Section A-Research paper

Integrative Harmonizing Hypertension Management: A Study on Sustained Release of Losartan Potassium Coupled with Immediate Release of Hydrochlorothiazide

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Abstract

The objective of this study was to develop a losartan potassium sustained-release and hydrochlorothiazide immediate-release formulation for the treatment of hypertension. This can be achieved by formulating microbeads on the basis of a regular 32-factorial design. The microbeads of Losartan Potassium were prepared by an ionotropic gelation technique using excipients such as gellan gum, calcium chloride, and chitosan. Compatibility studies of drugs and polymers were performed by FTIR spectroscopy and DSC. A variety of measurements were carried out on the microbeads, such as measurement and drug entrapment efficiency, bulk density, compressebility index, Hausner's ratio, scanning electron microscopy, dissolution rate studies, and in vitro drug release. Sodium lauryl sulfate, sodium bicarbonate, croscarmellose, and sodium starch glycolate were used as excipients for hydrochlorothiazide immediate release granules. FTIR spectroscopy and DSC were used to conduct drug and polymer compatibility investigations for tablets made from hydrochlorothiazide quick-release granules. The tablets were then evaluated for bulk density, Carr's Compressibility index, Hausner's ratio, disintegration test, and uniformity of drug content. FTIR spectroscopy and DSC studies revealed that there was no possible interaction between drugs and polymers. The *in vitro* release of Losartan Potassium is within the limit. The minimum disintegration time of Hydrochlorothiazide immediate release tablets was found in formulation (GF7), which was selected as an optimized formulation. Granules of hydrochlorothiazide were found to contain the medicine in formulation (GF7), which was chosen as the best formulation. Losartan

potassium sustain-release microbeads and Hydrochlorothiazide immediate-release tablets were successfully prepared with improved bioavailability.

Keywords: Losartan potassium, Hydrochlorothiazide, Hypertension, Microbeads, Matrix tablet, Gellan gum, etc.

1. Introduction

An oral active nonpeptide angiotensin II (AII) receptor antagonist is losartan potassium. It is the first medication in a new class to be available for clinical use in treating hypertension. Greater blood pressure lowering occurs when losartan potassium and hydrochlorothiazide are taken together than when either medication is taken alone. The combination product has shown positive results in about one-third of individuals with severe hypertension. In senior patients, losartan potassium seems to be useful. It's quite easy to tolerate losartan potassium (Goa & Wagstaff, 1996; Kalra et al., 2010). One of the most commonly used antihypertensive drugs is diuretics (primarily thiazides), and diuretics are commonly recommended for beginning antihypertensive therapy alone or in combination with other antihypertensive medications. Cardiac Fibrosis, Cardiac Hypertrophy, and Rho-Kinase Activation are Reduced in DOCA-Salt-Induced Hypertension by Hydrochlorothiazide (Masumoto et al., 2001; Mondaca-Ruff et al., 2021). There is a need for frequent dosing of drugs that are easily absorbed by the gastrointestinal tract. In addition, there are drugs with a short half-life that can be eliminated rapidly from the systemic circulation. To triumph over this problem, gastro-retentive drug shipping systems, which offer powerful plasma drug awareness for longer intervals thereby lowering the dosing frequency, are being formulated. By administering the medication in a regulated and repeatable manner, it also has the benefit of minimizing changes in plasma drug concentration. The microbeads of Losartan Potassium were prepared by ionotropic gelation technique and Gellan gum, calcium chloride and chitosan are the excipients (Fareez et al., 2015; Panda et al., 2021). These formulation act as sustain release drug delivery system. Uniform dry powder mixture containing hydrochlorothiazide and excipients such as MCC (Avicel PH 101), sodium starch glycolate/croscarmellose/Crospovidone sodium, sodium lauryl sulfate (SLS), and sodium bicarbonate are used for the preparation tablet (Park et al., 2021; Ye et al., 2022). These formulation act as immediate release drug delivery system. Ionotropic Gelation Method involves the interaction of an ionic polymer with oppositely charged ions to initiate crosslinking. Unlike simple monomeric ions, the electro-neutrality principle cannot completely explain polyanion interaction with cations. Polyanions can form ion pairs with cations, resulting in complex electrostatic interactions. These ion pairs can further form

hydrogen bonds and other non-covalent interactions, which are key to polyanion stabilization. Cations' ability to conjugate with anionic functions or vice versa depends on their three-dimensional structure and other groups. Beads can be produced in two ways using the Ionotropic gelation procedure. The methods differ from each other in the source of the crosslinking ion (Adamiak & Sionkowska, 2020; Perez-Puyana et al., 2019). The cross-linker ion is externally positioned in one method while passively integrated into the polymer solution in the other. Ionotropic gelation techniques can be categorized as either external or internal. External methods involve the application of an external stimulus to cause gelation, while internal methods rely on the reaction of the components within the system to cause gelation. The external gelation method involves the use of a metal ion solution as a source of the crosslinking ion. A needle is used to inject the drug-containing polymer solution into this solution while gently stirring it. When the polymeric drop interacts with the metal ion solution, instantaneous gelation takes place, resulting in self-sustaining beads. The very porous surface of these beads enables the quick absorption of metal ions. The beads are therefore effective at adsorbing heavy metal ions from aqueous solutions. The beads are placed into the gelation medium and allowed to cure for a predetermined amount of time before being retrieved and dried. Once the beads are dry, they can be used in a variety of applications. The beads are highly durable and can be reused multiple times. They are also able to withstand extreme temperatures and pressures. The cross-linker ions diffuse quickly into the partially gelled beads, which causes the external gelation to happen. This process occurs rapidly, allowing for the formation of a strong gel matrix that can be used to immobilize and separate biological molecules. The gel matrix can then be used for a variety of applications, such as chromatography and electrophoresis. When adopting the internal gelation process, the cross-linker ion is created "in situ". In this method, insoluble metal salts like calcium carbonate and barium carbonate are used to form the cross-linking cation. The metal salt dissolves when the solution pH is lowered, releasing the metal ion and the cation in situ. This method is advantageous because the cross-linker ion is created as part of the gelation process rather than added separately. This saves time and resources, making it a more efficient process (Mikula et al., 2019; Qasem et al., 2021). Emulsion gelation procedures are another way to prepare microbeads. The sodium alginate solution is made by dissolving the weighed quantity of sodium alginate in deionized water. The solution is then stirred until a homogeneous mixture is obtained. The solution is then heated and stirred until all of the sodium alginate is dissolved. The solution is then cooled before use. To create a homogenous drug polymeric mixture, a precisely weighed amount of drug is added to the sodium alginate polymeric solution and swirled magnetically with low heat. A specific volume of the crosslinking agent is added to form a viscous dispersion, which is then extruded through a syringe with a flat-tipped needle of size no.23 into oil containing span 80 and 0.2% glacial

acetic acid being stored below magnetic. Oral administration is the most favored route for systemic effects because of its simplicity, absence of discomfort, avoidance of adverse effects, adaptability, and most importantly, patient compliance. However, there are also drawbacks associated with oral administration. For example, substances taken orally are often rapidly metabolized by the digestive system and may not reach the desired target area in their active form. Additionally, some substances are not able to be absorbed through the digestive system and must be administered through other routes. Additionally, since they don't have to be created in sterile circumstances, solid oral delivery systems are less expensive to manufacture. This cost savings is passed on to the consumer, making solid oral delivery systems an affordable option for those who need medication. Solid oral delivery systems also offer better bioavailability, meaning the body absorbs the medication more quickly and effectively. Tablets are the preferred solid dosage form because to patient compliance, highly precise dosing, and efficient production. These selections will have a big impact on excipient and equipment choices if solid dosage form technologies develop in response to amazing advancements in drug discovery, including genomics. These selections will have a big impact on the cost and efficiency of manufacturing, as well as the design of the final product. In addition, the selection of excipients and equipment will need to be tailored to the specific drug, dosage form, and desired release profile. Patients typically do not choose to use injections until sophisticated auto injectors make it possible. Although inhalation is a viable alternate delivery method for many medications, current biopharmaceutical research has largely produced chemical compounds with modest molecular weights. The development of improved oral protein delivery technology via instant-release tablets, which may release pharmaceuticals at a faster pace, is particularly promising for the delivery of poorly soluble drugs such as high-molecular-weight proteins and peptides. This technology has the potential to revolutionize the way drugs are delivered, allowing for a more rapid onset of therapeutic effects and improved patient compliance. Furthermore, this could reduce the number of doses needed and potentially provide improved drug delivery to hard-to-reach areas of the body. The oral route is still the most effective means of administering therapeutic medications. This is because of its low therapy cost, ease of manufacture, and high patient acceptance. Furthermore, oral medications are absorbed more efficiently than other routes of administration, such as intravenous or subcutaneous injections. Additionally, they have fewer adverse effects than other types of medications due to the fact that they are not instilled directly into the bloodstream (Baryakova et al., 2023; Gupta et al., 2022). This is a new enhanced oral product that has emerged in this market segment and is applicable to a wide range of

medicinal agents. Approximately one-third of patients require immediate therapeutic activity from a medicine, resulting in poor adherence to conventional drug therapy and diminished total therapy effectiveness. This new product helps reduce the number of doses needed, leading to improved patient compliance. It also improves the therapeutic activity of the medicine, providing better outcomes for the patient. A new dosage format, the immediate release pharmaceutical form has been developed which offers the combined advantages of ease of dosing and convenience of dosing.These pills are designed to launch the medicaments with an more advantageous rate. Due to the limitations of current technologies, as discussed above, there is an unmet need for enhanced manufacturing methods for immediate-release pharmaceutical forms that are mechanically strong, allow for ease of handling and packaging, and have production costs comparable to conventional tablets. To meet these medical needs, formulators have worked hard to create a novel tablet dosage form for oral administration. This is one that disintegrates and dissolves quickly with increased solubility. An extension of market exclusivity, which can be granted by an immediate-release dosage Form, ends in extended sales even as additionally focused on underserved and undertreated affected person populations. This type of dosage form provides faster and more efficient medication delivery while improving patient compliance and satisfaction. Furthermore, it can improve clinical outcomes and reduce healthcare costs. The use of sustained release microbeads and immediate release granules can create a more effective and efficient delivery of drugs to the body. Sustain release microbeads are used to create targeted drug delivery systems, allowing for more efficient and accurate treatments. The development of immediate release granules has the potential to revolutionize the pharmaceutical industry.

2. Material and Methods

2.1. Chemicals and excipients

The gift sample comes from Scan Research Laboratories in Bhopal and contains hydrochlorothiazide and losartan potassium. Hydrochloride, sodium chloride, dipotassium hydrogen orthophosphate, and disodium hydrogen phosphate are all produced by S. D. Fine Chem. Ltd. in Mumbai. Methanol, ethanol, and chloroform are available from Mumbai's Qualigens Fine Chemicals. Mumbai-based Meru Chem Pvt. Ltd.'s sodium hydroxide Chitosan from Mumbai's Hi Media. From Loba Chemie Pvt Ltd. in Mumbai, we

can obtain calcium chloride, sodium starch glycolate, croscarmellose sodium, crospovidone, sodium lauryl sulfate, microcrystalline cellulose, and talc.

2.2. Making microbeads

Losartan Potassium microbeads were created using ionotropic gelation. Microbeads have effective drug loading and release properties and are well-suited to oral and topical delivery. They also have a high degree of drug stability and are resistant to enzymatic degradation. This makes them a promising option for pharmaceutical applications (Mokale et al., 2014; Pedroso- Santana & Fleitas- Salazar, 2020). First, gellan gum was dissolved in deionized water, and then the solution was heated to 60 °C. Each batch was given 50 ml of gellan gel. A different drug concentration was uniformly dissolved in the gel while held at 40°C and continually stirred. The gel was then poured into a Petri dish for cooling and solidification. After solidification, the gel was cut into 1-cm cubes and placed into individual vials for further testing.

The churning was continued until the medicine was evenly distributed. The resultant homogeneous slurry was mixed with a 50-ml solution of calcium chloride and chitosan in different concentrations. The mixture was stirred for 15 minutes and then allowed to settle for 30 minutes. The settled material was collected and dried for 48 hours at room temperature. The dried material was then subjected to further analysis. Table 1 lists the ingredients of the various formulations created for the current study.

2.3. Preparation of granules for tablet

In a polyethylene bag, a uniform dry powder mixture containing hydrochlorothiazide and excipients such as MCC (Avicel PH 101), sodium starch glycolate/croscarmellose/crospovidone sodium, sodium lauryl sulfate (SLS), and sodium bicarbonate was placed. The powder mixture was compressed into tablets using a single-punch tablet machine. The tablets were then evaluated for hardness, friability, weight variation, and drug content. The results showed that the tablets had satisfactory physical characteristics (De Oliveira et al., 2014; De Salvi et al., 2015).

The mixture was then granulated using 1% w/w PVP K-30 in water as granulation fluid. Following extrusion, the extrudates of the wet granulation mixture became spherical. The pellets were dried in a hot air oven at 40°C for 10–12 hours. After drying, the pellets were loaded and stored in screw-capped high-density polyethylene bottles. The pellets were then sieved using a sieve shaker to obtain particles in the size

range of 0.5–1 mm. Finally, the pellets were subjected to a hardness test to ensure reliability and uniformity.

2.4. Compatibility Study

In order to determine the compatibility, FT-IR spectroscopy and DSC were used to characterise the pure drugs Losartan Potassium and Hydrochlorothiazide as well as the solid admixer of drug and various excipients used in the creation of sustained release capsule formulation and immediate release tablet formulation.

2.5. Evaluation of Microbeads and Granules

Microbeads were tested for parameters such as beads size, drug entrapment efficiency, bulk density, compressibility index, surface morphology, and dissolution rate studies. Granules were tested for bulk density, compressibility index, disintegration time, and drug content uniformity. The results of these tests showed that microbeads had a higher drug entrapment efficiency and a larger particle size than granules. Granules, however, had a higher bulk density and compressibility index.

2.6. Beads size

Beads size of prepared microbeads was determined using zeta sizer (Malvern zetasizer instrument, India) (Doherty et al., 2011; Lu et al., 2018). The microbeads formulation was diluted with deionized water and analysed for average size.

2.7. Drug entrapment efficiency

The amount of drug in the beads was estimated using the digestion method. This required grinding up a known quantity of drug-loaded beads (20 mg) in a glass mortar and pestle before soaking them in 0.1 N HCl at room temperature for an hour to extract the drug fully. The solution was then filtered, and the drug concentration was determined by UV spectrophotometry. The amount of drug present in the beads was calculated using a standard curve. Based on the results, the drug was released from the beads controlled by the experiment (Kiran et al., 2019; Zhang et al., 2017).

2.8. Bulk density

The bulk density can be determined by measuring the volume of a known quantity of powder sample that has been passed through a screen and into a graduated cylinder or cup. The volume of the powder sample is then compared to the mass of the sample to calculate the bulk density. Bulk density is a measure of the mass of a given volume of

powder and is used to determine proper packaging and storage (Nayak AK et al., 2011). It can be calculated as per given formula:

Bulk density = Bulk Mass/ Bulk Volume

2.9. Compressibility index (C.I.)

It is an effective measure based on bulk and tapped densities. Carr's index is a free-flowing material with values ranging from 20% to 30%. It is defined as a substance that flows freely. Bulk density measures the mass of a given volume, and tapped density measures the mass of a given volume of the material that is tapped or vibrated. Carr's Index is a ratio of the tapped to bulk density to determine the degree of cohesiveness of a material. It can be calculated as per given formula:

$$C.I. = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} x100$$

2.10. Surface morphology

The scanning electron microscope was used to analyze the surface morphology of the beads. The results showed that the beads had a granular structure with an average particle size of 7.2 μm. The surface of the beads had a small number of cracks and pores, indicating a high degree of porosity (Jeol, JSM, 35CF, Japan) (Gazmer et al., 2023; Patil et al., 2011). The beads were attached to unique stabs and covered in 100- and 50-thick layers of gold and carbon, respectively. The coated samples were examined using a 7 kV scanning electron microscope. The samples showed that the gold and carbon layers were homogeneously distributed. The results proved that the coating method was successful in creating the desired surface finish.

2.11. Disintegration Time

The disintegration time of the granules was measured in water (37 ± 2°C) according to using Digital Tablet Disintegration Tester (EI, India) Markl & Zeitler, 2017; Steffens & Wagner, 2021). The duration in seconds required for the tablet to completely dissolve with no discernible bulk remaining inside the device was calculated. The tubes were filled with 100 mg of pellets and put in the typical tablet disintegration testing. The disintegration period of six dried samples at 37°C was calculated at 30 dips. The results showed that the disintegration time increased with the increase in the number of dips. The maximum disintegration time was observed at 30 dips. The results were consistent with the expected results. For each formulation, a disintegration test was conducted three times, with the results being expressed.

2.12. Drug content uniformity

The formulations (F1 to F9) were each finely dissolved in 10 ml of 0.1N HCl (simulated gastric fluid of pH 1.2 without enzymes), sonicated for 20 minutes to cause the entire drug to leach out of the complex, and then the solution was filtered through Whatman filter paper No. 41. 1 ml of this solution was taken, diluted with 0.1 N HCl to 100 ml, and tested spectrophotometrically for hydrochlorothiazide at 282.0 nm. The absorbance was measured and compared with the standard curve of hydrochlorothiazide. The amount of drug present in each formulation was then calculated. The results were tabulated and compared with the theoretical value (Bhoyar et al., 2010).

2.13. Dissolution rate studies

A USP-type II dissolution device (the paddle type) was used to administer the drug in vitro. The dissolution flask was filled with 900 ml of 0.1 N HCl and kept at a constant temperature and rotational speed of 75. Every dissolution device container was filled with one microbead of losartan potassium. The mechanical setup operated for ten hours. 5 ml of the sample was taken back using a 10-ml pipette every hour for up to 2 hours. Each time, a comparable volume of the material was added to the freshly prepared disintegration medium (37 oC), and the absorbance at 276.0 nm was measured using spectroscopy. The sample was stirred at 100 rpm for 30 minutes. The supernatant was then filtered, and the absorbance of the filtrate was determined. The rate of dissolution was calculated from the absorbance data.

3. Results

The different batches of Losartan Potassium microbeads were by ionic gelation method using various ingredients like gellan gum, chitosan, calcium chloride and different batches of Hydrochlorothiazide instant layer tablets were prepared by using various ingredients such as sodium starch glycolate, croscarmellose sodium, crospovidone, sodium lauryl sulfate, microcrystalline cellulose etc (Table 1).

Table 1: Array layout as 3^2 factorial screening designs between Batch F1-F17

F. Code	Std	Run	Factor 1:A Gellan gum	Factor 2:B Chitosan	Factor 3:C Calcium chloride
F1	7	1	50	25	5
F2	15	2	100	25	3.5
F3	12	3	100	40	5
F4	9	4	100	10	2
F5	13	5	100	25	4
F6	16	6	100	25	2
F7	17	7	100	25	5
F8	3	8	50	40	3.5
F9	4	9	150	40	3.5
F10	6	10	150	25	2
F11	8	11	150	25	5
F12	14	12	100	25	4.5
F13	2	13	150	10	3.5
F14	10	14	100	40	2
F15	5	15	50	25	2
F16	11	16	100	10	5
F17	1	17	50	10	3.5

Table 2: Wet granulation formulation of Batch GF1-GF9.

Ingredients(mg)	Formulation code								
	GF1	GF2	GF3	GF4	GF5	GF6	GF7	GF 8	GF 9
Hydrochlorothiazide	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Sodium Starch glycolate	10	20	30	-	-	-	-	-	-
Croscarmellose sodium		-	-	10	20	30	5	10	15
Crospovidone		-	-	-	-	-	5	10	15
Sodium lauryl sulfate	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose	80	80	80	80	80	80	80	80	80
Talc	10	10	10	10	10	10	10	10	10
Total weight	100	100	100	100	100	100	100	100	100

The findings from the FT-IR and DSC analysis indicated no evidence of interaction occurring between Losartan potassium and the excipients, as well as between Hydrochlorothiazide and

the excipients (Figure 1 and 2 for FT-IR) and Figure 3 for DSC). Melting point of Losartan potassium and Hydrochlorothiazide are found to be 263-265°C and 273-275 °C.

Losartan potassium was found to be freely soluble in water, 0.1 N HCl, ethanol, and methanol, soluble in 7.4 pH phosphate buffer, slightly present in chloroform and 0.1 N NaOH, and hydrochlorothiazide was found to be freely available in water, 0.1 N NaOH, ethanol, and 0.1 N HCl, sparingly found in chloroform, and slightly present in water. Losartan potassium was also found to be insoluble in acetone, ether, and ethyl acetate, while hydrochlorothiazide was insoluble in acetone and ether. Both substances were slightly soluble in ethyl acetate.

The percentage of loss on drying of Losartan potassium and Hydrochlorothiazide were found to be 0.178±0.003% w/w and 0.124±0.005% w/w respectively. Losartan potassium has a larger percentage of loss on drying than Hydrochlorothiazide, indicating it is more water-soluble. The developed formulation's beads size was between 335.65 and 520.36nm. The entrapment efficiency of produced microbeads ranged from 65.21 to 75.23 percent. The microbeads were found to be spherical in shape. The results showed that the microbeads had better physicochemical characteristics compared to the physical mixture. The results suggested that the microbeads could be an effective way to deliver the drugs.

Four formulations were chosen as optimized formulations for the manufacturing of sustained-release microbeads since the experimental values for microbead composition are more or less identical to the expected values and are also within limits (Table 3). The optimized formulation was found to have superior properties, such as sustained release, compared to conventional formulations. Therefore, it can be concluded that the optimized formulation is suitable for sustained-release drug delivery.

Table 3: Experimental results with predicted responses

Formulation	Composition (mg) Gellan gum (mg) /Chitosan (mg)/ Calcium chloride (%)	Response	Experimental value	Predicted value
OF1	100/25/3.5	Beads size (nm)	425.85	425.37
		Entrapment Efficiency (%)	75.23	74.72
OF2	100/25/2	Beads size (nm)	462.45	459.68
		Entrapment Efficiency (%)	74.69	76.39
OF3		Beads size (nm)	435.87	440.22

	100/25/4.5	Entrapment Efficiency (%)	74.65	72.75
OF4	100/40/2	Beads size (nm)	375.65	373.79
		Entrapment Efficiency (%)	77.85	77.16

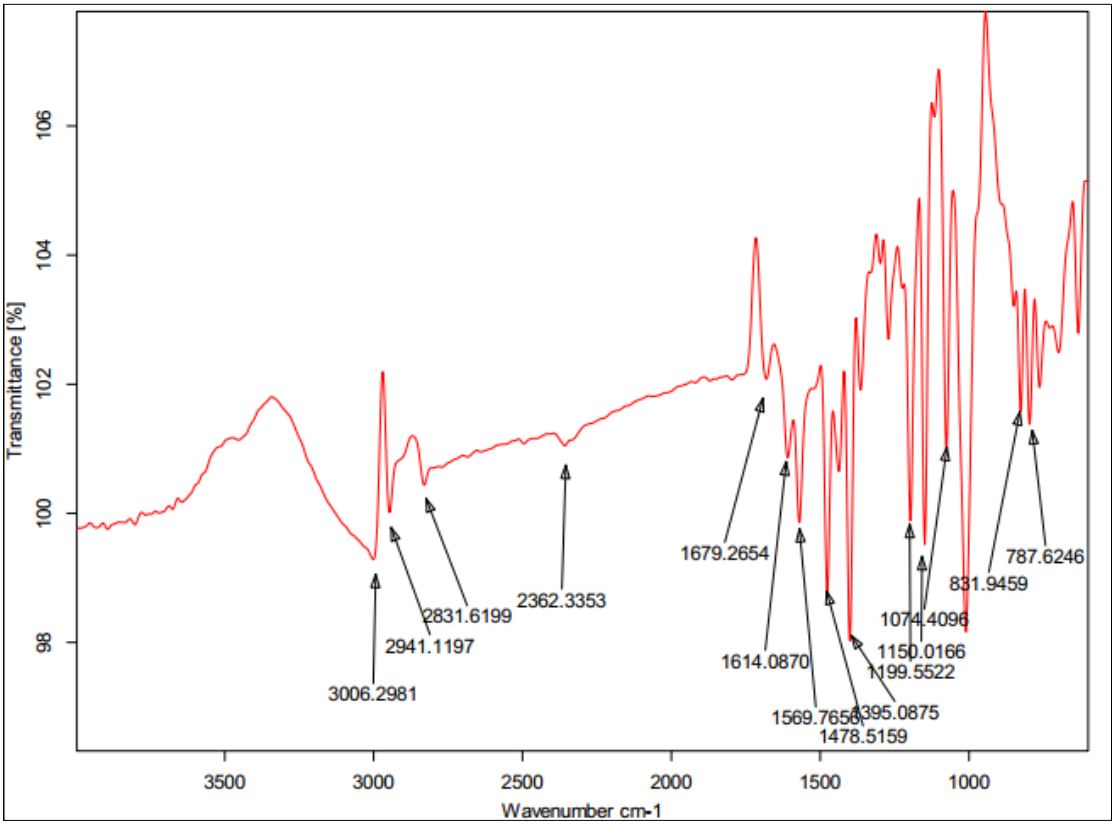


Figure 1: Pure medication (Losartan potassium) FT-IR spectrum

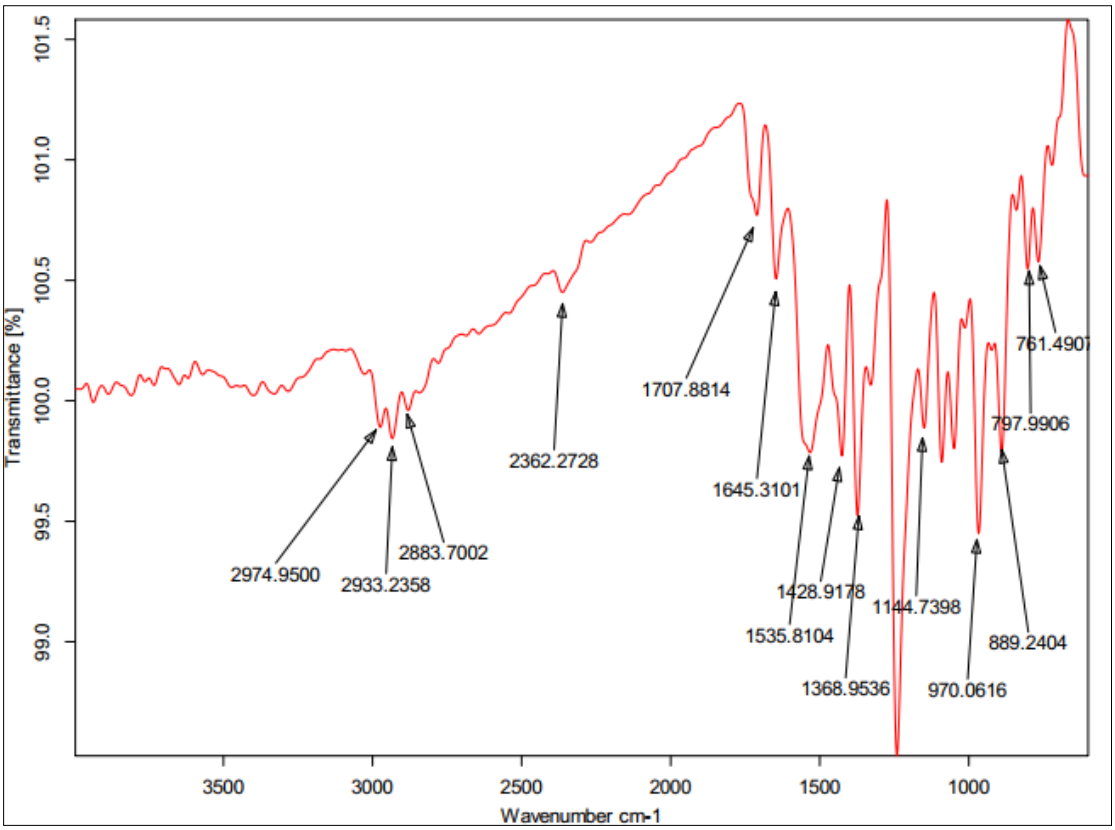
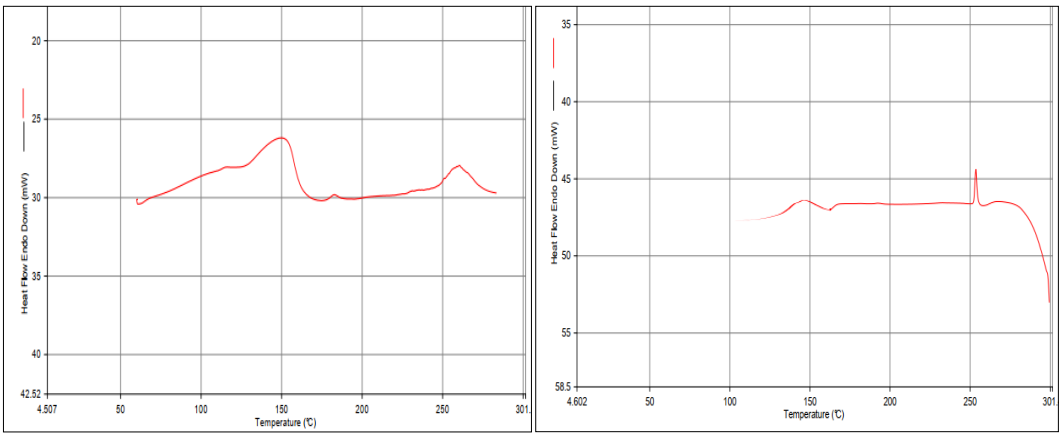
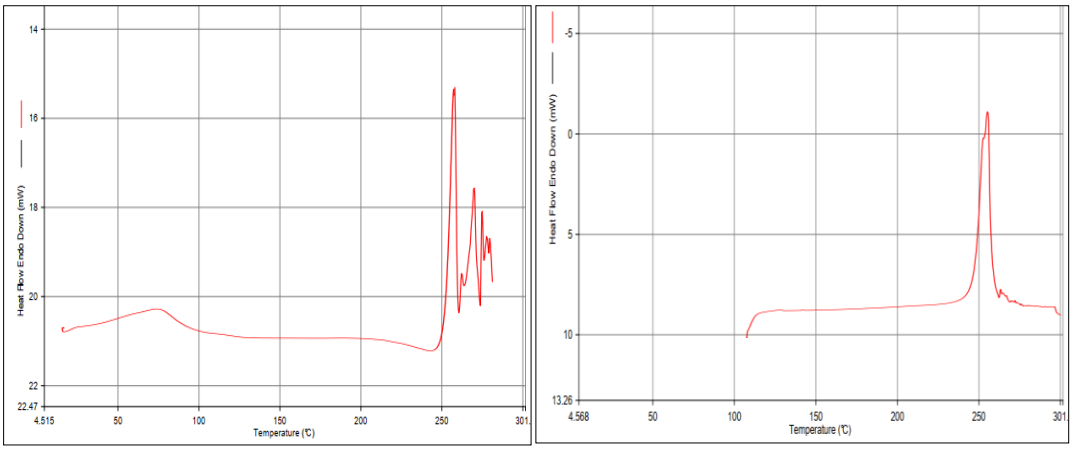


Figure 2: Pure medication (Hydrochlorothiazide) FT-IR spectrum



(a) **(b)**



(c) **(d)**

Figure 3: DSC thermogram of (a) pure drug Losartan Potassium, (b) Hydrochlorothiazide, (c) Losartan Potassium and All Excipient, (d) Losartan Potassium and Hydrochlorothiazide

In-vitro drug release investigations were conducted using the USP XXIII dissolution test apparatus II at 50 rpm and 900 mL of 1.2 pH buffer kept at 370.5 oC as the dissolving medium. When compared to other batches, batch OF4 exhibits sustained drug release (Figure 4). The cumulative% drug release for batch OF4 ranged from 25.65 to 99.45. Batch OF4 was found to have the best drug release profile. The release rate was found to be sustained over a period of 12 hrs. The drug release was found to follow Higuchi Kinetics.

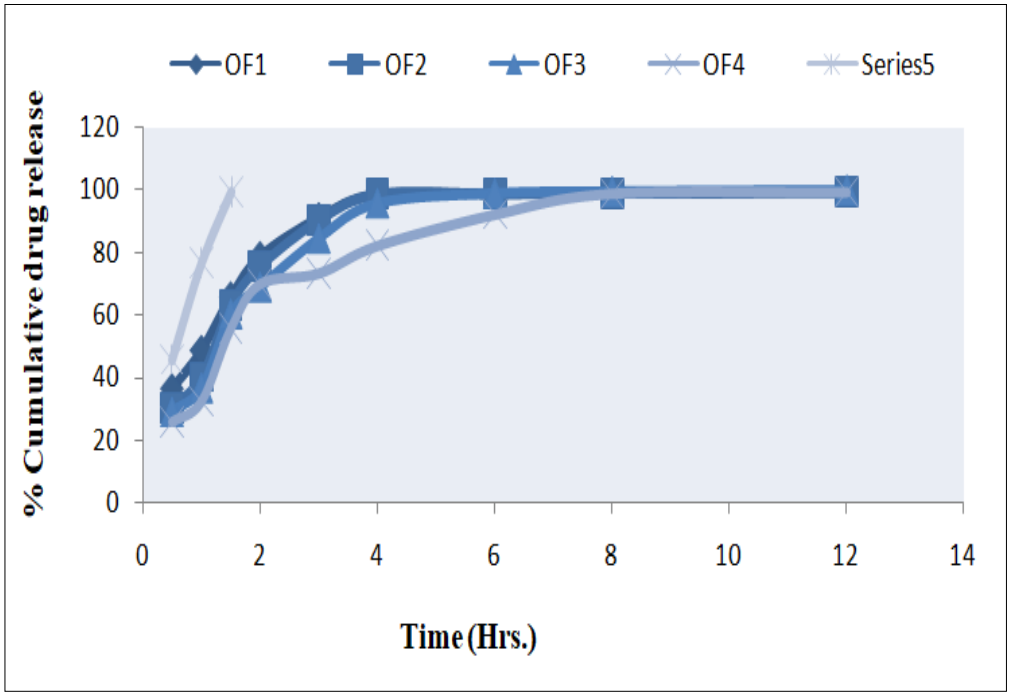


Figure 4: *In-vitro* drug release study of matrix tablets

The granules of various formulations were examined for their loose bulk density (LBD) and tapped bulk density (TBD). For all formulations, the bulk density and tapped density ranged from 0.365 to 0.385 g/cm3 and 0.431 to 0.469 g/cm3, respectively. The LBD and TBD values of the granules were found to be in the acceptable range. The results showed that the formulations had good flow properties and could be easily filled in the capsules. All formulas' Hausner's ratio results range from 1.278 to 1.321. This indicates that the formulas are cohesive and free-flowing. The uniformity of the results suggests that the formulas are well-balanced and consistent. This is an important factor when assessing the quality of a product. The compressibility index ranges from 21.748% to 24.274% for all formulations. The disintegration time of hydrochlorothiazide granule formulation batches GF1–GF9 is between 105 ± 3 and 75 ± 2. The dissolution time of hydrochlorothiazide granule formulation batches GF1–GF9 is between 9.06 and 8.48 minutes. The dissolution efficiency of the granules is between 68.35% and 74.15%. The flowability of granules is good for all formulations. The minimum disintegration time was found in formulation GF7 (45±5). The drug content of hydrochlorothiazide granules are found to be between 98.85±0.15 and 96.85±0.22. The minimum disintegration time and maximum percentage assay was found in formulation formulation GF7.

When the regression coefficient values were compared, it was discovered that Korsmeyer-Peppas had the highest r-value, 0.938, showing that drug release from these formulations followed Korsmeyer-Peppas release kinetics. This demonstrates that Korsmeyer-Peppas is the most suitable model to predict drug release from these formulations. The results are also consistent with previous studies on drug release from polymeric matrices (Table 4).

Table 4: Regression analysis data of matrix tablets

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	r^2	r^2	r^2	r^2
OF4	0.773	0.961	0.908	0.938

4. Discussion

The different batches of Losartan potassium sustain release beads were prepared by the ionotropic gelation method using various ingredients such as gellan gum, chitosan, and calcium chloride. Four formulations with varying quantities of gellan gum, chitosan, and calcium chloride were created and tested. The results showed that the formulation with the

highest amount of gellan gum had the best stability. This suggests that gellan gum could be an effective stabilizer for this product. Wet granulation was used to make and test hydrochlorothiazide immediate-release tablets with various additives such as sodium starch glycolate, croscarmellose sodium, crospovidone, sodium lauryl sulfate, and others. Table 3 shows the results. The tablets produced were evaluated for their hardness, friability, disintegration time, and dissolution profiles. The results showed that all the tablets had acceptable hardness, friability, and disintegration times. However, the dissolution profiles varied significantly depending on the type of additive used. The results of the FT-IR and DSC studies show that there is no potential for interaction between hydrochlorothiazide and its excipients or between losartan potassium and excipients. A binding agent is gellan gum, and a dissolving agent is sodium starch glycolate. As an optimized formulation, batch OF4 and GF7 were chosen. After one month, according to the stability study, there was no change

5. Conclusion

Losartan potassium sustained-release microbeads offer a slow and sustained release of the medication over some time. This permits a quick release and a more consistent, stable therapeutic impact. Granules of hydrochlorothiazide provide a quicker onset of action, which is advantageous for patients with sudden symptoms. Combining the two medications can be beneficial for patients with hypertension as they can provide both immediate and sustained relief from symptoms. Combining losartan potassium sustained-release microbeads with immediate release Hydrochlorothiazide granules can be a beneficial treatment option for patients with hypertension. The two drugs taken together relieve symptoms quickly and over time. Before starting any prescription regimen, it is crucial to speak with a healthcare provider. The healthcare provider can advise on the best medication and provide guidance to ensure the best results. It is important to follow the healthcare provider's instructions and take medications as prescribed. It is also important to report any side effects to the doctor.

Conflict of interest statement

We declare that we don’t have conflict of interest.

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