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FORMULATION AND EVALUTION OF ACEBUTOLOL MICROSPHERES

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ABSTRACT

In the present work, Microspheres of Acebutolol using Chitosan and PLGA as polymers were formulated to deliver Acebutolol via oral route. The results of this investigation indicate that Ionotropic gelation technique can be successfully employed to fabricate Prepared formulations are evaluated for bulk density, tapped density, percent mucoadhesion, Percent compressibility, hausner's ratio, percentage yield, size and interaction study by FTIR and in vitro drug release. Formulation which passed all the evaluation parameters was considered as the best formulation of Acebutolol. The present study concluded that Acebutolol microspheres could be prepared successfully and formulation **A5** showed satisfactory results.

Keywords: Acebutolol, Chitosan ,PLGA and Microspheres,Mucoadhesion,Ionotropic gelation method.

Introduction:

Oral route drug administration is by far the most preferable route for taking medications. However, their short circulating half life and restricted absorption via a defined segment of intestine limits the therapeutic potential of many drugs. Such a pharmacokinetic limitation leads in many cases to frequent dosing of medication to achieve therapeutic effect. Rational approach

to enhance bioavailability and improve pharmacokinetic and pharmacodynamics profile is to release the drug in a controlled manner and site specific manner.

Small, spherical particles, **microspheres**[1] typically range in size from **1 to 1000** μm. Both natural and synthetic polymers can be used to make them. Microspheres have several uses in medication delivery since they may control release rates and target particular parts of the body. They are particularly useful for applying medication to mucosal surfaces, such as those of the gastrointestinal tract, nose, eyes, and urinary tract. Long-lasting therapeutic advantages can be obtained via the controlled or prolonged release of drugs from microspheres. Additionally, by combining mucoadhesive properties, microspheres can adhere to mucosal surfaces, enhancing drug absorption and bioavailability. Drug distribution to the appropriate locations in the body is facilitated by this adherence.

The term **"mucoadhesive properties"** describes a substance's capacity to stick to mucosal surfaces, including those in the vaginal tract, ocular surface, nasal cavity, and gastrointestinal system. This characteristic is especially useful in drug delivery systems because it can increase the duration that medications remain at the site of action, promote drug absorption, and enable targeted distribution to particular tissues or cells. such as Van der Waals forces, electrostatic interactions, and hydrogen bonds[2]. Getting entangled and mixing Polymers or macromolecules with appropriate adhesive qualities, whether natural or manufactured, can be used as mucoadhesive materials. Natural mucoadhesive polymers include hyaluronic acid, alginate, chitosan, and other polysaccharides derived from plants. Various copolymers, polyethylene glycol (PEG), and polyacrylic acid are examples of synthetic mucoadhesive polymers.

Materials :

Table 1: List Of Materials Used In The Formulation

List of Chemicals	Manufacturing Company
Acebutolol	Procured from Hetero Pharma limited Hyd, provided by **SURA LABS**, Dilsukhnagar, Hyderabad
Chitosan	Merk specialiities Pvt Limited
PLGA	Merk specialiities Pvt Limited
Sodium alginate (w/v)	Merk specialiities Pvt Limited
Calcium Chloride (w/v)	Merk specialiities Pvt Limited

Instruments:

Table 2: List Of Instruments Used

S.NO	Instruments/Equipments	Model and Manufacturer/Supplier
1	UV-Visible spectrophotometer	Lab India, India
2	Electronic weighing balance	Sartorious
4	Magnetic stirrer	Remi Laboratories
5	Dissolution Apparatus	Lab India, Lab India
6	Ultrasonic cleaner	Remi Laboratories
7	FT – IR Spectrometer	Bruker Alpha
8	SEM	SEM (JEOL Ltd, Japan).

Method of preparation:

Ionotropic gelation method:

The microspheres were prepared by the Ionotropic gelation technique. The sodium alginate solution was prepared by dispersing the sodium alginate in deionized water under continuous stirring for 30 minutes. The weighed amount of the drug was thoroughly mixed with sodium alginate dispersion. By following the same procedure the alginate beads of different ratios of drug: polymer were prepared. The resulting homogeneous dispersion was extruded into the 5% calcium chloride solution through hypodermic syringe with flat tip needle (20G) and stirred for 15 minutes at 100 rpm using a magnetic stirrer. The formed microbeads were allowed to cure for 30 minutes in the calcium chloride solution to complete the gelation reaction. The microspheres were then filtered and dried in a hot air oven at 60ºC for 3 hr.

Preparation of Standard Calibration Curve of Acebutolol:

1. 10 mg of Acebutolol[3] was accurately weighed and dissolved in 10ml of methanol (Stock Solution – I) to get a concentration of 1000 µg/ml.
2. 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.
3. 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 10 to 50µg/ml. The absorbance of these samples were analyzed by using UV-Visible Spectrophotometer at 231nm against reference solution 0.1N HCl (pH 1.2). The procedure repeated to pH 6.8 phosphate buffer and pH 7.4 phosphate buffer.

Characterization of microspheres

Table3: Prepared formulation of Microspheres

INGREDIENTS	FORMULATION CODES					
	F1	F2	F3	F4	F5	F6
Acebutolol	50	50	50	50	50	50
Chitosan	25	50	75	-	-	-
PLGA	-	-	-	25	50	75
Sodium alginate (w/v)	6%	6%	6%	6%	6%	6%
Calcium Chloride (w/v)	10%	10%	10%	10%	10%	10%

RESULTS AND DISCUSSION

Calibration curve of Acebutolol in simulated gastric fluid pH 1.2

Table 4 shows the calibration curve data of Acebutolol in simulated gastric fluid pH 1.2 at 255 nm. shows the standard calibration curve with a regression value[4] of 0.9997, slope of 0.0037 and intercept of 0.009 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 10-50µg/ml.

Table 4: Calibration curve data for Acebutolol in simulated gastric fluid pH 1.2

Concentration (µg /ml)	Absorbance
0	0
10	0.141
20	0.266
30	0.389
40	0.526
50	0.658

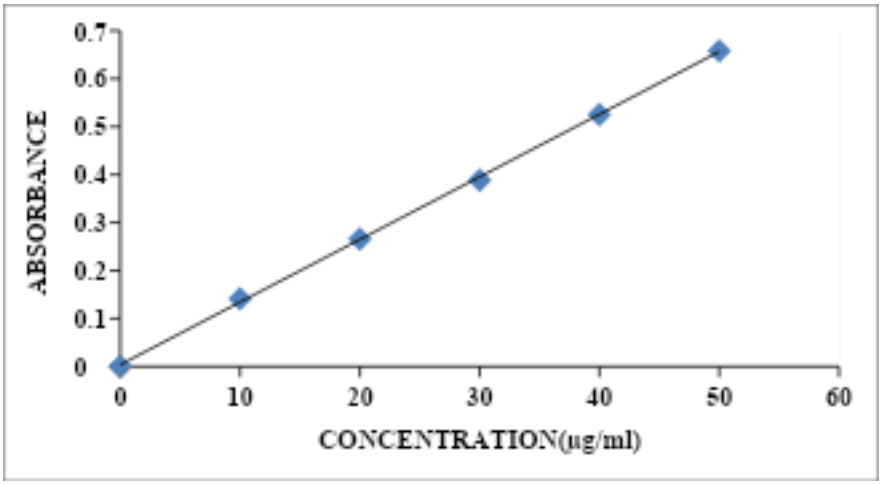

Figure1 : Standard graph Of Acebutolol in simulated gastric fluid pH 1.2

Calibration curve of Acebutolol in pH 7.4 phosphate buffer

Table shows the calibration curve data of Acebutolol in pH 7.4 phosphate buffer at 231 nm. Fig. shows the standard calibration curve with a regression value of 0.999, slope of 0.0091and intercept of 0.020 in simulated gastric fluid pH 1.2. The curve was found to be linear in the concentration range of 10-50µg/ml.

Table 5 : Calibration curve data for Acebutolol in pH 7.4 phosphate buffer

Concentration (µg /ml)	Absorbance
0	0
10	0.124
20	0.235
30	0.341
40	0.442
50	0.554

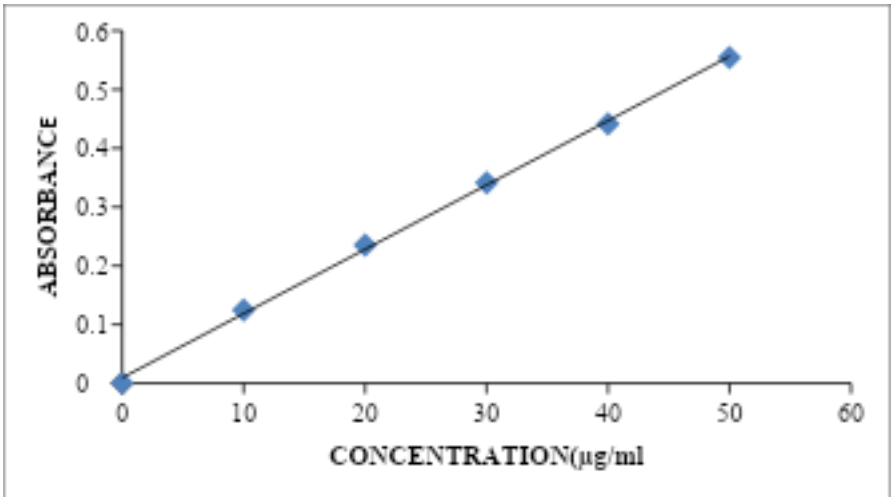

Figure2 : Standard graph Of Acebutolol in pH 7.4 phosphate buffer

Evaluation and characterization of microspheres

Micromeritic property of microspheres of Acebutolol

Formulation code	Mean partical size	Bulk density ((gm./cm^3))	Tapped density (gm./cm^3)	Hausener's ratio	Carr's Index	Angle of repose
A1	423.15	0.598 ± 0.42	0.747 ± 0.36	1.25	19.89	25.29 ± 0.25
A2	443.96	0.618 ± 0.85	0.772 ± 0.67	1.25	20	26.44 ± 0.9
A3	451.65	0.602 ± 0.31	0.762 ± 0.81	1.26	21.04	27.33 ± 0.77
A4	435.14	0.619±0.22	0.725 ± 0.75	1.17	14.62	21.01 ± 0.2
A5	442.69	0.638 ± 0.37	0.785 ± 0.83	1.22	18.20	29.89 ± 0.18
A6	454.54	0.618 ± 0.85	0.772 ± 0.67	1.25	20	24.08 ± 0.26

Drug Entrapment Efficiency[5]

Percentage yield and percentage drug entrapment efficiency of the prepared microspheres

S.No.	Formulation code	% Yield	Drug Content (mg)	% Drug entrapment efficiency
1	A1	86.47	60.15	69.56
2	A2	94.19	70.24	74.57
3	A3	99.42	65.24	65.62
4	A4	96.93	67.36	69.49
5	A5	97.25	72.25	74.29

6	A6	96.74	68.36	70.66

Swelling studies[6]

The swelling ratio is expressed as the percentage of water in the hydrogel at any instant during swelling. Swell ability 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 the amount of polymer plays an important role in solvent transfer. It can be concluded from the data shown in Table 8.5 that with an increase in polymer concentration, the percentage of swelling also increases. Thus we can say that the amount of polymer directly affects the swelling ratio. As the polymer to drug ratio increased[7], the percentage of swelling increased from 88.86 to 96.21% for microspheres containing PLGA as polymer, 88.86 to 92.92% for microspheres containing Chitosan as polymer. The percentage of swelling of the prepared microspheres is displayed in Figures. The percentage of swelling of the prepared microspheres is displayed in Figures. The effect of drug to polymer ratio on percentage swelling is displayed in Figure Table 8.5: Percentage swelling of the prepared microspheres[8].

Table5 : Swelling studies

S.NO.	FORMULATION CODE	INITIAL (Wt)	FINAL (Wt)	PERCENTAGE SWELLING
1	A1	10	13.54	35.4
2	A2	10	12.26	22.6
3	A3	10	14.85	48.5
4	A4	10	13.69	36.9
5	A5	10	14.59	45.9
6	A6	10	12.68	26.8

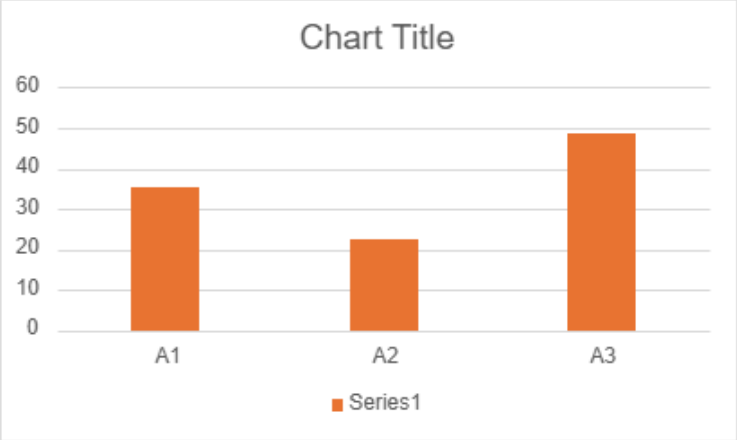

Figure 3 : Percentage swelling of microspheres containing Chitosan

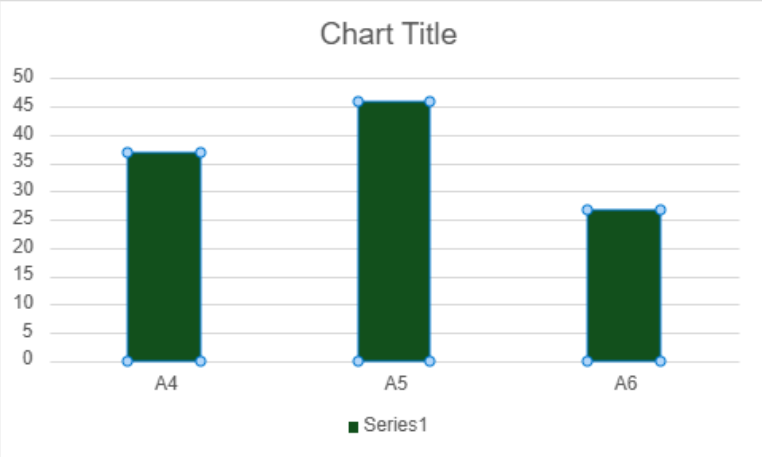

Figure4 : Percentage swelling of microspheres containing PLGA

IN VITRO MUCOADHESION TEST[9]

As the polymer to drug ratio increased, microspheres containing Chitosan exhibited % mucoadhesion ranging from 61 to 70%, microspheres containing PLGA[10] exhibited % mucoadhesion ranging from 75 to 95%. The results of the in-vitro mucoadhesion test are compiled in Table Effect of polymer proportion on % mucoadhesion is depicted in Figures and comparative depiction of % mucoadhesion[11] is depicted in Fig. Table Percentage mucoadhesion of the prepared microspheres.

Table6 : *In Vitro* Mucoadhesion Test of all Formulations[12]

S.NO.	FORMULATION CODE	No. OF MICROSPHERES		PERCENTAGE MUCOADHESION
		INITIAL	FINAL	
1	A1	20	13	65
2	A2	20	15	75
3	A3	20	17	85
4	A4	20	12	60
5	A5	20	18	90

6	A6	20	16	80

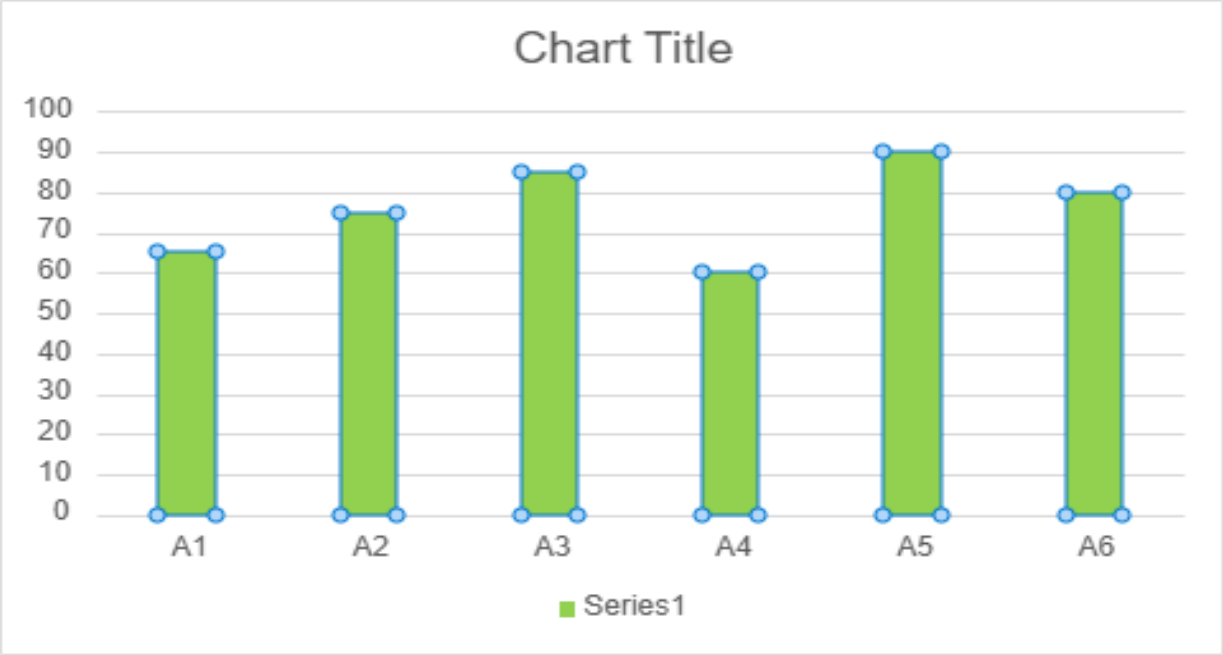

Figure5 : Percentage mucoadhesion of microspheres of all the formulations

IN-VITRO DRUG RELEASE STUDIES[13]

Table7 : *In-vitro* drug release data of Acebutolol microspheres

TIME (H)	Cumulative percentage of drug release					
	A1	A2	A3	A4	A5	A6
0	0	0	0	0	0	0
1	8.93	11.51	14.09	17.67	15.19	15.56
2	16.25	13.69	22.63	22.57	19.86	27.23

3	21.08	23.28	26.12	28.09	26.09	41.76
4	27.39	31.65	33.98	35.38	36.35	54.32
5	33.82	35.92	42.32	42.76	49.59	56.74
6	38.32	39.57	45.51	47.29	54.81	58.26
7	43.62	47.15	53.28	55.67	65.78	63.38
8	49.16	51.81	65.79	64.18	69.65	68.67
9	58.74	65.23	74.65	72.74	77.79	71.19
10	64.41	79.96	83.01	78.83	86.82	76.45
11	78.54	87.28	89.46	86.01	93.48	85.34
12	84.91	91.35	95.87	94.71	99.89	92.72

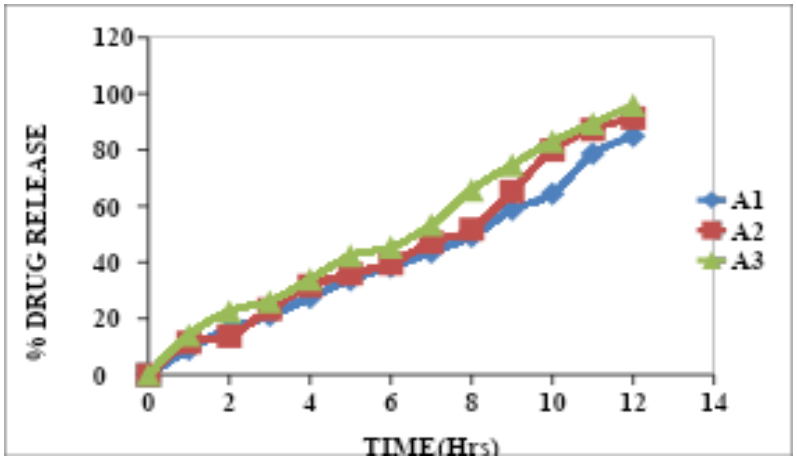

Figure6 : *In-Vitro* drug release profile of Acebutolol microspheres containing Chitosan

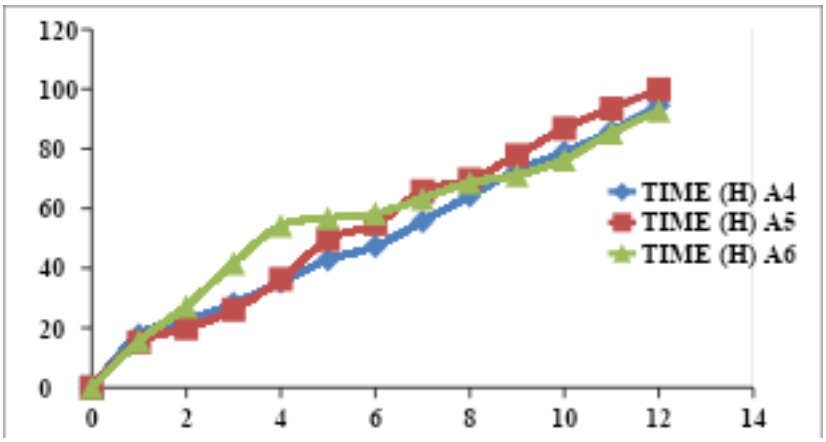

Figure7 : *In-Vitro* drug release profile of Acebutolol microspheres containing PLGA

IN-VITRO DRUG RELEASE KINETICS

COMPATIBILITY STUDIES

Drug polymer compatibility studies[14] 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[15] of the pure drug.

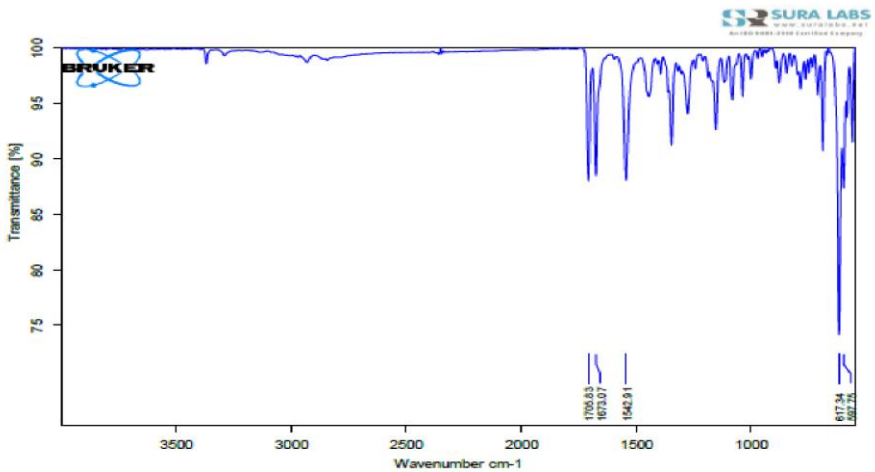

Figure8: FT-IR spectra of Pure drug

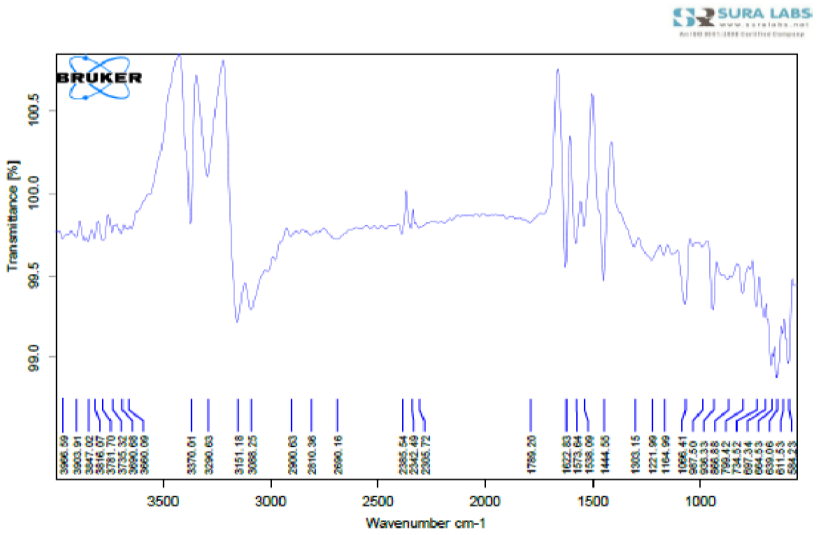

Figure9 : FT-IR spectra of Optimised formulation

SEM :

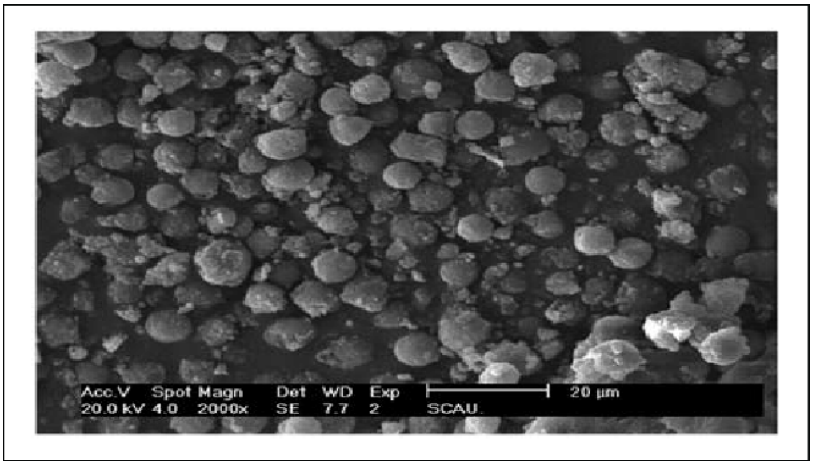

Figure10 : SEM of Optimised formulation

CONCLUSION

Microspheres are one of the micro-particle systems[16] and are prepared to obtain prolonged or controlled drug delivery to improve bioavailability or stability and target drugs to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance. Microspheres are prepared with Chitosan and PLGA[17] successfully by the ionotropic gelation technique. Microspheres of Acebutolol showed excellent mucoadhesive, % yield, Drug Content[19], % Drug entrapment efficiency[18] and prolonged drug release up to 12 hours. Microspheres of different size and drug content could be obtained by varying the formulation variables. Thus the prepared microspheres may prove to be potential candidates for oral delivery devices. Formulation Batch A5 showed the best appropriate balance between mucoadhesivity and drug release rate, which can be considered as a best fit for microspheres. Analysis of drug release mechanisms showed that the drug release from the formulations of the best fit model was found to be zero order release kinetics[20].

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