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DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE PELLETS OF LOSARTAN POTASSIUM BY EXTRUSION-SPHERONIZATION TECHNIQUE

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ABSTRACT

The Losartan potassium is an angiotensin-receptor blocker (ARB), is used alone or with other agents to treat hypertension. Losartan potassium lower blood pressure by antagonizing the renin-angiotensin-aldosterone system (RAAS).It has short plasma half-life, low absolute bioavailability. The objective of present work was to develop oral sustained release pellets of losartan potassium by extrusion–spheronization method, using hydrophilic hydroxyl propyl methylcellulose (HPMC), xanthan gum and carbopol polymer as rate controlling polymer. The pellets were evaluated for micrometric properties, surface morphology, drug content, *in-vitro* drug release and dissolution kinetic model. The drug-polymer interaction results suggested no interaction between drug and polymer. SEM photomicrographs of optimized batch of pellet formulation (L7) showed the uniform spherical surface. Formulation (L7) containing HPMC (5%) and Xanthan gum (15%) gives 13.36% release at the 2 hrs and 96.38% release at 10 hrs. The optimized formulation (L7) follows zero order drug release kinetic conforming sustained release over a period of 10 hours.

KEYWORDS: Losartan potassium, Extrusion-spheronization, Pelletization, sustained release, in vitro drug release

1. INTRODUCTION

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.[1]

Sustained release preparations are useful to reduce the dosage frequency to improve patient convenience. Sustained release pellets are easy to formulate by incorporating drug molecule in a slowly disintegrating and inert porous swellable polymers.[2] Pellets are a small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. The release of drug application within the pharmaceutical industry require consistent smooth surface with a narrow size distribution, to ensure uniform coating and accurate free flow of granules for filling operations (like capsule filling), and this can be achieved by extrusion spheronization technique. Losartan potassium salt, is a strong antihypertensive agent, non-peptide, and exerts its action by specific blockade of angiotensin II receptors.[1] Losartan potassium absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 hours.[2] Present study is aimed to prepare sustained release pellets to improve patient compliance and decrease drug load in body.[2] It is also possible to prepare/sustained release pellets without coating of the pellets by extrusion spheronization process. Low plasma half-life and low oral bioavailability of losartan potassium make it a perfect candidate or preparation of sustained release pellet formulation, which will releases the drug up to 10 hours following zero order kinetics.[2] The sustained release pellets of losartan potassium decrease frequency of dosing, increase elimination half-life, increase residence time and thus increase therapeutic efficasy.

2. MATERIALS AND METHODS

Losartan potassium was kindly supplied by from IPCA laboratories India Pvt. Ltd., Mumbai. Microcrystalline cellulose (MCC) from Loba Chemie Pvt. Ltd., Mumbai. All other chemicals and excipients used in this study were of analytical grade.

2.1 Preparation of pellets

On the basis of literature survey & preformulation studies hydrophilic polymers like HPMC K 100 M and Xanthan gum are selected for pellets formulation. The result obtained from preformulation studies, the following process parameters were optimized for preparation of pellets.

Table 1. Process parameters for preparation of pellets.

Parameter	optimized conditions
Batch size	25 gm.
Extruder speed	60 rpm.

Powder consumption	3 to 4 gm
Spheronization speed	500 rpm.
Spheronization time	15-20 min.
Temperature	R.T.
Batch running time	20-25 min

2.2 Preparation of losartan potassium sustained release pellets

To prepare sustained release pellets, Drug-polymer pellet were prepared by extrusion–spheronization [Extruder Spheronizer Model EXT 30/ SPH 150] using various concentrations of HPMC K 100 M alone & in combination with xanthan gum or carbopol (Table 2). Losartan potassium, MCC 101, HPMC K 100 M and Xanthan gum or carbopol were mixed in mortar pestle. The granulating liquid (PVP K 30 aqueous solution) was added slowly to the powder blend, which was then mixed until a homogeneous, cohesive wet mass was obtained. The resulting wet mass was extruded at a speed of 80 rpm and mesh of size 1.5 mm. Then spheronization was performed in a spheronizer with a rotating chequered plate with cross-hatch geometry (size -3.25 mm) at a speed of 450 rpm for 3 min. Then prepared pellets were air dried.

Table 2.Composition of various batches for the SR pellets containing losartan potassium

	Amount of ingredients (% w/w)									
Ingredients	**L1**	**L2**	**L3**	**L4**	**L5**	**L6**	**L7**	**L8**	**L9**	**10**
Drug	40	40	40	40	40	40	40	40	40	40
Microcrystalline cellulose (MCC)	30	30	30	30	30	30	30	20	20	20
HPMC k 100 M	20	15	10	5	15	10	5	20	10	15
Xanthan gum	--	--	--	--	5	10	15	20	20	15
Carbopol	--	5	10	15	--	--	--	--	--	--
PVP K 30	10	10	10	10	10	10	10	10	10	10
Total	100	100	100	100	100	100	100	100	100	100

2.3 Evaluation of pellets

2.3.1 Size Distribution

The pellets were sieved using nest of standard sieves (1680. 1180, 1000, 850,710, 420 and 355µm) for 10 min on a sieve shaker. The pellets retained on each sieve were weighed and the obtained data was used to construct a frequency distribution curve. The size range of 710-1680µm was considered appropriate and the weight of pellets in this range was reported as yield of pellets.

2.3.2 Particle Size

For determination of particle size of pellets stage micrometer and eye piece micrometer (model KG-3,micron optik) were employed. It is necessary to calibrate eye piece micrometer in order to get exact value of its 1 division in terms of micron. Therefore calibration of eye piece micrometer was carried out. The prepared slide of pellets under consideration was placed on stage and divisions occupied by the pellets were counted.

2.3.3 Micrometric Properties [3,4]

Pellets were evaluated for bulk density, tap density. It was measured by using 50ml graduated measuring cylinder. Ten gram pellets were poured in measuring cylinder. The volume of pellets was measured and the bulk density was calculated using following formula, then cylinder was tapped mechanically for 100 times, then tapped volume was noted down and tapped density was calculated.

$$Bulk.density = \frac{Weight.of.sample}{Volume.of.sample}$$

$$Tapped.density = \frac{Weight.of.sample}{tapped.volume}$$

Compressibility index or Carr's index value of pellets was computed according to following equation:

$$Carr's.index(\%) = \frac{Tapped - Bulk.density}{Tapped.density} \times 100$$

Haussner's ratio of pellets was determined by comparing the tapped density to bulk density using the equation:

$$\textbf{Haussner's Ratio} = \frac{\textbf{Tapped Density}}{\textbf{Bulk Density}}$$

The angle of repose of the pellets was determined by using funnel method. The accurately weighed powder blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The diameter of the powder cone was measured and angle of repose was calculated by using the equation.

$$\tan = \frac{h}{r}$$

2.4 Scanning Electron Microscopy (SEM)

The shape, surface characteristics and appearance of pellets were examined by scanning electron microscopy (SEM) (Bruker,x-flash 6130,USA) at kV.

2.5 *In-Vitro* release study[5, 6, 7]

The *in vitro* release of losartan potassium from pellets was measured using basket type dissolution apparatus. Losartan potassium pellets equivalent to 40 mg were filled in to capsule shell and placed in the basket type dissolution test apparatus. The volume of dissolution medium was 900 ml and maintained at 37±0.5ºC at a rotation speed of 100 rpm. The dissolution medium was 0.1N HCL (pH 1.2) solution for 2 hr. and then changed to phosphate buffer pH 6.8 for 8 hrs. Aliquots of 5ml of dissolution medium were withdrawn at predetermined time interval and replaced by 5ml of fresh dissolution medium immediately. The samples were assayed using UV visible spectrophotometer (Shimadzu japan) at 252 nm after filtration and dilution. The dissolution medium 0.1N HCL (pH 1.2) & phosphate buffer pH 6.8 were used as reference while UV analysis of the samples. All measurement was performed in triplicate.

2.6 Release Kinetics [9, 10]

Kinetic parameters were obtained by mathematical processing of data obtained from *in vitro* release studies and data was fitted to various kinetics equations to find out the mechanism of drug release from the pellets using PCP disso software.

To evaluate the influence of formulation variable on release rate constant k, various kinetic models studies were zero order, first order, Hixson-Crowell, Higuchi and peppas model. The rate constant and similarity factor were also calculated for the respective models.

2. RESULT AND DISCUSSION

3.1 Size Distribution

The size range of 710-1680 µm was considered appropriate and the weight of pellets in this range was reported in table no 3. In all the formulation L7 batch showing good size distribution i.e. 81.15±1.55 than other formulation.

Table No 3. Pellets Distribution frequency.

Batches	% 710-1680 µm pellet yield
L1	69.86 ±1.43

L2	76.15 ±0.59
L3	79.39 ±0.91
L4	77.13 ±2.14
L5	72.36 ±1.76
L6	72.06 ±1.05
L7	81.15 ±1.55
L8	80.26 ±0.68
L9	75.39 ±0.86
L10	78.46±0.97

Mean±S.D n=3

3.2 Particle Size

The particle size of all formulation was obtained showed in table no 4. In which L7 formulation has optimum particle size in the range of 0.5-1.5 mm

Table No 4. Pellets of particle size.

Batches	Particle size(mm)
L1	0.4-1.7
L2	0.2-1.9
L3	0.7-2.0
L4	1.2-3.2
L5	0.8-1.8
L6	0.5-2.2
L7	0.5-1.5
L8	0.7-2.4
L9	0.1-3.2
L10	1.5-2.5

Mean±S.D n=3

3.3 Evaluation of Losartan potassium Pellets

The Losartan potassium sustained release capsule were off-white, flat shaped in appearance. Bulk density may influence compressibility and flow and rate flow properties. The physicochemical properties and drug content of all formulation were given in table.5. The bulk density of pellets was found to be between 0.7964 ±0.002 to 0.8533 ± 0.016g/cm^3. The tapped density densities were found to be in range of 0.8693 ±0.009 to 0.9123 ± 0.007 g/cm^3, shows good packability of pellet. The value of Carr's index below 5-15 % shows excellent flow properties but readings above 23% indicate poor flowability. Carr's index was found in range between 5.605% ±2.189 to 10.54 ± 0.528 % indicating excellent flow properties or flowability. It was ranging from 1.060 to 1.099 i.e. all the formulation showed that they had

good flow properties. Haussner's ratio is simple method to estimate flow properties. Low range (less than 1.11) was observed of Haussner's ratio that indicates good flow properties.

Table 5. Physical Properties of pellets

Batches	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (0)	Drug Content
L1	0.8533 ±0.016	0.8723 ±0.003	5.605 ±2.189	1.060 ±0.024	15º5´ ±0.29	96.93 ±0.52
L2	0.8229 ±0.003	0.9077 ±0.004	9.336 ±0.807	1.103 ±0.009	19º2´ ±0.27	97.03 ±0.31
L3	0.8126 ±0.003	0.9123 ±0.007	10.54 ±0.528	1.117 ±0.006	15º5´ ±0.33	98.23 ±0.41
L4	0.8383 ±0.004	0.9106 ±0.001	8.435 ±0.268	1.092 ±0.003	16º2´ ±0.19	92.43 ±0.25
L5	0.7964 ±0.002	0.8697 ±0.009	8.427 ±0.200	1.094 ±0.005	14º6´ ±0.48	96.56 ±0.89
L6	0.8178 ±0.003	0.8939 ±0.003	8.518 ±0.425	1.093 ±0.005	14º4´ ±0.17	97.36 ±1.02
L7	0.8254 ±0.002	0.9064 ±0.004	9.496 ±0.766	1.098 ±0.005	18º4´ ±0.27	98.97 ±0.92
L8	0.8120 ±0.008	0.8791 ±0.001	7.641 ±0.766	1.087 ±0.005	19º5´ ±018	97.83 ±0.79
L9	0.8094 ±0.002	0.8901 ±0.003	9.173 ±0.313	1.099 ±0.002	14º1´ ±0.86	99.12 ±1.03
L10	0.8263 ±0.003	0.9124 ±0.003	9.184 ±0.702	1.110 ±0.006	18º6´ ±0.25	96.27 ±0.74

mean±S.D n=3

3.4 Scanning Electron Microscopy (SEM)

SEM photomicrographs in optimized batches of pellets formulated shows the uniform result that the formation of matrix of drug and polymer with desired particle size. SEM photomicrograph of Losartan potassium pellets of optimized batch (L7) was given in Fig.1.

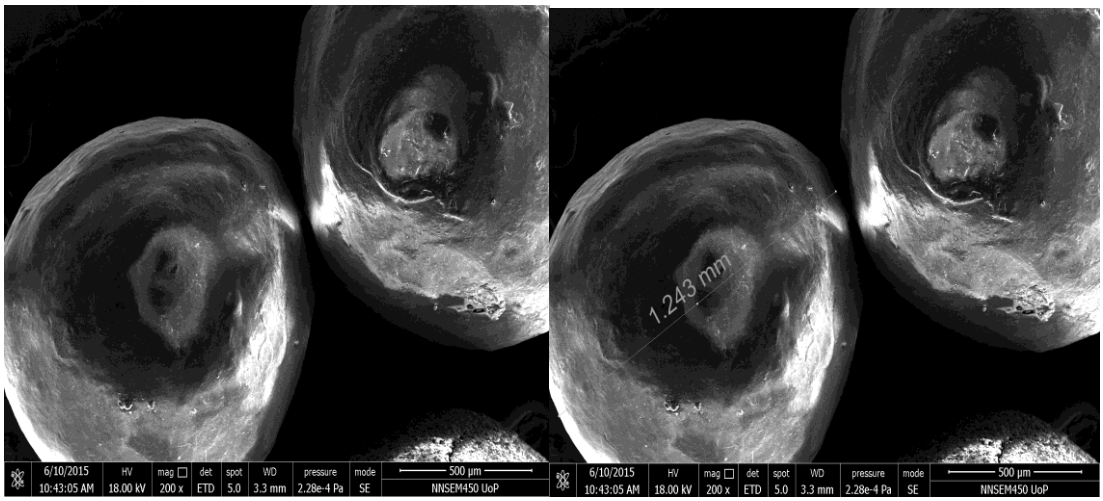

Fig 1. SEM study of Losartan potassium pellets of optimized batch (L7).

3.5 *In-Vitro* dissolution studies

In vitro release of drug from capsule was done in o.1 N HCL for 2 hrs and further in phosphate buffer pH 6.8 for 8 hrs. *In vitro* percent drug release from capsule is plotted against time as shown in fig. 2 and 3 respectively. The total drug release from optimized batch (L7) capsule in 10 hrs was 96.38%. The batch L7 shows more sustained drug release as compared to the other formulation due to combination of HPMC K 100(5%) and Xanthan gum (15%)which showed good physical and chemical properties.

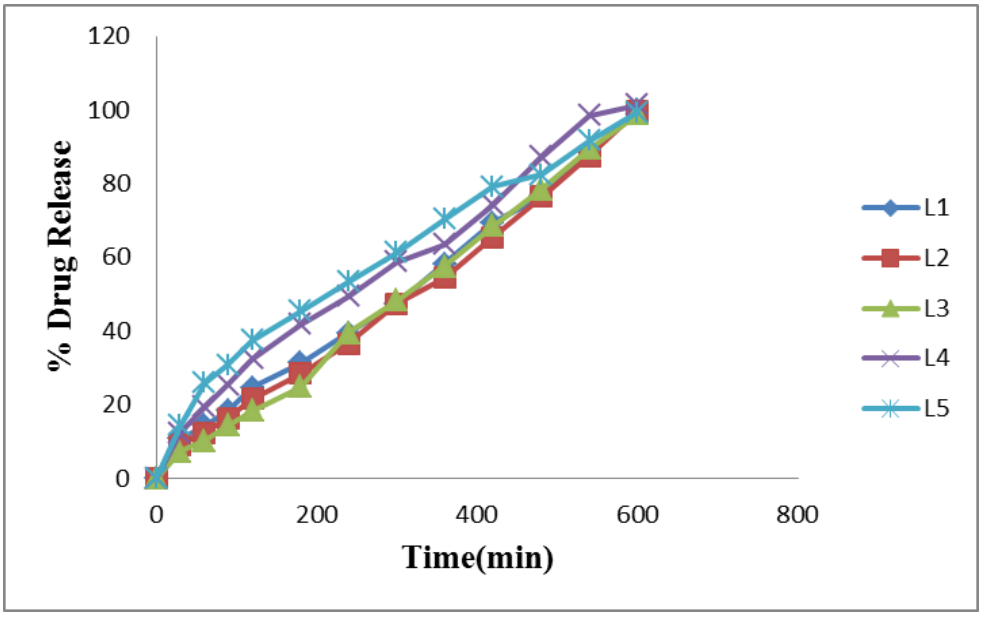

Fig. 2 *In-vitro* Drug release profile of L1 to L5 Batches

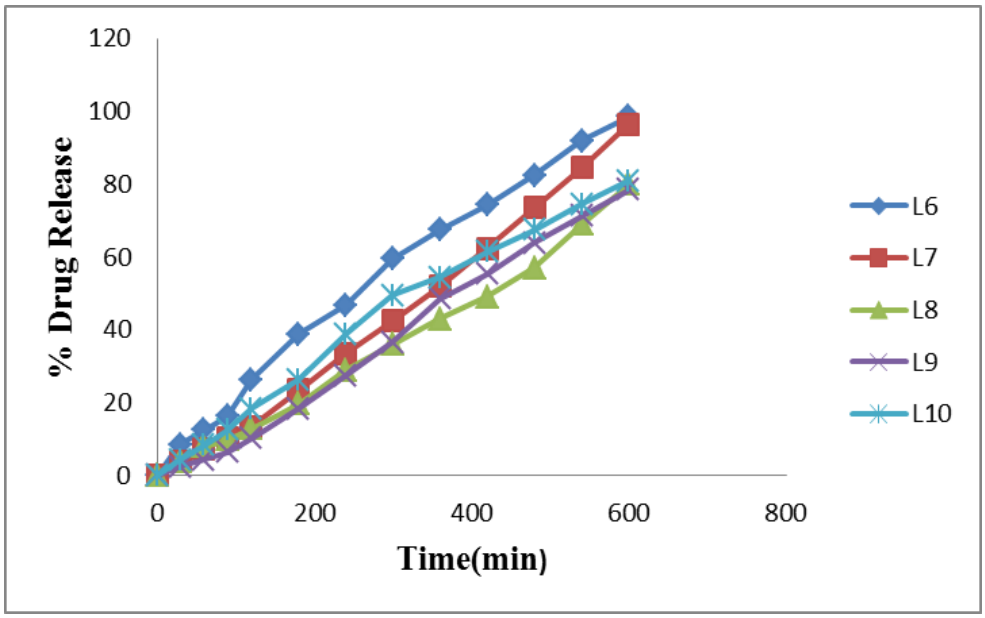

Fig.3 *In-vitro* Drug release profile of L6 to L10 Batches

3.6 Release kinetics

The data obtained from in vitro dissolution studies were fitted in different models viz. zero order, first order, Hixon crowell and Korsemeyer-Peppas equation, the results were shown in Table 6. It was also observed that highest correlation was found for Zero order profile (R2 > 0.99), which indicates the drug release via diffusion mechanism from hydrophilic matrices.[14] Results of Different kinetic models for Losartan potassium pellets were given in table.5.

Thus, the release of Losartan potassium was controlled by zero order dissolution model:

$$\text{Log \% R} = \log K + n \log t$$

Where, % R is percentage drug release: K is release ratio constant and n is the diffusional release exponent that could be used to characterize the different release mechanism. The value of exponent n can be used to characterize the release mechanism of controlled release formulation.[15] The mean diffusional exponent value (n) ranged from 0.2795 to 0.3373 indicating that formulations present a dissolution behavior controlled by Fickian Diffusion mechanism. The correlation coefficient revealed that zero order model was better applicable to release data for optimized batch formulations. The data obtained were plotted as cumulative percentage drug release versus square root of time. Result of drug release of Losartan potassium optimized batch Show zero order model.

Table 6 Different dissolution kinetic models for Losartan potassium pellets

Codes	Zero order		First order		Hixon Crowell		Peppas		Best fit Model
	R	K	R	K	R	K	R	K	
L1	0.9932	0.1863	0.9852	0.1864	0.8537	0.1978	0.9942	0.798	Peppas
L2	o.9832	0.1692	0.9763	0.1886	0.8975	0.1495	0.9921	0.8636	Peppas
L3	0.9945	0.3217	0.9763	0.1785	0.9852	0.1868	0.9964	0.1937	Peppas
L4	0.9837	0.1887	0.9836	0.1864	0.9736	0.2873	0.9954	0.2832	Peppas
L5	0.9764	0.1373	0.9853	0.1836	0.9673	0.1294	0.9948	0.1837	Peppas
L6	0.9945	0.1426	0.9736	0,1374	0.9736	0.2753	0.9948	0.1386	Peppas
L7	0.9961	0.1799	0.9923	0.1635	0.8291	0.1758	0.9942	0.0370	**Zero Order**
L8	0.9864	0.2981	0.9826	0.2716	0.9625	.01376	0.9915	0.1754	Peppas
L9	0.9736	0.1358	0.9875	0.1763	0.9764	0.1937	0.9917	0.3278	Peppas
L10	0.9943	0.2654	0.9746	0.1726	0.9868	0.1863	0.9946	0.1757	Peppas

4. CONCLUSION

The aim of the study was to study demonstrate that the hydrophilic matrix of HPMC alone could not control the Losartan potassium release for 10 hrs whereas when combined with xanthan gum could slow down the release of drug from their matrices and successfully for sustained-release pellets. Thus it can reduce frequency of administration and increasing plasma elimination half-life. Formulation L7 showed sustained drug release for 10 hours so it was selected as the best formulation among all the ten formulations. The kinetics of drug release was best explained by zero order equation. The drug release from the pellets was sufficiently sustained and non-Fickian transport of the drug from pellets was confirmed.

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