technique cost effective dosage form can be prepared as it lowers the number of trials and developed product will have scientific background as well.

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Nil.

CONFLICT OF INTEREST

All authors declares no conflict of interest.

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