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DESIGN AND DEVELOPMENT OF INVITRO CHARACTERIZATION OF FLOATING MICROSPHERES OF RANOLAZINE

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ABSTARCT

Ranolazine (RZ) is an antianginal agent employed in therapy of cardiovascular diseases such as myocardial infarction, variant and exercise-induced angina and arrhythmias constipation, headache, nausea and dizziness are the most common side effects. So the aim of the present research work was to formulation and in vitro evaluation of ranolazine microspheres using Sodium alginate along with Carbopol 934, Carbopol 971, HPMC K4M as copolymers The results of this work indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Ranolazine microspheres.Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion. The *in-vitro* mucoadhesive study demonstrated that microspheres of Ranolazine using sodium alginate along with Carbopol934 as copolymer adhered to the mucus to a greater extent The *invitro* drug release decreased with increase in the polymer and copolymer concentration. FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymers used.

KEYWORDS: Ranolazine, Carbopol, Microspheres.

INTRODUCTION

The oral route for drug delivery is the most popular, desir able, and most preferred method for administrating therapeutically agents for systemic effects because it is a natuural, convenient, and cost effective to manufacturing process. Oral route is the most commonly used route for drug administration.

Although different route of administration are used for the delivery of drugs, oral route remain the preferred mode. Even for sustained release systems the oral route of administration has been investigated the most because of flexibility because of flexibility in designing dosage forms.

Present controlled release drug delivery systems are for a maximum of 12 hours clinical effectiveness. Such systems are primarily used for the drugs with short elimination half life

Introduction To Oral Controlled Release Dosage Form

The treatment of acute diseases or chronic illnesses has been achieved b y delivery of drugs to the patients for many years. These drug delivery systems include tablets, indictables, suspensions, creams, ointmestnts,liquids and aerosols. Todaythese conventional drug delivery systems are widely used. The term drug delivery canbeedefined as techniques that are used to get the therapeutic agents inside the human body. Conventional drug therapy require periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability.

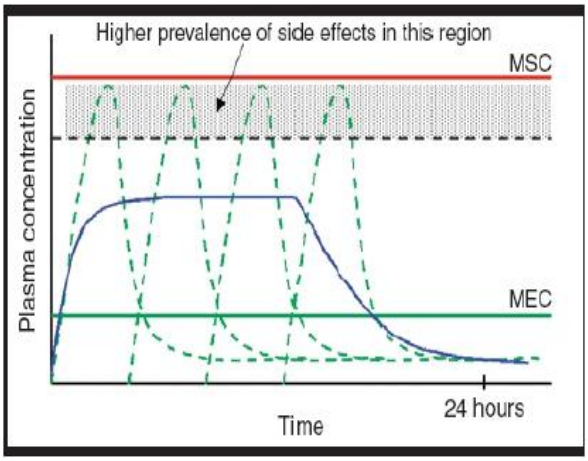

Figure 1. Plasma drug concentration profiles for conven tional tablet or capsule formulation and a zero order controlled release formulation,

MEC = Minimum Effective Concentration; MSC = Maxi mum Safe Concentration For most drugs, conventional methods of drug administration are effective, but some

drugs are unstable or toxic and have narrow therapeutic ranges. Some drugs also possess solubility problems.

In such cases, a method of continuous administration of t herapeutic agent is desirable to maintain fixed plasma levels as shown in figure 1**.**

Introduction To Microspheres

For many decades, medication of an acute disease or a chronic disease has been accomplished by delivering drugs to the patients via various pharmaceutical dosage[1] forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories as carriers. To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to take this type of drug delivery systems several times in a day. This results in a fluctuated drug level and consequently undesirable toxicity and poor efficiency. This factor as well as other factors such as repetitive dosing and unpredictable absorption leads to the concept of controlled drug delivery systems.[2-3] The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while Temporal delivery refers to controlling the rate of drug delivery[4-8] to the target tissue.

Definition And General Description

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats, and waxes. The natural polymers include albumin and gelatin[9-10] the synthetic polymers include polylactic acid and polyglycolic acid.[11-12] Fig. 2 shows two types of microspheres: Microcapsules, where the entrapped substance is completely surrounded by a distinct capsule wall, and micromatrices, where the entrapped substance is dispersed throughout the microsphere matrix.

Microspheres are small and have large surface to volume ratios. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important, often dictating their activity.

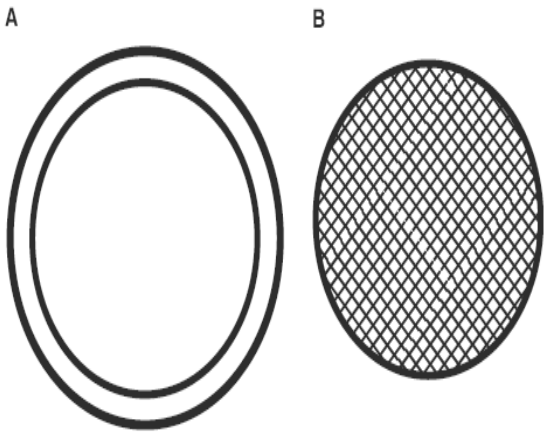

Figure: 2. Schematic diagram illustrating microspheres. (A) Microcapsule consisting of an encapsulated core particle and (B) micromatrix consisting of homogeneous dispersion of active ingredient in particle.

Mucoadhesion / Bioadhesion.[13]

Mucoadhesive drug delivery system are the systems which utilizes the property of bio adhesion of certain polymers which become adhesive on hydration and can be used for targeting a drug to a particular region of the body for extended periods of time.

The term "mucoadhesion" was coined for the adhesion of the polymers with the surface of the mucosal layer. Bio adhesions are a phenomenon in which two materials at least one of which is biological and are held together by means of interfacial forces. In biological systems, bio adhesion can be classified into 3 types:

1. Adhesion between two biological phases, for example, platelet aggregation and wound healing.
2. Adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and bio film formation on prosthetic devices and inserts.
3. Adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues and adhesion of sealants to dental enamel.

Mechanism of Mucoadhesion.[14]

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. Several theories have been proposed to explain the fundamental mechanism of adhesion. A general mechanism of mucoadhesion drug Delivery system is show in Figure 1.3.

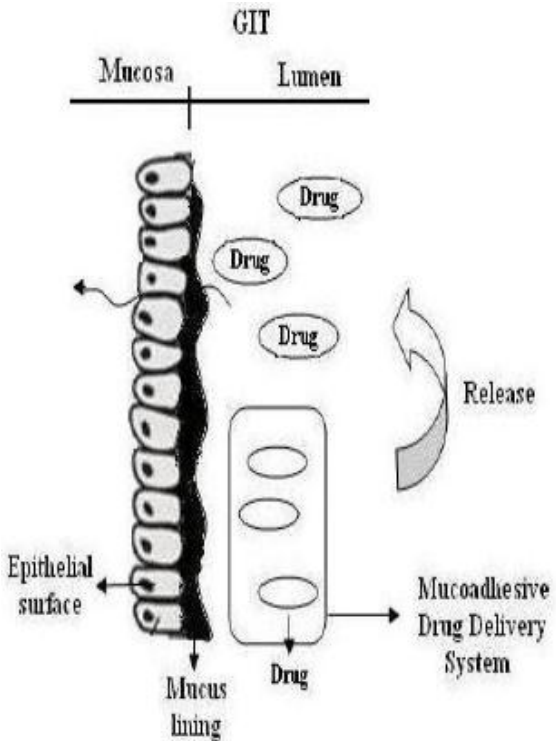

Figure: 3 Mechanism of Mucoadhesion

Methods of Preperation of Microspheres

Emulsion solvent evaporation technique.
Emulsion cross linking method.
Emulsion solvent diffusion method.
Multiple emulsion method.
Ionic gelation.
Co-acervation method.
Spray drying technique.

Polymers Used For Mucoadhesive System.[15-16]

Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular location / site. Polymers have played an important role in designing such systems so as to increase the residence time of the active agent at the desired location. Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, joined by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. An ideal polymer for a bio adhesive drug delivery system should have the following characters is as follows.

- Polymer and its degradation products should be nontoxic, non absorbable & nonirritant.
- It should preferably form a strong non covalent bond with the mucus or epithelial cell
- Surface & adhere quickly to moist tissue and possess some site specificity.
- It should allow easy incorporation of the drug and offer no hindrance to its release.
- Polymer must not decompose on storage or during the shelf life of the dosage form.
- Cost of the polymer should not be high so that prepared dosage form remains competitive.
- Polymers that adhere to biological surfaces can be divided into three broad categories, Various polymers and their mucoadhesive properties shown in table 1.

Table: 1 Polymer and their mucoadhesion properties

Polymers	Bioadhesive property
Carboxy methyl cellulose	+++
Carbopol 934	+++
Polycarbophil	+++
Tragacanth	+++
Poly(acrylic acid /divinyl benzene)	+++
Sodium alginate	+++
Hydroxy ethyl cellulose	+++
Gum Karaya	++
Gelatin	++
Guargum	++
Thermally modified starch	+
Pectin	+
Polyvinyl pyrrolidone	+
Acacia	+
Polyethylene glycol	+
Psyllium amberlite-200 resin	+
Hydroxy propyl cellulose	+
Chitosan	+
Hydroxy ethyl methacrylate	+

+++Very High, ++High, +Moderate.

Application Of Mucoadhesive Microspheres

- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control.
- Microsphere in vaccine delivery have a specific advantage like improved antigenicity by adjuvant action, modulation of antigen release, stabilization of antigen.
- Passive targeting of leaky tumour vessels, active targeting of tumour cells, antigens, by intra arterial / intravenous application.

METHODOLOGY

Preformulation Studies: **Spectroscopic Studies**

Preparation Of 0.1N HCl (pH 1.2)

Take 8ml of HCl in a 1000ml volumetric flask and make up the volume with distilled water.

Determination Of λmax

Stock solution (1000µg/ml) of Ranolazine was prepared in methanol. This solution was appropriately diluted with 0.1N HCl(pH 1.2) to obtain a concentration of 10µg/ ml. The resultant solution was scanned in the range of 200nm to 400nm on UV-Visible spectrophotometer. The drug exhibited a λmax at 269nm.

Preparation Of Standard Calibration Curve Of Ranolazine

- 10 mg of Ranolazine was accurately weighed and dissolved in 10ml of methanol (Stock Solution – I) to get a concentration of 1000 µg/ml.
- From the stock solution- I,1ml of aliquots was taken and suitably diluted with 0.1N HCl (Stock Solution- II) to get concentrations of 100µg/ml.
- From the stock solution- II,aliquots were taken and suitably diluted with 0.1N HCl (pH 1.2) to get concentrations in the range of 2 to 10µg/ml.The absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 269nm against reference solution 0.1N HCl (pH 1.2).

The Linear Regression Analysis

- The linear regression analysis was done on Absorance points. The standard calibration curve obtained had a Correlation Coefficient of 0.998 with of slope of 0.028 and intercept of 0.004.
- Compatibility Studies
- Fourier Transform Infrared Spectroscopy (Ft-IR).

METHOD OF PREPARATION

Ionotropic Gelation Method

Batches of microspheres were prepared by ionotropic gelation method which involved reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate and the mucoadhesive polymer were dispersed in purified water (10 ml) to form a homogeneous polymer mixture. The API, Ranolazine (100 mg) were added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added through a 22G needle into calcium chloride (4% w/v) solution. The addition was done with continuous stirring at 200rpm. The added droplets were retained in the calcium chloride solution for 30 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then air-dried.

Figure: 5 Photograph of prepared microspheres

Table 2: Prepared formulation of Biooadhesive Microspheres

Excipients	F1	F2	F3	F4	F5	F6
Drug	300	300	300	300	300	300
Carbopol	100	200	300			
Eudragit S-100				100	200	300
Sod CMC	50	50	50	50	50	50
Methanol	10	10	10	10	10	10
Sod alginate	100	100	100	100	100	100
Water	20	20	20	20	20	20

CHARACTERIZATION OF MICROSPHERES

- Percentage yield,
- Drug entrapment efficiency,
- Particle size analysis,
- Swelling study,

Evaluation of mucoadhesive property

In vitro drug release study

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^0C, 50 rpm) using the USP type – I rotating basket method in simulated gastric fluid pH 1.2 (900ml). A quantity of accurately weighed microspheres equivalent to 100mg Ranolazine each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 269nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed simulated gastric

fluid pH 1.2 maintaining sink conditions throughout the experiment.

In-Vitro Drug Release Kinetics

The release data obtained was fitted into various mathem atical models.The parameters 'n' and time component 'k', the release rate constant and 'R', the regression coefficient were determined by Korsmeyer-Peppas equation to understand the release mechanism.

RESULTS AND DISCUSSION

Preformulation Studies: Spectroscopic Studies

Determination of λmax:

A solution of 10µg/ml of Ranolazine was scanned in the range of 200 to 400nm. The drug exhibited a λmax at 269nm in simulated gastric fluid pH 1.2 and had good reproducibility. Correlation between the concentration and absorbance was found to be near to 0.998, with a slope of 0.028 and intercept of 0.004.

Calibration curve of Ranolazine in simulated gastric flui d pH 1.2

Table 3 shows the calibration curve data of Ranolazine in simulated gastric fluid pH 1.2 at 269nm. Fig.3 shows the standard calibration curve with a regression value of 0.998, slope of 0.028 and intercept of 0.004 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 2-10µg/ml.

Table 3: Calibration curve data for Ranolazine in simulated gastric fluid pH 1.2

CONCENTRATION (µg /ml)	ABSORBANCE
2	0.051
4	0.110
6	0.163
8	0.221
10	0.290

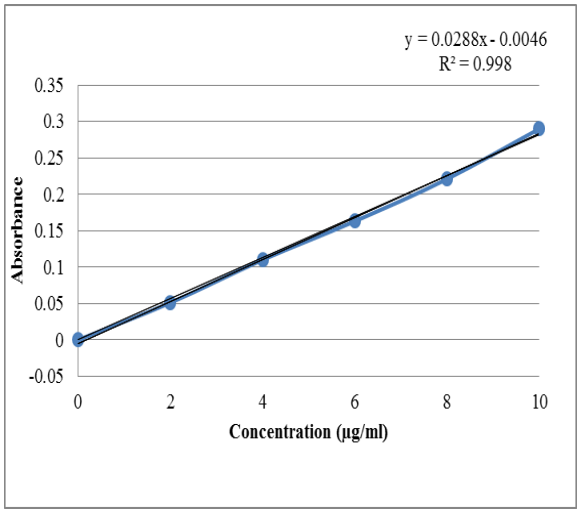

Figure: 6 Standard graph Of Ranolazine in simulated gastric fluid pH 1.2

Compatibility Studies

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish any possible interaction of Drug with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FTIR spectra of the pure drug.

FTIR STUDIES

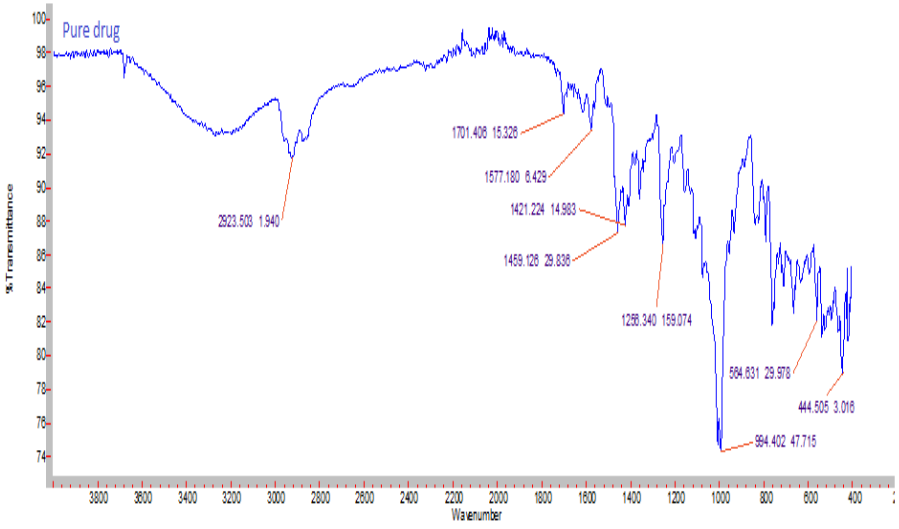

Fig No. 7: FTIR of pure drug

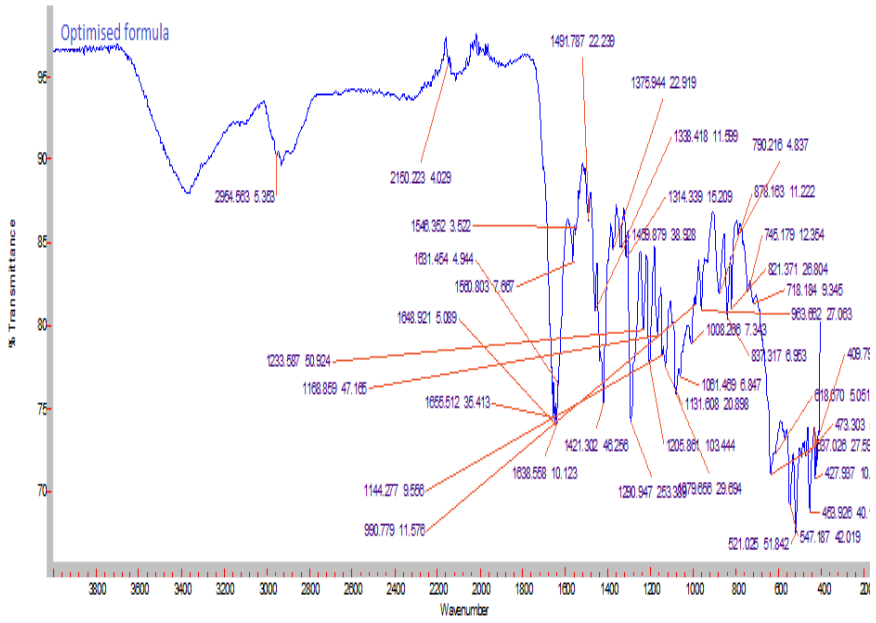

Fig No. 8: FTIR of OPTIMISED FORMULATION

Evaluation And Characterisation Of Microspheres

Percentage Yield

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle and wastage of the drug-polymer solution, adhesion of polymer solution to the magnetic bead and microspheres lost during the washing process. The percentage yield was found to be in the range of 80 to 88% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 62.22 to 87% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 80 to 87.5% for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The percentage yield of the prepared microspheres is recorded in Table 4 and displayed in Figures9, 10.

Drug Entrapment Efficiency

Percentage Drug entrapment efficiency of Ranolazine ranged from 82.66 to 88.66% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 53.2 to 76.66% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 66.73 to 79.2% for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The drug entrapment efficiency of the prepared microspheres increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases expone- ntially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared microspheres is displayed in Table 4, and displayed in Figures.

Table 4: Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% yield	Drug Content (mg)	% Drug entrapment efficiency
1	F1	80	12.40	82.66
2	F2	83.33	12.66	84.4
3	F3	85	12.70	84.66
4	F4	88	13.29	88.66
5	F5	62.22	8.07	53.2
6	F6	80	8.25	55

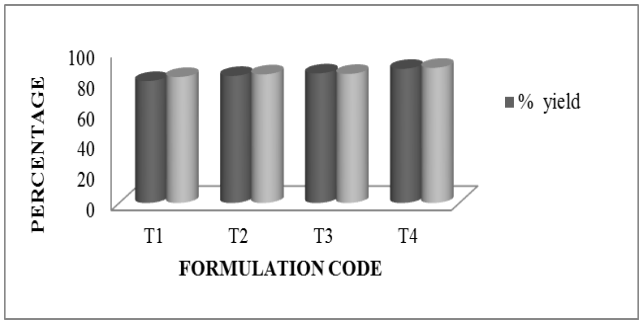

Figure 9: Comparison of % Yield and % drug entrapment efficiency microspheres containing sodium alginate along with carbopol 934 as copolymer

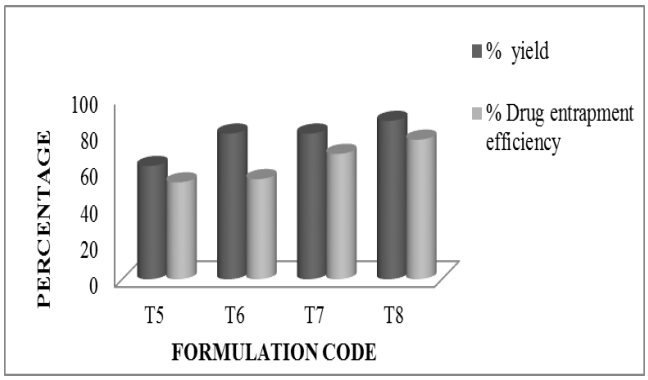

Figure 10: Comparison of % Yield and % drug entrapment efficiency microspheres containing sodium alginate along with carbopol 971 as copolymer

Particle Size Analysis

The mean size increased with increasing polymer concentration which is due to a significant increase in the viscosity, thus leading to an increased droplet size and finally a higher microspheres size. Microspheres containing sodium alginate along with carbopol 934 as copolymer had a size range of 512µm to 826µm, microspheres containing sodium alginate along with carbopol 971 as copolymer exhibited a size range between 517µm to 834µm and microspheres containing sodium alginate along with HPMC K 4 M as copolymer had a size range of 664µm to 903µm. The particle size data is presented in Tables 5 to 10. The effect of drug to polymer ratio on particle size is displayed in Figure. The particle size as well as % drug entrapment efficiency of the microspheres increased with increase in the polymer concentration.

Table 5: Particle size data of F_1

PARTICLE SIZE RANGE (µm)	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	AVERAGE PARTICLE SIZE (µm)
200-300	250	9	512 µm
300-400	350	13	
400-500	450	17	
500-600	550	29	
600-700	650	32	
		∑n=100	

Table 6.: Particle size data of F_2

PARTICLE SIZE RANGE (µm)	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	AVERAGE PARTICLE SIZE (µm)
300-400	350	15	617 µm
400-500	450	13	
500-600	550	18	
600-700	650	12	
700-800	750	28	
800-900	850	14	
		∑n=100	

Table 7: Particle size data of F_3

PARTICLE SIZE RANGE (µm)	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	AVERAGE PARTICLE SIZE (µm)
500-600	550	6	826 µm
600-700	650	12	
700-800	750	16	
800-900	850	32	

900-1000	950	34	
		∑n=100	

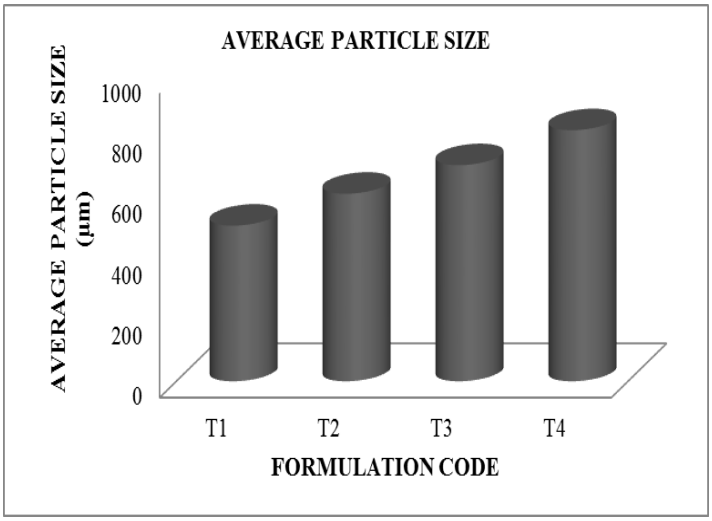

Figure 12: Average particle size of microspheres containing sodium alginate along with carbopol 934 as copolymer

Table 8: Particle size data of F_4

PARTICLE SIZE RANGE (µm)	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	AVERAGE PARTICLE SIZE (µm)
500-600	550	6	826 µm
600-700	650	12	
700-800	750	16	
800-900	850	32	
900-1000	950	34	
		∑n=100	

Table 9: Particle size data of F_5

PARTICLE SIZE RANGE (µm)	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	AVERAGE PARTICLE SIZE (µm)
200-300	250	8	517 µm
300-400	350	12	
400-500	450	18	
500-600	550	29	
600-700	650	33	
		∑n=100	

Table 10: Particle size data of F_6

PARTICLE SIZE RANGE (µm)	MIDPOINT SIZE RANGE (d)	FREQUENCY (n)	AVERAGE PARTICLE SIZE (µm)
300-400	350	12	642 µm
400-500	450	11	
500-600	550	15	
600-700	650	14	
700-800	750	31	
800-900	850	17	
		∑n=100	

The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swellability is an important characteristic as it affects mucoadhesion as well as drug release profiles of polymeric drug delivery systems. Swellability is an indicative parameter for rapid availability of drug solution for diffusion with greater flux. Swellability data revealed that amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in Table 11, that with an increase in polymer concentration, the percentage of swelling also increases. Thus we can say

that amount of polymer directly affects the swelling ratio. As the polymer to drug ratio increased, the percentage of swelling increased from 28 to 85% for microspheres containing sodium alginate along with carbopol 934 as copolymer, 24 to 64% for microspheres containing sodium alginate along with carbopol 971 as copolymer and 31 to 85 for microspheres containing sodium alginate along with HPMC K 4 M as copolymer. The percentageof swelling of the prepared microspheres is displayed in Figures. The effect of drug to polymer ratio on percentage swelling is displayed in Figure 13-16.

Table 11: Percentage swelling of the prepared microspheres

S.NO.	FORMULATION CODE	INITIAL (Wt)	FINAL (Wt)	PERCENTAGE SWELLING
1	F_1	10	12.8	28
2	F_2	10	14.2	42
3	F_3	10	16.2	62
4	F_4	10	18.5	85
5	F_5	10	12.4	24
6	F_6	10	13.9	39

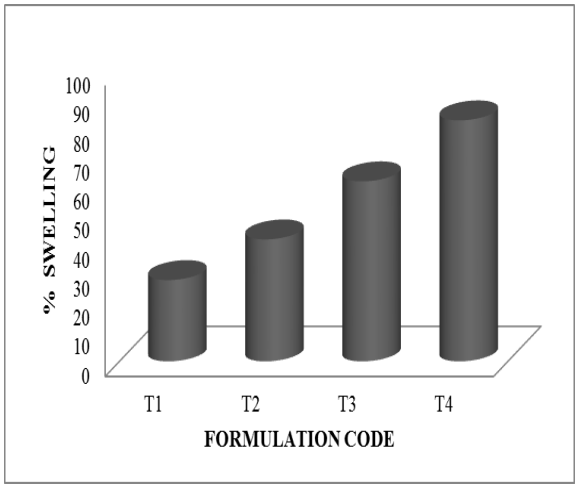

Figure 13: Percentage swelling of microspheres containing sodium alginate along with carbopol 934 as copolymer

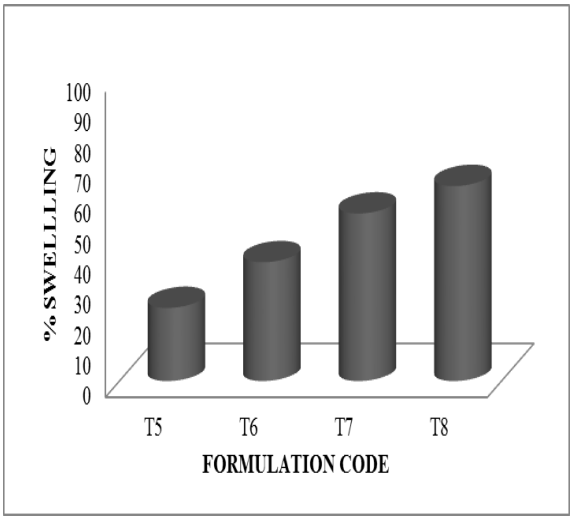

Figure 14: Percentage swelling of microspheres containing sodium alginate along with HPMC K 4 M as copolymer

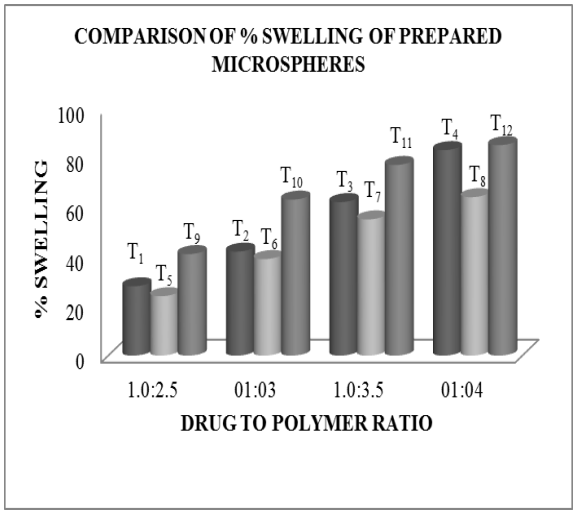

Figure 15: Comparison of percentage swelling of prepared microspheres

IN-VITRO MUCOADHESION TEST

As the polymer to drug ratio increased, microspheres containing sodium alginate along with carbopol 934 as copolymer exhibited % mucoadhesion ranging from 65 to 85%, microspheres containing sodium alginate along with carbopol 971 as copolymer exhibited % mucoadhesion ranging from 60 to 75% and microspheres containing sodium alginate along with HPMC K 4 M as copolymer exhibited % mucoadhesion ranging from 60 to 80%.

The rank of order of mucoadhesion is carbopol 934 > HPMC K 4 M > carbopol 971. The results of in-vitro mucoadhesion test are compiled in Table 12.

Table 12: Percentage mucoadhesion of the prepared microspheres

S.NO.	FORMULATION CODE	No. OF MICROSPHERES		PERCENTAGE MUCOADHESION
		INITIAL	FINAL	
1	F_1	20	13	65
2	F_2	20	14	70
3	F_3	20	15	75
4	F_4	20	17	85
5	F_5	20	12	60
6	F_6	20	13	65

in-vitro drug release studies

Dissolution studies of all the formulations were carried out using dissolution apparatus USP type I. The dissolution studies were conducted by using dissolution media, pH 1.2. The results of the in-vitro dissolution studies of formulations F_1 to F_{12} are shown in table. The plots of Cumulative percentage drug release Vs Time.

The formulations F_1, F_2, F_3 and F_4 containing Sodium alginate along with Carbopol 934 as copolymer showed a maximum release of 92.66% after 9 hours, 90.66% after 10 hours, 90.6% after 11 hours and 97.66% after 12 hours respectively.

This shows that more sustained release was observed with the increase in percentage of polymers. As the polymer to drug ratio was increased the extent of drug release decreased. A significant decrease in the rate and extent of drug release is attributed to the increase in density of polymer matrix that results in increased diffusion path length which the drug molecules have to traverse. The releaseof the drug has been controlled by swelling control release mechanism. Additionally, the larger particle size at higher polymer concentration also restricted the total surface area resulting in slower release.

Table 13: *In-Vitro* drug release data of Ranolazine microspheres containing sodium alginate along with carbopol 934 as copolymer.

TIME (h)	CUMULATIVE PRECENT OF DRUG RELEASED			
	F1	F2	F3	F4
0	0	0	0	0
1	24.88	21.11	18.66	15.88
2	31.55	31.55	25.11	24.22
3	42.44	39.77	35.44	32.66
4	53.55	47.77	40.66	39.33
5	62	56.66	52	47.55
6	74.66	62.44	57.33	55.77
7	83.55	69.55	63.11	61.77
8	89.33	75.33	69.11	69.55
9	92.66	84.66	75.33	77.55
10	85.55	90.66	82.66	85.55
11	80.22	84.22	90.66	90.66
12	78.88	80.88	89.55	97.66

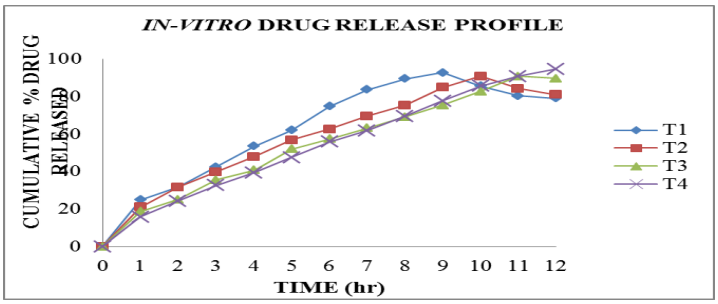

Figure 17: Comparison of *In-Vitro* drug release profile of Ranolazine microspheres containing sodium alginate along with carbopol 934 as copolymer

Table .14: *In-Vitro* drug release data of Ranolazine microspheres containing sodium alginate along with carbopol 971 as copolymer

TIME (h)	CUMULATIVE PRECENT OF DRUG RELEASED				
	F5	F6	F7	F8	F9
0	0	0	0	0	0
1	27.77	22.44	18.44	17.11	25.77
2	36.44	32.22	29.33	26.44	35.33
3	43.77	40.88	39.55	37.55	43.55
4	54.66	48.66	45.55	46.88	54
5	64.01	57.55	57.33	55.77	63.55
6	75.77	63.55	65.33	63.55	75.33
7	84.65	70.44	71.55	71.33	84
8	90	76.55	77.56	75.77	89.77
9	92.22	85.55	81.55	79.77	92.66
10	84.88	91.33	83.33	82.44	85.11
11	79.55	85.77	89.55	86.88	80.66
12	77.55	81.11	87.55	90.66	78

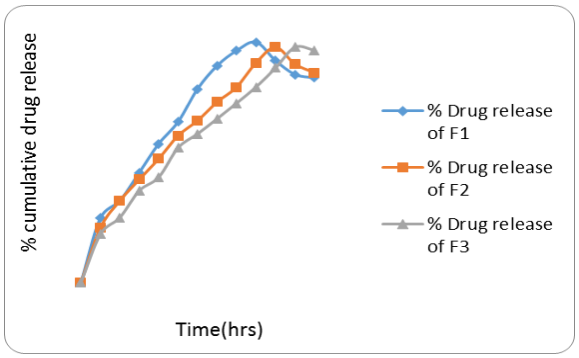

Figure 18: Korsmeyer-Peppas plots of Ranolazine microspheres formulations T_1, T_2 and T_3

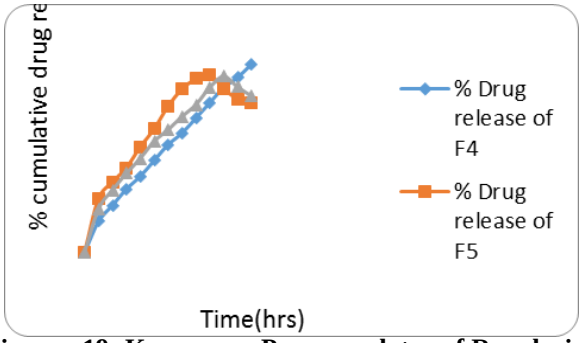

Figure 19: Korsmeyer-Peppas plots of Ranolazine microspheres formulations T_4, T_5 and T_6

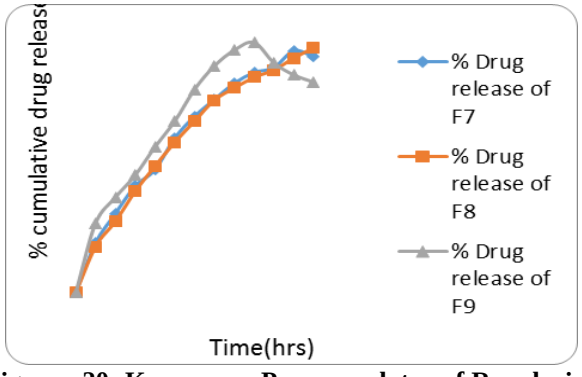

Figure 20: Korsmeyer-Peppas plots of Ranolazine microspheres formulations T_4, T_5 and T_6

In-Vitro Drug Release Kinetics

For understanding the mechanism of drug release and rel ease rate kinetics of the drug from dosage form, the in-vitro drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi matrix, and Krosmeyer-Peppas model. The values are compiled in Table 15. The coefficient of determination (R^2) was used as an indicator of the best fitting for each of the models considered. The kinetic data analysis of all the formulations reached higher coefficient of determination with the Korsmeyer-Peppas model (R^2 = 0.914 to 0.996) whereas release exponent value (n) ranged from 0.498 to 0.743. From the coefficient of determination and release exponent values, it can be suggested that the mechanism of drug release follows Korsmeyer-Peppas model along with non-Fickian diffusion mechanism which leading to the conclusion that a release mechanism of drug followed combination of diffusion and spheres erosion.

Table 15: Release Kinetics Studies Of The Prepared Formulations

Formulation code	Release model								
	Zero order		First order		Higuchi matrix		Koresmeyer-peppas		
	K	R^2	K	R^2	K	R^2	N	K	R^2
T_1	21.6	0.797	1.923	0.720	-0.313	0.912	0.556	1.388	0.925
T_2	16.39	0.908	1.991	0.890	-3.945	0.970	0.595	1.326	0.983
T_3	10.45	0.976	2.062	0.945	-8.966	0.975	0.673	1.233	0.991
T_4	7.434	0.990	2.118	0.914	-12.25	0.962	0.743	1.171	0.996
T_5	24.34	0.768	1.897	0.689	2.624	0.903	0.498	1.442	0.914
T_6	17.19	0.904	1.990	0.885	-3.333	0.971	0.579	1.346	0.981

SUMMARY AND CONCLUSION

In the present work, bioadhesive microspheres of Ranolazine using Sodium alginate along with Carbopol 934, Carbopol 971, HPMC K4M as copolymers were formulated to deliver Ranolazine via oral route.

From the study following conclusions could be drawn:-

- The results of this investigation indicate that ionic cross linking technique Ionotropic gelation method can be successfully employed to fabricate Ranolazine microspheres. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. Other methods utilize larger volume of organic solvents, which are costly and hazardous because of the possible explosion, air pollution, toxicity and difficult to remove traces of organic solvent completely.
- FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymers used.
- Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range of 512-903µm and are suitable for bioadhesive microspheres for oral administration.
- Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion.
- The *in-vitro* mucoadhesive study demonstrated that microspheres of Ranolazine using sodium alginate along with Carbopol934 as copolymer adhered to the mucus to a greater extent than the microspheres of Ranolazine using sodium alginate along with Carbopol 971 and HPMC K4M as copolymers.
- The *invitro* drug release decreased with increase in the polymer and copolymer concentration.
- Analysis of drug release mechanism showed that the drug release from the formulations followed non-Fickian diffusion and the best fit model was found to be Korsmeyer-Peppas.
- Based on the results of evaluation tests formulation coded F_4 was concluded as best formulation.

REFERENCES

1. Mulugeta Fentie*, Anteneh Belete and Tsige Gebre-Mariam Formulation of Sustained Release Floating Microspheres of Furosemide from Ethylcellulose and Hydroxypropyl Methylcellulose Polymer Blends J Nanomed Nanotechnol 2015, 6:1 http://dx.doi.org/10.4172/2157-7439.1000262
2. Abhijeet A. Durgavale* , Archana R. Dhole, Shrinivas K. Mohite, Chandrakant S. Magdum Formulation and Evaluation of Floating Microsphere of Captopril using Different Gas Forming Agents. Am. J. Pharm Tech Res, 2012; 2(2)
3. A Salomy Monica Diyya*, V Rakesh Kumar Formulation and In Vitro Evaluation of Floating Microspheres of Glipizide, 2015; 3(2): 606-615 606. IIIIIIIII© International Journal of Pharma Research and Health Sciences. All rights reserved CODEN (USA)-IJPRUR, e-ISSN: 2348-6465
4. Megha Sharma[a, c], Seema Kohli[b,], Agnimitra Dinda *In-vitro* and *in-vivo* evaluation of repaglinide loaded floating microspheres prepared from different viscosity grades of HPMC polymer Saudi Pharmaceutical Journal Available online 27 February 2015
5. Pavan Kumar Perumandla *, Sree Priya Formulation And In Vitro Evaluation Of Floating Microspheres Of Dextromethorphan Hydrobromide International Journal of Pharmacy and Pharmaceutical Sciences ISSN- 0975-1491, 2014; 6(4).
6. S.K.Senthilkumar1*,B.Jaykar 2 , S.Kavimani3 Formulation, Characterization and Invitro Evaluation of Floating Microsphere Containing Rabeprazole Sodium /JITPS, 2010; 1(6): 274-282.
7. V. Sai Kishore*, B. Tejeswara Rao, K. Pavani, D. Nagasen, K. Rakesh Varma and D. Gowtham Plantago Ovata Seeds And Bhringaraj Leaves As Superdisintegrants: Formulation And Evaluation Of Sotalol Hydrochloride Orodispersible Tablets IJPCBS, 2013; 3(4): 1040-1046.
8. Sanjeev Kumar 1*, Tara Chand 1 Formulation and Development of Floating and Mucoadhesive Microspheres of Clarithromycin The Pharma Innovation – Journal, 2013; 2(5).
9. Mukesh P. Ratnaparkhi*,Formulation and in-vitro characterization of floating microspheres of Metfomin HCl Scholars Research Library Der Pharmacia Lettre, 2012, 4 (5): 1390-1400.
10. Kapil Kumar1* and AK Rai2 Development and Evaluation of Floating Microspheres of Curcumin Tropical Journal of Pharmaceutical Research October, 2012; 11 (5): 713-719
11. Parmar Kunal Vinodbhai a, Sustained Release Floating Microspheres of Acyclovir: Formulation,

Optimization, Characterization And In Vitro Evaluation International Journal of Drug Development & Research., Jan-March, 2011; 3(1). ISSN 0975-9344. Available online http://www.ijddr.in

12. Kumar Darapu B.N*,Formulation And In-Vitro Evaluation Of Gastroretensive Floating Microspheres Of Ranitidine Hydrochloride, Nov-Dec, 2010; 1(2). An International Journal of Advances In Pharmaceutical Sciences
13. Pandey Manisha*, Saraf Shubhini A. Formulation and Evaluation of Floating Microspheres of Famotidine International Journal of PharmTech Research CODEN (USA): IJPRIF ISSN: 0974-4304, April-June 2010; 2(2): 1415-1420,
14. M.K. Deepaa,*, Cefpodoxime Proxetil Floating Microspheres: Formulation and In Vitro Evaluation Iranian Journal of Pharmaceutical Sciences Spring, 2009: 5(2): 69-72. ijps.sums.ac.in.
15. Patel Asha, Ray Subhabrata and Thakur Ram Sharnagat, In Vitro Evaluation and Optimization of Controlled Release Floating Drug Delivery System of Metfo.