2. LITERATURE REVIEW

After thorough survey of literature there is no article related to the novel microencapsulation of losartan potassium in a controlled release pharmaceutical dosage form that has been reported in literature. The microencapsulation of drugs into solid non-biodegradable polymeric microspheres via solvent evaporation technique remain challenging especially with those having low molecular weight and high hydrophilicity nature. An ideal microencapsulating method is one that successfully encapsulates the standard drug and also modifies its release characteristics. Therefore, it was thought necessary to study the various microencapsulation techniques involving a potent hydrophilic compound and attempt could be done to successfully formulate and characterize the formulations products.

Reported reviews of literatures are as follows:

Freiberg S et al reviewed that the polymer microspheres can be employed to deliver medication in a rate-controlled and sometimes targeted manner. Medication is released from a microsphere by drug leaching from the polymer or by degradation of the polymer matrix. Since the rate of drug release is controlled by these two factors, it is important to understand the physical and chemical properties of the releasing medium. Author reviewed the methods used in the preparation of microspheres from monomers or from linear polymers and discusses the physio-chemical properties that affect the formation, structure, and morphology of the spheres. Topics including the effects of molecular weight, blended spheres, crystallinity, drug distribution,
porosity, and sphere size are discussed in relation to the characteristics of the release process.

Li M et al reviewed microencapsulation by solvent evaporation technique is widely used in pharmaceutical industries. It facilitates a controlled release of a drug, which has many clinical benefits. Water insoluble polymers are used as encapsulation matrix using this technique. Different kinds of drugs have been successfully encapsulation: for example hydrophobic drugs such as cisplatin, lidocaine, naltrexone and progesterone; and hydrophilic drugs such as insulin, proteins, peptide and vaccine. The choice of encapsulation materials and the testing of the release of drug have been intensively investigated. However process-engineering aspects of this technique remain poorly reported. To succeed in the controlled manufacturing of microspheres, it is important to investigate the latter. Author further reviews the current state of the art concerning this technique by focusing on the influence of the physical properties of materials and operating conditions on the microspheres obtained. Based on the existing results and authors’ reflection, it gives rise to reasoning and suggested choices of materials and process conditions.

Donnell O et al reviewed the microencapsulation process in which the removal of the hydrophobic polymer solvent is achieved by evaporation has been widely reported in recent years for the preparation of microspheres and microcapsules based on biodegradable polymers and copolymers of hydroxy acids. The properties of biodegradable microspheres of poly (lactic acid) (PLA) and poly (lactic co-glycolic acid) (PLGA) have been extensively investigated by the author. The encapsulation of highly water soluble compounds including proteins and peptides presents formidable challenges to
the researcher. The successful encapsulation of such entities requires high drug loading in the microspheres, prevention of protein degradation by the encapsulation method, and predictable release of the drug compound from the microspheres.

Freitas S et al reviewed the therapeutic benefit of microencapsulated drugs and vaccines brought forth the need to prepare such particles in larger quantities and in sufficient quality suitable for clinical trials and commercialization. Very commonly, microencapsulation processes are based on the principle of so-called solvent extraction/evaporation. While the author performed initial lab scale experiments in simple beaker/stirrer setups, clinical trials and market introduction require more sophisticated technologies, allowing for economic, robust, well-controllable and aseptic production of microspheres. In this article author reviews the current state of the art in solvent extraction/evaporation-based microencapsulation technologies.

Bodmeier R et al reported that Poly (DL-lactide) (PLA) microspheres containing quinidine or quinidine sulfate were prepared by the solvent evaporation technique. The successful entrapment of drug within the microspheres was associated with: (a) a fast rate of precipitation of the polymer from the organic solvent phase; (b) a low water solubility of the drug in the aqueous phase; and (c) a high concentration of the polymer in the organic phase. The author postulated that the rate of polymer precipitation was strongly affected by the rate of diffusion of the organic solvent into the aqueous phase. Organic solvents of low water solubility resulted in a slow polymer precipitation, causing the drug to partition completely into the
aqueous phase. Water-miscible organic solvents when added to the organic phase further enhanced the drug content in the microspheres.

Haznedar S et al investigated the influence of formulation factors (stirring speed, polymer: drug ratio, type of polymer, ratio of the combination of polymers) on particle size, encapsulation efficiency and in vitro release characteristics of the microspheres were investigated. The yields of preparation and the encapsulation efficiencies were high for all formulations the microspheres were obtained. Mean particle size changed by changing the polymer: drug ratio or the stirring speed of the system. Author proposed to prepare and evaluate Eudragit (RS and RL) microspheres containing acetazolamide. Microspheres were prepared by solvent evaporation method using acetone/liquid paraffin system. Although acetazolamide release rates from Eudragit RS microspheres were very slow and incomplete for all formulations, they were fast from Eudragit RL microspheres. When Eudragit RS was added to Eudragit RL microsphere formulations, release rates slowed down and achieved the release profile suitable for peroral administration.

Pe`reza M H et al reported the novel microencapsulation of both, lipophilic and hydrophilic drugs, in poly (e-caprolactone) (PCL) microparticles prepared either by the oil-in-water (o/w) or the water-in-oil-in-water (w/o/w) solvent evaporation method. Microparticles were characterized in terms of morphology, size, encapsulation efficiency and drug release. The physical state of the drugs and the polymer was determined by scanning electron microscopy (SEM), X-ray powder diffractometry, and differential scanning calorimetry (DSC). In vitro release studies revealed a controlled release of nifedipine and propranolol HCl from microparticles prepared by the o/w-
method; a burst release of propranolol HCl was observed from microparticles prepared by the w/o/w-method.

Kılıcarslan M et al in his study prepared the microspheres containing verapamil hydrochloride (VRP) with Eudragit RS 100 by solvent evaporation method. In the solvent evaporation method one of the parameters which affect to the formation and properties of the microsphere is the variations of drug/polymer ratios. The aim of author was to examine the effects of this parameter on the VRP loaded microspheres. To achieve this purpose, only drug/polymer ratio was altered while the other formulation parameters were kept constant and percentage yield value, incorporation efficiency, particle size and distribution of the microspheres were analyzed and micrographs of the microspheres were taken to determine the effects of the increase in the polymer amount of formulations. In vitro dissolution tests were done by using dissolution media with three different pH in sequence as half-change method with flow through cell and the effect of the variation in polymer ratio on drug dissolution was evaluated according to dissolution test results.

Mundargi RC et al in his study reports the preparation of starch-based tableted microspheres that are crosslinked with epichlorohydrin (EPI) using a modified water-in-oil (w/o) emulsification technique. Ampicillin (AMP), a broad spectrum antibiotic was encapsulated up to the extent of 70% into the microspheres. The microspheres were characterized by Fourier transform infrared spectroscopy (FT-IR) to confirm the crosslinking reaction and chemical stability of AMP. Differential scanning calorimetry (DSC) was studied on the placebo and drug loaded microspheres to confirm the polymorphism of AMP. Results of this study indicated a molecular level dispersion of AMP in
the developed microspheres. Scanning electron microscopy (SEM) confirmed the spherical nature and smooth surfaces of the microspheres produced. Mean particle size of the microspheres as measured by laser light scattering ranged between 96 and 158 µm. Diffusion coefficients (D) of water transport through the microspheres were determined using an empirical equation In-vitro release studies were performed in 1.2 and 7.4 pH media to simulate the gastric and intestinal conditions.

Aso Y et al reported changes in the physicochemical properties of poly(l-lactide) microspheres that occurred during storage were studied by X-ray powder diffraction, differential scanning calorimetry and scanning electron microscopy, in order to elucidate the factors that affect the stability of drug release characteristics. Progesterone-loaded microspheres with amorphous polymer matrices were stored at 50 and 30°C under desiccated and moist atmospheres. The author observed that the surface morphology did not change significantly during storage under any of the conditions studied. Storing the microspheres at a temperature above the glass transition temperature (T_g) of the polymer under moist conditions caused polymer matrix crystallization. The drug release rate of stored microspheres was faster than that of microspheres before storage, which indicates that matrix crystallization increased the drug release rate.

Vachon MG et al in their study prepared a series of homogeneous Eudragit® RS100 matrix microspheres containing molecularly dispersed acylated esterified homologues of salicylic acid, (acetylsalicylic acid, valeryl salicylic acid, or caprylsalicylic acid) in order to investigate the effect of encapsulation on solid-state orientation of the encapsulated molecule. Electrostatic
association of the drug with the charged quaternary residues in the polymer may be responsible for the previously observed stability of acetylsalicylic acid (ASA) in aqueous swollen ASA-loaded Eudragit® RS100 microspheres. Author carried out evaluation of the $^{13}$C nuclear magnetic resonance spectra for evidence of structural association of the incorporated probe molecules indicated that alteration of the microenvironment of the incorporated solutes had occurred.

**McIntyre M et al** in his article reviewed Losartan potassium, an angiotensin II receptor antagonist, is the first of a new class of agents to be introduced for the treatment of hypertension. In his review, author described the clinical pharmacology of losartan, including its pharmacokinetics in healthy, male volunteers and special patient groups, such as the elderly, patients with liver disease and patients with renal impairment. Author also reviews its pharmacodynamics, including safety and tolerability; specificity of action; and the effect of salt depletion. Author then reviewed the studies examining clinical efficacy and safety in hypertension.

**Eudragit Data Sheets**, Industrial Products Division, EVONIK Röhm Pharma GmbH, Weiterstadt, Germany gives property specifications and test methods for EUDRAGIT® RL 100 and EUDRAGIT® RL PO, EUDRAGIT® RS 100 and EUDRAGIT® RS PO.

**Kadian SS** in his review focuses on recent literature regarding use of Eudragit polymer in different drug delivery systems with special attention to used in its fabrication along with their physiochemical properties.
2.1 DRUG PROFILE

LOSARTAN POTASSIUM

Chemical Structure

![Chemical Structure Image]

IUPAC Name: 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl) benzyl] imidazole-5-methanol monopotassium salt.

Molecular weight: 461.01 g/mol

Molecular formula: C_{22}H_{22}ClKN_{6}O

Colour: White to off-white

Odor: Odorless

Appearance: Crystalline Solid

Solubility:
- Freely soluble in water.
  - Solubility in Water: 10 mg/ml* at 25°
  - Other Solubility Notes: *PBS pH 7.2, soluble in EtOH, DMSO & DMF.
- Soluble in alcohols.
- Slightly soluble in common organic solvents, such as acetonitrile and methyl ethyl ketone.
- Sparingly soluble in methanol.
- Practically insoluble in chloroform.

**Melting point** : 243.5-244.5 °C

**Pka** : 4.9

**Description** : Losartan potassium is the prototype of this new class of cardiovascular drug, and it offers the advantages of increased selectivity, specificity, and maintained blockade of the circulating and tissue renin-angiotensin system at the AT1 receptor level without the adverse reactions associated with ACE inhibitors. Losartan has now been approved for use in the treatment of hypertension in Scandinavia, the UK, several European countries, and the USA.

**Category** : A non-peptide molecule and an angiotensin II receptor (type AT1) antagonist.
Medicinal chemistry and mechanism of action: Losartan and other AT₁ receptor antagonists being developed are phenyl tetrazole substituted imidazoles. Losartan potassium is a low molecular weight, non-peptide, hence orally active. It binds with high affinity and specificity to the AT₁ receptor with a slow dissociation rate, and is 30,000-fold more selective for the AT₁ receptor. The renin-angiotensin system is a bioenzymatic cascade in which renin acts on angiotensin to form Angiotensin I which is then converted by ACE to Angiotensin II. Angiotensin II is the end-product of the process and all known effects of the renin-angiotensin system can be accounted for by the multiple actions. Therefore, what is physiologically important is the level of Angiotensin II, not the activity of the regulating enzymes. Angiotensin II interacts with at least two known membrane receptors, type 1 and type 2 (AT₁ and AT₂). Other possible angiotensin Receptors have been proposed, particularly in non-primate tissues and cell lines. The well-known physiological effects of angiotensin such as vasoconstriction, aldosterone stimulation, and salt and water homoeostasis seem to be mediated via stimulation of the G-protein-coupled AT₁ receptor.

Losartan and its principal active metabolite block the vasoconstrictor and aldosterone-secreting effects of Angiotensin II by selectively blocking the binding of Angiotensin II to the AT₁ receptor found in many tissues.
(e.g., vascular smooth muscle, adrenal gland). In vitro binding studies indicate that losartan is a reversible, competitive inhibitor of the AT$_1$ receptor.

Dose

**Dose**: Oral

**Adult**: Losartan can be administered once or twice daily with total daily doses ranging from 25 mg to 100 mg.

**Available Dosage forms**

**Dosage**: COZAAR 25 mg, 50 mg and 100 mg tablets contain potassium in the following amounts: 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq) and 8.48 mg (0.216 mEq), respectively. COZAAR 25 mg, COZAAR 50 mg, and COZAAR 100 mg may also contain carnauba wax.

**Bioavailability**: 33%
**Half-life**  
1.5 to 2.5 hr

**Metabolism**  
Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows losartan treatment. The terminal half-life of losartan is about 2 hours and of the metabolite is about 6-9 hours. The pharmacokinetics of losartan and its active metabolite are linear with oral losartan doses up to 200 mg and do not change over time. Neither losartan nor its metabolite accumulates in plasma upon repeated once-daily dosing.

**Excretion**  
Renal excretion.

When losartan is administered orally, about 4% of the dose is excreted unchanged in the urine and about 6% is excreted in urine as active metabolite.

**Plasma protein binding**  
Both losartan and its active metabolite are highly bound to plasma proteins, primarily albumin, with plasma free fractions of 1.3% and 0.2%, respectively. Plasma protein binding is constant over the concentration range achieved with recommended doses.
Volume of Distribution: The volume of distribution of losartan is about 34 liters and of the active metabolite is about 12 liters. Total plasma clearance of losartan and the active metabolite is about 600 mL/min and 50 mL/min, respectively, with renal clearance of about 75 mL/min and 25 mL/min, respectively.

Adverse Effect: The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, edema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis, diarrhea, dyspepsia, myalgia, insomnia, cough disorder.

Drug Interaction: Co-administration of losartan and phenobarbital led to a reduction of about 20% in the AUC of losartan and that of its active metabolite. A somewhat greater interaction (approximately 40% reduction in the AUC of active metabolite and approximately 30% reduction in the AUC of losartan) has been reported with rifampin. Fluconazole, an inhibitor of cytochrome P450 2C9, decreased the AUC of the active metabolite by approximately 40%, but increased the AUC of losartan by approximately 70%.
Reported analytical methods for quantification of Losartan potassium in In- vitro and in biological fluids are available. Most of the biological methods were developed from plasma samples. Analytical tools used in the quantification of Losartan potassium included UV spectroscopic determination, High performance liquid chromatography with UV detection, etc.

**HPLC condition for Losartan potassium determination**

**Column**: Symmetry C8 columns (150×3.9 mm I.D., 5 µm particle size) purchased from Waters Corporation (Milford, MA, USA).

**Mobile phase**: Phosphate buffer solution of KH₂PO₄ and Na₂HPO₄ (pH 7.0, 0.02 M). This buffer solution was then mixed with acetonitrile in ratios of 85:15 (v/v) and 93:7 (v/v) buffer–acetonitrile to yield Mobile Phase A. Mobile Phase B is 100% acetonitrile for both methods. Mobile phases for pH robustness studies involved pH adjustment of the 0.02M Phosphate buffer with NaOH or H₃PO₄ prior to mixing with
acetonitrile

Detector : UV/VIS detector
Flow rate : 1.0 mL/min
Injection volume : 10 mcL

$\lambda_{\text{max}}$ : 248.7 nm

2.2 POLYMER PROFILE

EUDRAGIT® RL 100 / EUDRAGIT® RS 100

2.2.1 Commercial Form
Solid substances EUDRAGIT® RL 100 (Type A) and EUDRAGIT® RS 100 (Type B) Solutions of EUDRAGIT® RL 100 and EUDRAGIT® RS 100, respectively, with 12.5 % (w/w) dry substance in a mixture of 60% (w/w) Isopropyl Alcohol Ph. Eur. / USP and 40 % (w/w) Acetone Ph. Eur. / NF.

2.2.2 Structure

The average molecular weight is approx. 150,000.

2.2.3 Characters

2.2.3.1 Description

EUDRAGIT® RL 100 and EUDRAGIT® RS 100: colorless, clear to cloudy granules with a faint amine-like odor.

EUDRAGIT® RL PO and EUDRAGIT® RS PO: white powders with a faint amine-like odor.
2.2.3.2 Solubility

1 g of the substances dissolves in 7 g aqueous methanol, ethanol and isopropyl alcohol (containing approx. 3 % water), as well as in acetone, ethyl acetate and methylene chloride to give clear to cloudy solutions. The substances are practically insoluble in petroleum ether, 1 N sodium hydroxide and water.

2.2.4 Tests

2.2.4.1 Test solution

A 12.5 % solution of the dry substance is used for the test solution: a quantity of the substance of corresponding to 12.5 g dry substance is dissolved in a mixture of 60 % (w/w) isopropyl alcohol and 40 % (w/w) acetone.

2.2.4.2 Particle size

EUDRAGIT® RL PO / RS PO: at least 90 % < 0.315 mm

Particle size is determined according to Ph. Eur. 2.1.4 or USP <811>.

2.2.4.3 Film formation

When the test solution is poured onto a glass plate, a clear film forms upon evaporation of the solvents.

2.2.4.4 Dry substance / Residue on evaporation

Not less than 97.0 %.

1 g of the substances is dried in an oven for 5 hrs in vacuum at 80 °C.

2.2.4.5 Loss on drying

Max. 3.0 % according to "Dry substance / Residue on evaporation."

2.2.4.6 Assay

EUDRAGIT® RL 100 / RL PO: 8.85 - 11.96 % ammonia methacrylate units on dry substance (DS).
Alkali value: 23.9 - 32.3 mg KOH per g DS

EUDRAGIT® RS 100 / EUDRAGIT® RS PO: 4.48 - 6.77 % ammonia methacrylate units on DS

Alkali value: 12.1 - 18.3 mg KOH per g DS

The alkali value (AV) is defined similarly to the acid value. It states how many mg KOH are equivalent to the basic groups contained in 1 g dry substance (DS).

The assay is performed according to Ph. Eur. 2.2.20 "Potentiometric titration" or USP <541>. 1 g EUDRAGIT® RL 100 / RL PO or 2 g EUDRAGIT® RS 100 / RS PO are dissolved in 96 ml glacial acetic acid and 4 ml water. 0.1 N perchloric acid is used as the titrant after adding 5 ml mercury (II) acetate solution (5 % solution in glacial acetic acid).

Ammonia methacrylate units (%) on DS = AV (mg KOH / g DS) = ammonia methacrylate units (%). 2.701

2.2.4.7 Viscosity / Apparent viscosity

Maximum 15 mPa

The viscosity of the Test solution is determined by means of a Brookfield viscometer (UL adapter / 30 rpm / 20 °C).

2.2.4.8 Refractive index

ND 20: 1.380 - 1.385

2.2.4.9 Relative density

D 20/ 20: 0.816 - 0.836

The relative density of the Test solution is determined according to Ph. Eur.
2.2.5 Storage

Store at controlled room temperature (USP, General Notices). Protect against moisture. Any storage between 8°C and 25°C fulfils this requirement. EUDRAGIT® RL 100 and EUDRAGIT® RS 100 tend to form lumps at warm temperatures. This has no influence on the quality. The lumps are easily broken up again.