



Design and Evaluation of Losartan Potassium Sustained and Hydrochlorothiazide Immediate Release Formulation

Bimal Debbarma* and Chandra Kishore Tyagi

School of Pharmacy, Sri Satya Sai University of Technology and Medical Sciences, Sehore - 466002, Madhya Pradesh, India.

Received: 20 Jul 2022/ Accepted: 22 Aug 2022 / Published online: 1 Oct 2022

*Corresponding Author Email: bimald32@gmail.com

Abstract

Regioselective dual components technology is utilized to develop sustain release and immediate release formulation for a single drug or combination of drugs. The main objective of the present research work was to prepare dual components of hydrochlorothiazide and losartan potassium in separate layers for desired release patterns and thus maximize the efficacy of both drugs in combination for the effective treatment of hypertension. In the dual component capsule, an immediate release layer of hydrochlorothiazide was prepared by dry granulation method using crospovidone as super disintegrants, and sustain release layer of losartan potassium microbeads was prepared using sodium alginate adopting ionotropic gelation method using calcium chloride and blend of chitosan employing ionic and covalent cross-linking method. Preformulation studies were performed before compression. The microbeads were evaluated for drug entrapment efficiency, swelling index, and in-vitro drug release studies. The drug excipients compatibility studies were carried out using ATR and DSC. Spectra revealed that there was no interaction found between drugs and excipients used in the formulations. All the pre-compression studies revealed that the results were found to be within the official limits. In-vitro release studies reveal that the hydrochlorothiazide immediate release layer was found to be 98.41% within 120 minutes and the losartan potassium sustained release layer was 99.14% at the end of 12 hrs. Release kinetics showed good linearity by best fitting into the Higuchi model and stability studies showed no changes after exposing to accelerated conditions for 1 month for physical characteristics and in-vitro drug release studies. From the above study, it can be concluded that the prepared region-selective dual component capsule achieved the objective of the research work in treating hypertension.

Keywords

Hydrochlorothiazide, Losartan potassium, Sodium alginate Crospovidone, Ionotropic gelation, Dry granulation, Simultaneous Estimation, UV spectrophotometry.

INTRODUCTION:

Hypertension is one of the most common diseases affecting humans throughout the world. It also

known as high blood pressure or arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is persistently

elevated. Blood pressure is expressed by two measurements, the systolic and diastolic pressures; those are the maximum and minimum pressures respectively in the arterial system. The systolic pressure occurs when the left ventricle is most contracted; the diastolic pressure occurs when the left ventricle is most relaxed before the next contraction. The definition of abnormally high blood

pressure is extremely difficult and arbitrary. A level for high BP must be agreed upon in clinical practice for screening patients and for instituting diagnostic evaluation and initiating therapy, because the risk to an individual patient may correlate with the severity of hypertension. Thus, there is a need to develop effective strategies to improve management [1,2].

Table 1: Classification of Hypertension

Classification	Systolic pressure	Diastolic pressure
	mmHg	mmHg
Normal	90–119	60–79
Pre hypertension (High Normal)	120–139	80–89
Stage 1 Mild hypertension	140–159	90–99
Stage 2 Moderate hypertension	160 -- 179	100 -- 109
Stage 3 Severe hypertension	180 -- 209	110 -- 119
Stage 4 Very Severe hypertension	≥ 210	≥ 120
Malignant hypertension	≥200	≥ 140

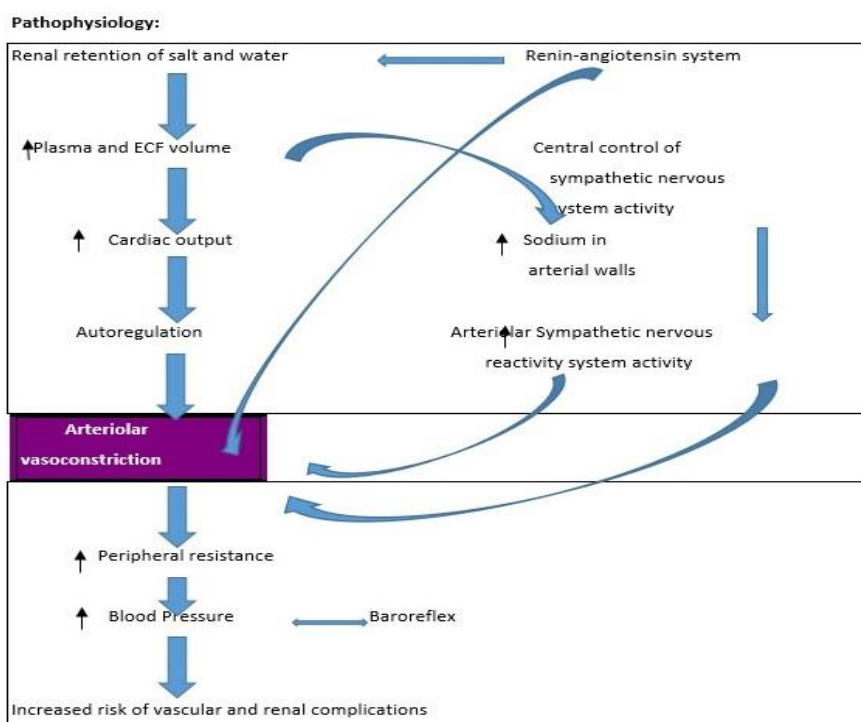


Figure 1: Pathophysiology of Hypertension

Signs and Symptoms of Hypertension:

Severe headache, fatigue or confusion, vision problems, chest pain, difficulty breathing, irregular heartbeat, blood in the urine, and pounding in your chest, neck, or ears.

Hypertension risk factors:

Although the exact cause of hypertension (high blood pressure) is unknown, some several factors and conditions that may increase the risk. These are overweight and obesity, smoking, little or no exercise, too much salt in the diet, drinking too much alcohol, stress, ethnic background (black person of African or Caribbean descent or South Asian descent), and history of high blood pressure in the family.

Management of Hypertension:**Monotherapy:**

Mono drug therapy in hypertension control has been the traditional route for many years. Yet the use of only one drug to control arterial pressure is successful in 50 to 60 percent of all patients. One reason for the low success rate is the ritual increase in the dose of the sole drug prescribed, leading to prolonged treatment with high doses and, thus, an increase in side effects. Patients, in turn, become non-compliant. Another reason for the failure to control blood pressure is that one drug addresses only one physiological pathway of many that lead to hypertension. Multiple mechanisms are involved in the pathogenesis of hypertension. Monotherapy in general will only interfere with one of these mechanisms, thereby potentially allowing the other mechanisms to compensate. Therefore, given that hypertension is a multi-factorial condition, combination therapy makes more therapeutic sense [3].

Combination Therapy:

By taking two drugs from appropriate classes of agents, the primary actions of drugs acting through different mechanisms are put into play, while they oppose the homeostatic compensations that limit the fall in blood pressure. Combination therapy may have an advantage in that it synergistically interferes with pathogenetic mechanisms. Thus, lower doses can be used and the problem of dose-dependent side effects is minimized. Another rationale for combination therapy is that sustained hypertension often leads to target organ disease in the heart, the kidneys, and the brain. Certain antihypertensive drugs, such as angiotensin-converting enzyme inhibitors (ACE inhibitors), affect target organ disease independent of their antihypertensive efficacy. Antihypertensive efficacy of a single drug is often lowered due to the potential stimulation of compensatory mechanisms serving to restore blood

pressure to its preset levels. Combination therapy allows the use of lower doses of each antihypertensive agent; therefore, compensatory stimulation may be diminished, and, conceivably, the second component of the combination may counteract this stimulation.

Drugs used for the marketed product:

Diuretics ("water pills") increased the amount of sodium and water excreted into the urine by the kidneys. It is thought that they lower blood pressure mainly by reducing the volume of fluid in the blood vessels [3,4].

SIMULTANEOUS ESTIMATION

Combinations of two or more drugs in the pharmaceutical dosage forms are very much useful in multiple therapies. Analytical monitoring of pharmaceutical products or specific ingredients within the product is necessary to ensure its safety and efficacy throughout the shelf life, including storage, distribution, and use [5].

The oral route of drug administration is perhaps the most appealing route for the delivery of drugs because of its patient acceptance, ease of administration, accurate dosing, cost-effective manufacturing methods, and stability when compared to other dosage forms. Combination therapy has various advantages over monotherapy. A low dose combination of two different agents reduced the dose-related risk; minimizes the clinical and metabolic effects that occur with a maximal dosage of individual components.

SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Oral drug delivery is the most preferred and convenient route as it provides maximum active surface area among all drug delivery systems for administration of various drugs because of certain advantages such as unit dosage form, low cost, and simple packaging. The aim of designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at the site of action, reducing the dose required, and providing uniform drug delivery. A sustained release system is a type of modified drug delivery system that can be used as an alternative to a conventional drug delivery system. These systems sustain the release of drugs and maintain the plasma drug concentration in the therapeutic window except for any fluctuation and increase the therapeutic efficacy of the drug. A sustained release system has benefits like patient compliance, avoiding multiple dosing, increasing plasma drug concentration, avoiding side effects, and overcoming the problems associated with the conventional system [6].

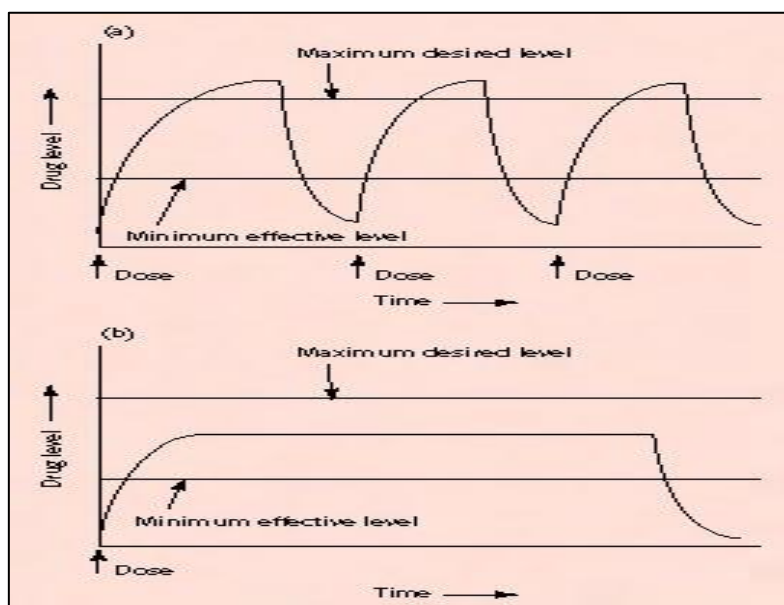


Figure 2: Drug levels in the blood with (a) Conventional drug delivery systems. b) Controlled drug delivery dose systems.

The basic goal of therapy is to achieve a steady state blood level that is therapeutically effective and nontoxic for an extended period. The design of proper dosage regimens is an important element in accomplishing this goal. Sustained release, sustained action, controlled release, extended-release, timed release, depot, and repository dosage forms are terms used to identify drug therapy systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period after administration of a single dose. The oral route of administration for sustained release systems has received greater attention because of more flexibility in dosage form design. The design of oral sustained release delivery systems are subject to several interrelated variables of considerable importance such as the type of delivery system, the disease being treated, the patient, the length of therapy, and the properties of the drug [7].

Limitations:

- If the active compound has a long half-life (over six hours), it is sustained on its own.
- If the pharmacological activity of the active compound is not related to its blood levels, slow releasing then has no purpose.
- If the absorption of the active compound involves an active transport; the development of a time-release product may be problematic.
- Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose. In this case, a broad therapeutic window is necessary to avoid toxicity;

otherwise, the risk is unwarranted and another mode of administration would be recommended.

- Not effectively absorbed in the lower small intestine [8].

The rationale for Developing Sustain Release Matrix Drug Delivery Systems:

- To extend the duration of action of the drug.
- To minimize the fluctuations in plasma level.
- Improved drug utilization.
- To reduce the frequency of dosing providing uniform drug delivery.

The basic rationale for sustained drug delivery is to alter the pharmacokinetics and pharmacodynamic properties of pharmacologically active moieties by using a novel drug delivery system [9].

Factors Affecting Oral Sustained Release Dosage Form Design:

Pharmacokinetics and Pharmacodynamics Factor:

Biological half-life:

Drugs with a biological half-life of 2 to 8 hours are considered a suitable candidate for sustained release dosage form since this can reduce dosing frequency.

Absorption:

The rate of absorption of a sustained formulating depends upon the release rate constant of the drug from the dosage form, and for the drugs that are absorbed by active transport, the absorption is limited to the intestine.

Distribution:

It reduces the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extravascular tissue, consequently, the apparent

volume of distribution assumes different values depending on the time course of drug disposition.

Metabolism:

The metabolic conversion to a drug is to be considered before converting into another form. As long as the location, rate, and extent of metabolism are known a successful sustain release product can be developed.

Drug Properties Relevant to Sustain Release Formulation:

Dose size:

A dose of 500-1000mg is considered maximal for a conventional dosage form. Since dose size consideration serves to be a parameter for the safety involved in the administration of large amounts with a narrow therapeutic range.

Ionization, pka, and aqueous solubility:

Most drugs are weak acids or bases and for a drug to get absorbed, it must dissolve in the aqueous phase surrounding the site of administration and then partition into the absorbing membrane.

Partition coefficient:

The bioavailability of a drug is largely influenced by the partition coefficient because the biological membrane is lipophilic, and the transport of drugs across the membrane largely depends upon the partition coefficient of the drug. Drugs having lower partition coefficients are considered a poor candidate for the sustain release formulation as they will be localized in the aqueous phase.

Drug stability:

Orally administered drugs come across acid-base hydrolysis and enzymatic degradation. If the drug is unstable in the stomach, a drug release system that provides medication over an extended time is preferred [10].

Methods to achieve oral sustained drug Delivery:

These are Hydrophilic matrix, Plastic matrix, Barrier resin beads, Fat embedment, Repeat action, Ion exchange resin, soft gelatin depot capsules, and Drug complexes [11].

IMMEDIATE RELEASE DOSAGE FORM

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of the drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, the immediate release may be provided for by way of appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Thus, the term excludes formulations which are adapted to provide for "modified", "controlled", "sustained",

"prolonged", "extended" or "delayed" release of drug [12].

Advantages of Immediate Release Drug Delivery System:

- Improved compliance/added convenience.
- Improved stability.
- Suitable for controlled/sustained release actives.
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery.
- Cost-effective.

Desired Criteria for Immediate Release Drug Delivery System:

- In the case of solid dosage, it should dissolve or disintegrate in the stomach within a short period.
- In the case of liquid dosage form it should be compatible with taste masking.
- Be portable without fragility concerns.
- Have a pleasing mouth feel.
- It should not leave minimal or no residue in the mouth after oral administration.
- Be manufactured using conventional processing and packaging equipment at low cost.
- Rapid dissolution and absorption of the drug, which may produce rapid onset of action.
- Exhibit low sensitivity to the environmental condition as humidity and temperature [13].

Conventional Technique used in the Preparation of Immediate Release Tablets:

Tablet molding technique, direct compression technique, wet granulation technique, mass extrusion technique, by solid dispersions [14].

MICROBEADS:

Microbeads are small, solid, and free-flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release profiles for treatment with various active agents without major side effects. Microbeads provide better control of the release of the active ingredients compared with monolithic formulations. Through the oral route due to the presence of food, the release from microbeads is less affected because it takes time to pass through the intestinal tract.

Microbeads are uniform polymer particles, typically 0.5 to 1000 μm in diameter. Bio-reactive molecules can be adsorbed or coupled to their surface and used to separate biological materials such as cells, proteins, or nucleic acids. They are small, solid, and free-flowing particulate carriers containing dispersed drug particles either in solution or crystalline form that allow a sustained release or multiple release

profiles of treatment with various active agents without major side effects [15].

Multiple unit dosage forms such as microspheres or microbeads have gained in popularity as oral drug delivery systems because of more uniform distribution of the drug in the gastrointestinal tract, more uniform drug absorption, reduced local irritation, and elimination of unwanted intestinal retention of polymeric material when compared to the non-disintegrating single unit dosage form.

The microbeads release the active ingredient through a double mechanism: diffusion and/or biodegradation of the polymer. Microbeads can be administered orally, parentally, or topically as an alternative to conventional injectable formulations. However, the success of these Novel DDS is limited due to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing intimate contact of the DDS with absorbing membranes. It can be achieved by coupling mucoadhesion characteristics to mucoadhesive microbeads and developing novel delivery systems referred to as "microbeads" [16]. Microbeads are at present the most common and rapidly expanding technology for controlled drug delivery systems. It is one of the convenient dosages which is more advantageous, because of good patient compliance and ease of formulation. It is formulated with drugs for sustained release or action by using different polymers, which improves the bioavailability of some drugs and it is more economical too [17].

They also maintain functionality under physiological conditions and can incorporate drugs to deliver locally at high concentrations ensuring that therapeutic levels are reached at the target site while reducing the side effects by keeping systemic concentration low. The microbeads are produced from several polymers such as cationic polymers e.g. chitosan, anionic polymers e.g. sodium alginate, and binding components e.g. gelatin, chondroitin sulfate, and avidin in the predetermined ratio [18].

Hydrogel beads or Hydrocolloids:

The basic rationale of a controlled release drug delivery system is to optimize the biopharmaceutical, pharmacokinetic and pharmacodynamic properties of a drug administered by the most suitable route to achieve its maximum utility, to control conditions within the shortest possible time by using the smallest quantity of the drug. It also provides constant drug levels in the blood with reduced dosing frequency and reduced side effects, thus increasing patient compliance and decreasing adverse drug effects. In these systems, the dosage of the drug substances is divided into a plurality of subunits,

typically consisting of thousands of spherical particles with a selective diameter range. To deliver the recommended total dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet [19].

Hydrophilic polymers derived from plant, animal, microbial, or synthetic sources when added to water, hydrocolloids are formed which disperse evenly as microscopic particles. At sufficiently high concentrations, the polymers become entangled with each other, forming loose networks that change the rheological properties of solutions. Many hydrocolloids, such as gelatin and pectin can also form gels by hydrogen bonding within and between polymers. Formulations based on hydrocolloids may have some advantages over other sustained release formulations, for instance, different structures can be obtained upon dehydration of the hydrocolloid formulations which can be modified by the drying conditions and formulation composition. Structural characteristics such as porosity may affect the penetration rate of liquid into the formulations and thus modify the release pattern of the drug. Moreover, the stability and physical properties (dimensions, strength, etc.) of various hydrocolloids are affected by factors such as swelling in water, pH value, and enzymes, and therefore vary in different parts of the gastrointestinal tract. Changes in the physical properties of the formulations may also lead to different drug-release patterns in different parts of the gastrointestinal tract, thus providing a wide scope to be utilized as carriers for the controlled release of drugs [20]. In addition, hydrocolloid formulation preparation procedures are generally quite simple and the cost of such materials is low. Beads formulated from hydrocolloid polymers are called hydrogel beads whose size ranges from 0.2 to 3 mm and are mostly spherical to give them the desired properties regarding eye appeal, release properties, or technical demands in general.

Commonly employed polymers in hydrogel beads:

Sodium alginate, pectin, chitosan, gellan gum, guar gum, and gum karaya.

Formulation Techniques of Hydrogel Beads:

Preparation of Ionotropic Gelation Method

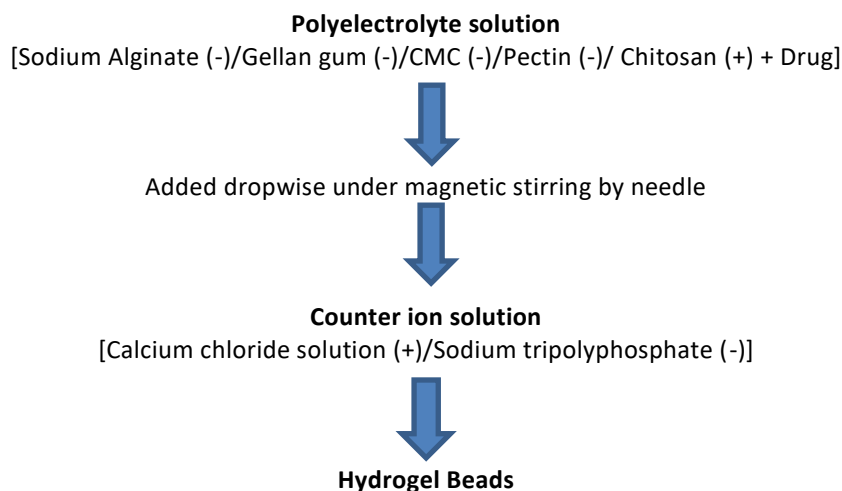


Figure 3: Schematic representation of the preparation of hydrogel beads by Ionotropic gelation method.

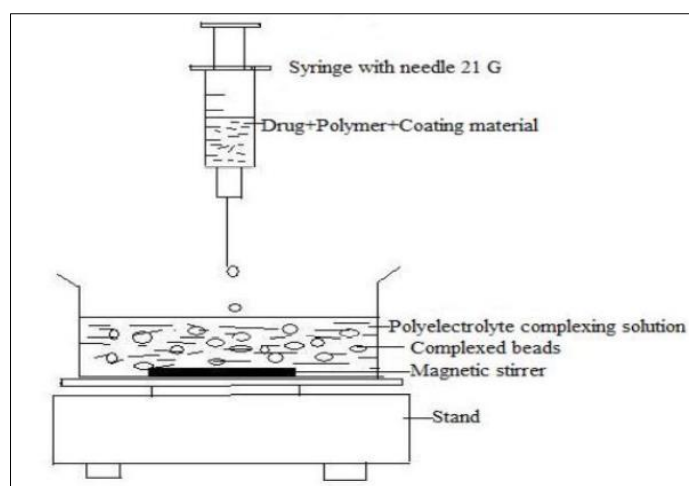


Figure 4: Schematic representation and diagram of the preparation of hydrogel beads by Ionotropic gelation and polyelectrolyte complexation.

Polyelectrolyte complexation:

The quality of hydrogel beads prepared by the ionotropic gelation method can also be further improved by the polyelectrolyte complexation technique. The mechanical strength and permeability barrier of hydrogels can be improved by the addition of oppositely charged polyelectrolytes to the ionotropically gelated hydrogel beads. For instance, the addition of polycations allows a membrane of polyelectrolyte complex to form on the surface of alginate beads.

Syringe dropping /extruding method:

The hydrogel beads can be produced widely by dropping an aqueous solution of poly anion solution into a solution of cation usually calcium chloride.

Although this is a simple and fast way of obtaining particulate drug carriers, the method presents a major limitation of drug loss during formulation. The matrix formed is usually very permeable and little or no drug release can be controlled in the core of soluble drugs. Hence, a preferential use for these hydrogel beads in the delivery of low solubility or micro molecular drugs has been suggested.

Air atomization method:

Beads can also be prepared by vibration system or air atomization method. Relatively smaller droplets can be formed using a vibration system or air atomization method to extrude the poly anion solution. The later involves a "Turbotak air-atomizer" in which pressurized air is fed to mix with the poly anion

solution, and thereby forcing tiny liquid droplets out through the orifice of the nozzle. The cations cross-link the droplets of poly anions on contact to form micro gel droplets which were further cross-linked by poly electrolytes such as poly-L-lysine to form a membrane on the droplets [15].

Factors Affecting Iontropic Gelation Method:

Polymer and cross-linking electrolyte concentration

Polymer and electrolyte concentration has a major effect on the formulation of beads by the ionotropic gelation method. The concentration of both should be in the ratio calculated from the number of cross-linking units. Percentage entrapment efficiency varies on the type of electrolytes and also the concentration of electrolytes.

Temperature

Temperature also plays an important role in the size of beads formed by the ionotropic gelation method and also in the curing time i.e., time required for cross-linking.

pH of cross-linking solution

The pH of the cross-linking solution is also a considerable factor during the formulation as it shows an effect on reaction rate, shape, and size of beads.

Drug concentration

The drug to be entrapped in the beads should be in the proper ratio with the polymer, as the drug concentration greatly affects the entrapment efficiency, if the drug: polymer ratio exceeds the range then the bursting effect may observe, and the density of gel spheres enhances and the size and shape of gel spheres also increases.

Gas-forming agent concentration

Gas-forming agents such as calcium carbonate and sodium bicarbonate are added to the formulation to develop porous gel spheres, which tremendously affect the gel sphere's size and shape.

Evaluation of Microbeads:

Yield Value, Drug content, *In-vitro* Swelling Study, *In-vitro* Drug release, Drug-excipient compatibility by FTIR Spectroscopy, Particle Size Determination, Release Kinetics, SEM analysis [21].

GRANULES:

Many components of solid dosages form including excipients and drug substances are passed through multiple processes of manufacturing and thus end with the final product. The pharmaceutical industry uses granulation methods to enlarge and densify small powder particles into larger ones that improve powder flow without segregation so that the material can be processed effectively and efficiently into solid dosage forms. There are two pharmaceutical methods of granulation, wet granulation, and dry granulation. Roller compaction

is a unit operation in the dry granulation process, a pressure-induced agglomeration technique in which granules are prepared with acceptable flowability, compaction properties, compositional uniformity, and chemical stability, especially for moisture and heat-sensitive drug formulations. During the dry granulation process the dry powders of the active ingredient and excipients, e.g., dry binders, disintegrants, diluents, and lubricants, are mixed in a blender. The powder mixtures are then roller compacted and size reduced to form granules.

Ideal characteristics of granules:

The ideal characteristics of granules include usually spherical in shape, smaller particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-3%), good flow, good compressibility, and sufficient hardness. The effectiveness of granulation depends on the particle size of the drug and excipients, type of binder (strong or weak), the volume of binder (less or more), wet massing time (less or more), amount of shear applied, drying rate (Hydrate formation and polymorphism) [22].

Granulation method:

Granulation may be defined as a size enlargement process that converts small particles into physically stronger and larger agglomerates. The granulation method can be broadly classified into three types:

Wet granulation:

The wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing, and drying.

Disadvantages:

- Process is expensive because of labor, space, time, special equipment, and energy requirement.
- Multiple processing steps involved in the process add complexity.
- Loss of material during various stages of processing.
- Moisture-sensitive and thermolabile drugs are poor candidates.
- Any incompatibility between the formulation components is aggravated during the processing.

Dry granulation:

In the dry granulation process, the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact material by compression and then to mill the compact to obtain granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is precompressed and the resulting tablet or slug is milled to yield the granules. The other method is to precompress the

powder with pressure rolls using a machine such as Chilsonator.

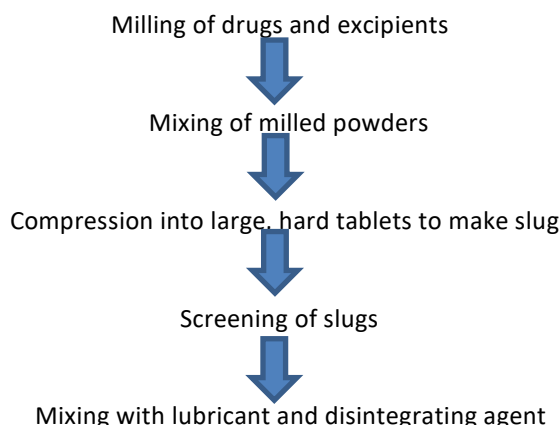


Figure 5: Steps involved in the dry granulation

Disadvantages:

- It requires a specialized heavy-duty tablet press to form a slug.
- It does not permit uniform color distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.
- The process tends to create more dust than wet granulation, increasing the potential contamination [23,24].

SUPERDISINTEGRANTS:

Superdisintegrants are nothing but super absorbing materials with tailor-made swelling properties. They are not planned to absorb significant amounts of water or aqueous fluids but are planned to swell very fast. Superdisintegrants are usually employed as structural weakeners for the disintegrable solid dosage forms. They are physically dispersed within the matrix of the dosage form and will expand when the dosage form is exposed to the wet environment. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength.

Mechanism of Action of Superdisintegrants:

Five major mechanisms for tablet disintegration are as follows-

Swelling:

Swelling is believed to be a mechanism in which certain disintegrating agents (such as starch) impart the disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart.

Porosity and Capillary Action (Wicking):

Effective disintegrants cannot swell that impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into tablets. The disintegrant particles (with low cohesiveness & compressibility) themselves act to enhance porosity and provide these pathways into the tablet. The liquid is drawn up or "wicked" into these pathways through capillary action and ruptures the inter particulate bonds causing the tablet to break apart. E.g., croscopolidone, croscarmellosesodium.

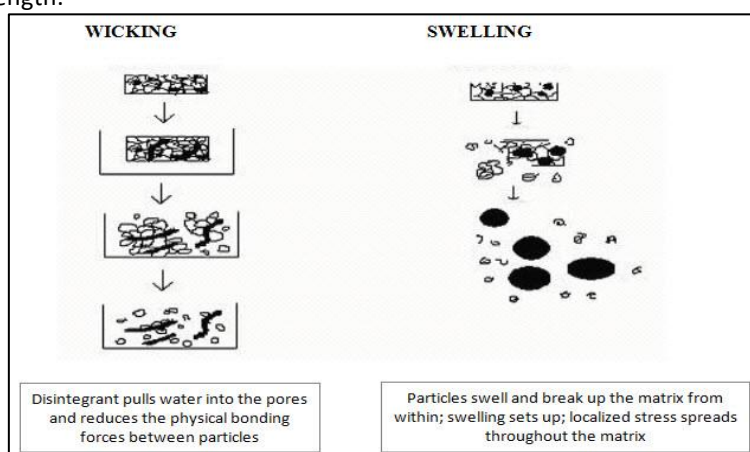


Figure 6: Wicking property of granules and swelling of granules.

Deformation:

Starch grains are generally thought to be “elastic” in nature i.e., grains are deformed under pressure will return to their original shape when that pressure is removed. But, due to the compression forces involved in tableting, these grains are believed to be deformed more permanently and are said to be “energy rich” with this energy being released upon exposure to water. The ability for starch to swell is higher in “energy rich” starch grains than it is for

starch grains that have not been deformed under pressure.

Repulsive forces:

This mechanism of disintegration explains the swelling of tablet made with “non swellable” disintegrants. Guyot Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

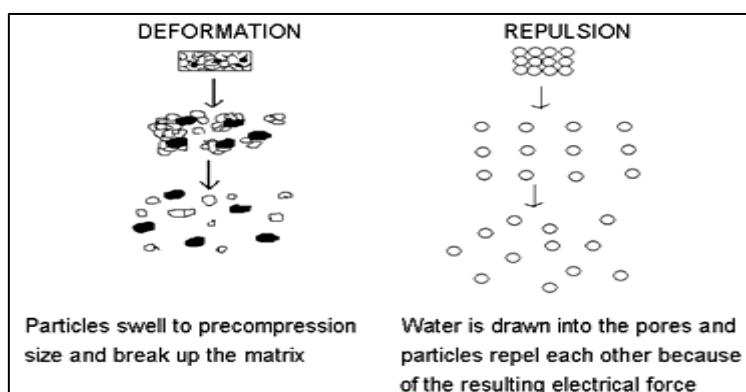


Figure 7: Repulsion of granules and deformation of granules.

Enzymatic Reaction:

Enzymes present in the body also act as disintegrants. These enzymes dearth the binding action of binder and helps in disintegration. Due to swelling, pressure is exerted in the outer direction

that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration [25,26].

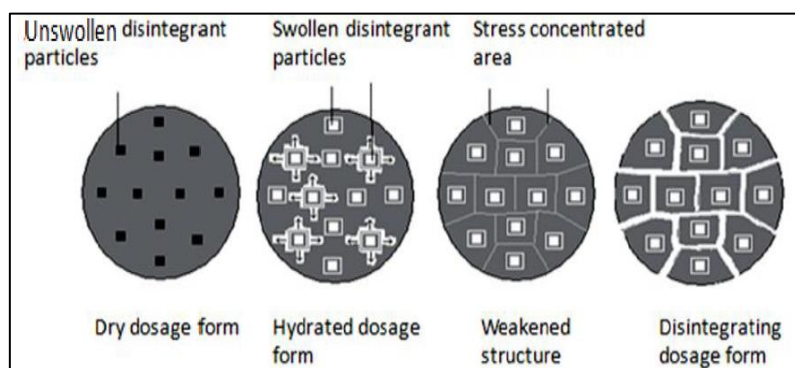


Figure 8: Enzymatic reaction of granules.

MATERIAL AND METHODS:

Drugs and chemicals

Losartan Potassium was procured from Embiotic Laboratories Ltd. Bengaluru and Hydrochlorothiazide was procured from Centurion Laboratories, Gujarat. Polymers and other excipients such as Sodium Alginate, Chitosan, Cross Povidone, Starch, Acetic Acid, Calcium Chloride, Lactose Monohydrate, Magnesium Stearate, Talc, Sodium Hydroxide, Potassium Dihydrogen Orthophosphate, Potassium

Chloride, Hydrochloric Acid are purchased from S.D. Fine Chem. Ltd., Mumbai.

METHODS

PREFORMULATION STUDIES:

Determination of Melting Point:

The melting point of losartan potassium and hydrochlorothiazide was determined by placing a small quantity of drug sample into a capillary tube (previously sealed at one end) and was kept in the digital melting point apparatus and the temperature

range where the drug melted was noted. The mean of three readings was recorded.

Drug excipients compatibility studies:

ATR and DSC studies can be used to investigate any physicochemical interaction between components in a formulation; therefore, these studies were applied for the selection of suitable chemically compatible excipients [27].

Attenuated Total Reflectance (ATR):

Attenuated total reflection (ATR) is a sampling technique used in conjunction with infrared spectroscopy which enables samples to be examined directly in the solid or liquid state without further preparation.

ATR uses a property of total internal reflection resulting in an evanescent wave. A beam of infrared light is passed through the ATR crystal in such a way that it reflects at least once off the internal surface in contact with the sample. This reflection forms the evanescent wave which extends into the sample.

Procedure:

The integrity of the pure drug and physical mixture of pure drug with excipient was checked by taking an IR spectrum. The spectra were obtained using a Shimadzu ATR spectrophotometer.

Little quantity of pure drugs, polymers, and physical mixtures were placed in the testing chamber and a peak was observed [28].

Differential Scanning Calorimetry:

The thermal properties of the samples were investigated with a differential scanning calorimeter. DSC thermograms were taken for pure drug(s) drug and respective formulations with various polymers. The dynamic scans were taken in a nitrogen atmosphere at the heating rate of 100C/min with a flow rate of 10ml/min. DSC studies were routinely conducted on drug interaction in the formulations [29].

ANALYTICAL METHODS

Preparation of Standard Solution:

Losartan Potassium:

An accurately weighed quantity of 100 mg of the drug transferred into a 100 ml volumetric flask and dissolved in a small quantity of 1.2 & 7.4 pH buffer solutions separately.



The required volume was made with the respective buffers to get the concentration of 1000 µg/ml. i.e. Stock solution-1.



Pipette out 2 ml exactly from the stock solution-1 into another 100 ml volumetric flasks separately and made the volume with respective buffers to get concentration of 20 µg/ml. i.e. stock solution-2 [30].

Figure 9: Preparation of Standard Solution of Losartan Potassium

Hydrochlorothiazide:

Weigh accurately 100 mg of hydrochlorothiazide transferred into two different 100 ml volumetric flask and dissolved in a small quantity of 1.2 & 7.4 pH buffer solutions separately.



The required volume was made with the respective buffers to get the concentration of 1000 µg/ml. i.e. Stock solution-1.



Pipette out 2 ml exactly from the stock solution-1 into another 100 ml volumetric flasks separately & make the volume with respective buffers to get the concentration of 20 µg/ml. i.e. stock solution-2.

Figure 10: Preparation of Standard Solution of Losartan Potassium

Determination of analytical wavelength of Drugs:

Losartan potassium and Hydrochlorothiazide:

Most of the drugs absorb light in the UV region (200 nm - 400 nm) since they are generally aromatic or having double bonds. The solution containing 20 µg/ml of losartan potassium and hydrochlorothiazide in 1.2 pH and 7.4 pH buffers were prepared and scanned over the range of 200 nm – 400 nm against the 1.2 pH and 7.4 pH buffers as blank using double beam UV spectrophotometer respectively. The maximum peak obtained was considered as λ max.

Simultaneous Estimation of LP and HCTZ in Acidic & Phosphate Buffers:

Most of the drugs absorb light in the UV region (200 nm - 400 nm) since they are generally aromatic or have double bonds. The solution containing 20 µg/ml of losartan potassium and hydrochlorothiazide in 1.2 pH and 7.4 pH buffers was prepared and scanned over the range of 200 nm – 400 nm against the 1.2 pH and 7.4 pH buffers as blank using double beam UV

spectrophotometer respectively. The maximum peak obtained was considered as λ max.

Simultaneous Estimation of LP and HCTZ in Acidic & Phosphate Buffers:

A simple procedure for the simultaneous estimation of prepared capsules containing losartan potassium-loaded microbeads and a hydrochlorothiazide granules formulation was developed. It involves absorption ratio method of analysis was based on the absorbance at two selected wavelengths (i.e. 257 nm for LP and 272 nm for HCTZ), one of which was an iso-best point and the other being the wavelength of maximum absorption of one of two components.

The calibration curve of LP and HCTZ in 1.2 pH and 7.4 pH buffers has been constructed at 257 nm and 272 nm respectively. Losartan potassium and hydrochlorothiazide solutions of known concentrations were scanned on UV spectrophotometer.

Quantitative estimation of LP and HCTZ was carried out by solving the following simultaneous equations:

$$C_x = \frac{Q_m - Q_y}{Q_x - Q_y} \times \frac{A_1}{a_{x1}} \quad C_y = \frac{Q_m - Q_x}{Q_y - Q_x} \times \frac{A_1}{a_{y1}}$$

$$\text{Where, } Q_m = \frac{A_2}{A_1}, Q_x = \frac{a_{x2}}{a_{x1}}, Q_y = \frac{a_{y2}}{a_{y1}}$$

Where, A1 and A2 were the absorbances of the sample at 257 nm and 272 nm respectively, ax1 and ax2 were the absorptivities of sample 1 at 257 nm and 272 nm respectively and ay1 and ay2 were the absorptivities of sample 2 at 257 nm and 272 nm respectively [31].

PREPARATION OF DRUG-LOADED MICROBEADS: ^{32, 33}

Here Ionotropic gelation method was employed for the preparation of losartan potassium-loaded

microbeads. Hydrogel beads were prepared by using sodium alginate as a gelating agent, while chitosan solution was added as a coating solution. Calcium chloride helps in the hardening of microbeads.

Table No. 2: Composition of losartan potassium-containing microbeads.

FORMULATION CODE	DRUG: POLYMER RATIO	CHITOSAN(W/V)	CALCIUM CHLORIDE(W/V)
B1	1:1 Ratio	0.5%	4%
B2	1:1.5 Ratio	0.5%	4%
B3	1:2 Ratio	0.5%	4%
B4	1:2.5 Ratio	0.5%	4%

Method of Preparation of Microbeads:

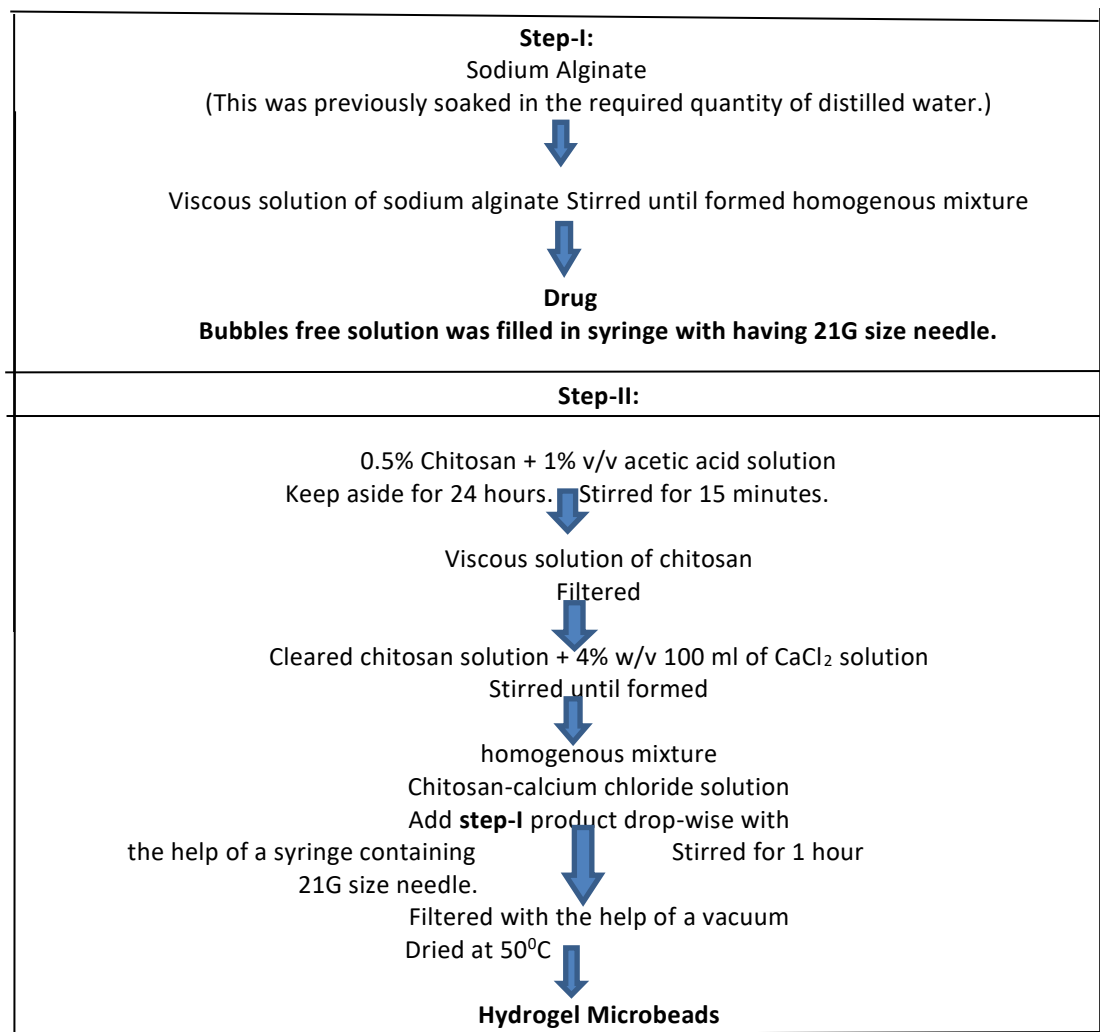


Figure 11: Flow diagram for the preparation of hydrogel microbeads containing losartan potassium.

PREPARATION OF IMMEDIATE RELEASE GRANULES

In this work hydrochlorothiazide containing an immediate release, granules were prepared by dry granulation technique using croscopovidone as super disintegrants.

All the ingredients were accurately weighed and passed through sieve no. 80.

Accurately weighed quantity of lactose monohydrate was transferred into a cleaned mortar followed by hydrochlorothiazide and mixed thoroughly with the help of a pestle.

Added croscopovidone into the above mixture and mixed it well.

The remaining excipients were added in geometrical proportions and mixed till a homogenous mixture was formed [32,33].

Figure12: Preparation of immediate release granules

Table 3: Composition of hydrochlorothiazide containing granules.

INGREDIENTS	QUANTITY (mg)
Hydrochlorothiazide	12.5
Lactose monohydrate	13
Crospovidone	2.5
Starch mucilage	8
Magnesium stearate	1
Talc	1
Total Weight	38

EVALUATION PARAMETERS OF FORMULATED MICROBEADS: Determination of Yield Value:

The prepared microbeads were assessed for the yield value. The batch was weighed after total drying and

the % yield was calculated using the formula given below. Each batch was formulated in triplicate batches (n=3) to get a reproducible yield.

It can be calculated by using the following formula:

$$\text{Percentage Yield} = \frac{\text{Weight of microbeads}}{\text{Weight of drug} + \text{Weight of polymer}} \times 100 \%$$

Determination of Particle Size:

The size distribution study was carried out using an optical microscope, and the mean particle size was calculated by measuring 300 particles with the help

of a calibrated ocular micrometer. Calibration of the optical microscope was carried out using a micrometer.

The size of each division of the eyepiece micrometer was determined by using the following formula:

$$\text{Size of each division} = \frac{\text{Number of the division of stage micrometer}}{\text{Number of the division of eyepiece micrometer}} \times 100$$

The microbeads were mounted on a slide and placed on a mechanical stage. The microscope eye-piece was fitted with a micrometer by which the size can be determined. The field was projected onto the screen and the particles were measured along an arbitrarily chosen fixed line horizontally across the center of the particles. A size-frequency distribution curve was plotted.

Flow Properties of Beads:
Angle of Repose:

Good flow properties are critical for the development of any pharmaceutical dosage forms such as tablets, capsules or powder formulations. The angle of repose is defined as a possible maximum

angle (θ) formed between the surface of a pile of powder and the horizontal plane.

Procedure:

A funnel was kept vertically at a specified height and the funnel bottom was closed. Sample of granules was filled inside the funnel. Then funnel was opened to release the powder to form a smooth conical heap which just touches the tip of the funnel. From the powder cone, the radius and height of the heap was measured. The angle of repose is represented as ' θ ' and is calculated using the following equation [34]:

$$\text{Angle of Repose } (\theta) = \tan^{-1} (h/r)$$

Where, h = height of the pile, r = radius of the base.

Table No. 4: Flow properties and corresponding angle of repose.

FLOW PROPERTIES	ANGLE OF REPOSE
Excellent	<25
Good	26-30
Moderate	31-40
Poor	>40

Surface Morphology:

The external and internal morphology of the microspheres were studied by scanning electron microscopy (SEM). The samples for SEM were prepared by lightly sprinkling the powder on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken with a scanning electron microscope (Jeol JSM-1600, Tokyo, Japan).

Estimation of Drug Content:

Accurately weighed 50 mg equivalent weights of losartan potassium-loaded microbeads were placed

in a 7.4 buffer solution overnight. The solution was mixed using a magnetic stirrer. After suitable dilution drug content was determined by using a double beam UV spectrophotometer (Shimadzu, UV-1700) [35].

In-vitro Swelling study:

The release of the entrapped drug from hydrogels depends on the swelling behavior because in the case of hydrogels swelling is directly proportional to the release of the drug. As the hydrogel swells, the pores of the network open as a result release of entrapped solute occurs. Therefore, the dynamic swelling study of the prepared beads was carried out. The swelling behavior of the prepared beads can be analyzed by mass measurement.

Procedure:

The 50 mg of beads were incubated into the glass vials, initially with 10 ml of 1.2 pH buffer and then 7.4 pH phosphate buffer solutions.



The beads were taken out at different time intervals and blotted carefully without pressing hard to remove the excess surface liquid.



The swollen beads were weighed using the electronic microbalance.



The weights determined were used for plotting the swelling profile.

Fig.13. Procedure of swelling study

The swelling index was calculated using the following equation:

$$Q = [(W_2 - W_1) / W_1] \times 100$$

Where, Q = percentage of swelling

W_1 = mass of the dry beads

W_2 = the mass of swollen beads.

In-vitro Dissolution Studies:

Dissolution studies were carried out by using dissolution apparatus USP XXII (Electrolab). Drug-loaded microbeads equivalent to 50 mg of the drug were introduced into the 900 ml of acidic buffer pH 1.2 ± 0.1 for initial 2 hours and in phosphate buffer pH 7.4 ± 0.1 up to 12 hours. The medium was maintained at $37 \pm 2^\circ\text{C}$ at 50 rpm. Aliquots of 5ml were withdrawn at regular intervals up to 12 hours and analyzed spectrophotometrically (UV 1700, Shimadzu, Japan) at 257nm. Three trials were carried out for all formulations. Sink condition was maintained throughout the study by replacing an equal volume

of fresh dissolution medium. Dissolution studies profile can be calculated by using simultaneous equations [36].

Release Kinetics of Microbeads:

To analyze the mechanism of drug release from the microbeads the results of in-vitro release data were plotted in various kinetic models like zero order, first order, Higuchi model, Korsmeyer-Peppas equation, and Hixson-Crowell model [37].

Zero-order kinetics:

Cumulative percent drug released versus time. It can be predicted by the following equation.

$$A_t = A_0 - K_0 t$$

Where, A_t = drug release at time 't'

A_0 = initial drug concentration.

K_0 = Zero-order rate constant (hr^{-1})

First order kinetics:

Log cumulative percent drug remaining versus time. A first-order would be predicted by the following equation.

$$\log C = \log C_0 - 303.2Kt$$

Where, C = amount of drug remained at time 't'

C₀ = initial amount of drug.

K = first-order rate constant (hr⁻¹)

Higuchi model:

Cumulative percent drug released versus square root of time. Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = \left(\frac{De}{t} (2A - eC_s) C_s t \right)^{1/2}$$

Where, Q = amount of drug released at the time, "t"

D = diffusion coefficient of the drug in the matrix.

A = total amount of drug in a unit volume of the matrix.

C_s = the solubility of the drug in the diffusion medium.

ε = porosity of the matrix.

τ = tortuosity.

t = time (hrs.) at which 'Q' amount of drug is released.

The equation may be simplified by assuming that, D, C_s, and A are constant. Then the equation becomes:

$$Q = Kt^{1/2}$$

Korsmeyer and Peppas release model:

The release rates from controlled release polymeric matrices can be described by the equation proposed by Korsmeyer et al.

$$Q = K_1 t^n$$

Where, Q = Percentage of drug released at the time 't'

K = Kinetic constant incorporating structural and geometric characteristics of the tablets and

'n' = Diffusional exponent indicative of the release mechanism.

Hixson and Crowell:

To account for the particle size decrease and change in surface area accompanying dissolution, Hixson and Crowell's cubic root law of dissolution is used [38]:

$$W_0^{1/3} - W^{1/3} = Kt$$

EVALUATION PARAMETERS OF IMMEDIATE RELEASE GRANULES

Bulk Density:

It is the ratio of the total mass of powder to the bulk volume of powder. The bulk density of the granules was determined by pouring the sample through a glass funnel into a 5 ml measuring cylinder. The volume occupied by the sample was recorded. Bulk density can be determined by using the following formula:

$$\text{Bulk Density} = \frac{\text{Mass of Powder}}{\text{Bulk volume of powder}}$$

Tapped Density:

It can be determined by placing the sample of granules into a 10 ml graduated measuring cylinder. The initial volume was noted. The cylinder was tapped 100 times from a distance of 14±2 mm. The tapped volume was measured to the nearest graduated unit. The tapped density can be determined by using the following formula:

$$\text{Tapped Density} = \frac{\text{Mass of Powder}}{\text{Tapped volume of powder}}$$

Carr's consolidation index:

Carr developed an indirect method of measuring powder flow from bulk densities. The % compressibility of the powder was a direct measure of the potential powder arch or bridge strength or stability. Carr's index can be calculated using the following formula:

$$\text{Carr's Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Hausner's Ratio:

It indicates the degree of densification which could result from the vibration of the feed hopper. Lower the Hausner's ratio better is the flowability. It can be calculated by using the formula:

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Angle of Repose:

Good flow properties are critical for the development of any pharmaceutical dosage form such as tablets, capsules, or powder formulations. The angle of repose is defined as a possible maximum angle (θ) formed between the surface of a pile of powder and the horizontal plane.

$$\text{Angle of Repose } (\theta) = \tan^{-1} (h/r)$$

Where,

h = height of the pile from the horizontal powder surface.

r = radius of the powder surface.

Estimation of Drug Content:

Accurately weighed 10 mg equivalent weight of hydrochlorothiazide containing granules was placed in a 1.2 pH buffer solution. The solution was mixed in a magnetic stirrer. After suitable dilution drug content was determined by using a double beam UV spectrophotometer (Shimadzu, UV-1700).

In-vitro dissolution studies:

Dissolution studies were carried out by using dissolution apparatus USP XXII (Electrolab). Drug-loaded microbeads equivalent to 12.5 mg of the drug were introduced into the 900 ml of acidic buffer pH 1.2 ± 0.1 up to 2 hours, then in phosphate buffer of 7.4 pH up to 12 hours. The medium was maintained at $37 \pm 2^\circ\text{C}$ at 50 rpm. Aliquots of 5 ml were withdrawn at regular intervals for up to 2 hours and analyzed spectrophotometrically (UV 1700, Shimadzu, Japan) at 272nm. Three trials were carried out for all formulations. Sink condition was maintained throughout the study by replacing an equal volume of fresh dissolution medium [39].

RESULTS AND DISCUSSION:

Melting point:

The melting point of losartan potassium was found to be 265.0°C which is within the reported range of 259.0°C – 266.0°C and hydrochlorothiazide was found to be 268.0°C which is within the range of 265.0°C – 268.0°C . It complies with the official standard. Thus, indicating the purity of the sample.

Drug excipients compatibility studies:

Attenuated Total Reflectance (ATR):

As described in the methodology compatibility studies were performed using an ATR spectrophotometer. The IR spectrum of pure drug, polymers, and physical mixture of drug and polymer were studied. The peaks obtained in the spectra of optimized formulation were correlated with the peaks of the drug spectrum. This indicates that the drug was compatible with the formulation components.

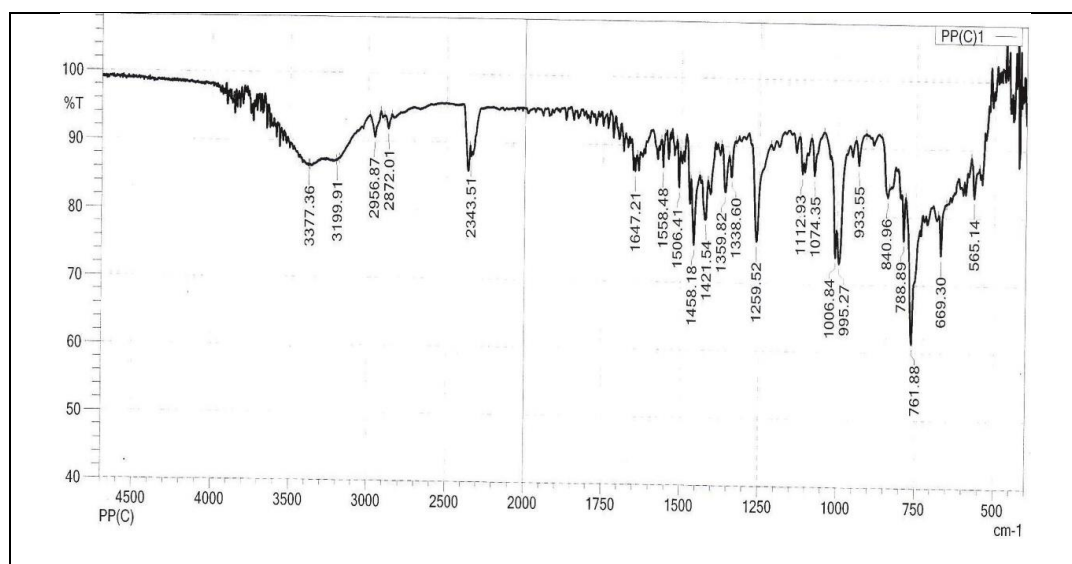


Figure 14: ATR spectra of Losartan Potassium

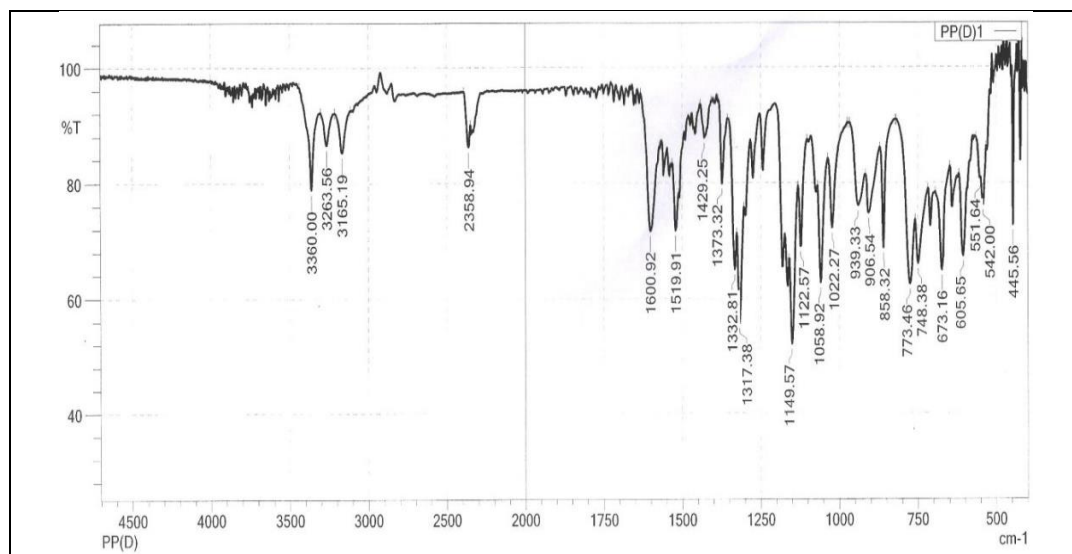


Figure 15: ATR spectra of Hydrochlorothiazide

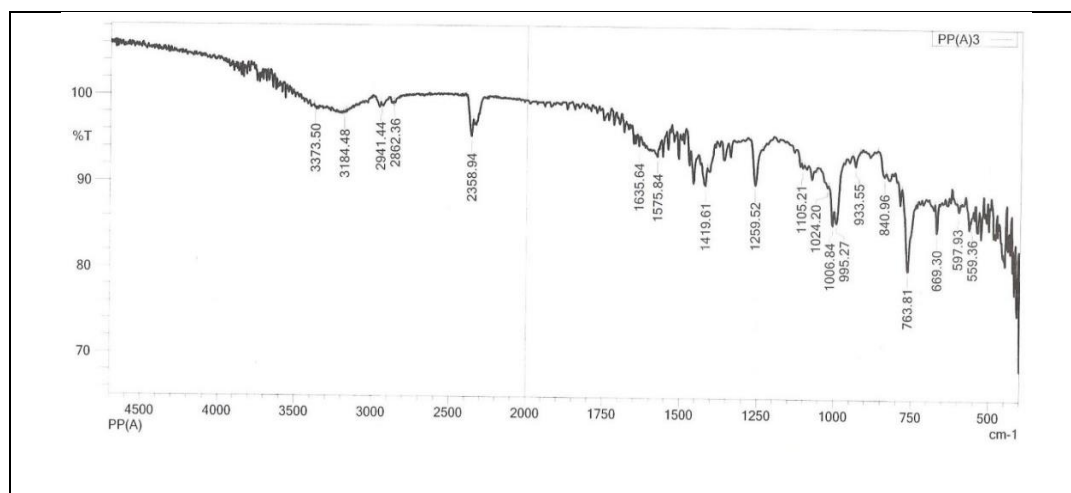


Figure 16: ATR spectra of Microbeads (LP+Sodium alginate+Chitosan)

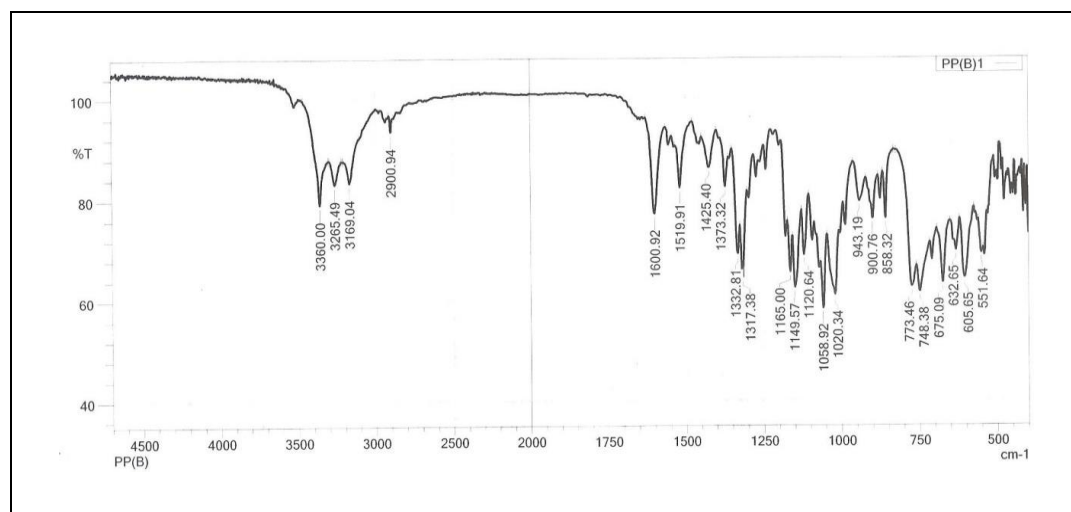


Figure 17: ATR spectra of granules (HCTZ+Crospovidone+Lactose+Starch)

Differential Scanning Calorimetry (DSC) Analysis:

As described in the methodology compatibility studies were performed using an ATR spectrophotometer. The IR spectrum of pure drug, polymers, and physical mixture of drug and polymer

were studied. The peaks obtained in the spectra of optimized formulation were correlated with the peaks of the drug spectrum. This indicates that the drug was compatible with the formulation components.

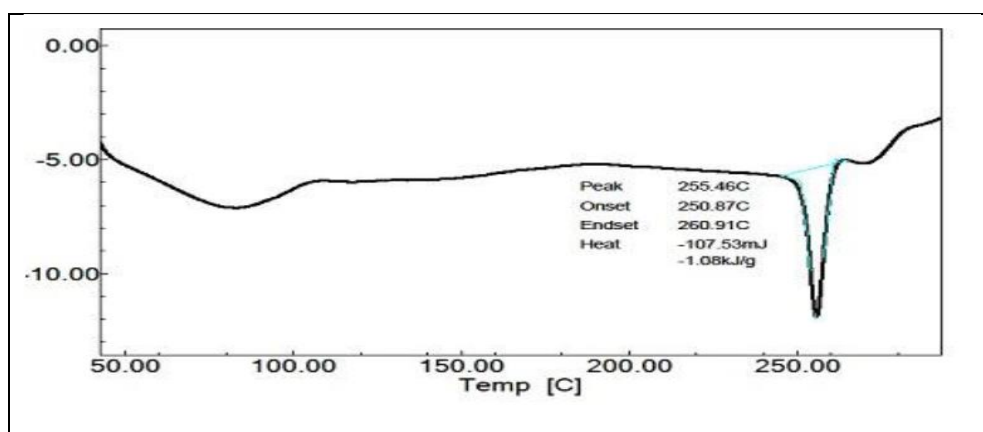


Figure 18: DSC thermogram of Losartan potassium

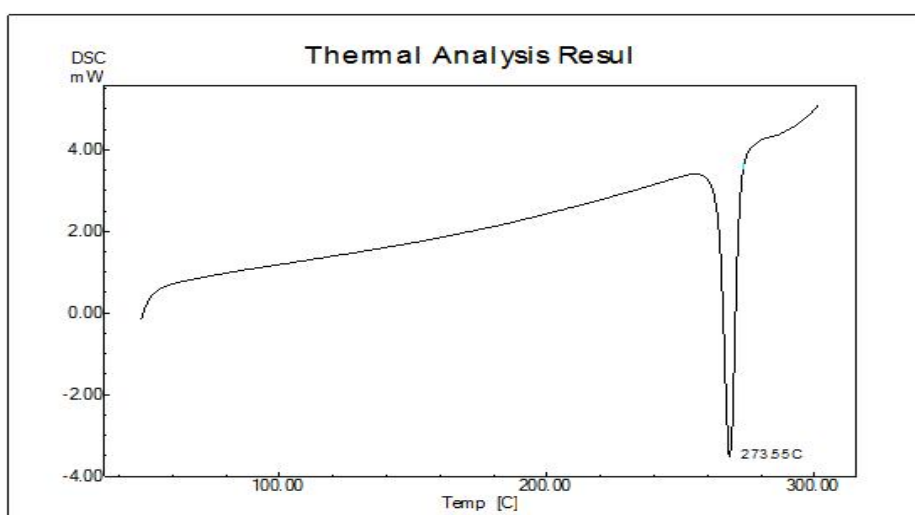


Figure 19: DSC thermogram of Hydrochlorothiazide

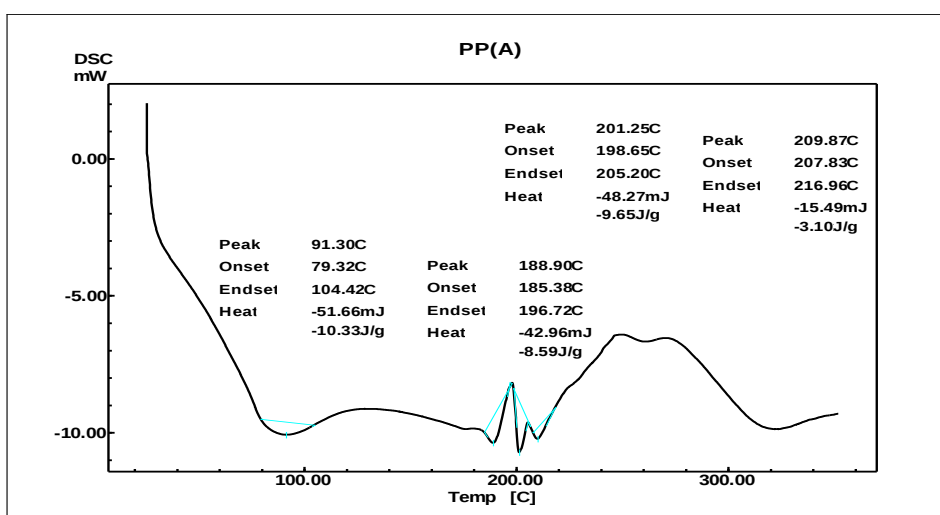


Figure 20: DSC thermogram of Losartan potassium-containing microbeads.

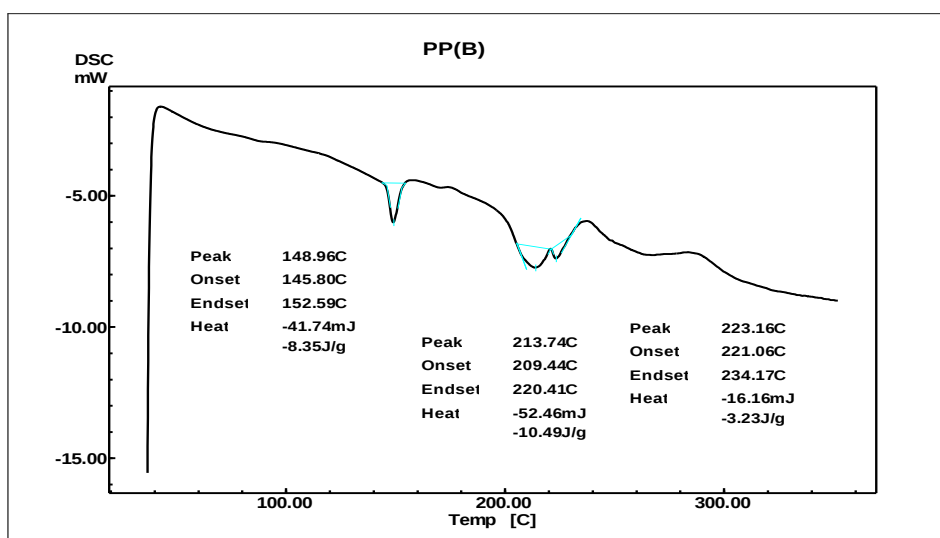


Figure 21: DSC thermogram of Hydrochlorothiazide containing granules.

ANALYTICAL METHOD

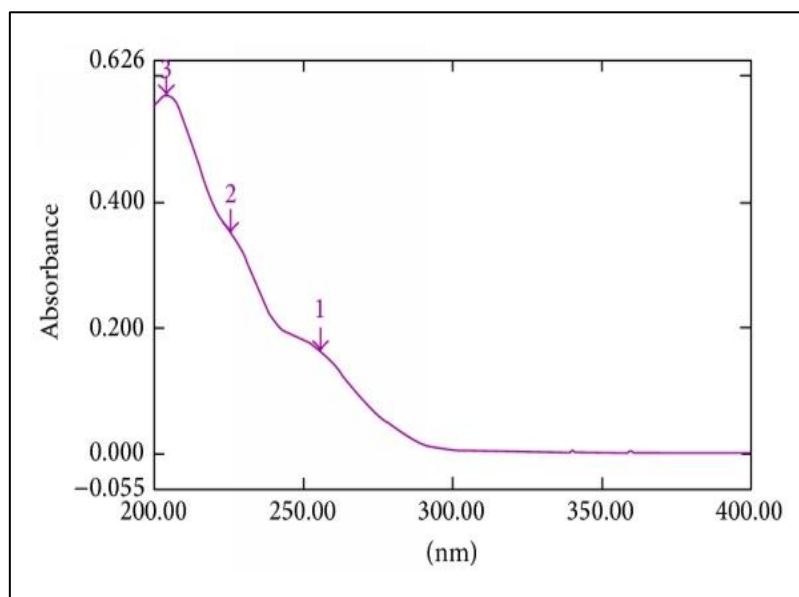


Figure 22: Analytical wavelength of Losartan potassium

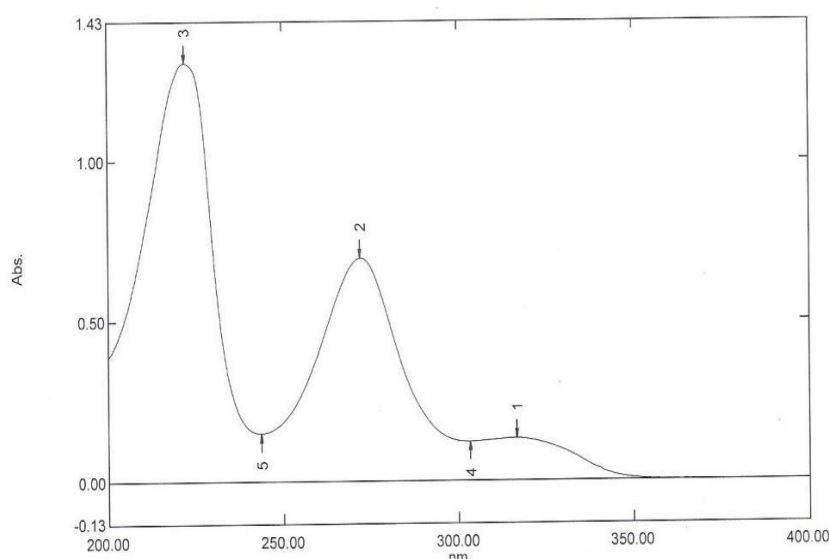


Figure 23: Analytical Wavelength of Hydrochlorothiazide.

CHARACTERIZATION

Immediate Release Hydrochlorothiazide Formulation:

Granule Properties:

The prepared granules were evaluated for the blend properties like bulk density, tapped density, carr's index, angle of repose, and Hausner's ratio.

Drug content:

The drug content of the immediate release formulation batch was found to be $91.94 \pm 0.53\%$.

Losartan Potassium Loaded Sustained Release Formulation:

Losartan potassium-loaded microbeads were prepared by using the ionic gelation method. Sodium alginate was used as a gelling agent followed by 0.5% chitosan and 4% calcium chloride were selected as coating solution and hardening agents respectively. Four different ratios of gelling agent and drug were taken for the preparation of losartan potassium entrapped microbeads.

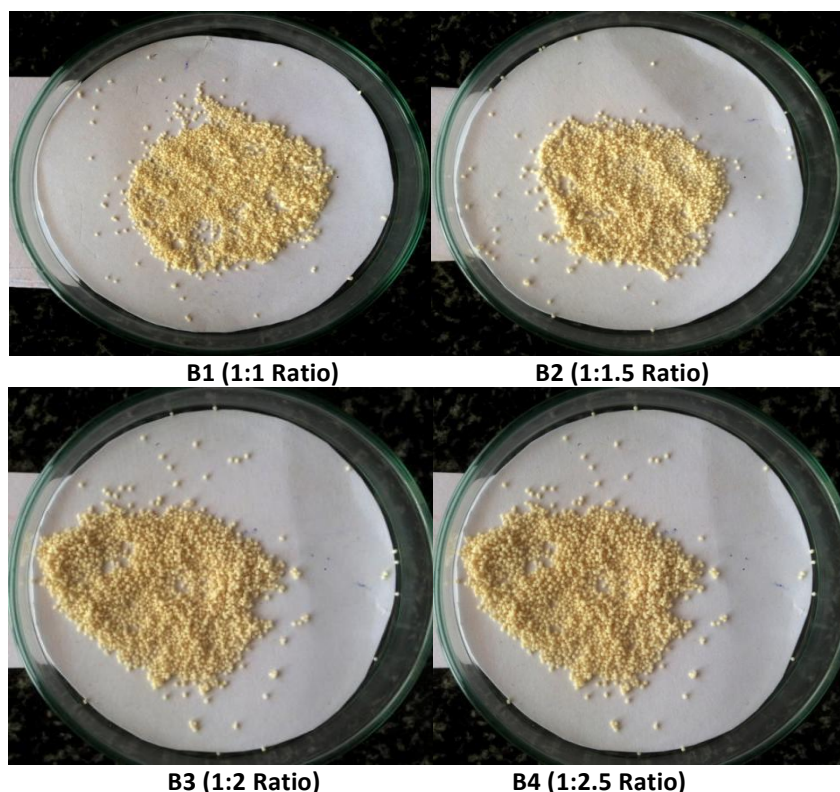


Figure 24: Microbeads prepared using different concentrations of drug and polymer ratio.

CHARACTERISATION OF MICROBEADS AND GRANULES:

Percentage Yield of Microbeads:

The percentage yield was increased with an increase in the concentration of the polymer. This may be due to the addition of more amount of polymer in the same volume of the continuous phase.

Particle size:

It has been stated that when a drop of alginate solution comes in contact with Ca^{2+} , gelation occurs instantaneously. As alginate Ca^{2+} penetrates interior droplets water is squeezed out of the interior of droplets resulting in a concentration of beads. Thus, an increase in the concentration of sodium alginate solution will significantly affect the beads leading to an increase in diameter.

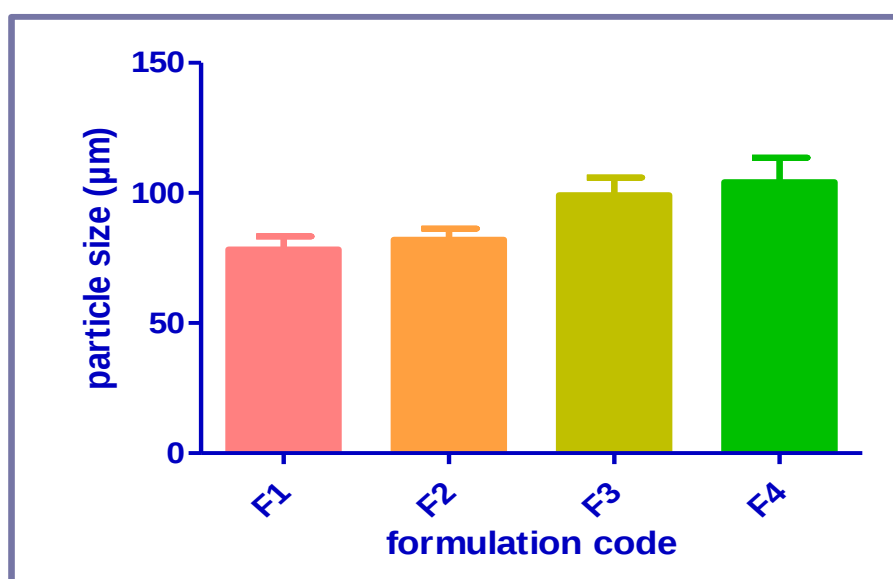


Figure 25: Average particle size of losartan potassium-loaded microbeads.

Drug Entrapment Efficiency:

The drug entrapment efficiency of microbeads an increased with increase in the concentration of sodium alginate.

Surface Morphology:

SEM of the microbeads prepared from sodium alginate was spherical and exhibits uniformity and

rough wrinkle on the surface. This may be due to collagens and fusion to the colloidal aqueous polymer dispersion in the alginate matrix. From the photo micrographic observation, it can be stated that the bridging and dense nature of the formulations were responsible for prolonged drug release.

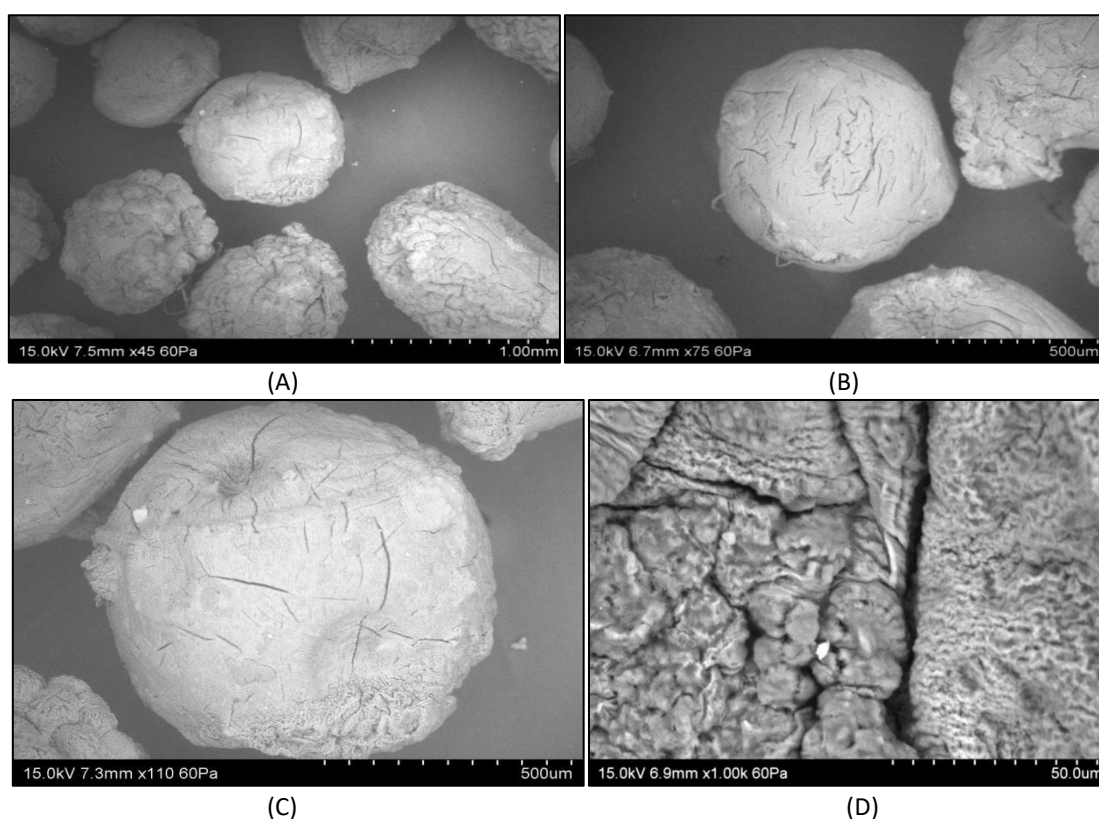


Figure 26: SEM photographic image of microbeads

Swelling Studies:

The result showed that the swelling was related to the polymer concentration with swelling being more

significant for beads containing high polymer content.

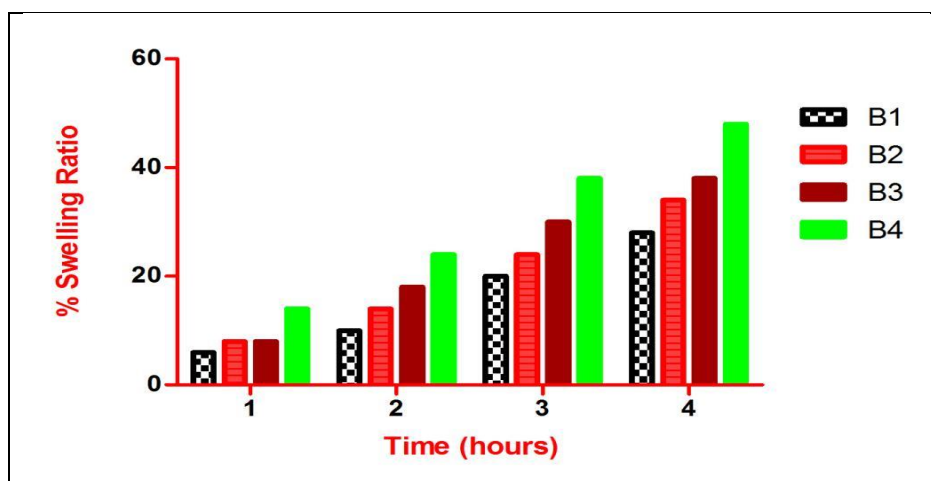


Figure 27: In-vitro swelling index profile of microbeads.

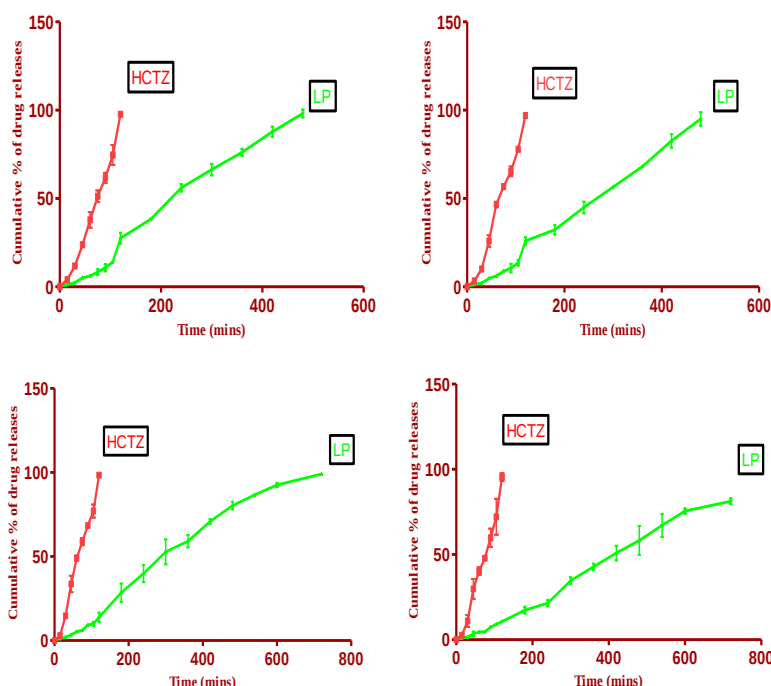


Figure 28: In-vitro drug release profile of B1, B2, B3, and B4

In-vitro drug release:

The dissolution studies were conducted for microbeads using different dissolution mediums simultaneously in pH 1.2 buffer for 2 hours and pH 7.4 buffer for remaining studies i.e. up to 12 hours. In general, the drug release behavior of the losartan potassium microbeads in acidic (pH 1.2) buffer was very slow due to the low solubility of the drug in an acidic medium. The swelling behavior of the microbeads also affects the release rate of the drug. The drug release behavior increased in pH 7.4 buffer in almost all the batches due to an increase in the swelling behavior of the polymer. The in-vitro drug release observation was continued for 12 hours to estimate the sustained release property of the prepared formulations. It proves that all these formulation batches showed sustained release behavior.

From the results, the drug release of hydrochlorothiazide from immediate-release granules was found to be fast-release, which may be due to the presence of croscopovidone as the super disintegrating agent.

Drug Release Kinetics Losartan Potassium Containing Microbeads:

On analyzing regression coefficient values of all batches, it was found that all microbeads exhibited almost zero-order kinetics. The in-vitro release profiles of drugs from all these formulations could be best expressed by Higuchi's equation as the plots showed the highest linearity ($r^2 = 0.902$ to 0.937). To

confirm the diffusion mechanism, the data were fitted into the Korsmeyer-Peppas equation. The formulations showed good linearity ($r^2 = 0.849$ to 0.863) with a slope (n) between 0.845 - 0.905 , which appears to indicate a non-fickian diffusion mechanism.

STABILITY STUDIES:

Stability studies of optimized formulation in a capsule containing immediate-release granules and sustained release microbeads of hydrochlorothiazide and losartan potassium were subjected to accelerated stability studies. The optimized capsule was packed in an aluminum pouch and placed in an accelerated stability chamber at 40°C with 75% RH for 1 month. Samples withdrawn after one month showed no significant change in the appearance of a capsule and drug content uniformity.

CONCLUSION:

The present study demonstrated the successful formulation and evaluation of a regioselective dual component capsule. In the dual component capsule, an immediate release layer of hydrochlorothiazide was prepared by dry granulation method using croscopovidone as super disintegrants and sustain release layer of losartan potassium microbeads using sodium alginate adopting ionotropic gelation method employing calcium chloride and blend of chitosan employing ionic and covalent crosslinking method. The drug excipients compatibility studies

were carried out using ATR and DSC. Spectra revealed that there was no interaction found between drugs and excipients used in the formulations. All the pre-compression studies revealed that the results were found to be within the official limits. In-vitro release studies reveal that the hydrochlorothiazide immediate release layer was found to be 98.41% within 120 minutes and the losartan potassium sustained release layer was 99.14% at the end of 12 hrs. Release kinetics showed good linearity by best fitting into Higuchi's model and stability studies showed no changes after exposing to accelerated conditions for a period of 1 month with respect to physical characteristics and in-vitro drug release studies.

From the above study, it can be concluded that the prepared regioselective dual component capsule achieved the objective of the research work in treating hypertension with the sequential release of two drugs. As these capsules reduce the dosage frequency and are cost-effective, they can be the best alternative to conventional dosage forms having more frequency of administration.

ACKNOWLEDGEMENT:

The authors are very thankful to the Sri Satya Sai University of Technology and Medical Sciences, Sehore, Bhopal (MP) for helping.

REFERENCE:

- [1] www.wikipedia.com.
- [2] Enyoma N Obineche. Management of hypertension: update and review. Bull The Kuwait Ins Med Spe. 2003; 2: 73-82.
- [3] www.webMD.com.
- [4] Ron Gasbarro. Hypertension: the use of combination therapy. 1999; 86-90.
- [5] Poonam Patil, Daksha Chavanke, Milind Wagh. A review on ionotropic gelation method: A novel approach for controlled gastroretentive gelspheres.
- [6] Kube Rahul S, Kadam V S, Shendarkar G R, Jadhav S B, Bharkad V B. Sustained release drug delivery system: a review. Int J Res Ph Biotech. 2015; 3(3): 246-251.
- [7] M M Gupta, Ray Brijesh. A review on sustained release technology. Int J Thera App. 2012; 8: 18-23.
- [8] N Anuj Patnaik, T Nagarjuna, T V Thulasiramaraju. Sustained release drug delivery system: a modern formulation approach. Int J Res Pharm Nano Sci. 2013; 2(5): 586-601.
- [9] Audumbar Digambar Mali, Ritesh Suresh Bathe. A review on sustained release drug delivery system. GCC J Sci Tech. 2015; 1(4): 107-123.
- [10] Pharma tutor.
- [11] K P Sampath Kumar, Debjit Bhowmik, Shweta Srivastava³, Shravan Paswan, A S Dutta. Sustained release drug delivery system potential. The Pharm Inno. 2012; 1(2): 46-56.
- [12] Vishal G Rathod, Vaishali Kadam¹, S B Jadhav, Md. Zamiruddin, V B Bharkad, Suprabha P Biradar. Immediate release drug delivery system: areview. World J Ph Pharm Sci; 2014; 3(6): 545-558.
- [13] Bhandari Neeraj, Kumar Abhishek, Choudhary Abhilash, Choudhary Rubia, Bala Rajni. A review on immediate release drug delivery system. Int Res J Pharm App Sci. 2014; 4(1): 78-87.
- [14] Nyol Sandeep, Dr. M M Gupta. Immediate release dosage form: A review. J Drug Deli Thera. 2013; 3(2): 155-161.
- [15] Arpita R Jaiswal, Maulesh R Vyas, Dr. Atanu Kumar Behera¹, Dr. Dhananjay B Mesharam. Colon targeted multiparticulate system: hydrogel beads. World J Ph Pharm Sci. 2014; 3(4): 507-525.
- [16] Krishnaveni Manubolu¹, Byna Sujatha¹, Munna Sreenivasulu, S RupeshKumar, S Naveen Kumar, K Bhaskar Rao. Formulation and in-vitro evaluation of gliclazide microbeads. World J Pharm Res. 2015; 4(5): 1970-1982.
- [17] Yogyata S Pathare, Seema Hiray, Fayeza A H. Formulation and characterization of micro particulate carriers for diclofenac sodium. The Pharm Inno J. 2013; 2(4): 92-96.
- [18] Avinash G K, S Parthiban, S K Senthil Kumar. Formulation and evaluation of ramipril beads for gastro-mucoadhesive drug delivery. Int J Curr Pharm Clini Res. 2013; 3(2): 55-63.
- [19] Kundlim M Girhepunje, Krisnapillai, Ranju S Pal, Hitesh B Gevariya, N Thiunmoorthy. Celecoxib loaded microbeads: a targeted drug delivery for colorectal cancer. Int J Curr Pharm Res. 2010; 2(1): 46-55.
- [20] Bhatt M B, Panchal B P, Patel N N, Bhimani B V, Patel G V, DR. Patel U L. Formulation and evaluation of ionotropically gelled novel hydrogel beads of valsartan. Int J Pharm Res Bio Sci. 2014; 3(2): 845-859.
- [21] W Zam, G Bashour, W Abdelwahed, W Khayata. Formulation and in-vitro release of pomegranate peels polyphenols microbeads. Int J Pharm Sci Res. 2013; 4(9): 3536-3540.
- [22] Himanshu K Solanki, Tarashankar Basuri, Jalaram H Thakkar, Chirag A Patel. Recent advances in granulation technology. Int J Pharm Sci Rev Res. 2010; 5(3): 48-54.
- [23] Sheth Vijay P, Ranpura Vicky D, Patel Vipul P, Atara Samir A, Desai Tusharbindu R. Steam granulation: novel aspects in granulation techniques. Int J Pharm Sci. 2012; 3(3): 2170-2184.
- [24] P Thejaswini, B Suguna, N Sumalatha¹, K Umasankar, P Jayachandra Reddy. Advanced granulation techniques for pharmaceutical formulations. Int J Res Pharm Nano Sci. 2013; 2(6): 723 - 732.
- [25] Patil Rohit, Dr. V A Jagtap, Dr. A V Patil, Dr. Suraj Sarode. A review on role of novel super disintegrants in pharmacy. Euro J Pharm Med Res. 2015; 2(3): 390-400.
- [26] www.Pharmatutor.org
- [27] Organic laboratory techniques.
- [28] Justin Bueno, Igor K Lednev. Attenuated total reflectance FTIR imaging for rapid and automated detection of gunshot residue. Anal Chem. 2014; 86(7): 3389-3396.

- [29] Subhash Chandra BP, Srikanth RP, Valluru R. Formulation and evaluation of sustained release floating tablets of diltiazem HCl using xanthan gum. *Res J Pharm Biological Chem Sci.* 2011; 2(2): 319-28.
- [30] Indian pharmacopoeia 2007; (1): 245-246.
- [31] Jani B R, Shah K V. Development and validation of analytical method for simultaneous estimation of valsartan and pioglitazone hydrochloride by simultaneous equation method. *Int J Pharm Res Scholars.* 2014; 3(3): 186-196.
- [32] J S Patil, S V Mandave, S M Jadhav. Ionotropically crosslinked and chitosan reinforced losartan potassium loaded complex alginate beads: design, characterization and evaluation. *Malaya J Bio Sci.* 2014; 1(3): 126-133.
- [33] Bhatt M B, Panchal B P, Patel N N, Bhimani B V, Patel G V, Dr. Patel U L. Formulation and evaluation of ionotropically gelled novel hydrogel beads of valsartan. *Int J Pharm Res Bio Sci.* 2014; 3(2): 845-859.
- [34] Anuranjita Kundu. Preparation and evaluation of sustained release microbeads of norfloxacin using sodium alginate. 2012; 2(3): 647-651.
- [35] Thulasi V Menon, C I Sajeeth. Formulation and evaluation of sustained release sodium alginate microbeads of carvedilol. *Int J Pharm Tech Res.* 2013; 5(2): 746-753.
- [36] J S Patil, S V Mandave, S M Jadhav. Ionotropically crosslinked and chitosan reinforced losartan potassium loaded complex alginate beads: design, characterization and evaluation. 2014; 1(3): 126-133.
- [37] B V Ramana, C S Parameswari, C Triveni, T Arundathi, Venkateswara Reddy, G Nagarajan. Formulation and evaluation of sodium alginate microbeads of simvastatin. *Int J Ph Pharm Sci.* 2013; 5(3): 410-416.
- [38] Vishal G Rathod, Vaishali Kadam¹, S B Jadhav, Md. Zamiruddin¹, V B Bharkad, Suprabha P Biradar. Immediate release drug delivery system. *World J Ph Pharm Sci.* 2014; 3(6): 545-558.