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FORMULATION, DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE MICROSPHERES OF LOSARTAN POTASSIUM BY SPRAY DRYING TECHNIQUE

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ABSTRACT

Losartan Potassium is antihypertensive agent called angiotensin II receptor blockers (ARBs).is a highly water soluble drug. Losartan Potassium has shorter half-life of 2.1± 0.70 Hrs and after oral conventional administration mostly it is degraded in the liver and does not show prolonged effect.To overcome these problems the sustained release microspheres of Losartan Potassium is developed which will deliver the drug over a longer period of time. Microspheres of Losartan Potassium were prepared by spray drying technique using the lipophillic polymers i.e.EudragitRS100 and Ethyl Cellulose in drug:polymer ratio 1:8.The microsphere of Losartan Potassium showed an increasing trend of entrapment efficiency and in-vitro drug release. The in vitro drug release study suggests the sustained release of drug despite being highly water soluble.Scanning electron microscopy, differential scanning calorimetry and FT-IR study of the drug and formulation was carried out.

KEY WORDS: antihypertensive, microspheres, spray drying, Losartan Potassium.

1. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systematic delivery of drugs via various pharmaceutical products of different dosage forms. Conventional oral dosage forms like tablets, capsule, pills, powders, emulsion, suspension, offer no control over drug delivery leading to fluctuations in plasma drug level. When such conventional dosage forms is administered the concentration of drug in systemic circulation gradually rises to attain a therapeutic range in short time, and this concentration is maintained for some time

and finally decreases to sub-therapeutic value rendering the drug pharmacologically inactive. Ideally the drug concentration should be continuously maintained within therapeutic level. However, for the drug with short half-life, it is not possible to maintain the drug concentration within therapeutic range without frequent dosing. Frequent dosing may lead to patient non-compliance and drug toxicity and the suitable alternative is sustained release product.

Sustained-Release Formulations

Time release technology also known as sustained-release or time-release formulations are prepared to dissolve slowly and release a drug over time. The advantages of this dosage forms are that oftenly being taken less frequently than instant-release formulations of the same drug, and keeping steadier levels of the drug in the blood stream. Generally, sustained-release formulas are formulated so that the active ingredient is embedded in a matrix of insoluble substance so that the dissolving drug has to find its way out through the holes in the matrix. In some sustained-release formulations the matrix physically swells up to form a gel, so that the drug has first to dissolve in matrix, and then exit through the outer surface. Sustained release formulations are employed for many oral dosage forms to enable time-controlled release of active ingredients throughout the whole gastro-intestinal tract for increasing therapeutic effect and patient compliance.

Microspheres

Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers having a particle size ranging from 1-1000µm. Microspheres as carriers for drugs also known as microparticles. It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest. Microspheres are matrix systems and essentially spherical in shape.

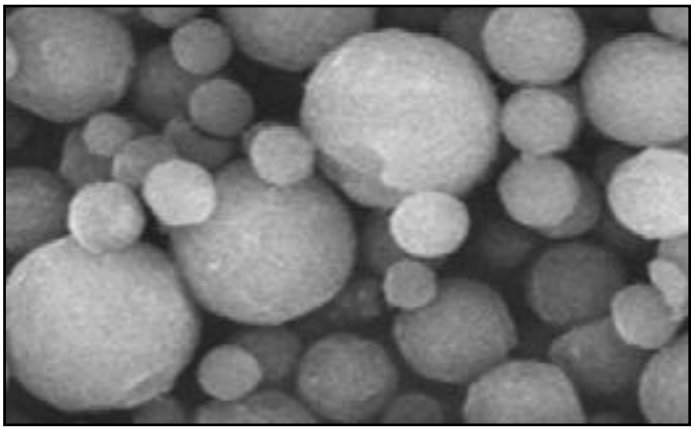

Fig1: Microspheres

Techniques For The Preparation Of Microspheres

The main techniques for the preparation of microspheres are

Phase separation coacervation

Coacervationterm was introduced by Bungerberg de Jong and Kruyt in 1929 to describe macromolecular aggregates or separation of liquid phases in aqueous solutions where, at least one of the phases contained a hydrocolloide. If one starts with a solution of a colloid in an appropriate solvent, then according to the nature of the colloid, various changes can bring about a reduction of the solubility of the colloid. Coacervation may be initiated in a number of different ways. Examples are changing the temperature, changing the pH or adding a second substance such as a concentrated aqueous ionic salt solution, other polymer or a non-solvent. As a result of this reduction a large part of the colloid can be separated out into a new phase. The original one phase system becomes two phases. One is rich and the other is poor in colloid concentration. The colloid-rich phase in a dispersed state appears as amorphous liquid droplets called coacervate droplets. Upon standing these coalesce into one clear homogenous colloid-rich liquid layer, known as the coacervate layer which can be deposited so as to produce the wall material of the resultant capsules. As the coacervate forms, it must wet the suspended core particles or core droplets and coalescence into a continuous coating for the process of microencapsulation to occur. The final step for microencapsulation is the hardening of the coacervate wall and the isolation of the microcapsules, usually the most difficult step in the total process.

Solvent evaporation technique

Is the most extensively used method of microencapsulation, first described by Ogawa in 1988. It is based on the evaporation of the internal phase of an emulsion by agitation. A buffered or plain aqueous solution of the drug (may contain a viscosity building or stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents like dichloromethane (or ethyl acetate or chloroform) with vigorous stirring to form the primary water in oil emulsion. This emulsion is then added to a large volume of water containing a surfactant like PVA or PVP to form the multiple emulsions (w/o/w). The double emulsion, so formed, is then subjected to stirring until most of the organic solvent evaporates, leaving solid microspheres in suspension in the continuous phase. The microspheres can be recovered by filtration or centrifugation, washed and dried.

Spray drying

Recently, spray drying techniques has gained the attention as a method for preparing sustained release formulation. Spray drying is a solvent evaporation process where the solvent in the droplets is removed very quickly due to heat energy provided in the spray dryer. Spray drying has been used routinely for the preparation of microspheres and other controlled-release formulations. The process involves three steps of operation: atomization during which the polymer and drug solution are atomized in the nozzle at a very high inlet temperature, drying which occurs within a chamber, and powder collection which is achieved by means of a cyclone separator. Smaller particle sizes, however, are difficult to attain due to the low efficiency for cyclone collectors to retain them. Compared to other methods of microsphere preparation, product yield from the spray-dryer is much higher, i.e., it is a one-step process and much less laborious. The high inlet temperature (>120 ºC) of the nozzle ensures instant drying of droplets and is safe for most drug molecules. Attempts have been made to investigate the potential use of the spray drying as an alternative to the conventional microencapsulation methods generally based on organic solvents. For microparticulate systems, the spray drying can be applied to both hydrophilic and hydrophobic drugs and polymers. It is a one stage continuous process and it can be adaptable in an industrial scale, which is superior to most of other fabrication procedures being only good for laboratory-scale operation. It is a simplified procedures and consuming low costs. To prepare drug loaded microparticle with a slow release character using the spray drying method, using of lipophilic matrices is a rational approach.

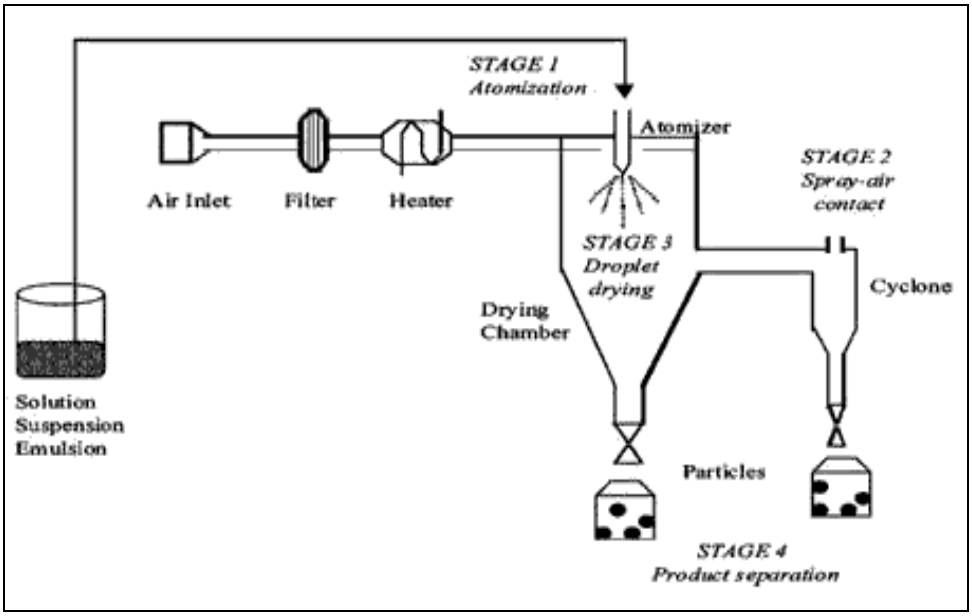

Fig2. Spray Drying Process.

Principle

There are three fundamental steps involved in spray drying.

1. Atomization of a liquid feed into fine droplets.
2. Mixing of these spray droplets with a heated gas stream, allowing the liquid to evaporate and leave dried solids.
3. Dried powder is separated from the gas stream and collected.

Atomization

The atomizing device, which forms the spray, is the ´heart´ of the spray drying process. Atomizer: Equipment that breaks bulk liquid into small droplets, forming a spray. Prime functions of atomization are:

1. A high surface to mass ratio resulting in high evaporation rates,
2. Production of particles of the desired shape, size and density. In order to produce top-quality products in the most economical manner, it is crucial to select the right atomizer.
3. Three basic types of atomizers are used commercially:

1. Rotary atomizer (atomization by centrifugal energy)
2. Pressure nozzle (atomization by pressure energy)
3. Two-fluid nozzle (atomization by kinetic energy)

Mixing and drying

Once the liquid is atomized it must be brought into intimate contact with the heated gas for evaporation to take place equally from the surface of all droplets within the drying chamber. The heated gas is introduced into the chamber by an air disperser, which ensures that the gas flows equally to all parts of the chamber.

Air Disperser

The air disperser uses perforated plates or vaned channels through which the gas is directed, creating a pressure drop and, thereby, equalizing the flow in all directions.

The drying chamber

The largest and most obvious part of a spray-drying system is the drying chamber. This vessel can be taller and slander or have large diameter with a short cylinder height. Selecting these dimensions is based on two process criteria that must be met. First, the vessel must be of adequate volume to provide enough contact time between the atomized cloud and the heated glass.

Powder separation

In almost every case, spray-drying chambers have cone bottoms to facilitate the collection of the dried powder. When the coarse powder is to be collected, they are usually discharged directly from the bottom of the cone through a suitable airlock, such as a rotary valve. The gas stream, now cool and containing all the evaporate moisture, is drawn from the center of the cone above the cone bottom and discharge through a side outlet. In effect, the chamber bottom is acting as a cyclone separator. Because of the relatively low efficiently of collection, some fines are always carried with the gas stream. This must be separated in high-efficiency cyclones, followed by a wet scrubber or in a fabric filter (bag collector). Fines are collected in the dry state (bag collector) are often added to the larger powder stream or recycled.

Parameters to be controlled

The pharmaceutical spray-dried products have important properties like

-Uniform Particle size,

-Nearly spherical regular particle shape,

-Excellent Flowability,

-Improved Compressibility,

-Low Bulk Density,

-Better Solubility,

-Reduced Moisture Content,

-Increased Thermal stability, and suitability for further applications.

Such product characteristics majorly depend on the physical properties of feed, equipment components and processing parameters. By modifying the spray drying process, it is possible to alter and control the mentioned properties of spray-dried powders. It is certainly very useful for the development of drug delivery systems.

Advantages of spray drying

1. Able to operate in applications that range from aseptic pharmaceutical processing to ceramic powder production.
2. It can be designed to virtually any capacity required. (Feed rates range from a few pounds per hour to over 100 tons per hour).
3. The actual spray drying process is very rapid, with the major portion of evaporation taking place in less than a few seconds.

4. Adaptable to fully automated control system that allows continuous monitoring and recording of very large number of process variables simultaneously.
5. Wide ranges of spray dryer designs are available to meet various product specifications.
6. It has few moving parts and careful selection of various components can result in a system having no moving parts in direct contact with the product, thereby reducing corrosion problems.
7. It can be used with both heat-resistant and heat sensitive products.
8. As long as they are can be pumped, the feedstock can be in solution, slurry, paste, gel, suspension or melt form.
9. Offers high precision control over Particle size, Bulk density, Degree of crystallinity, organic volatile impurities and residual solvents.
10. Powder quality remains constant during the entire run of the dryer. Nearly spherical particles can be produced, uniform in size and frequently hollow, thus reducing the bulk density of the product.

Losartan Potassium

Losartan is the first of a class of antihypertensive agents called angiotensin II receptor blockers (ARBs). Losartan and its longer acting active metabolite, E-3174, are specific and selective type-1 angiotensin II receptor (AT1) antagonists which block the blood pressure increasing effects of angiotensin II via the renin-angiotensin-aldosterone system (RAAS). Losartan PotassiumHalf-life is 2.1± 0.70 hrs, well absorbed from GIT, the systemic bioavailability of Losartan is approximately 33%.

MATERIAL AND METHODOLOGY

Materials

Losartan potassium was received a generous gift sample from Alkem lab ltd, Mumbai. Eudragit RS100 were procured from Evonik Degussa India Pvt.Ltd, Mumbai. Ethyl cellulose were procured from LobaChemie, Mumbai. All other excipients were procured from Lobachemie, Mumbai.

Methodology

Preparation of microspheres

Losartan Potassium microspheres were prepared by spray drying technique as described elsewhere. Briefly, different amount of Eudragit RS100 and Ethyl cellulose was dissolved in 100 mL of mixture of dichloromethane and ethanol in the ratio 1:1 by using a magnetic stirrer

for all batches that are shown in **Table no.1** To this the required proportion of ethyl cellulose was added and continued stirring until a uniform dispersion was ensured. The proportions of Eudragit RS100: ethyl cellulose, were varied. The required quantity of Losartan Potassium was kept constant and was dispersed in the polymer mixture. The polymeric solution was allowed to flow through the feed pipe at 1 mL/min. flow rate. The inlet and outlet temperatures were set as shown in **Table no.2**

Table 1 :Formulations of Losartan Potassium Microspheres.

Drug	Drug:Polymer (Ratio)	Batch no.	Polymers(Ratio)	Solvents Used(Ratio)
		C1A	Eudragit-RS100:Ethyl Cellulose (1:1)	
Losartan Potassium	1:4	C1B	Eudragit-RS100: Ethyl Cellulose (2:1)	Ethanol:Dichloromethane (1:1)
		C1C	Eudragit-RS100: Ethyl Cellulose (1:2)	
Losartan Potassium	1:5	C2	Eudragit-RS100: Ethyl Cellulose (1:1)	Ethanol:Dichloromethane (1:1)
Losartan Potassium	1:6	C3	Eudragit-RS100: Ethyl Cellulose (1:1)	Ethanol:Dichloromethane (1:1)
Losartan Potassium	1:7	C4	Eudragit-RS100: Ethyl Cellulose (1:1)	Ethanol:Dichloromethane (1:1)
Losartan Potassium	1:8	C5	Eudragit-RS100: Ethyl Cellulose (1:1)	Ethanol:Dichloromethane (1:1)

Table 2: Spray Drying Conditions for Microspheres.

Batch No.	Inlet temperature (^{0} c)	Outlet Temperature (^{0} c)	Feed rate(mL/min)	AspiratoreFlow (Nm3/hr)
C1A	78	60	1	40
C1B	78	60	1	40
C1C	78	60	1	40
C2	78	60	1	40
C3	78	60	1	40
C4	78	60	1	40
C5	78	60	1	40

RESULT AND CONCLUTION

Evaluation Parameters Of Losartan Potassium Microspheres

Table no.3: Evaluation parameters of Losartan Potassium microspheres

Batch No.	% yield	% Drug Loading	Entrapment efficiency
C1A	48.77%	6.2%	31%
C1B	47.14%	6.4%	32%
C1C	46%	6.0%	30%
C2	46 %	6.6%	40%
C3	44.51%	6.3%	44%
C4	44%	5.8%	47%
C5	42%	6.4%	58%

Table no.4: Evaluation parameters of Losartan Potassium microsphere

Batch code.	Bulk density(g/cm3)	Tapped density(g/cm3)	Carr's index	Hausner ratio	Angle of repose
C5	0.405	0.461	12.14	1.138	26.18

Table 5 : In Vitro % Cumulative Drug Release of Losartan Potassium microsphere.

Time(Hr)	Drug Release (%)						
	C1A	C1B	C1C	C2	C3	C4	C5
1	33.61	31.45	27.94	26.89	23.74	21.57	18.55
2	46.20	42.01	44.32	32.56	33.69	35.59	22.60
3	63.54	58.46	62.66	45.12	40.53	40.78	26.12
4	85.20	82.20	88.87	60.78	51.41	51.20	31.47
5	97.20	102	100	70.47	60.98	60.13	35.65
6				90.65	64.74	70.68	40.74
7				104	85.87	78.10	49.85
8					94.34	84.62	60.98
9					98.52	90.25	70.91
10						95.21	78.19
11						103	81.14
12							85.71
13							94.25
14							98.68

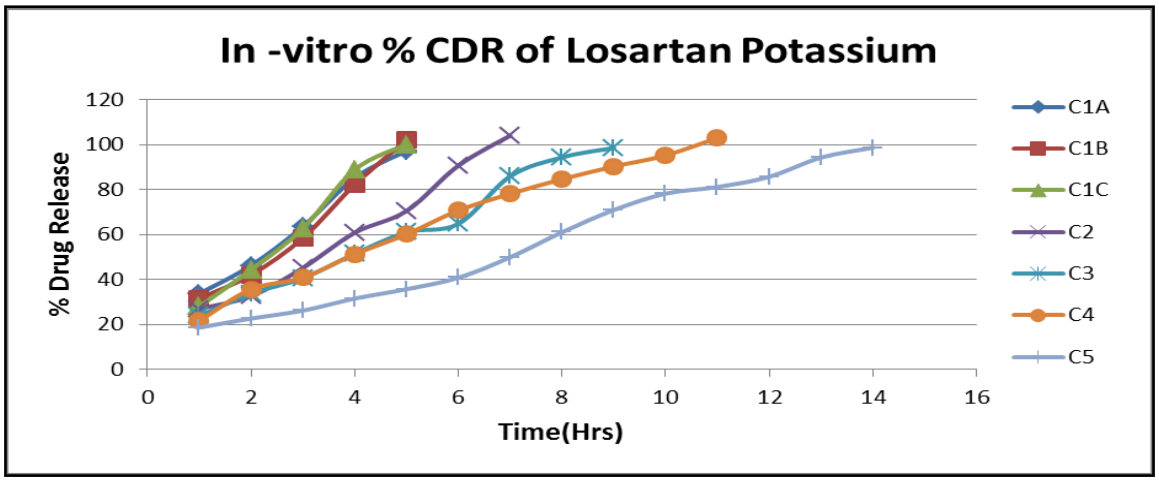

Figure no.3: In- Vitro % CDR of Losartan Potassium microspheres

From result it was found that as the concentration of Eudragit RS100 and ethyl cellulose with Drug, increases up to optimum ratio (8:1), microspheres showed good yield, particle size, entrapment efficiency and drug release. The drug entrapment efficiency of different batches of microspheres of Eudragit RS100 and Ethyl Cellulose was found in the range of 31.00-58.00%, microspheres showed good entrapment efficiency than other formulations.

Percentage drug loading of all formulations were in the range of 5.8-6.6%. Percentage of drug loading was obtained in C5 formulation (6.4%). Microspheres of C5 formulations showed particle size in the range of 90-130µm. Optimum size of microspheres was obtained for C5 formulation. Tapped density for C5 formulations was found to be 0.461gm/cm^3 and Bulk densities were 0.405gm/cm^3. *In-Vitro* drug release study of Eudragit RS100 and ethyl cellulose ratio with Drug.(8:1) for C5 showed 98.68% drug release upto 14 hour.

Table no.6:In vitro drug release study of Losartan Potassium microspheres formulation C5 in triplicate

	% Drug release													
Time	1	2	3	4	5	6	7	8	9	10	11	12	13	14
C5a	18.6	22.60	26.1	31.5	35.7	40.7	49.9	61	70.9	78.2	81.1	85.7	94.3	98.70
C5b	16.9	21.48	27.08	33.00	36.20	40.87	51.37	60.89	70.04	79.19	83.43	86.11	93.71	99.37
C5c	19.19	21.18	29.13	34.18	37.09	41.99	52.74	62.27	72.38	80.07	84.01	87.29	94.12	100.15
Avg.	18.23	21.75	27.43	32.89	36.60	41.19	51.33	61.38	71.10	79.15	82.84	86.36	94.04	99.40
SD	1.19	0.75	1.55	1.34	0.70	0.70	1.42	0.77	1.18	0.94	1.54	0.83	0.30	0.73

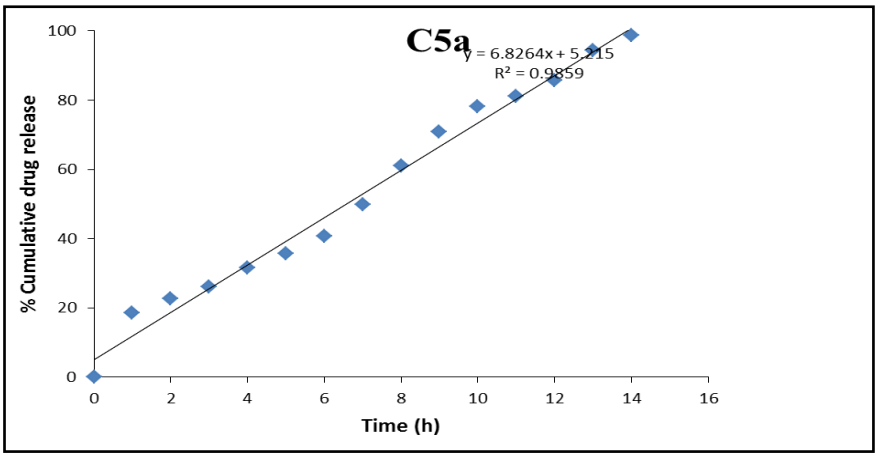

Fig.no.4: C5a

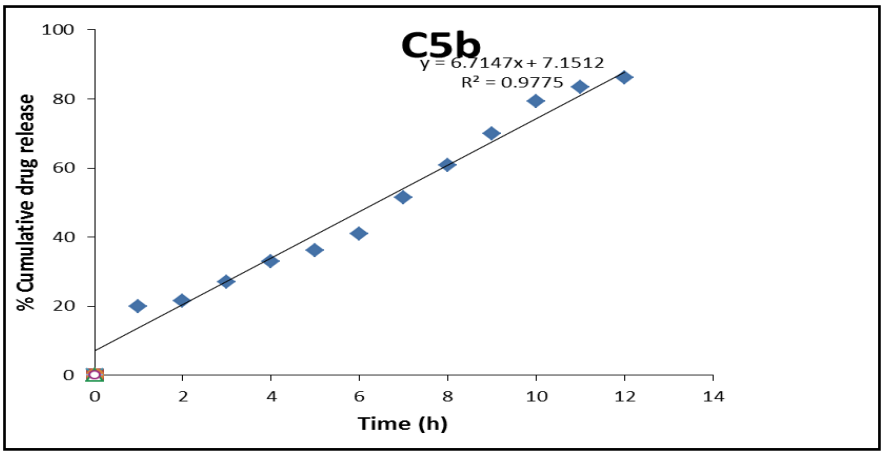

Fig.no.5: C5b

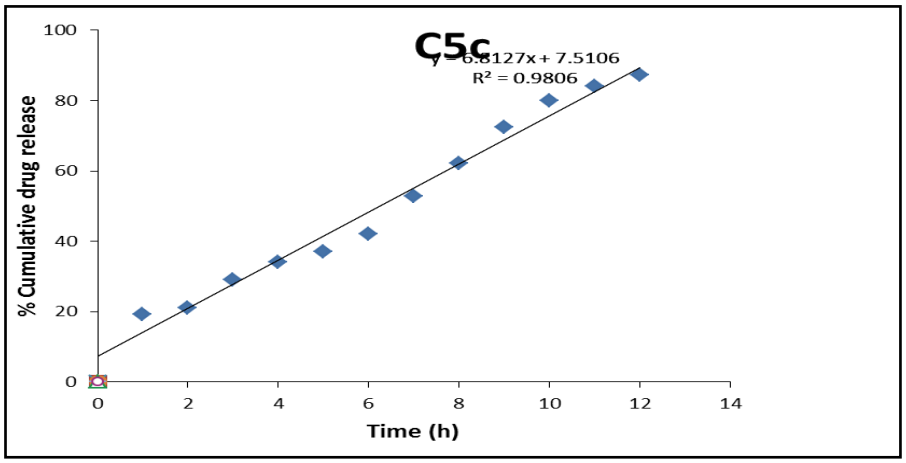

Fig.no.6: C5c

PARTICLE SIZE ANALYSIS

Scanning Electron Microscopy of Losartan Potassium microspheres showed spherical shape with no visible major surface irregularity. Few wrinkles were appeared as shown in **Fig,no.7,8.**

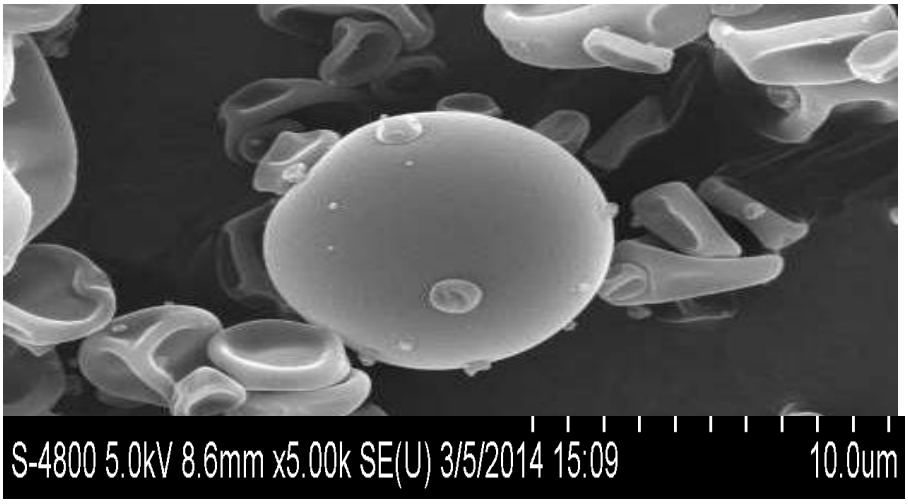

Fig.7 Scanning Electron Microscopy of Losartan Potassium microspheres

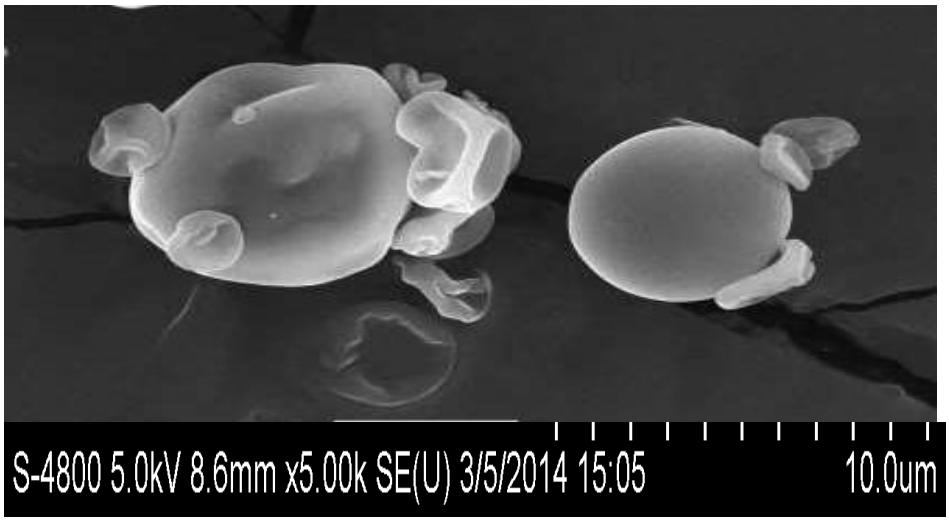

Fig.8 Scanning Electron Microscopy of Losartan Potassium microspheres

Tableno.7: Release kinetics study of Losartan Potassium microspheres of C5 formulation.

Code	Zero Order	First Order	Higuchi	KorsmeyerPeppas	Hixson crowell
	R^2	R^2	R^2	R^2	R^2
C5	0.9773	0.7859	0.8284	0.969	0.8736

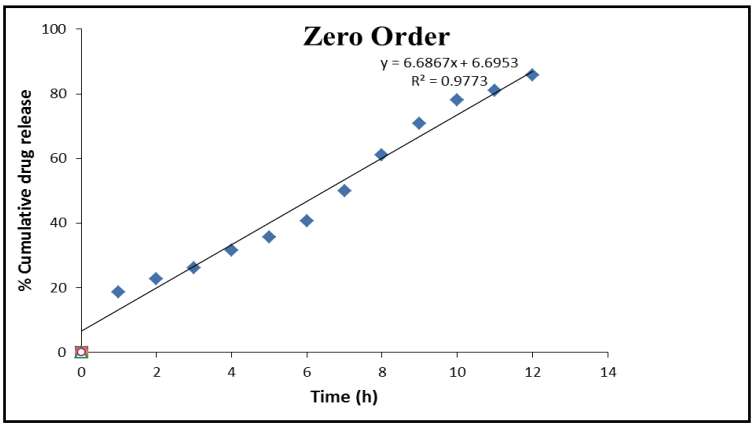

Fig9 : Zero order release study of C5 batc

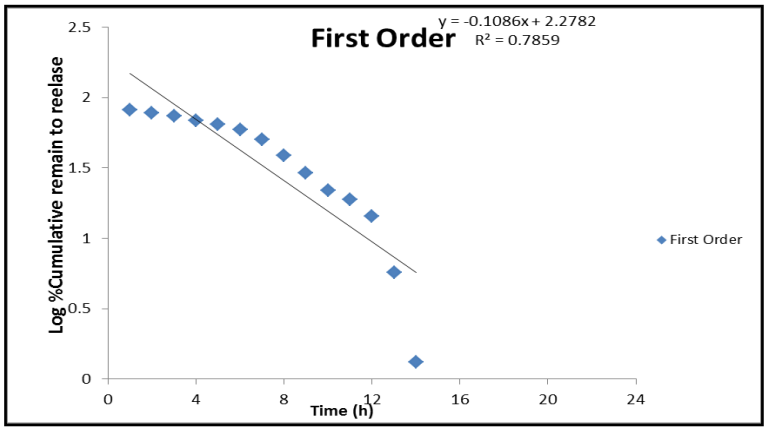

Fig10 : First order release study of C5 batch.

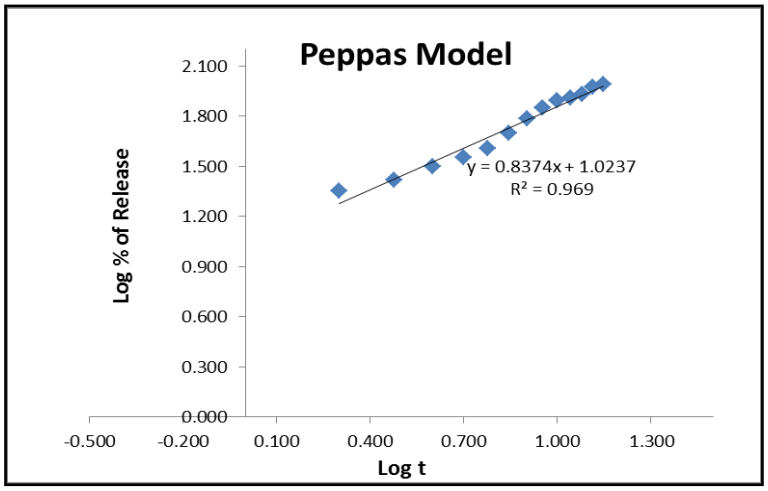

Fig11 :KorsemeyerPeppas model

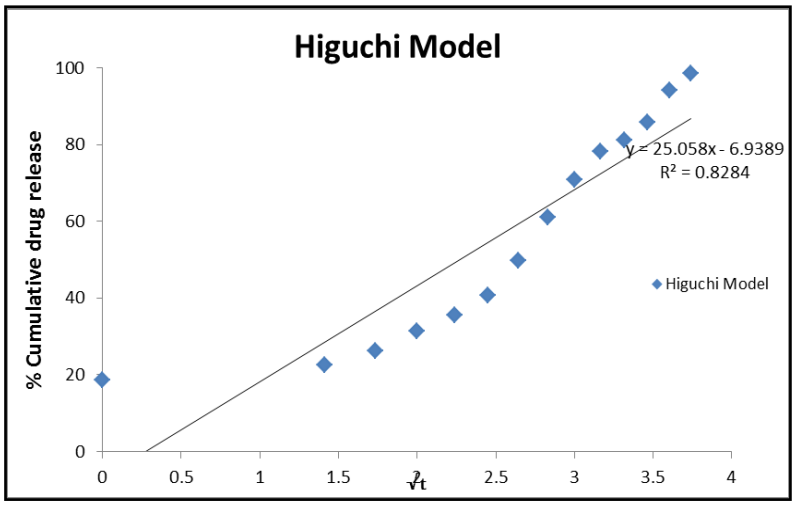

Fig12: Higuchi model study of C5 batch

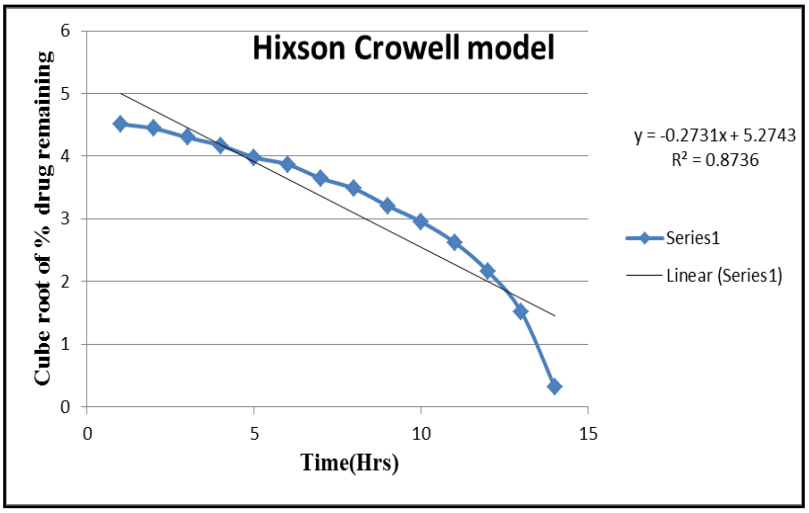

Fig13 :Hixson Crowell model study of C5 batch.

Losartan Potassium microspheres showed Zero order drug release and followed KorsmeyerPeppas model.

DSC of Formulation

From DSC graph of formulation, the drug started to melt at 182 ^{0}C and end at 185.5^{0}C. The drug formulation showed sharp endothermic peak at 183^{0}C. The DSC of drug formulation is as shown in **Figure14 .**DSC of the Losartan Potassium was performed for the identification purpose; it is also helpful in stability study of dosage form.

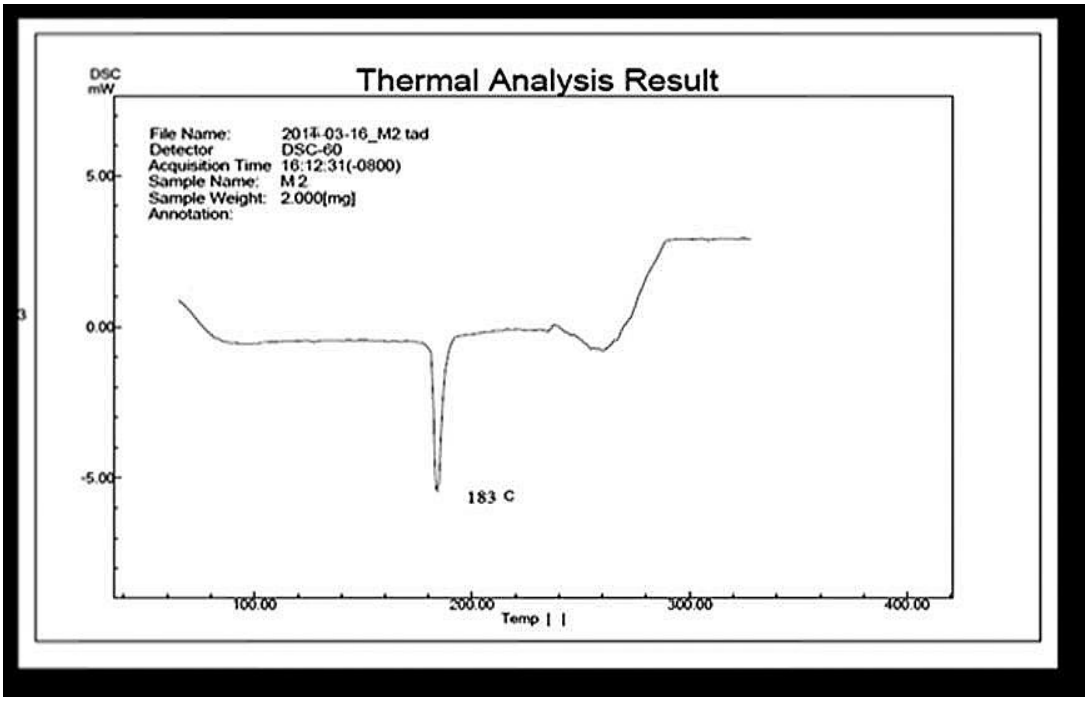

Figure 14 : DSC of Formulation

CONCLUSION

Sustained release microspheres of Losartan Potassium were successfully prepared using Eudragit RS100 and Ethyl Cellulose by spray drying technology.Microspheres were prepared at different concentration of Eudragit RS100 and Ethyl Cellulose with Drug. It was found that as the concentration of Eudragit RS100 and ethyl cellulose with Drug, increases up to optimum ratio (8:1), microspheres showed good yield, particle size, entrapment efficiency and drug release. The drug entrapment efficiency of different batches of microspheres of Eudragit RS100 and Ethyl Cellulose was found in the range of 31.00-58.00%, microspheres showed good entrapment efficiency than other formulations. Percentage drug loading of all formulations were in the range of 5.8-6.6%. Percentage of drug loading was obtained in C5 formulation (6.4%). Microspheres of C5 formulations showed particle size in the range of 90-130µm. Optimum size of microspheres was obtained for C5 formulation. Tapped density for C5 formulations was found to be 0.461gm/cm^3 and Bulk densities were 0.405gm/cm^3. *In-Vitro* drug release study of Eudragit RS100 and ethyl cellulose ratio with Drug.(8:1) for C5 showed 98.68% drug release upto 14 hour.formulation showed microspheres of Losartan Potassium were spherical and smooth with particle size of 90-130 µm. Microspheres of Losartan Potassium in formulation C5 showed drug release in slow and sustained manner over 14 hours. The *In-Vitro* release data was applied to various kinetic models. The correlation coefficient (r^2) for different kinetic studies was in the range of 0.7859-0.9773 for

microspheres of C5 formulation. Losartan Potassium microspheres showed Zero order drug release and followed KorsmeyerPeppas model.Present research work has successfully developed at different processing and formulation parameters for sustained release Losartan Potassium microsphere.

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