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Formulation and Evaluation of Mucoadhesive Microspheres of Ritonavir

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ABSTRACT- Microspheres are charectically free flowing powder consisting of protein or synthetic polymers which are biodegradable in nature. Microspheres are particle between 0.1 and 200um in size. A well designed controlled drug delivery system can overcome some of the polymer of the problem of convention therapy and enhances the therapeutic efficacy of given drug. The microspheres were prepared by Ionotropic gelation method dispersing Ritonavir separately in to mixture of ionic sodium alginate. As primary polymer with oppositely charged counter ion polymer, namely HPMC and carbopol of both polymer, in to a solution of aluminium sulphate solution. Microspheres constitute an important part of novel drug delivery system by virture of their small size and efficient carrying capacity. the micro carrier were evaluate for micrometric properties, production yield, drug loading and in vitro drug released studies .the size of prepared microcarrieres were in the range of 447.1umto 650.2 um The result of this study indicate that HPMC K4M gives fast released pattern of the drug as compare to carbopol. The formulation with combination of hydrophilic and hydrophobic polymer also show a good released pattern as compare to f4 to f6 and f7 to f9 and prolonged drug released up to 24 hours. It is important carrier for safe and effective in vivo drug delivery.

KEYWORDS - Microspheres, controlled released novel drug delivery, target site, sodium alginate, Mucoadhesive microspheres, Ritonavir.

I. INTRODUCTION

Mucoadhesive micro carriers has been a topic of interest in the development of drug delivery systems to prolong the residence time at the site of application or absorption [1] Mucoadhesive microspheres become adhesive on hydration, and hence can be used for localizing the drugs to a particular target site of gastrointestinal tract (GIT) for prolong periods of time [2,3]. Mucoadhesive microspheres have advantages like efficient absorption, enhanced bioavailability of the drugs, maximum utilization of drugs, much more intimate contact with intestinal cells, better patience compliance and targeting to specific absorption site can be achieved by using suitable Mucoadhesive polymers on the surface of micro carriers [4,5].

Among the various methods developed for formulation of Mucoadhesive microsphere, the Ionotropic gelation method has gained much attention due to its easy, rapid fabrication and does not involve the use of toxic organic solvent [6,7]. Ritonavir is an antiretroviral agent used in treatment of HIV and viral diseases, belongs to class II under BCS and exhibits low & variable oral bioavailability due to poor aqueous solubility. Ritonavir is a peptidomimetic inhibitor of both the HIV-1 and HIV-2 proteases [8]. Ritonavir having narrow therapeutic index, low bioavailability (65%) and short biological half life (3-5hrs). The usual dose of Ritonavir is 100 mg twice daily; moreover it is primarily absorbed from stomach [9].

All the shortcomings necessitate the development of gastrorentensive Mucoadhesive microspheres for enhancing retention of formulation in GIT which could utilize all the efficacy of Ritonavir, thereby reduced dosing frequency, improve the bioavailability and to enhance the quality of HIV infected patients. All the

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Volume 2, Issue 7, July 2016

drawbacks necessitated the development of Mucoadhesive microspheres for improving residence of dosage form in GIT, which could utilize all the efficacy of Ritonavir, thereby reduced dosing frequency and enhance bioavailability. Therefore, Mucoadhesive microspheres are promising candidate for delivery of Ritonavir for treatment of HIV/AIDS patients.

Materials Used[10, 11]

A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres. These materials include and also modified natural substances. Synthetic polymers employed as carrier materials are methyl methacrylate, acrolein, lactide, glycolide and their copolymers, ethylene vinyl acetate copolymer, polyanhydrides, etc. The natural polymers used for the purpose are albumin, gelatine, starch, collagen and carrageen an. the polymers of natural and synthetic origin

Ritonavir was a gift sample from freedom pharma pvt.ltd.mumbai. Polymers were received as gift sample from HPMC K4Mand carbopol Evonik Degussa India Pvt. Ltd., Mumbai and HPMC K4M Unichem laboratories, Mumbai. Other ingredients used were Of analytical grade.

II. REVIEW OF LITERATURE

Syed. E.et.al. (2013) Floating microspheres of Ritonavir were prepared by ionic gelation method with an aim of increasing the gastric residence time and for controlled release. Oral controlled release dosage forms (OCRDFS) are being developed for the past three decades due to their advantages. The design of oral controlled drug delivery system is primarily aimed at achieving more predictable and increased bioavailability, thereby obtaining a maximum therapeutic effect.[18]

Ankita guarg et.al(2012) Recently the novel dosage forms which can control the release rate and target the active drug molecule to a particular site have attained a great formulation interest. Microspheres are one of the novel drug delivery system which posses several applications and are made up of assorted polymers Novel drug delivery systems achieved a great interest in recent years in the field of modern pharmaceutical formulations. Mucoadhesive microspheres have been proved as a promising tool in delivery of drugs to a particular site in controlled or sustained manner, as they deliver the drug to a particular site for longer duration, the absorption of drug increased and hence, the bioavailability of the drug get increased. [19]

Patil.p.b.et.al. (2009). Mucoadhesive microspheres were prepared by an interpolymer complexation poly(acrylic acid) (PAA) withpoly(vinyl pyrrolidone) (PVP) to increase gastric residence time and a solvent diffusion method. The complexation betweenpoly(acrylic acid) and poly(vinyl pyrrolidone) as a result of hydrogen bonding was confirmed by the shift in the carbonyl absorption bands of poly(acrylic acid) using FT-IR. A mixture of ethanol/water was used as the internal phase, corn oil wasused as the external phase of emulsion, and span 80 was used as the surfactant. Spherical microspheres were p repaired Mucoadhesive microsphere was prepared by a solvent evaporation and interpolymer complexation method. The dissolution rate of the complex microspheres was significantly retarded when compared with that of the PVP microspheres, particularly at pH 2.0.[18]

liu z et al. (2010) were prepared Amoxicillin Mucoadhesive microspheres (Amo-ad-ms) using ethyl cellulose (Ec) as matrix and carbopol 934P as Mucoadhesive polymer for the potential use of treating gastric and duodenal ulcers, which were seen associated with Helicobacter pylori. The morphological characteristics of the Mucoadhesive microspheres have been studied under scanning electron microscope. In vitro release test have been shown that amoxicillin released faster in pH 1.0 hydrochloric acid (HCl) than in pH 7.8 phosphate

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Volume 2, Issue 7, July 2016

III. PREPARATION OF MUCOADHESIVE MICROSPHERES OF RITONAVIR

The Ritonavir Mucoadhesive microspheres were prepared by Ionotropic external gelation technique.

↓

Ritonavir and Mucoadhesive polymers were individually passed through sieve ≠ 60.

↓

The weighed quantity of the Ritonavir was added to 50 mL of purified water the Mucoadhesive polymers and thoroughly mixed with a stirrer at 400 rpm to form a homogenous polymer solution.

↓

The resulting homogeneous dispersion was sonicated for 30 minutes to remove any air bubbles.

↓

For the formation of microspheres the dispersion was extruded drop-wise from a needle of 22 G in diameter from a height of about 5 cm into aqueous aluminum sulphate solution (10%) and stirred at 400 rpm.

↓

The added droplets were retained in the aluminum sulphate solution for 30 minutes to complete the curing reaction and to produce spherical rigid Ritonavir microspheres.

↓

Then the solution containing formed microspheres was filtered by using Whatman filter paper.

↓

The Mucoadhesive microspheres were allowed to dry at 45°C for 12 hrs and stored in well-closed container for further use.

The composition of various formulations was mentioned in

Drug: sodium alginate: HPMC

Drug: sodium alginate: guar gum

Drug: sodium alginate: carbopol

IV. CHARECTERIZATION AND EVALUATION OF MICROSPHERES

- **Percentage Yield:**

The prepared microspheres of all batches were accurately weighed. The measured weight of prepared microspheres was divided by the total amount of all the excipients and drug used in the preparation of the microspheres, which give the total percentage yield of floating microspheres. It was calculated by using following equation,

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of excipients and drug}} \times 100$$

- **Particle Size and Shape**

Light microscopy (LM) and scanning electron microscopy (SEM) both can be used to determine the size, shape and outer structure of microspheres

1. Micromeritic studies

The microspheres were evaluated for micromeritic properties such as bulk density, tapped density, angle of Repose, Carr's index and Hausner's ratio.

a. Bulk density

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Bulk density is the ratio of the weight of the powder and the volume it occupies. It is expressed in gms/ml. Bulk Density is imparted in determining the size of the container needed for handling and processing. A weighed Quantity of the microspheres (W) was carefully taken into a graduated measuring cylinder and the volume Occupied by it (V0) was measured. The bulk density was calculated using the formula

$$\text{Bulk density (B.D)} = \frac{\text{Weight of microspheres (W)}}{\text{Initial volume occupied by the microspheres' } v_0}$$

b. Tapped density

Tapped density is the ratio of the weight of the powder and the volume occupied by it after a specified Compaction process, usually involving vibration of the container. It is obtained by mechanically tapping a Graduated cylinder containing the powder until a little change from the initial volume is observed. It is expressed in gms/ml. A weighed quantity of the microspheres (W) was carefully taken into a graduated measuring cylinder and its initial volume (V0) is noted. The measuring cylinder was closed with a lid and the bulk density apparatus was set for 100 tappings. After the tappings were done, the final volume (VF) was measured and the procedure was continued till the consecutive readings were equal. The tapped density was measured by the formula

$$\textbf{Tapped density (T.D)} = \frac{\textbf{Weight of microspheres (W)}}{\textbf{Final volume occupied by the microspheres (VP)}}$$

c. Carr's compressibility index

The Carr's compressibility index is indirectly related to flow rate, cohesiveness and particle size of a powder. It is a simple, fast and popular method of predicting powder flow characteristics. It was estimated from the bulk Density and tapped density of the powder using the formula

$$\textbf{Carr's compressibility index} = \frac{\textbf{Tapped density- Bulk density}}{\textbf{Tapped density}} \textbf{ X 100}$$

Table:- 1 Carrs index as an indication of powder flow

Carr's index	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	poor
33-38	Very poor
>40	Extremely poor

d. Hausner's ratio

Hausner's ratio is an indirect measure of the flow property of a powder. It is estimated by the following formula

$$\textbf{Hausner's ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk density}}$$

e. Angle of repose

Angle of repose is the maximum angle possible between the surface of the pile of the powder and the horizontal Plane. The frictional forces in the loose powder can be measured by angle of repose. The tangent of the angle of Repose is equal to the coefficient of friction (μ) between the particles. Hence, the rougher and more irregular the Surface of the particles, the greater will be the angle of repose. The angle of repose of the microspheres was determined by the funnel method. Accurately weighed quantity of microspheres were taken in a funnel and the height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the microspheres inside. The microspheres were allowed to flow through the funnel freely onto the surface.

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Volume 2, Issue 7, July 2016

The diameter of the pile of the microspheres was measured and the angle of repose was calculated using the following equation:

$$\tan \Theta = \frac{h}{r}$$

$$\Theta = \tan^{-1} \frac{h}{r}$$

Where, θ = angle of repose, h = height of the heap (in cms) and r = radius of the base (in cms).

Table:-2 Relationship between angle of repose (Θ) and flow ability:-

Angle of repose Θ	flow ability
<25	Excellent
25-30	Good
30-40	Passable
40	Very poor

f. Drug Loading and Drug Entrapment: [13]

Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1MHCl repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using 0.1M HCl The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically Systronic (2201)at 212 nm against appropriate blank. The amount of drug loaded and entrapped in the microspheres was calculated by the following formulas:

$$\% \text{ Drug loading} = \frac{\text{Weight of the drug loaded in the microspheres (DC)}}{\text{Total weight of the microspheres}} \times 100$$

$$\% \text{ Drug entrapment} = \frac{\text{Amount of drug actually present (DC)}}{\text{Theoretical drug load expected}} \times 100$$

Where ;-(DC- Actual Drug Content)

g. Swelling Index

Swelling index illustrate the ability of the Mucoadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption ,which is a primary requirement for initiation of Mucoadhesion. The percent swelling value can be determined using following equation.

Percent swelling = DT - D0 / D0 × 100

Where, D0 = weight of dried microspheres

DT = weight of swelled microspheres

h. *In- Vitro* Release Study

Standard IP/BP/USP dissolution apparatus is used to study *in-vitro* release profile in the dissolution media that is similar to the fluid present at the absorption site as per monograph, using rotating basket or paddle type dissolution apparatus [14].

1. *Ex-Vivo* Mucoadhesion Study

The Mucoadhesive property of the microspheres is evaluated on goat's intestinal mucosa by using phosphate buffer, as per monograph. Weighed microspheres are spread onto wet rinsed tissue specimen and immediately thereafter the slides are hung onto the arm of a USP tablet disintegrating test machine with suitable support at

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Volume 2, Issue 7, July 2016

370C. The weight of microspheres leached out at different intervals is measured. The % Mucoadhesion is calculated by the following equation .

2.Mucoadhesive test

The Mucoadhesive property of prepared Ritonavir microspheres was evaluated by *in-vitro* wash off method. Briefly, a small portion of the goat intestinal mucosa was mounted on a glass slide and about 100 microspheres were spread onto wet rinsed tissue specimen and it was hung onto one of the grooves of a USP disintegration apparatus. Now operating the disintegration test apparatus, the goat intestinal mucosa was given regular up and down movement in test fluid (900 Ml of 0.1 N HCL/pH7.4 phosphate buffer) at 37±0.5°C. At every 1 hr intervals up to 8 hrs the apparatus was stopped and the number of Ritonavir microspheres still adhering to tissue was counted and percent Mucoadhesion was calculated [14].

3.Infrared Spectroscopy

IR spectra of the pure drugs and microspheres were recorded using Perkin Elmer model 883 IR-spectrophotometer between the ranges of 500 to 4000 cm-1 by making a pellet of the samples with KBr. The resultant spectra were then compared with standard reference (IP 1996) and observe for any type of deviation from the standard.

4.Differential Scanning Calorimeter Analysis (DSC)

DSC thermo gram of the pure drugs and the microspheres were recorded with a differential Scanning calorimeter (Universal V2.5H TAInstrument) from 20 to 550 ºC at a heating rate of 20 ºC/minute.

5.X-Ray Diffraction Spectroscopy (XRD)

X-ray diffraction spectrum of the pure drugand microspheres were recorded with Phillips PW 1830 X-ray generator fixed with PW 1710diffractometer (Phillips Industrial & Electro acoustic Systems Division, Almelo, the Netherlands). The XRD was performed at the angle between 5-60 ° 2.

6.Scanning Electron Microscopy (SEM)

Scanning electron microscopy (Hitachi S-3600N, Japan) was done to characterize Surface topography of the microspheres. Photomicrograph of the microspheres before and after the release of drugs was taken. The quality of the microspheres (with respect to surface properties) and the nature and size of pores developed on the surface can be studied. The changes that occur during in-vitro dissolution studies may have implications to the performance of the microspheres.

Table 3 COMPOSITION OF MICROSPHERES

Formulation code	Drug: Polymer ratio	Polymer ratio
F1	1:1	(Sodium alginate: Guar gum) (0.75:0:25)
F2	1:0.5	(Sodium alginate: Guar gum) (0.25:0.25)
F3	1:1	(Sodium alginate: Guar gum) (0.5:0.5)
F4	1:1.5	(Sodium alginate: HPMC) (0.75:0.75)
F5	1:1	(Sodium alginate: HPMC) (0.5:0.5)
F6	1:0.5	(Sodium alginate: HPMC) (0.25:0.25)
F7	1:0.5	(Sodium alginate: Carbopol 940)(0.25:0.25)
F8	1:1	(Sodium alginate: Carbopol 940)(0.75:0.25)
F9	1:1	(Sodium alginate: Carbopol 940) (0.5:0.5)

V. RESULT AND DISCUSSION

Table: 4 Average Particle Size of Ritonavir Mucoadhesive microspheres

Formulation Code	Average Particle Size (um)	Percentage Yield %
F1	**447.1±6.75**	78.35**%**
F2	**468.5±8.71**	63.94**%**
F3	**533.3±10.3**	78.25**%**

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Volume 2, Issue 7, July 2016

F4	**693.4±8.39**	87.6%
F5	**708.4±2.58**	96%
F6	**718.4±2.58**	79%
F7	**626.4±5.99**	58.10%
F8	**638.2±5.10**	54.32%
F9	**650.2±5.33**	52.21%

Percentage yield and micrometric studies: The production yields of microspheres prepared by Ionotropic gelation method were found to be between 78.35% and 96% as shown in Table 5. It was found that production yield of microspheres prepared by HPMC and carbopol was greater than guar gum. All Ritonavir microspheres formulations were evaluated for micromeritic properties. Results are shown in Table 3. Angle of repose of all microspheres batch varied from 20.34 to 33.94. Compressibility index varies from 7.80 to 10.49%. Hausner's ratio varies from 1.921 to 1.117. All formulations results revealed excellent flow property and compressibility.

Table:-5Micromeritic Properties of Mucoadhesive Ritonavir Microspheres

Formulation Code	**Bulk Density**(g/cm^3)	**Tapped Density** (g/cm^3)	**Compressibility Index** (%)	**Hausner's Ratio**	**Angle of Repose** (θ)
F1	**0.307**	**0.333**	**7.80**	**1.921**	**20.34**
F2	**0.221**	**0.269**	**17.12**	**1.212**	**24.94**
F3	**0.346**	**0.367**	**5.72**	**1.602**	**26.76**
F4	**0.307**	**0.350**	**12.28**	**1.187**	**23.75**
F5	**0.370**	**0.375**	**18.13**	**1.013**	**25.75**
F6	**0.304**	**0.340**	**10.46**	**1.112**	**27.58**
F7	**0.316**	**0.390**	**18.97**	**1.23**	**30.60**
F8	**0.300**	**0.331**	**9.36**	**1.103**	**33.72**
F9	**0.324**	**0.362**	**10.49**	**1.117**	**32.94**

Particle size

The average particle size of Ritonavir microspheres ranged from **447.1±6.75** to **650.2±5.33**

um. The mean particle size was significantly increases with increasing Mucoadhesive polymer concentration this may be attributed to high viscosity of Mucoadhesive polymer solution (Table 4).

Morphology of microspheres

The morphology of the Mucoadhesive microspheres of best formulation F4,F6was examined by SEM. The SEM photographs revealed that Ritonavir microspheres were discrete and spherical shape with a rough surface morphology (Fig. 1).

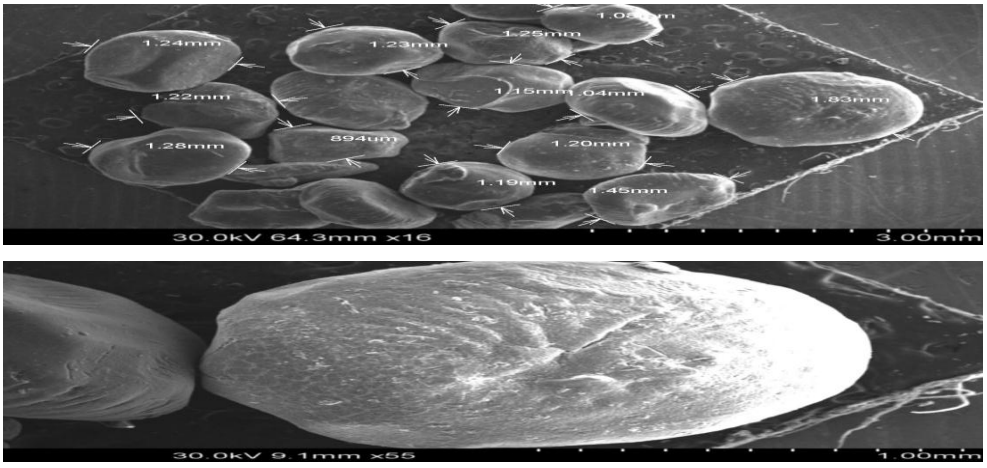

Fig. 1 SEM Photographs of Formulation F4 to F6

Entrapment efficiency

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Volume 2, Issue 7, July 2016

The percentage entrapment efficiency ranged from 76 to 93.00% (Table 6). The entrapment efficiency of the Ritonavir microspheres prepared with carbopol was higher than those of microspheres prepared with HPMC K4M. This may be attributed to higher molecular weight of carbopol than HPMC K4M. Increase in the molecular weight of the polymer increases the entrapment efficiency of the microspheres due to the formation of more intact matrix network.

Mucoadhesive test[16]

To assess the Mucoadhesive property of Ritonavir Mucoadhesive microspheres, *in-vitro* wash-off test was carried out for all batches, and the results are shown in Table 7. Percentage Mucoadhesion increased with the increase in concentration of Mucoadhesive polymer. The

Higher Mucoadhesion of ethyl cellulose microspheres may be attributed to the higher molecular weight of ethyl cellulose than guar gum. The rank order of percentage mucoadhesivity it of all the microsphere formulations after 8 hrs was found to be as follows: F1, F2, F3, <**F4.F5.F6,**>F7, F8, F9

Table:-6 Drug Loading and Drug Entrapment of RITONAVIR Mucoadhesive microspheres

Formulation Code	Actual Drug Content (mg)	Theoretical Drug Content (mg)	Total Weight of Microspheres (mg)	% Drug Loading	% Drug Entrapment
F1	19.18	25	50	38%	76%
F2	13.75	16.67	50	27.5%	82%
F3	19.72	25	50	39.44%	78%
F4	9.09	10	50	18.18%	90%
F5	9.30	10	50	18.6%	93%
F6	14.15	16.67	50	28%	84%
F7	14.75	18.12	50	29.5%	81%
F8	18.85	20.15	50	37%	93%
F9	15.21	18.45	50	30%	82%

***In vitro* dissolution studies**

The *in vitro* Ritonavir release profiles for all batches were shown in Fig. 2. Drug release from these Mucoadhesive microspheres was slow, controlled release and dependent upon the nature and concentration of Mucoadhesive polymers used. Among all the formulations F8 showed good dissolution profile with 75.33% of drug release in 12 hrs. Hence it is considered as the best microsphere formulation, which seems to be a good candidate for controlled release of Ritonavir.

Table 7: Results of *in vitro* wash off test {In 0.1 M HCL (pH 1.2)}

HRS	1	2	3	4	5	6	7	8
F1	0.75±0.21	1.74±0.78	2.75±1.35	3.53±1.73	5.67±0.57	7.22±0.74	10.24±1.73	13.35±1.39
F2	10.29±0.37	15.46±1.34	17.99±1.13	20.24±1,36	22.93±0.40	23.54±0.78	23.59±0.56	26,84±0.42
F3	17.89±0.57	20.56±0.75	20.64±0.58	23.11±0.39	24.32±0.95	30.61±0.74	30.61±0.74	37.81±0.77
F4	3.62±0.21	4.88±0.00	5.75±0.21	6.62±1.34	7.40±1.69	10.93±1.16	10.93±1.16	16.02±0.91
F5	3.11±1.13	6.83±38	8.64±6.70	11.46±0.74	12.12±1.77	12.19±0.76	19.05±0.91	20.13±0.78
F6	4.11±0.93	9.93±1.14	10.7±1.16	11.35±0.97	13.95±1.18	16.33±1.18	18.98±1.18	22.65±1.48
F7	13.37±0.57	15.25±0.78	17.15±0.76	18.45±1.00	19.89±0.80	20.85±0.81	19.71±0.06	24.49±0.41
F8	23.03±1.19	28.36±0.58	30.90±0.79	33.21±0.59	33.20±0.57	35.54±0.39	37.15±0.54	38.28±0.80
F9	29.09±0.98	30.28±0.57	30.28±0.57	33.57±0.58	34.92±0.39	36.53±0.59	38.90±0.76	40.54±0.74

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Volume 2, Issue 7, July 2016

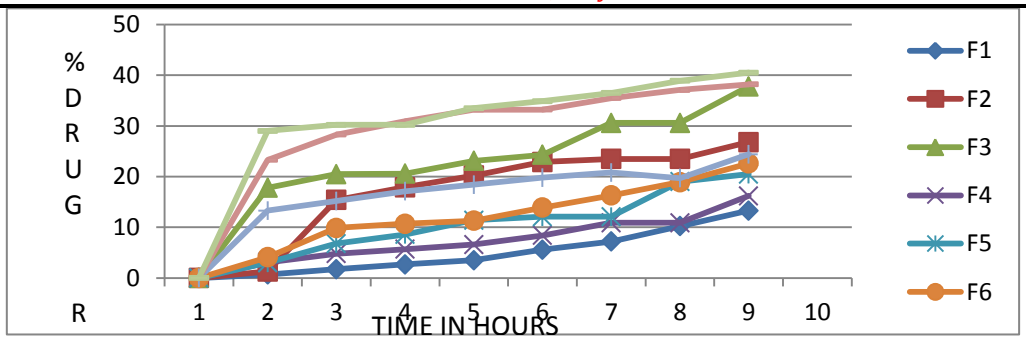

Fig. 2 Comparative release profile of formulation F1-F9

Release kinetic studies

Drug release kinetic data for Ritonavir Mucoadhesive microspheres was shown in Table 8. All the microsphere formulations (F1-F9) followed Kerseymeres-Peppas model and zero-order release kinetic with regression values ranging from 0.891 to 0.877. Nordmeyer- Peppas plots; "n" value ranges from0.964 to 0.950 indicating that the Ritonavir release mechanism followed super Case-II transport mechanism.

FTIR studies and DSC studies

Infrared (IR) spectra of pure drugs sample of Ritonavir were compared with IR spectra of Ritonavir loaded microspheres, as there was no significant change in the pattern of peaks of pure drug and Ritonavir loaded microspheres (Fig. 3). Hence, there was no interaction seen in

Between Ritonavir and polymers. The thermal behaviour of prepared Ritonavir microspheres was studied in comparison with thermo grams of pure Ritonavir as shown in Fig. 4. The thermo gram of pure Ritonavir showed a sharp endothermic peak at 125.1°C, which corresponds to its melting point. The characteristic peak of Ritonavir was well recognized. In the Ritonavir-loaded microspheres. Thus, there was no incompatibility between Ritonavir and Mucoadhesive polymers used in the formulation of microspheres.

XRD study

The XRD spectra's were recorded for Ritonavir, physical mixtures and Ritonavir loaded microspheres for investigating the crystalanity of the Ritonavir in the polymeric microspheres. The X-ray diffract gram of Ritonavir showed sharp peaks at diffraction angle 21.85° depicting a typical crystalline pattern. Physical mixtures showed less intense peaks, however Ritonavir loaded Mucoadhesive microspheres showed peaks, but of low intensity, revealing that some amount of Ritonavir was changed to amorphous form

Stability study[17]

Stability studies of the prepared Ritonavir Mucoadhesive microspheres were carried out by storing the optimized formulation F6 at 4°C/ambient, 25±2°C/60±5%, 40±2°C/75±5% RH for 3 months. The optimized batch F6show negligible change in entrapment efficiency and percentage Mucoadhesion as shown in Table 6. Hence, it can be said that Ritonavir Mucoadhesive microspheres prepared with HPMC K4M is stable.

Table:-8 Drug released kinetics

Sr.no	*Zero Order* r	*First Order r*	*Higuchi r*	*Peppas Plot R (n)*		*Hixson Crowell R*
F4	0.891	0.989	0.973	0.964	0.674	0.966
F5	0.899	0.983	0.974	0.961	0.705	0.963
F6	0.877	0.954	0.964	0.950	0.706	0.930

Mean=SD, n=3

ISSN (Online) : 2454-4159
International Journal of Advanced Research in Science Management and Technology
Volume 2, Issue 7, July 2016

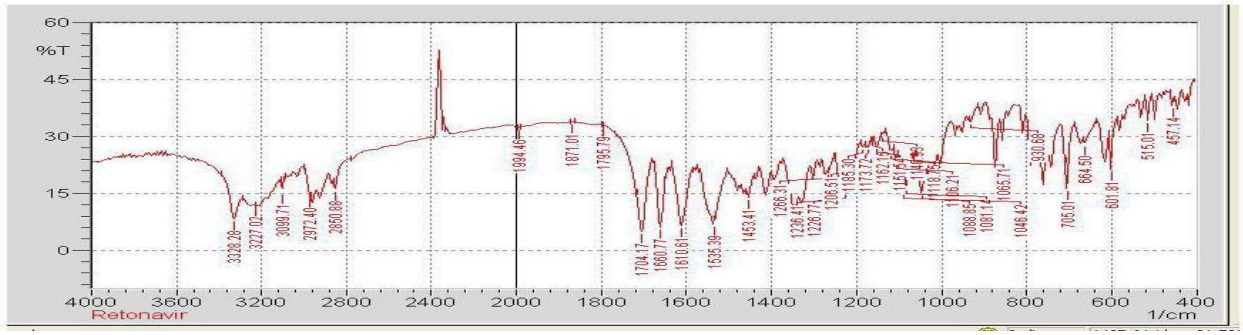

Fig.3 IR spectra of Ritonavir

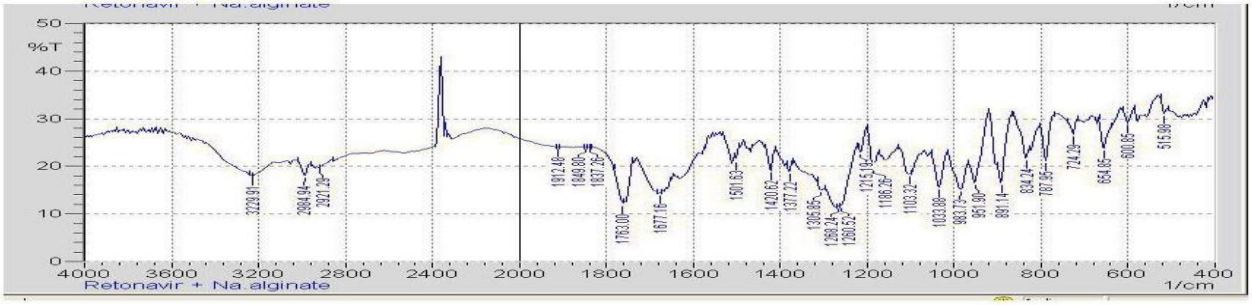

Fig. 4 IR spectra of Na.Alginate /Ritonavir

VI. CONCLUSION

In this study, controlled release Ritonavir microspheres were prepared successfully using the Ionotropic gelation method. This study has been a satisfactory attempt to formulate a Mucoadhesive micro particulate system of an anti-retroviral drug Ritonavir with a view of controlled delivery of the drug. Interaction studies (FTIR and DSC) data revealed that there was no interaction between Mucoadhesive polymers and Ritonavir, hence they are compatible. The prepared Ritonavir microspheres gave good micrometrics properties, percent yield, drug entrapment, Mucoadhesive property and *in vitro* release. SEM analysis of the Ritonavir microspheres revealed that F4 to F6 formulation was spherical shape with rough surface morphology. Among different formulations, the Ritonavir microspheres of batch F4 to F6 had shown the optimum percent drug entrapment of microspheres, Mucoadhesive properties and the controlled release of Ritonavir for about 12 hrs. Thus, the results demonstrate the potential use of HPMC K4M polymer for preparation of controlled delivery Ritonavir Mucoadhesive microspheres and prolonged residence at the absorption site.

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