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**DEVELOPMENT AND EVALUATION OF A COMBINATION
FORMULATION OF LOSARTAN POTASSIUM AS A SUSTAINED-
RELEASE COMPONENT AND HYDROCHLOROTHIAZIDE AS AN
IMMEDIATE-RELEASE COMPONENT**

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ABSTRACT

According to the Prospective Studies Collaboration, lowering blood pressure can significantly lower cardiovascular risk, cardiovascular mortality, and all-cause mortality. When baseline blood pressure is high, this risk reduction is steeper in younger people than in older subjects. Reducing both systolic and diastolic blood pressure was found to prevent cardiovascular events in a meta-analysis of 61 studies with more than a million hypertensive patients and 12.7 million years of follow-up (Turnbull *et al.*, 2005). The Box-Behnken design was effective in formulating microbeads of losartan potassium. The analysis of variance (ANOVA) revealed that the microbeads formulations were significantly affected by the independent variables. The interaction between two variables, namely, the amount of Gellan gum, Chitosan and Calcium chloride, had a significant effect on the properties of the microbeads. The microbeads with the highest encapsulation efficiency were obtained when the amount of Gellan gum was 100mg, Chitosan 40mg and 2% Calcium chloride. The optimized formulation of microbeads had a mean particle size of 375.65nm and a spherical shape with good flowability. These results suggest that the Box-Behnken design is an effective method for formulating losartan potassium microbeads. Further Hydrochlorothiazide granules were prepared and evaluated, the formulation of immediate release granules of hydrochlorothiazide is a promising approach to improve the bioavailability of the drug and reduce its side effects. Further research and

optimization of the formulation is necessary to fully understand the impact it can have on patient outcomes.

Keywords: Losartan potassium, Hydrochlorothiazide, Sodium alginate Crospovidone, UV spectrophotometry

INTRODUCTIONS

In India and other countries, high blood pressure (BP) is a significant public health issue. It is a significant cardiovascular risk factor and has a large impact on cardiovascular mortality [1]. Reducing both systolic and diastolic blood pressure was found to prevent cardiovascular events in a meta-analysis of 61 studies with more than a million hypertensive patients and 12.7 million years of follow-up [2]. A two-pronged strategy is used for the initial management of hypertension, with a focus on lifestyle changes and additional pharmacological management [3]. Exercise is crucial, especially for hypertensive children and adolescents who frequently have elevated sympathetic nervous system activity. Many hypertension patients experience stress, which worsens their blood pressure [4]. Numerous long-term studies, including phase 2 of the Trials of Hypertension Prevention (TOHP2) [5] and the Trials of Non-pharmacological Interventions in the Elderly (TONE), have addressed this topic [6]. Dietary changes are a mainstay for both hypertension prevention and beginning treatment. Moderation should be used when drinking [7]. The most convincing data regarding how salt affects

blood pressure comes from tightly controlled, dosage response experiments [8]. The DASH-Sodium trial [9], the largest dose response study, examined the effects of three different amounts of sodium intake in two different diets: the DASH diet and a control diet (more typical of what Americans eat). Additionally, studies have shown that decrease in salt consumption can lower blood pressure when using antihypertensive medications, prevent hypertension (relative risk reduction of roughly 20% with or without concurrent weight loss), and help manage hypertension [10]. High BP can be viewed as a sign to monitor the patients' clinical status; or a risk factor for atherosclerotic cardiovascular disease or as a disease and major contributor to death from cardiac, cerebrovascular, renal or peripheral vascular disease. It has been recommended that pharmacological therapy should be initiated early if the targets are not achieved by lifestyle changes alone [11]. Patients with diabetes mellitus and hypertension have twice the risk of cardiovascular disease as non-diabetic hypertensive patients. In addition, hypertension increases the risk of diabetic retinopathy and nephropathy [12].

Techniques used for formulation of microbeads:

Emulsion Gelation Method:

Another method of microbead preparation is emulsion gelation techniques. The sodium alginate solution is prepared by dispersing the weighed quantity of sodium alginate in deionized water. An accurately weighed quantity of drug is added to the polymeric

solution of Sodium alginate, and the drug is stirred magnetically with gentle heat to get a homogenous drug polymeric mixture. 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 kept under magnetic.

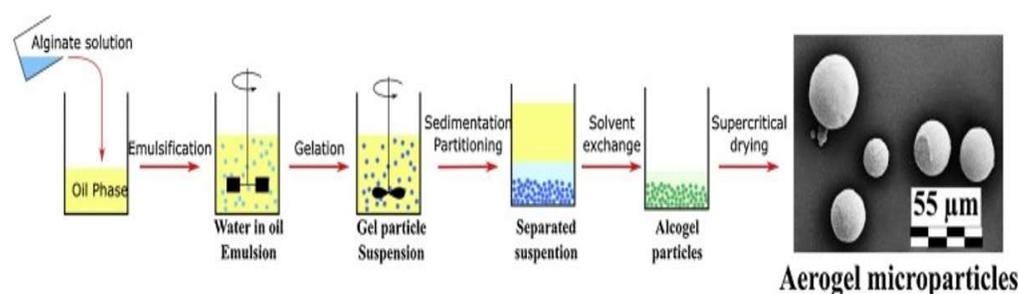


Figure 1: Emulsion Gelation Method

Immediate release dosage forms

The development of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. Because of the low cost of therapy, convenience of manufacturing, and high levels of patient compliance, the oral route is still the best way to administer therapeutic drugs [13].

MATERIAL AND METHODS

Losartan potassium and Hydrochlorothiazide from Gift sample from Scan Research Laboratories, Bhopal. Disodium Hydrogen Phosphate, Di potassium Hydrogen

Orthophosphate, Sodium Chloride from and Hydrochloride from S. D. Fine Chem. Ltd., Mumbai. Methanol, Ethanol and Chloroform from Qualigens Fine Chemicals, Mumbai. Sodium hydroxide from Meru Chem Pvt. Ltd. Mumbai, Chitosan from Hi media, Mumbai. Calcium chloride, Sodium Starch glycolate, Croscarmellose sodium, Crospovidone, Sodium lauryl sulfate, Microcrystalline cellulose and Talc from Loba Chemie Pvt Ltd. Mumbai.

Methods:

Results of preformulation studies

Preformulation studies are conducted to evaluate the physical and chemical properties of a drug substance, to determine its suitability for use in the formulation of a

drug product. The results of preformulation studies can include information about the physical state of the drug substance, its solubility in various solvents, its hygroscopicity, its melting point, its particle size and size distribution, its surface area and porosity, its physical stability, its chemical stability, and its compatibility with other ingredients in the formulation. Preformulation studies can also provide information about a drug substance's pharmacokinetic properties, including its absorption, distribution, metabolism, and excretion profile.

Preparation of calibration curve of Losartan potassium and Hydrochlorothiazide

(a) Calibration curve in 0.1 N HCl: 10 mg of Losartan potassium and Hydrochlorothiazide was weighed accurately and dissolved in 5 ml of 0.1 N HCl in a 10 ml of volumetric flask and volume was made up to 10 ml with the 0.1 N HCl. The resulted solution 1000 μ g/ml and from this solution 1 ml was pipette out, transferred to a 10 ml volumetric flask and volume was made up with 0.1 N HCl solution. Further, suitable dilutions from stock were made to a solution in concentration range of 5-25 μ g/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+). The absorbances of these solutions were measured at 276nm and

282nm against a blank 0.1 N HCl respectively. The calibration curve was obtained by plotting the absorbance versus the concentration. The straight line of best fit was obtained by using linear regression analysis program.

(b) Calibration curve in methanol: 10 mg of Losartan potassium and Hydrochlorothiazide was weighed accurately and dissolved in 5 ml of methanol in a 10 ml of volumetric flask and volume was made up to 10 ml with methanol. This resulted in a solution with 1000 μ g/ml concentration. From this solution 1 ml was pipette out, transferred to a 10 ml volumetric flask and volume made up with methanol. Suitable dilution was prepared to make different concentration in the range of 5-25 μ g/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+). The absorbances of these solutions were measured at 276nm and 282nm against a blank methanol respectively. The calibration curve was obtained by plotting the absorbance versus the concentration. The straight line of best fit was obtained by using linear regression analysis program.

Formulation of sustain release microbeads of Losartan potassium

Formulation development by box-behnken design

A 3-factor, 2-level BBD was used to explore and optimize the main effects, interaction

effects, and quadratic effects of the formulation ingredients on the performance of the microbeads. A 3-factor, 2-level BBD requires 17 experimental runs with three central points to determine the experimental

error and the precision of the design. A total of 17 experimental runs were generated and evaluated using Design-Expert software (11.0.4.0; Stat-Ease Inc., Minneapolis, Minnesota).

Table 1: List of variables employed in 3² factorial designs

Factors	Levels	
	Low (-1)	High (+1)
Losartan Potassium (mg)	50	
Gellan gum (mg)	50.00	150.00
Chitosan (mg)	10.00	40.00
Calcium chloride (%)	2.00	5.00

Method for preparation of microbeads containing Losartan Potassium:

The microbeads of Losartan Potassium were prepared by ionotropic gelation technique [14]. Firstly, gellan gum solution was prepared by dissolving gellan in deionized water and followed by heating it at 60°C. About 50 ml of the gellan gel from each batch was taken separately and a different concentration of drug was dispersed

uniformly in the gel maintained at 40°C, with continuous stirring. The stirring was further continued until uniform dispersion of drug was achieved. The resultant homogenous slurry was dropped into a 50 ml solution containing different concentrations of calcium chloride and chitosan. The compositions of various formulations designed in the present study are given in **Table 2**.

Table 2: Array layout as 3² factorial screening designs

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

ANOVA for Quadratic model

Table 2: Response (Bead size)

Source	Sum of Square	df	Mean Square	F-Value	P-Value	
Model	45468.73	9	5052.08	187.21	< 0.0001	significant
A-Gellan gum	1297.19	1	1297.19	48.07	0.0002	
B-Chitosan	53.77	1	53.77	1.99	0.2010	
C-Calcium chloride	1.32	1	1.32	0.0488	0.8315	
AB	15450.49	1	15450.49	572.53	< 0.0001	
AC	990.68	1	990.68	36.71	0.0005	
BC	21694.34	1	21694.34	803.91	< 0.0001	
A ²	19.76	1	19.76	0.7321	0.4205	
B ²	869.49	1	869.49	32.22	0.0008	
C ²	3703.74	1	3703.74	137.25	< 0.0001	
Residual	188.90	7	26.99			
Cor Total	45657.63	16				

Evaluation of flow properties of microbeads

There are many formulations and process variables involved in mixing step and all these can affect characteristics of prepared beads, bulk density, true density and percent compressibility index have been measured.

Bulk density

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup [15]. Calculate the bulk density, in gm per ml gm/ml, by the formula

$$\text{Bulk density} = \text{Bulk Mass} / \text{Bulk Volume}$$

Compressibility index (Carr's index):

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material. It can be calculated as per given formula:

$$C.I. = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio:

It indicates the flow properties of the powder and it can be measured by the ratio of tapped density to bulk density.

$$\text{Hausner ratio} = \text{Tapped density} / \text{Bulk Density}$$

Scanning electron microscopy (SEM)

The surface morphology of the beads was examined using scanning electron microscope (Jeol, JSM, 35CF, Japan) [16]. The beads were mounted onto individual stab and then coated with carbon and gold (100 and 50 Å thickness respectively). The coated samples were then observed under scanning electron microscope operated at 7Kv.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1 N HCl was set into the dissolution flask maintaining the temperature of 37±0.5°C and rpm of 75. One Losartan Potassium microbeads was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to

2 hours using 10ml pipette. The new disintegration medium (37°C) was supplanted each time with a similar amount

of the sample and takes the absorbance at 276.0 nm using spectroscopy.

Table 3: Interpretation of diffusional release mechanisms

Release exponent (<i>n</i>)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
$0.5 < n < 1.0$	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

Formulation of hydrochlorothiazide immediate release granules

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 taken in polyethylene bag as shown in Table 4 [17]. The mixture was then granulated using 1%

w/w PVP K-30 in water as granulation fluid. Then, the wet granulation mixture was extruded, and the extrudates were then immediately spheronized to yield the spherical pellets. The pellets were dried in hot air oven at 40°C for 10–12 h. After drying, pellets were then filled and stored in screw-capped, high-density polyethylene bottles.

Table 4: Composition of hydrochlorothiazide Instant layer tablets

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

Evaluation of hydrochlorothiazide immediate release granules

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined [18]. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and

estimated the LBD and TBD, calculated by using following formulas.

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Carr's Compressibility index: Percent compressibility of powder mix was

determined by Carr's compressibility index, calculated by using following formula:-

$$\text{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

$$\text{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{loose Bulk density}}$$

Hausner's ratio value <1.25 shows better flow properties

Disintegration Test

The disintegration time of the granules was measured in water ($37 \pm 2^\circ\text{C}$) according to using Digital Tablet Disintegration Tester (EI, India) [19]. 100 mg of pellets is filled in the tubes and they were placed in the standard tablet disintegration tester. The disintegration time of six dried samples at 37°C was determined at a speed of 30 dips.

Uniformity of drug content

Equivalent to 10mg of each formulation (F1 to F9) were finely dissolved in 10 ml 0.1 N HCl (simulated gastric fluid of pH 1.2 without enzymes) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 282.0nm for Hydrochlorothiazide [20].

RESULTS AND DISCUSSION:

Results of preformulation studies

The results of preformulation studies can include information about the physical state of the drug substance, its solubility in various solvents, its hygroscopicity, its melting point, its particle size and size distribution, its surface area and porosity, its physical stability, its chemical stability, and its compatibility with other ingredients in the formulation. Preformulation studies can also provide information about a drug substance's pharmacokinetic properties, including its absorption, distribution, metabolism, and excretion profile.

Fourier-transform infra red spectroscopy (FTIR)

The spectrum of Losartan potassium and Hydrochlorothiazide were authenticated by FTIR spectroscopy. The presences of characteristic peaks associated with specific structural characteristics of the drug molecule were noted. Various peaks of the drug are shown in **Figure 2, 3**.

Melting point determination

The melting point of Losartan potassium was $263-265^\circ\text{C}$ and for Hydrochlorothiazide it was $273-275^\circ\text{C}$.

Drug-excipient compatibility study

DSC thermogram of Losartan potassium and Hydrochlorothiazide exhibited melting point at 268°C and 266°C respectively. The mixture of drug and excipient which was kept in accelerated condition of $40^\circ\text{C}/75\%$ RH for 30 days and subjected to DSC analysis. The characteristic melting point of

Losartan potassium and Hydrochlorothiazide does not deviate from 268°C and 266°C that predicts that there is no interaction between drug and excipient (Figure 4a to Figure 4b).

Results of evaluation of prepared microbeads

The particle size (Beads size) of the prepared microbeads will vary depending on the type of microbeads being prepared. In general, microbeads are available in sizes ranging from 2 to 500 micrometers. The

Beads size of prepared formulation F1 to F17 was found to be 335.65 to 520.36nm. The entrapment efficiency of the prepared microbeads is determined by the size and shape of the microbeads as well as the type of material used to prepare them. Generally, the larger the microbead, the greater the entrapment efficiency. The entrapment efficiency can range from 0 to 100%. The entrapment efficiency of prepared microbeads was found to be 65.21 to 75.23 percentages (Figure 5).

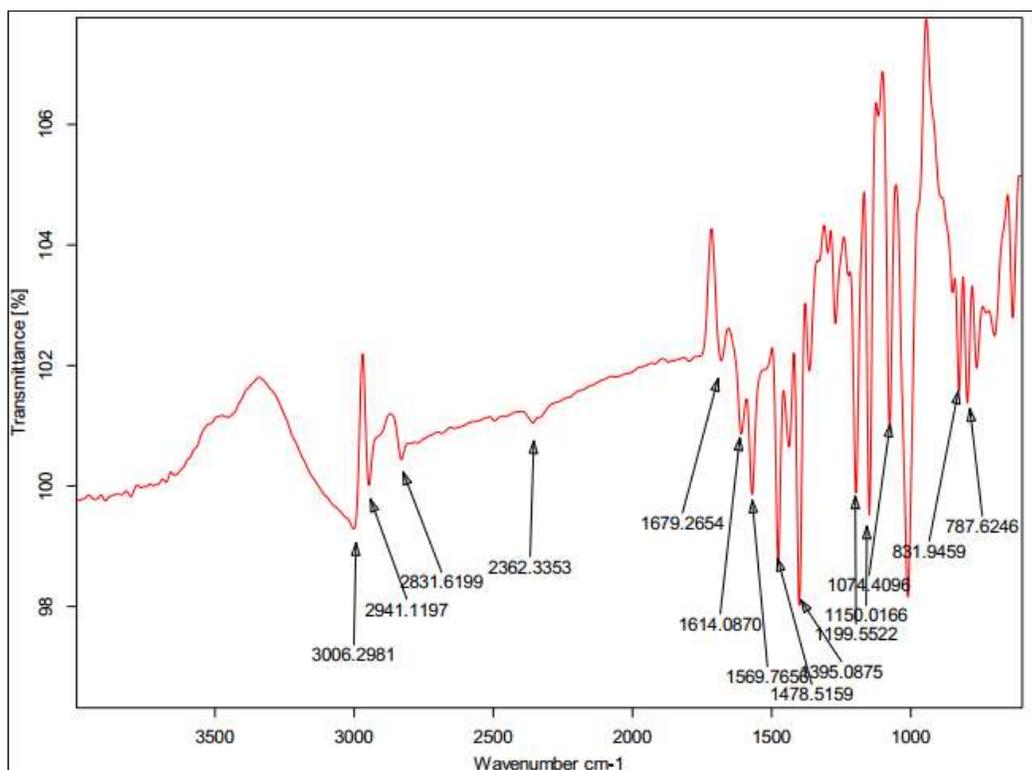


Figure 2: FT-IR Spectrum of pure drug (Losartan potassium)

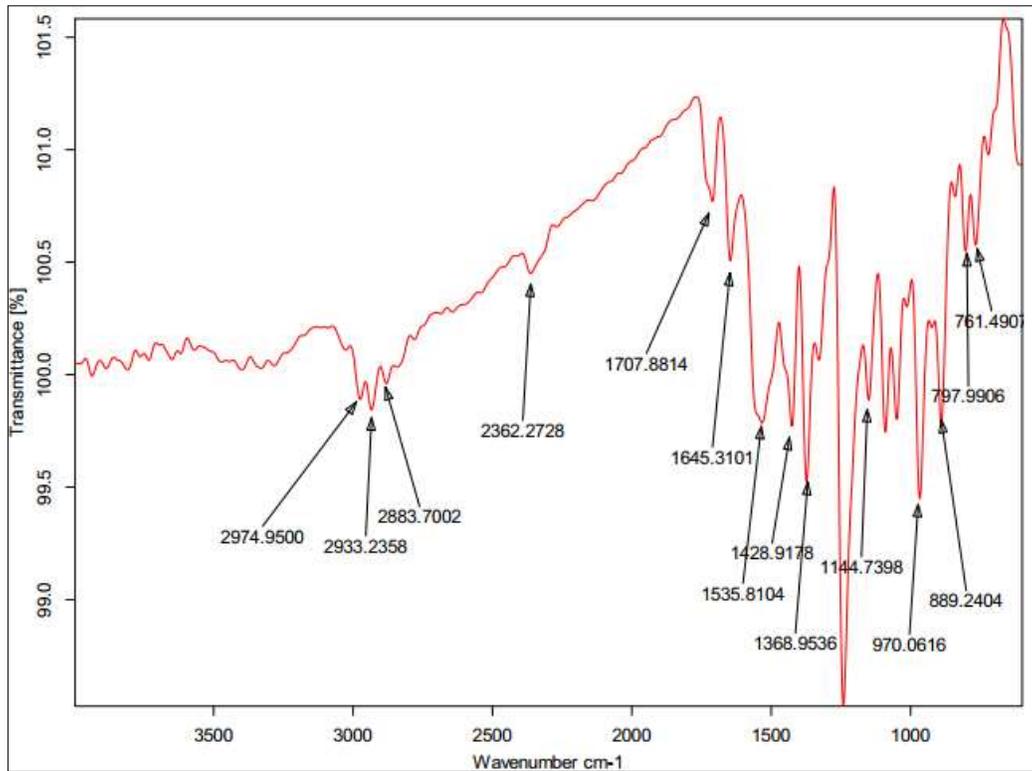


Figure 3: FT-IR Spectrum of pure drug (Hydrochlorothiazide)

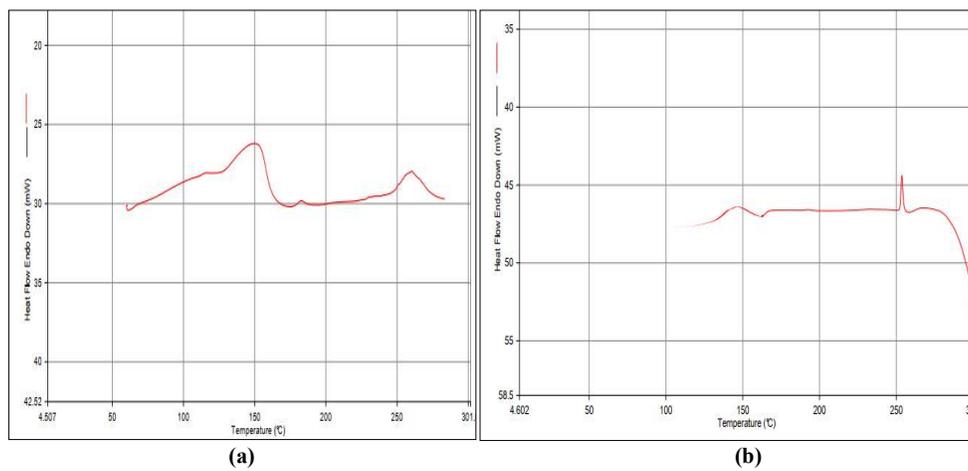


Figure 4: DSC thermogram of (a) pure drug Losartan Potassium, (b) Hydrochlorothiazide

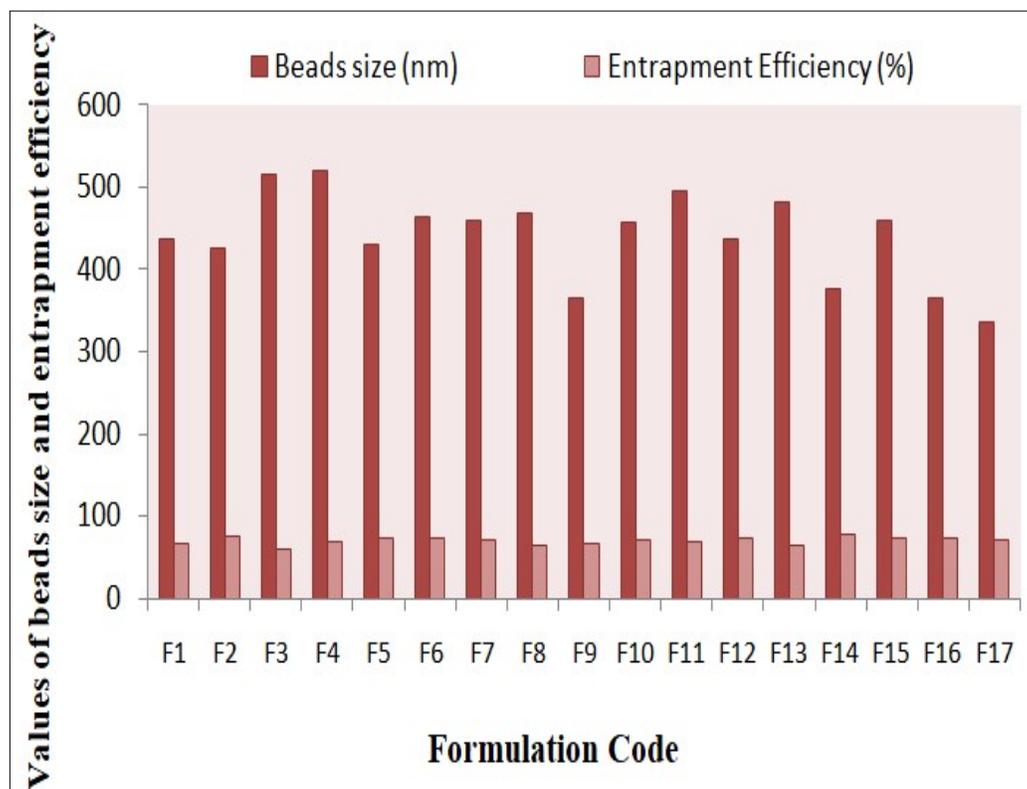


Figure 5: Graphical representation of results of Particle Size and Entrapment Efficiency Solubility study

An important physical-chemical property of a drug substance is solubility, especially aqueous solubility (Indian pharmacopeia, 2007). A drug must possess some aqueous solubility for therapeutic efficacy in the physiological pH range of 1 to 8. Solubility is expressed in terms of maximum volume or mass of the solute that dissolve in a given volume or mass of a solvent. Pharmacopoeias give solubility's in terms of the number of parts by volume of solvent required to dissolve one part by weight of a solid, or one part by volume of a liquid. The solubility of Losartan potassium and Hydrochlorothiazide were determined in various common solvents. Solubility studies

were performed in distilled water; 0.1 N hydrochloric acid, 0.1 N NaOH, ethanol, methanol, 7.4 pH phosphate buffer and chloroform at room temperature ($25 \pm 2^\circ\text{C}$) (IP, 2007). An excess amount of drug was added to 5 ml of solvent in screw-capped glass vials; these were shaken at 25°C until equilibrium was achieved. Aliquots were withdrawn, filtered through a membrane filter (0.45μ) and spectrophotometrically analyzed for solubility.

CONCLUSION

Losartan potassium sustained release microbeads offer a slow and sustained release of the medication over a period of time. This allows for a more consistent and

stable therapeutic effect and immediate release Hydrochlorothiazide granules allow for more rapid onset of action, which can be beneficial for patients with acute 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 combination of the two medications can provide both rapid and sustained relief from symptoms. However, it is important to consult with a healthcare professional before beginning any new medication regimen.

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