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EFFECT OF NATURAL POLYMERS ON CONTROLLED RELEASE OF IRBESARTAN FROM ACACIA AND KERNEL LOADED MICROSPHERES

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ABSTRACT: Microencapsulation for oral use has been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract which results in more reproducible drug absorption Irbesartan loaded microspheres were prepared using gelatin as a base material along with kernel powder (*Tamarindus indica* belonging to family Fabaceae) and acacia by phase separation and Coacervation method. Kernel powder loaded microspheres has shown better control over drug release than acacia. Microspheres shown lowered bursting effect and controlled release rate. The size and compatibility of microspheres were analyzed by using SEM and FTIR respectively. This was the first report on kernel powder which is obtained from Tamarind seeds used as a control releasing agent.

Keywords: Phase separation and Coacervation, Kernel powder, Acacia, SEM..

INTRODUCTION:

The objective of the present study is to prepare Irbesartan loaded microspheres by using natural polymers. Irbesartan is an angiotensin II type I receptor antagonist and therefore blocks the vasoconstriction and aldosterone-secreting effects of angiotensin II by which it produces antihypertensive effect [1-2]. Kernel powder is a natural polymer containing carbohydrates and proteins. It is obtained from tamarind seeds. It contains Galactoxyloglucan polysaccharide (55-65%), Lipids (6-10%), Proteins (18-20%) and a little amount of Fibers, Sugar etc. Tamarind Kernel Powder is also used in various food processing industries and applied largely in ketchups, ice creams, sauces, sherbet, baked food, pet food, meat product and instant noodles. Viscosity is ranging from 40,000 To 55,000 cps. It is off white in color. [12] The present study was conducted to control the release rate of Irbesartan using natural polymers to reduce the dose frequency.

MATERIALS AND METHODS:

Irbesartan (Hetero labs Hyderabad), Gelatin (food grade), acacia, Formaldehyde (25%), Sunflower oil (Sun drop sunflower oil), Hydrochloric acid, n-Hexane and Kernel powder (Tamarind seeds).

Preparation of microspheres:

Phase separaration and Coacervation method was selected to prepare irbesartan loaded microspheres. Weighed amount of gelatin was dispersed in distilled water by heating the solution. Equal amount of kernel powder was weighed and dispersed in gelatin dispersion. 75 mg irbesartan was added to the gelatin dispersion.

The suspension of Irbesartan in gelatin solution was homogenized using a magnetic stirrer. The suspension was then added gradually to 50 ml of sunflower oil which is previously heated (50°C) while stirring at 600 rpm using a magnetic stirrer up to 2 hrs. Then 0.5 ml of formaldehyde was added to the suspension/emulsion system. Stirring was continued for 30 mins to allow the cross linking of gelatin microspheres to be completed. Microspheres were then filtered and stored at 5°C overnight. Microspheres were then dried at 37°C and stored in colored glass containers. Gelatin is maintained in equal concentration throughout the formulations (1 part), where as the concentrations of kernel and acacia were changed (1, 2, 3 parts). F1, F2, F3 indicates kernel and gelatin microspheres and F4, F5, F6 indicates acacia and gelatin microspheres (1:1, 1:2, 1:3)

CHARACTERIZATION OF MICROSPHERES

Particle size Analysis: [3, 4, 5, 6]

Microspheres were evaluated for their size and shape by using optical microscope fitted with an ocular micrometer and a stage micrometer. The particle diameters of more than 100 microspheres were measured randomly by optical microscope. The particle size was calculated using the equation

$$Xg = 10 \times [(ni \times \log Xi) / N]$$

Particle Shape and Surface morphology: [2]

Particle shape and surface morphology was determined by scanning electron microscopy. The dried microspheres were coated with gold (100 A°) under an argon atmosphere in a gold coating unit and scanning electron micrographs were observed.

Swelling Index: [11, 12]

Swelling index was done for measuring the extent of swelling of microspheres in 0.1N HCl. Exactly weighed amount (50mg) of microspheres were allowed to swell in 0.1N HCl for a period of 36 hrs at room temperature. The adhered liquid drops to the surface of the microspheres were removed by blotting paper and the swollen microspheres were weighed by using microbalance. Swelling index was calculated by using the formula.

$$\mathrm{Wsi} = \frac{\mathrm{Ws} - \mathrm{Wi}}{\mathrm{Wi}}$$

W*si*= Swelling index of microspheres, Ws=Weight of the swelling microspheres, W*I*=Initial weight of the microspheres.

Estimation of drug content: [4, 5]

Drug loaded microspheres of 100 mg were powdered and suspended in 100 ml 50%ethanol and 50% 0.1N HCl. It was kept for shaking for 30 minutes and the resultant solution was filtered and subjected to analysis. The drug content was determined specrophotometrically (Systronics) at 244 nm using a regression equation derived from the standard curve (r^2=0.9901).

Entrapment Efficiency: [4, 5]

In order to evaluate the amount of entrapped drug in the microspheres, weighed amount of microspheres were dissolved in buffer and allowed for 24 hrs then filtered the solution. The filtered solution was assayed specrophotometrically at 244 nm using UV Visible spectrophotometer. The amount of drug entrapped was calculated from the difference between the total amount of drug added and the amount of drug found in the filtered solution. About 50 mg of microspheres were placed in 10ml of ethanol and 10ml of 0.1NHCl solutions and stirred for 1hr. Then, 2 ml of solution was filtered and the concentration of drug was determined specrophotometrically by UV. Efficiency of drug entrapment was calculated in terms of percentage drug entrapment by following formula

$$PDE = \frac{\text{Practical drug loading}}{Theoretical\ drug\ loading} \times 100$$

Percentage yield:

The yield was calculated as the weight of the microspheres recovered from each batch divided by total weight of drug and polymer used to prepare that batch multiplied by 100[4,5].

IR-Spectra: [7]

FTIR technique was commonly used to investigate the compatibility between the drug and the various excipients used in the formulation. The samples were prepared by physical mixture of drug and excipients (1:1) using a clean dried glass mortar and subjected to analysis by following further steps and Spectral scanning was done in the range of 4000 – 400^{-1} cm.

***In vitro* drug release:** [6]

The drug release study was performed using USP Dissolution Testing Apparatus I (Basket type) (Electrolab, TDT-06L, Mumbai, India) at 37°C ± 0.5°C and at 50 rpm using 900 mL of 0.1N HCl as a dissolution medium. Microspheres equivalent to 75 mg of irbesartan were used for the test. 5 ml of sample solution was withdrawn at predetermined time intervals, diluted suitably, and analyzed specrophotometrically. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved at different time intervals was calculated using the standard curve equation (r^2 value 0.990). All the experiments were carried out in triplicate (n=3). In order to study the exact mechanism of drug release from microspheres was analyzed according to Zero order [8], First order [8], Higuchi square root [9], Korsmeyer peppas model.[10]

RESULTS AND DISCUSSION:

The irbesartan loaded microspheres were prepared by Phase separation and Coacervation method. The data was discussed in the below mentioned tables.

Particle size and shape –optical microscopy and SEM analysis:

The obtained microspheres size was analyzed using SEM. The size of kernel powder microspheres was in the range of 250 µm to 310 µm and acacia powder microspheres was in the range of 270 µm to 300 µm (fig 1a, b). The size of the microspheres was found to be in the range of 290 µm to 340 µm by using optical microscopy.

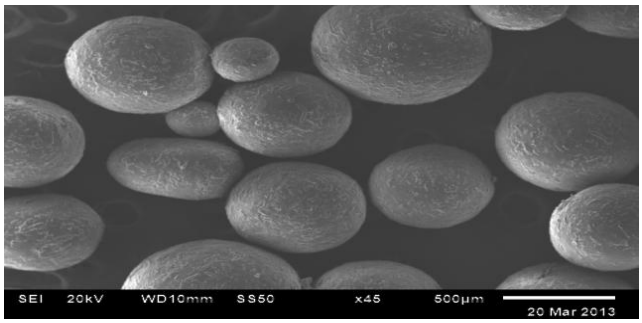


Fig.1(a). Microspheres of Kernel powder

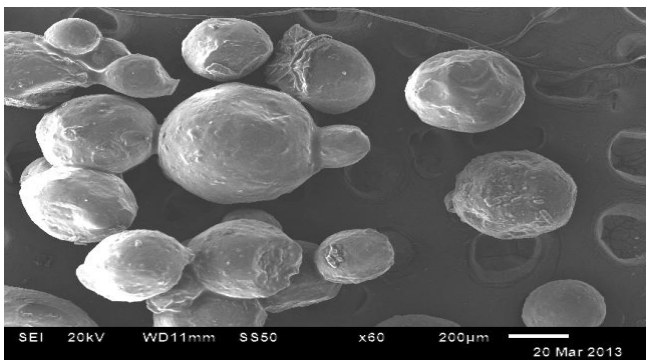


Fig.1 (b). Microspheres of Acacia powder

Swelling index:

The Swelling index of the microspheres was found to be 35% and 30% in the case of kernel powder microspheres and acacia powder microspheres.

FT-IR:

The reports of FTIR indicate that there is no interaction between the drug and the excipients which were illustrated in the figure.2 a, b, c.

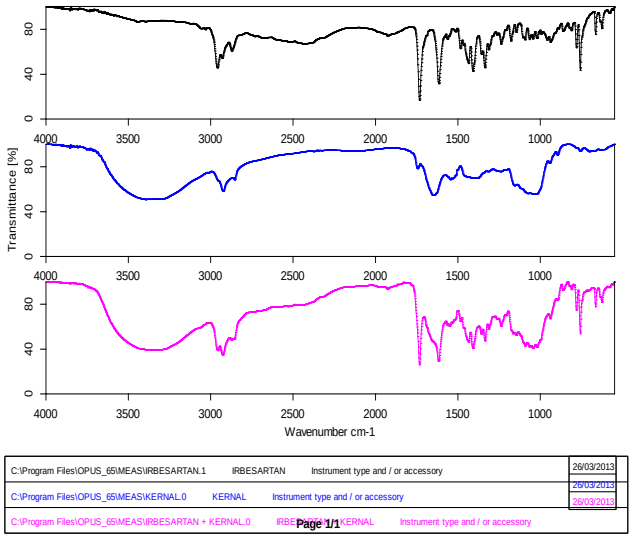


Fig.2(a). The combination of polymer and drug

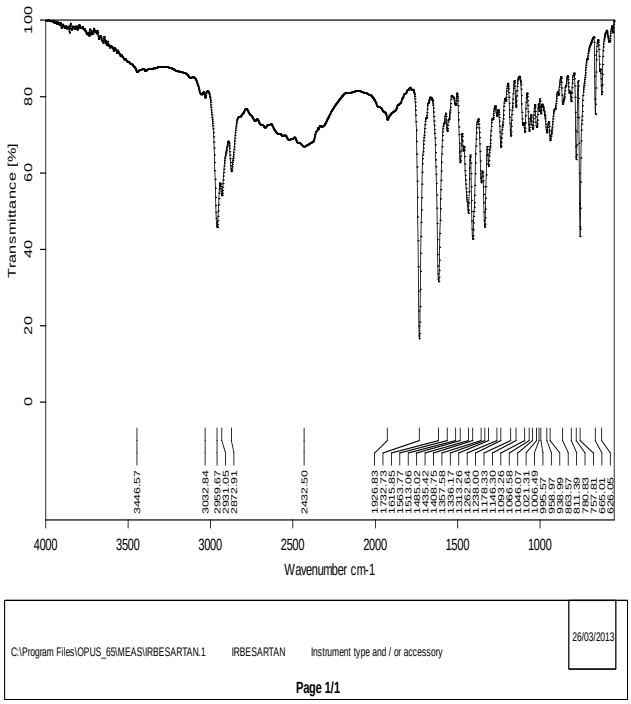


Fig .2(b).Spectra of kernel powder

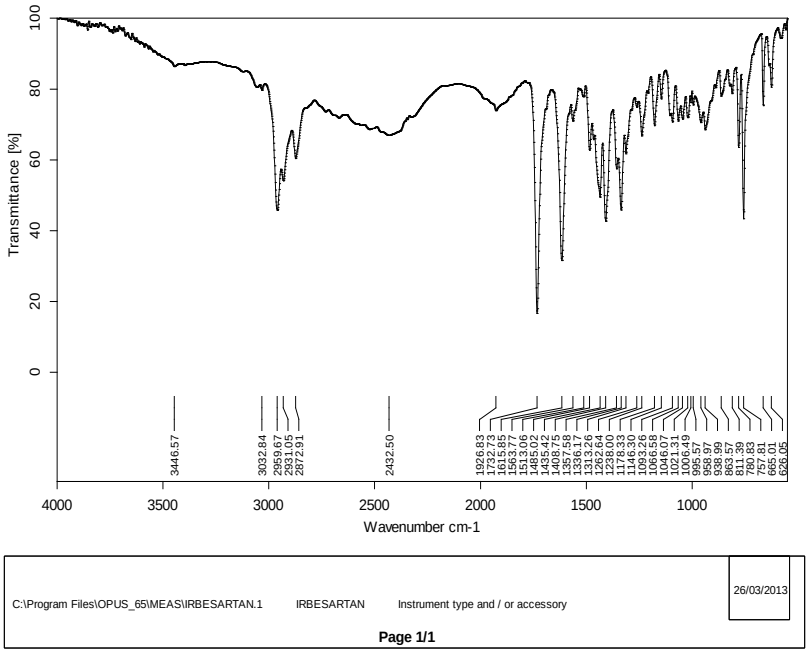


Fig .2(c).Spectra of drug

IR spectra results indicate that there is no interaction between the drug and polymers.

Table.1.Formulation of irbesartan loaded microspheres. (Method- Phase separation and Coacervation) polymer concentration (gelatin+ kernel and gelatin + acacia)

S.No	Formulation code	Drug concentration ratio	Gelatin+ Kernel concentration ratio
1	F1	1	1:1
2	F2	1	1:2
3	F3	1	1:3
S.No	**Formulation code**	**Drug concentration ratio**	**Gelatin+ Acacia concentration ratio**
4	F4	1	1:1
5	F5	1	1:2
6	F6	1	1:3

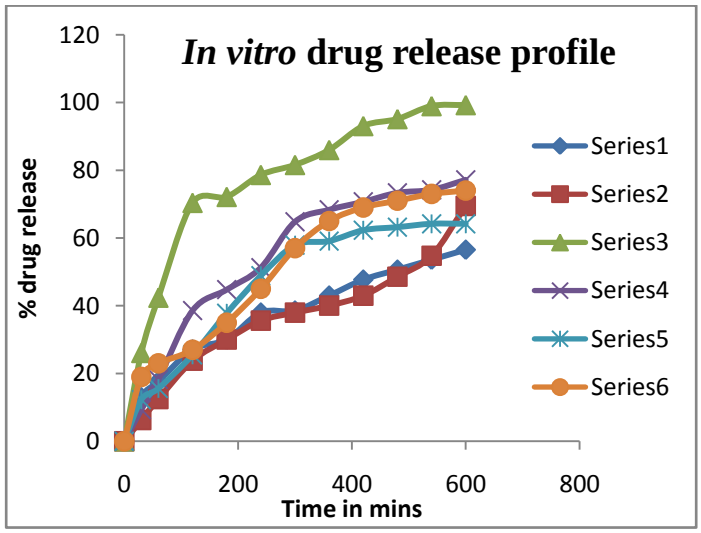
Table.2. Percentage yield, drug content and encapsulation efficiency of irbesartan loaded microspheres prepared by phase separation Coacervation technique.

S.No	Formulation	Percentage yield% X±S.D.	drug content X±S.D.	encapsulation efficiency X±S.D.
1	F1	80.1±0.412	55.5±0.12	73.1±0.21
2	F2	82.4±0.542	60.6±0.34	80.5±0.34
3	F3	81.2± 0.456	65.4±0.65	85.3±0.23
4	F4	79.3±0.213	50.6±0.34	66.3±0.54
5	F5	82.3±0.376	55.3±0.21	73.2±0.54
6	F6	80.4±0.467	62.2±0.54	82.1±0.57

Table .3.*In vitro* drug release kinetics of irbesartan loaded microspheres

S.No	Formulation code	Regression coefficient (r^2) value			
		Zero order	First order	Higuchi	Korsmeyer peppas
1	F1	0.9629	0.9656	0.9459	0.9946
2	F2	0.9429	0.9028	0.9929	0.9723
3	F3	0.8213	0.9183	0.9304	0.9362
4	F4	0.9181	0.9653	0.9688	0.9627
5	F5	0.9456	0.9213	0.9765	0.9435
6	F6	0.9575	0.9564	0.9543	0.9123

All the formulations found to release irbesartan in a controlled manner over seven hours. To describe the kinetic of drug release from microspheres, release data was analyzed according to different kinetic equations which were illustrated in the Table 3. Release data of F1, obeys first order kinetics where as F2, F3, F4, F5 obeys Higuchi square root kinetics and F6 obeys zero order kinetics (Tab-3).



Graph.1: *In vitro* drug release profile of different formulations formulated by Phase separation and Coacervation (Series 1,2,3,4,5,6 indicates different formulations-F1,F2,F3,F4,F5and F6)

DISCUSSION:

This was the first report on formulation of kernel powder loaded microspheres. Kernel powder plays an important role in controlling the release rate of irbesartan from the microspheres. The percent yield of the overall formulations were found to be 80% (Tab-2). F2 (drug:gelatin:kernel = 1:1:2) and F5 (drug:gelatin:acacia = 1:1:2) were found to be having better yield. Entrapment efficiency of the formulations was found to be 74%. Irbesartan loaded microspheres shown that microspheres obtained were discrete, spherical and uniform. Acacia and Kernel powder loaded microspheres were found to be similar in size. It was observed that all formulations follows non fickian diffusion model. Formulation F3 (drug:gelatin:kernel = 1:1:3) was found to be better formulation to control the release of irbesartan. 95% release was observed in 10 hrs. Out of all the findings, kernel powder was found to be better natural polymer to control the release rate.

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