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## DESIGN AND EVALUATION OF RIMONABANT LOADED SODIUM ALGINATE-GUAR-GUM MICROSPHERE FORMULATION

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### Keywords:

Guar gum,  
Microsphere,  
Rimonabant,  
Sodium Alginate

### ABSTRACT

Rimonabant is an anti-obesity drug which acts as Cannabinoid-1 receptor antagonist. Its main avenue of effect is reduction in appetite. The drug was formulated in the form of Sodium Alginate – Guar gum microspheres following ionotropic gelation method to reduce its dose related side effects. A detailed study of physical and chemical parameters including percentage drug loading and cumulative drug release was carried out and statistically evaluated. Each and every test on all batches was carried out in triplicate. After the experiment the microspheres showed good flow properties with drug entrapment efficiency recorded highest at 71.6%, drug loading results ranged from 12.91-18.20% and the yield percentage was recorded over 90% for all the formulations. The rate of drug release followed Higuchi matrix model equation.

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**INTRODUCTION:** Rimonabant is chemically 5- (4-chlorophenyl) - 1- (2, 4- dichlorophenyl) 4 methyl- N- (piperidin- 1- yl) - 1H- pyrazole- 3 carboxamide. It acts by blocking the CB1 receptor <sup>1, 2, 3</sup>, one of the two receptors found in the newly described physiological system called endocannabinoid system (EC), believed to play a critical role in regulation of food intake and energy expenditure. The drug has a severe side effect of mental depression leading to suicidal tendency. The drug was formulated in the form of microsphere to slower its release rate and minimize dose related side effects. Detailed physiochemical study of microsphere was carried out and statistically evaluated.

#### MATERIALS AND METHODS:

**Materials:** Rimonabant was obtained as a gift sample from Hetero Labs Ltd., Hyderabad. Sodium Alginate <sup>24</sup> (Viscosity of 2% aqueous solution at 25°C was 3500 cps) was obtained from Loba Chemie, Mumbai, Calcium Chloride Dihydrate (A.R. Grade, E Merck, Germany). Guar gum <sup>25</sup> (Merck Specialized Private Limited, Mumbai) and all other chemicals were purchased in A.R and L.R. grade as required. The experimental work was carried out at the laboratory of Calcutta Institute of Pharmaceutical Technology & AHS, Banitabla, Uluberia in 2010 and some instrumental analysis was also carried

out in Bose Institute, Central Drug Laboratory, Kolkata.

#### Methods:

**Preparation of Microspheres:** Rimonabant, Guar gum and Sodium alginate were weighed accordingly and the concentrations of Guar gum and Sodium Alginate were varied (**Table 1**). The two polymers Guar gum and Sodium alginate are water soluble in nature <sup>7, 8</sup>. 50 ml DM water and Sodium alginate were stirred in a mechanical stirrer (Remi, Mumbai) at a speed of 300 rpm to form a uniform solution. The drug was added to the solution and stirred for 30 minutes at the same speed of 300 rpm. Guar gum was then added to this solution and stirred for 1 hour at a speed of 400 rpm. Calcium Chloride (6% w/v) was added to DM water to form a 100 ml solution in a magnetic stirrer. Now the drug polymer solution was drop wise injected in the calcium chloride solution by a needle (21G) while being stirred in a mechanical stirrer at a speed varying from 300-400 rpm. Thus microspheres were formed. The microspheres were decanted from the solution within 5 minutes of formation and then air dried for 4 hours. The air dried microspheres were then put in the incubator at 30°C-40°C for 2 to 3 days. The #22 I.P standard sieve size fractions were used for further studies.

**TABLE 1: FORMULATION OF MICROSPHERES**

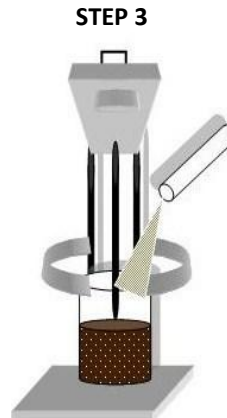
Formulation code	Drug (mg)	Sodium Alginate (mg)	Guar gum (mg)	Drug: Polymer	Polymer: Polymer	Total Polymer (mg)	Initial Weight (gm)
F1	400	1000	1000	1:5	1:1	2000	2.4
F2	400	800	1600	1:6	1:2	2400	2.8
F3	400	700	2100	1:7	1:3	2800	3.2
F4	400	640	2560	1:8	1:4	3200	3.6
F5	400	1600	800	1:6	2:1	2400	2.8
F6	400	2100	700	1:7	3:1	2800	3.2
F7	400	2560	640	1:8	4:1	3200	3.6



**STEP 1**  
Sodium Alginate added to 50ml DM water and stirred at 300 rpm to form a uniform solution.



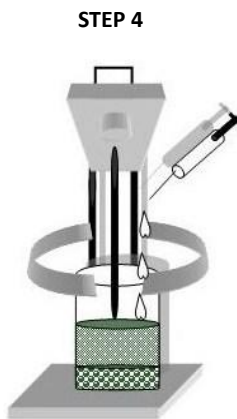
**STEP 2**  
Rimonabant was added to the Na alginate solution and stirred for 30 minutes at 300 rpm.



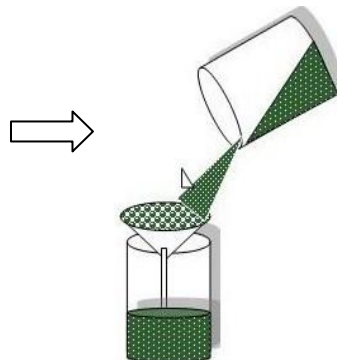
**STEP 3**  
Guar gum was added to the Na alginate and Rimonabant solution and stirred for 1 hour at 400 rpm.



**STEP 4**  
Calcium Chloride (6% w/v) added to DM water in a magnetic stirrer to form a 100ml solution.



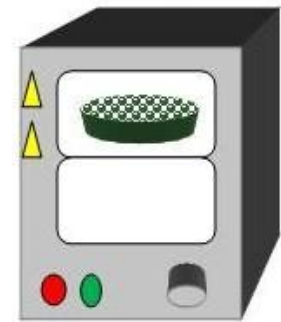
**STEP 4**  
The drug polymer solution was injected drop wise into the Calcium Chloride solution from a height of 5cm from the upper surface of the solution, while being stirred by mechanical stirrer at 300-400 rpm speed. Thus microspheres were formed.



The microspheres were decanted within 5 minutes of formation.



The microspheres were air dried for 4 hours.



The microspheres were then put in the incubator at 30°C-40°C for 2-3 days.

**Process Variables and Process Optimization:** In the preparation of microsphere, the percentage of Sodium Alginate and Guar gum was varied leading to different drug loading capacity<sup>4</sup>. The stirring time, stirring speed were varied in each formulation and different batches thus produced were analyzed for size, shape, ease of preparation, drug content and drug release (Table 2).

$$\text{Drug Entrapment Efficiency} = \left( \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \right) \times 100$$

±SD was calculated. Drug entrapment efficiency was calculated according to the formula:

$$\text{Drug Loading (\%)} = \left[ \frac{Q_m}{W_m} \right] \times 100,$$

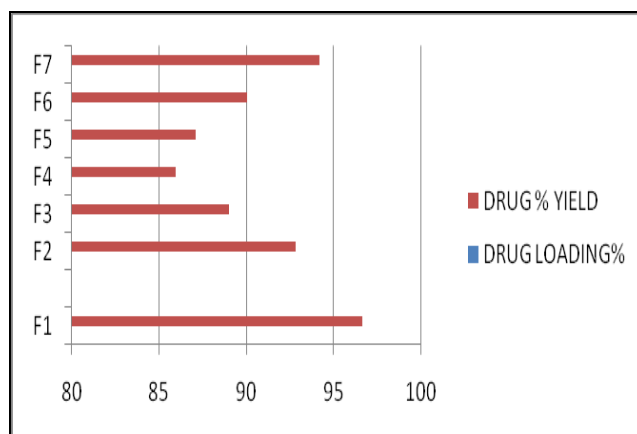
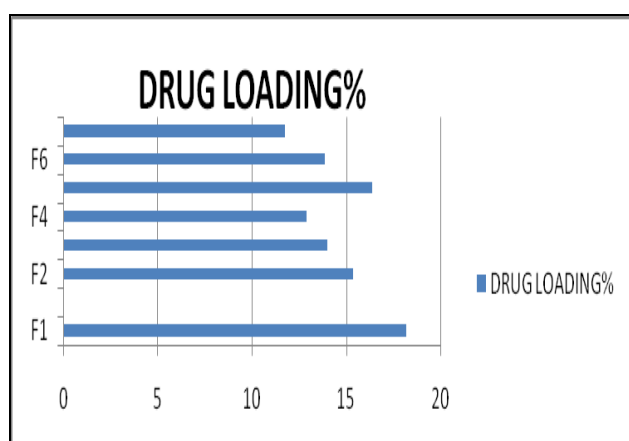
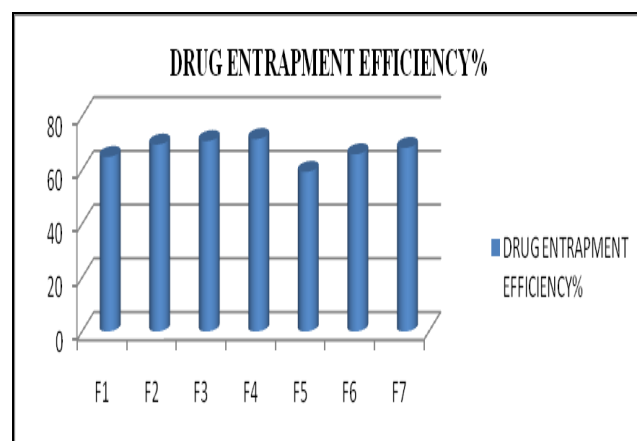
Where,  $W_m$  = Weight of the microsphere and  $Q_m$  = Quantity of drug present in the microsphere.

$$\text{Yield \%} = \left( \frac{M}{M_u} \right) \times 100,$$

Where  $M$  = weight of microsphere and  $M_u$  = Total weight of drug and polymer (table 3, Fig. 1, Fig. 2, Fig. 3).

**TABLE 2: PROCESS VARIABLES AND OPTIMIZATION**

Process Variables	Optimized Data
Bore Diameter of the needle	21G
Height of Dropping	5cm from the level of CaCl <sub>2</sub> solution
Drying time and Temperature	30°C - 40°C for 2-3 days
Guar gum Concentration	0.64% - 2.56%(w/v)
Sodium Alginate Concentration	0.64% - 2.56%(w/v)
Calcium Chloride Concentration	6% (w/v) solution
Mechanical Stirring Speed	300 - 400 rpm
Bore Diameter of the needle	21G

**FIG. 2: BAR DIAGRAM OF YIELD%****FIGURE 1. BAR DIAGRAM OF DRUG LOADING****FIG. 3: BAR DIAGRAM OF DRUG ENTRAPMENT EFFICIENCY****TABLE 3: PARTICLE SIZE ANALYSIS, DRUG ENTRAPMENT EFFICIENCY, DRUG LOADING AND YIELD PERCENTAGE**

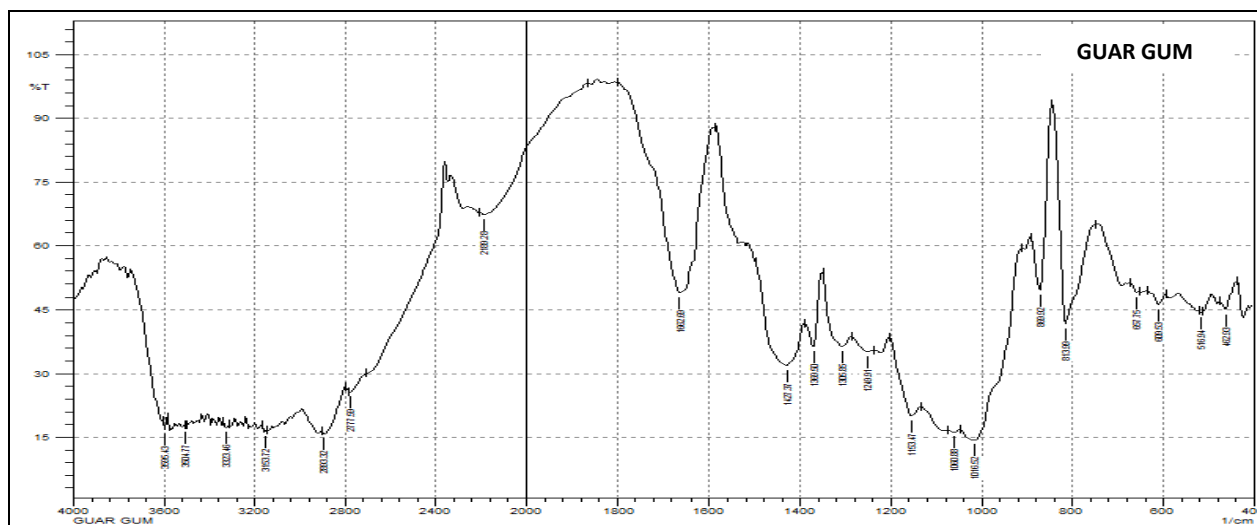
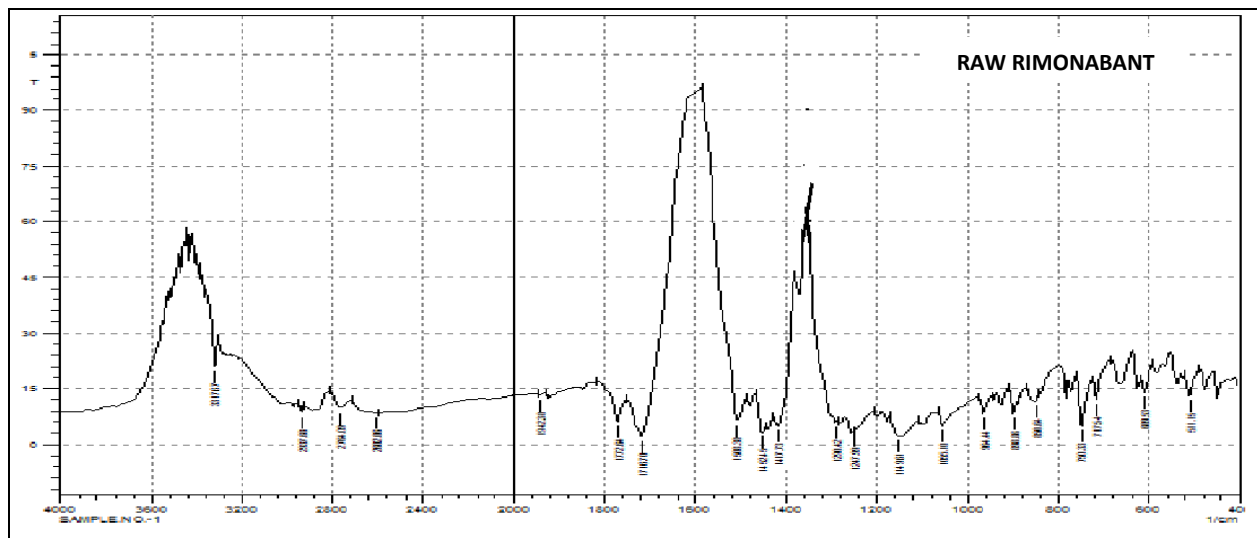
Sample No.	Formulation Code	Mean Particle size (±S.D.)*	Drug Entrapment Efficiency % (±S.D.)*	Drug Loading % (±S.D.)*	% Yield (±S.D.)*
1	F1	760±0.47	64.92±0.27	18.20±0.62	96.66±3.46
2	F2	753±0.01	69.53±0.41	15.30±0.34	92.85±2.03
3	F3	759±0.009	70.83±0.28	13.99±0.04	89.05±0.51
4	F4	757±0.01	71.6±0.21	12.91±0.01	86.01±0.13
5	F5	745±0.81	59.37±0.16	16.39±0.14	87.14±0.67
6	F6	755±0.004	65.93±0.094	13.87±0.11	90.1±0.73
7	F7	762±0.008	68.20±0.138	11.78±0.03	94.25±0.26

**Evaluation of Preparation Method:** In this project attempts have been made to prepare the guar gum-alginate microspheres bearing Rimonabant by ionotropic gelation technique<sup>5</sup>. Here, microspheres were formulated with guar gum which increased the entrapment efficiency, Sodium alginate maintain good percentage of yield value. The Guar gum concentration increased swell ability of formulation. The drug-polymer ratio of the formulation is described by the table 1<sup>28</sup>.

**Drug-Polymer Interaction (FTIR):** Pure drug, guar-gum, sodium alginate and drug loaded

microspheres were analyzed. KBr (I P grade) discs in a proportion of 1:100 samples: KBr were prepared from sample and analyzed in FTIR spectrophotometer (SHIMADZU FTIR- 8400S, Japan) over a range of 400- 4000  $\text{cm}^{-1}$ . Transmittance spectra were recorded and displayed (fig. 4).

From the FTIR reports we see that the peaks 1200, 1350, 1850, 1650, 1471.74, 1842.08 between the drug Rimonabant and polymers Guar gum and Sodium Alginate remain unchanged, thus indicating no drug polymer interaction.



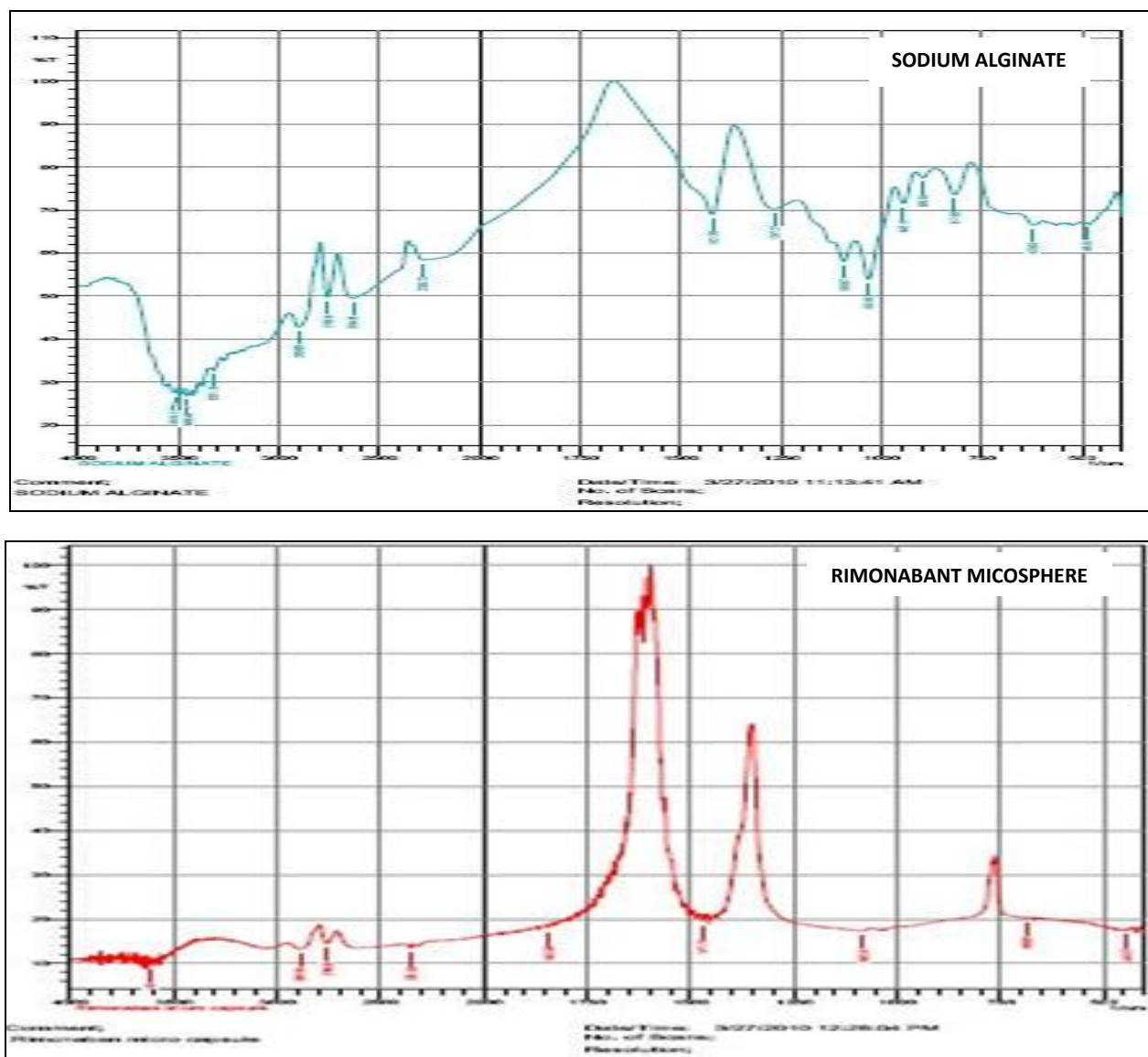


FIG. 4: FTIR REPORTS OF RAW RIMONABANT, GUAR GUM, SODIUM ALGINATE, RIMONABANT MICROSHERE

**Differential Scanning Colorimetric Study:** DSC thermogram of the pure drug and the microsphere were recorded with a differential scanning calorimeter (DSC131 evo, Setaram Instrumentation (Caluire, France) from 20°C-550°C at a heating rate of 20°C per minute. (Figure 5, Figure 6, Figure 7, Figure 8 and figure 9).

**Dissolution Test:** Drug release was performed using USP dissolution rate test apparatus paddle type (50 rpm, 37±0.5°C), at pH 7.4 of phosphate buffer solution for 10 hours. At predetermined time intervals 2ml samples were withdrawn and replaced by an equal volume of fresh medium. After that the samples were filtered, diluted, and assayed at each interval for rimonabant content released at  $\lambda_{max}$  230nm using double beam UV-spectrophotometer (Shimadzu – 1700, Japan). Three trials were carried out for all formulations

29. From this, percentage drug release was calculated and plotted against time.

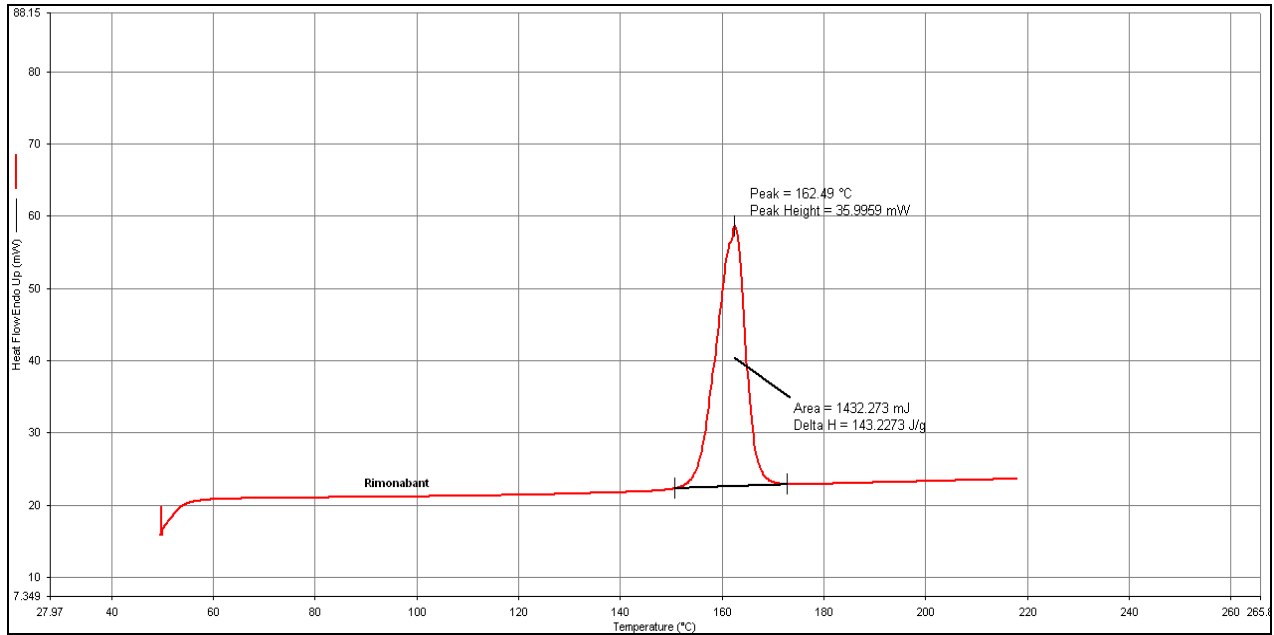


FIG. 5: DSC GRAPH OF RAW RIMONABANT

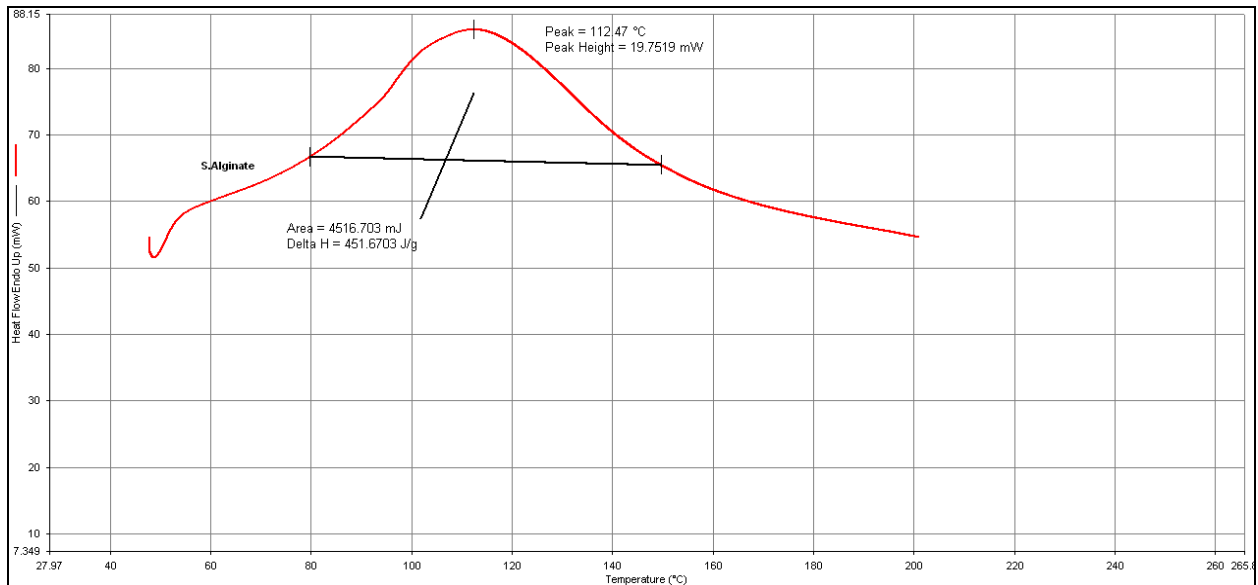


FIG. 6: DSC GRAPH OF GUAR GUM

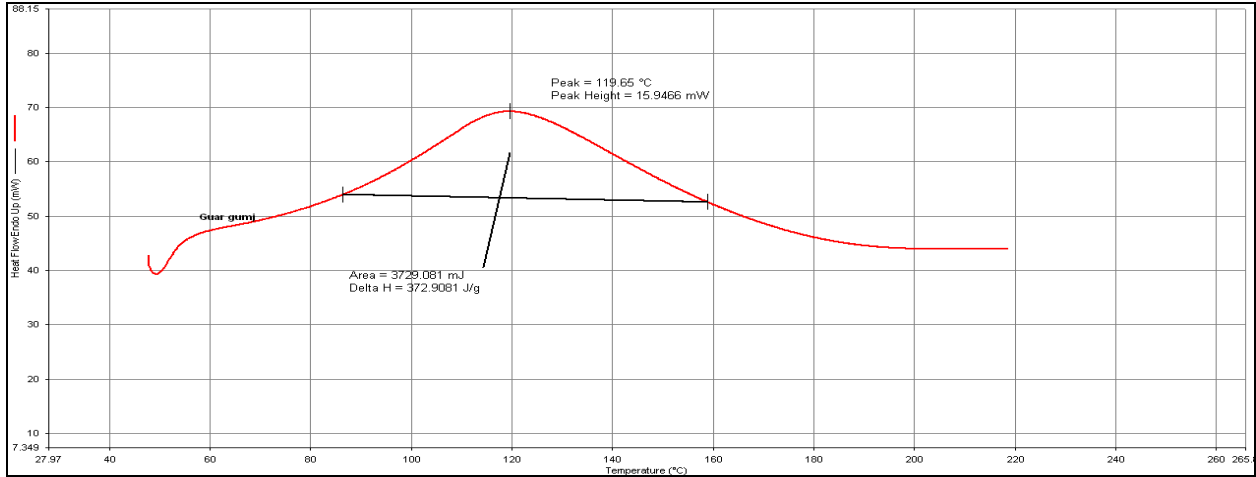


FIG. 7: DSC GRAPH OF SODIUM ALGINATE

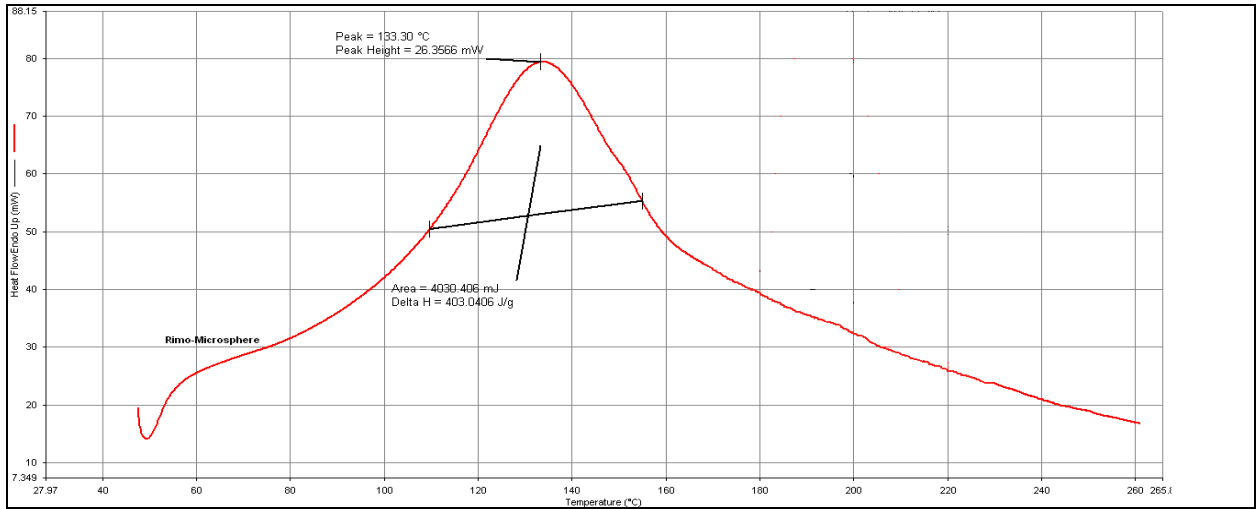


FIG. 8: DSC GRAPH OF RIMONABANT MICROSPHERE FORMULATION

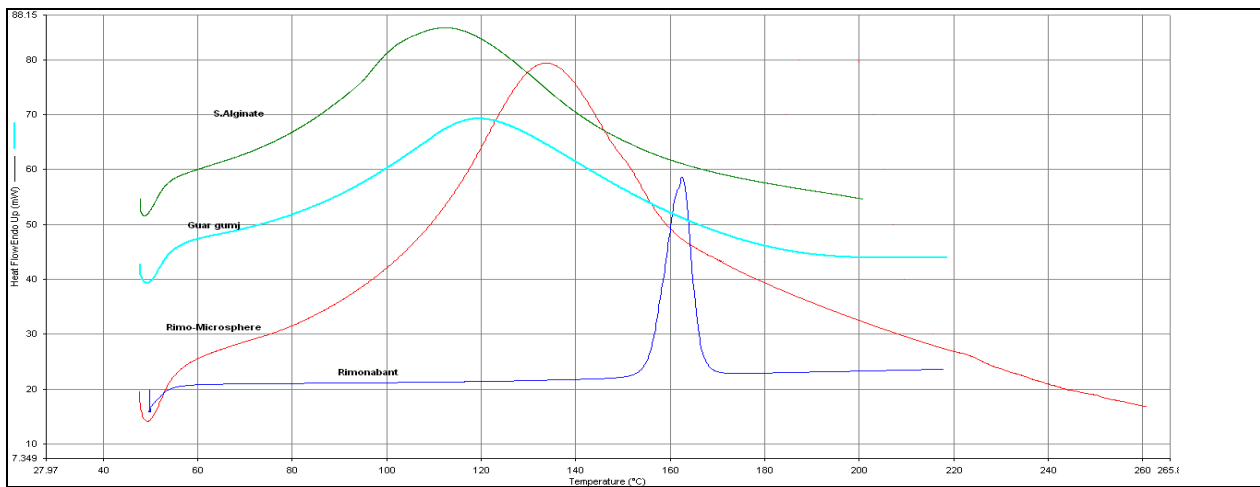


FIG. 9: COMPARITIVE DSC GRAPH OF RAW RIMONABANT, SODIUM ALGINATE AND GUAR GUM



**In vitro Drug Release Kinetics:** Drug release data were fitted into kinetic model including the zero order [Equation 1]<sup>13</sup>, first order [Equation 2]<sup>6</sup>, Higuchi matrix [Equation 3]<sup>10, 11</sup>, Korsmeyer-Peppas [Equation 4]<sup>12</sup> release equations to find the equation with the best fit<sup>6</sup>.

$$R = k_0t \quad [1]$$

$$\text{Log UR} = k_1t/2.303 \quad [2]$$

$$R = k_h\sqrt{t} \quad [3]$$

$$R = k_{kp}t^{n*} \quad [4]$$

Where R and UR are the released and unreleased percentages respectively, at time [t];  $k_0$ ,  $k_1$ ,  $k_h$ ,  $k_{kp}$  are the rate constants of zero order, first order, Higuchi matrix and Korsmeyer-Peppas respectively<sup>27</sup> (Table 4, Fig. 10, Fig. 11, Fig. 12 and Fig. 13). Time versus cumulative percentage of drug release data is shown in table 5. The rate of drug release followed Higuchi matrix model, where the mean  $r^2$  value is greater than the mean  $r^2$  value of zero order, first order or Korsmeyer-peppas models. According to the value of n (table 4) it can be stated that F4, the best optimized batch follows non-fickian super case II.

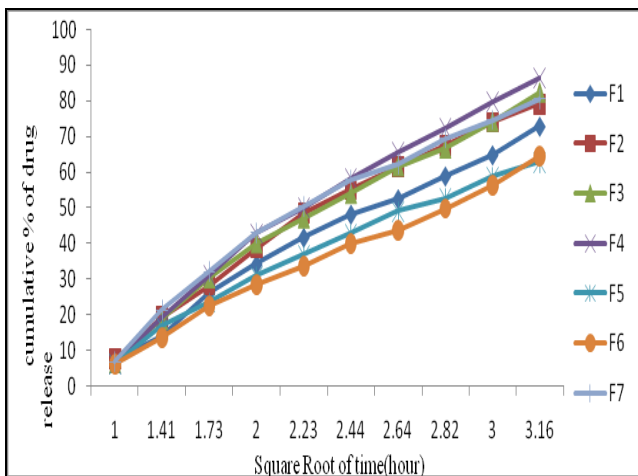


FIG. 10: COMPARITIVE STUDY OF DRUG RELEASE IN HIGUCHI MODEL

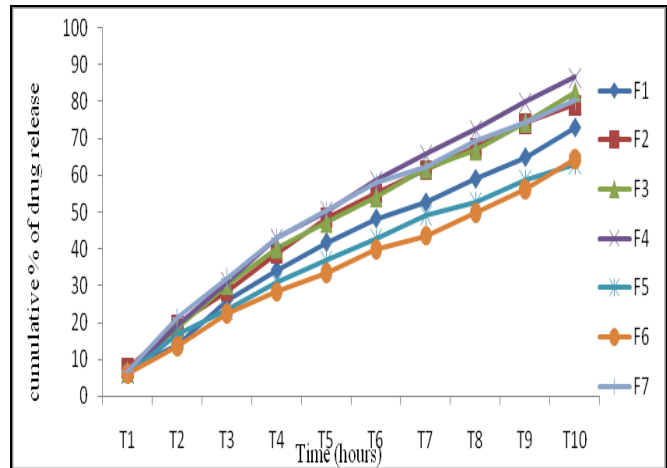


FIG. 11: COMPARITIVE STUDY OF DRUG RELEASE IN ZERO ORDER KINETICS

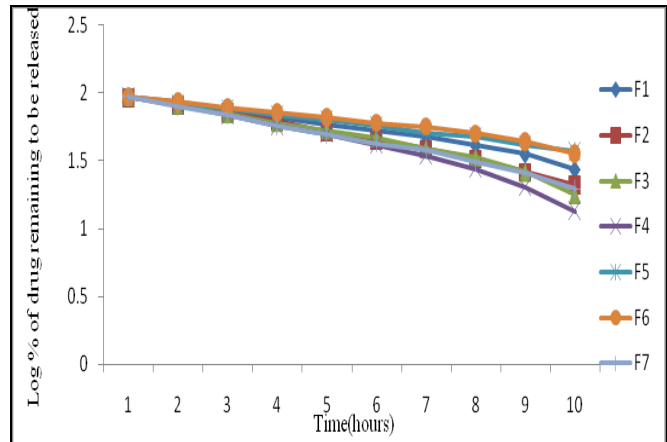


FIG. 12. COMPARITIVE STUDY OF DRUG RELEASE IN 1<sup>ST</sup> ORDER KINETICS

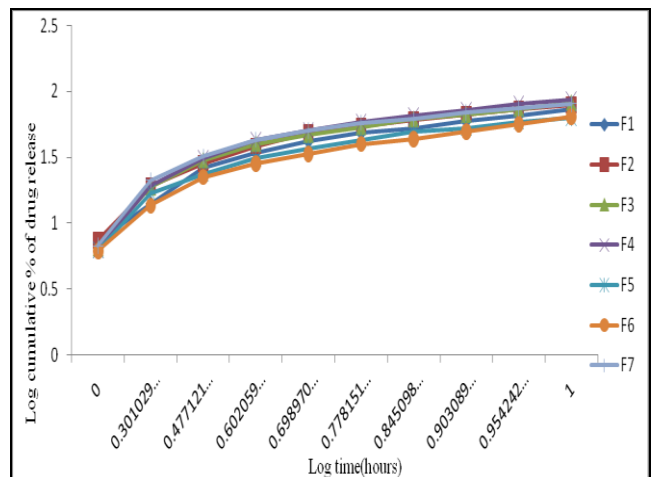


FIG. 13: COMPARITIVE STUDY OF DRUG RELEASE IN KORSMEYER-PEPPAS MODEL

**TABLE 4: IN VITRO RELEASE KINETIC PARAMETERS FOR RIMONABANT MICROSPHERE**

Formulation Code	Zero Order Model		First Order Model		Higuchi Matrix Model		Korsmeyer-Peppas Model	
	r <sup>2</sup>	k <sub>0</sub>	r <sup>2</sup>	k <sub>1</sub>	r <sup>2</sup>	k <sub>h</sub>	r <sup>2</sup>	n
F1	0.987	7.29	0.984	0.329	0.993	23.07	0.998	0.995
F2	0.983	7.91	0.902	0.303	0.998	25.05	0.984	0.999
F3	0.989	8.24	0.972	0.280	0.997	26.08	0.974	1.047
F4	0.983	8.65	0.971	0.259	0.998	27.39	0.971	1.089
F5	0.986	6.29	0.998	0.361	0.998	19.90	0.980	0.959
F6	0.993	6.44	0.978	0.356	0.985	20.39	0.992	0.979
F7	0.970	8.04	0.993	0.297	0.998	25.44	0.960	1.011

if value of n is less than 0.5, it implies Quasi-Fickian diffusion;

if value of n is equal to 0.5, it implies Fickian diffusion (first order release);

if value of n is more than 0.5 but less than 1.0, it implies anomalous (non-Fickian) diffusion;

if value of n is equal to 1.0, it implies non-Fickian case II (and zero order release rate);

if value of n is more than 1.0, it implies non-Fickian super case II

**TABLE 5: TIME VERSUS CUMULATIVE % DRUG RELEASE**

Batch No.	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
F1	7.32±0.008	14.13±0.009	26.21±0.012	34.27±0.012	41.83±0.008	48.33±0.012	52.66±0.004	59.08±0.016	65.02±0.016	73.07±0.009
F2	7.46±0.004	19.39±0.495	28.37±0.42	38.68±0.76	48.65±0.92	55.09±0.640	61.64±1.03	67.66±0.29	74.28±0.36	79.34±0.28
F3	6.48±0.27	18.7±0.31	30.3±0.29	40.18±1.83	47.21±0.76	54.07±0.66	61.83±0.66	66.83±0.37	74.35±0.5796	82.59±0.22
F4	6.24±0.10	19.2±0.17	31.13±0.13	42.98±0.62	50.31±0.36	58.58±0.69	65.78±0.31	72.49±0.33	79.99±0.13	86.75±0.06
F5	6.22±0.08	16.98±0.50	23.62±0.05	31.05±0.200	36.95±0.156	42.92±0.04	49.1±0.02	52.79±0.33	58.9±0.12	63.03±0.10
F6	6.18±0.008	13.68±0.37	22.54±0.03	28.51±0.05	33.7±0.140	39.99±0.52	43.73±0.05	49.86±0.31	56.38±0.47	64.58±0.07
F7	6.78±0.009	21.25±0.63	32.08±0.10	43.02±0.16	50.4±80.20	57.96±0.28	62.37±0.13	69.48±0.07	74.67±0.01	80.58±0.17

### Swelling Study (Degree of Swelling):

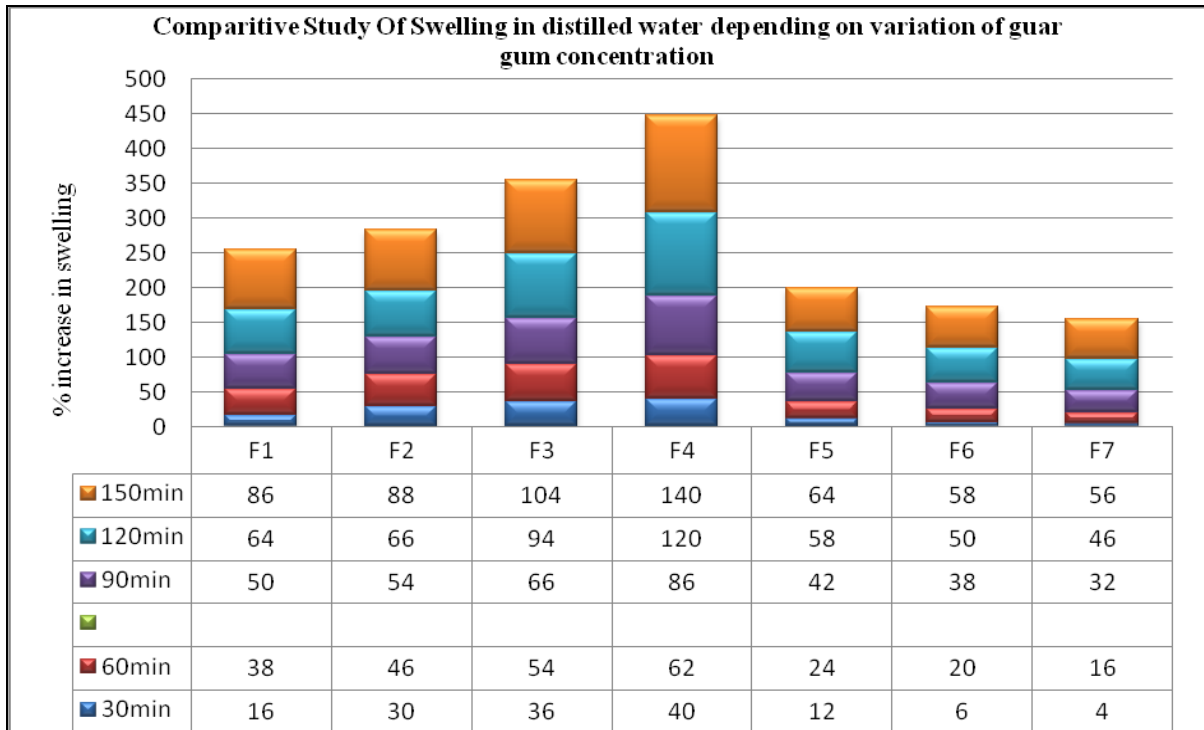
Microspheres (100mg) were placed in little excess of distilled water, 0.1N HCL and PBS (pH 7.4) and allowed to swell to constant weight. The microspheres were removed, blotted with filter paper and their changes in weight were measured at an interval period of 30 minutes and recorded. The degree of swelling [a] was then calculated from the formula <sup>6</sup>:

$$a = W_G - W_0/W_0$$

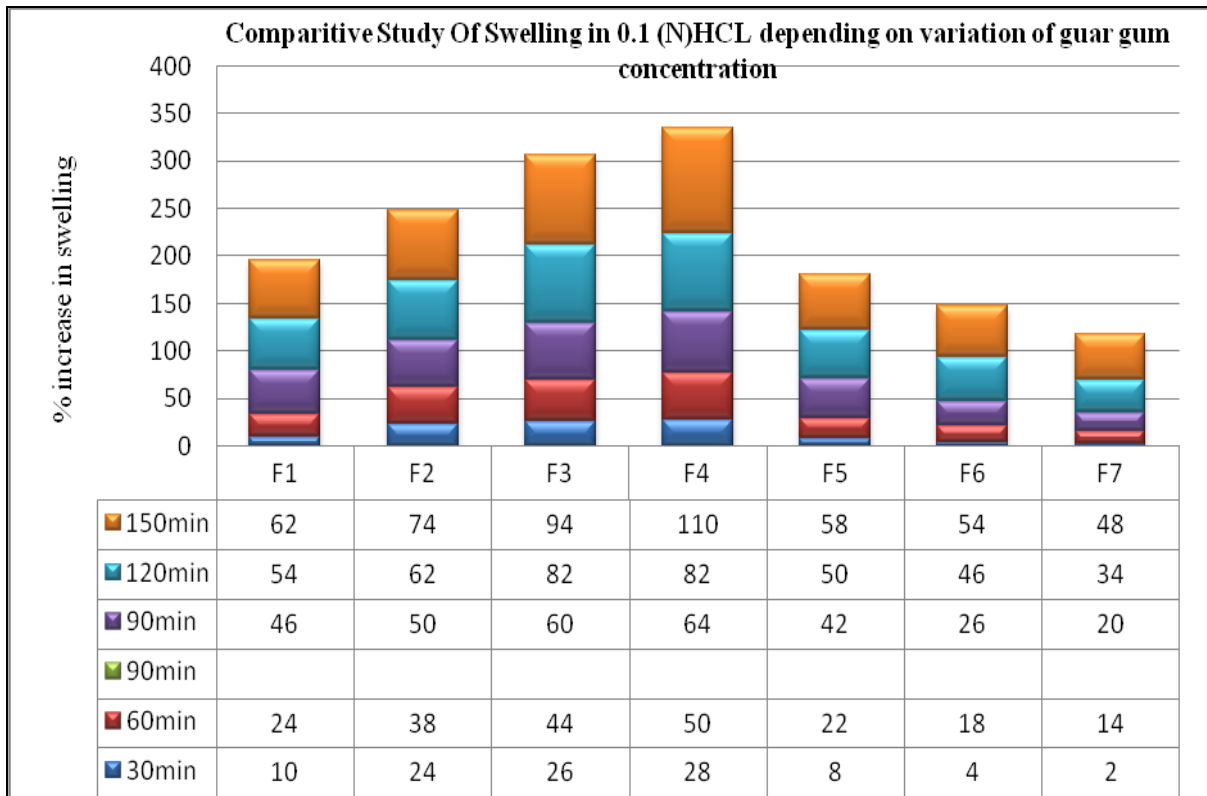
Degree of the swelling in percentage was calculated using the formula:

$$[a = W_G - W_0/W_0] \times 100$$

Where, W<sub>0</sub> is the initial weight of the beads at equilibrium swelling in the medium. Guar gum-alginate microspheres swell <sup>6</sup> in water, 0.1(N) HCL and phosphate buffer 7.4. As a result of decrease in the concentration of guar gum the swell ability study is decreased. Cross-linking with free access of water to the guar gum hydroxyl group, reduces the swelling properties of the cross linked polymer. The swelling percentage of all the batches in distilled water, 0.1 (N) HCL and phosphate buffer 7.4 depending on the variation of guar gum concentration are shown in **Fig. 14**, **Fig. 15**, and **Fig. 16**.



**FIG. 14: COMPARATIVE STUDY OF SWELLING % OF ALL BATCHES DEPENDING ON VARIATION OF GUAR GUM CONC. IN DISTILLED WATER**



**FIG. 15: COMPARATIVE STUDY OF SWELLING % OF ALL BATCHES DEPENDING ON VARIATION OF GUAR GUM CONC. IN 0.1 (N) HCl**

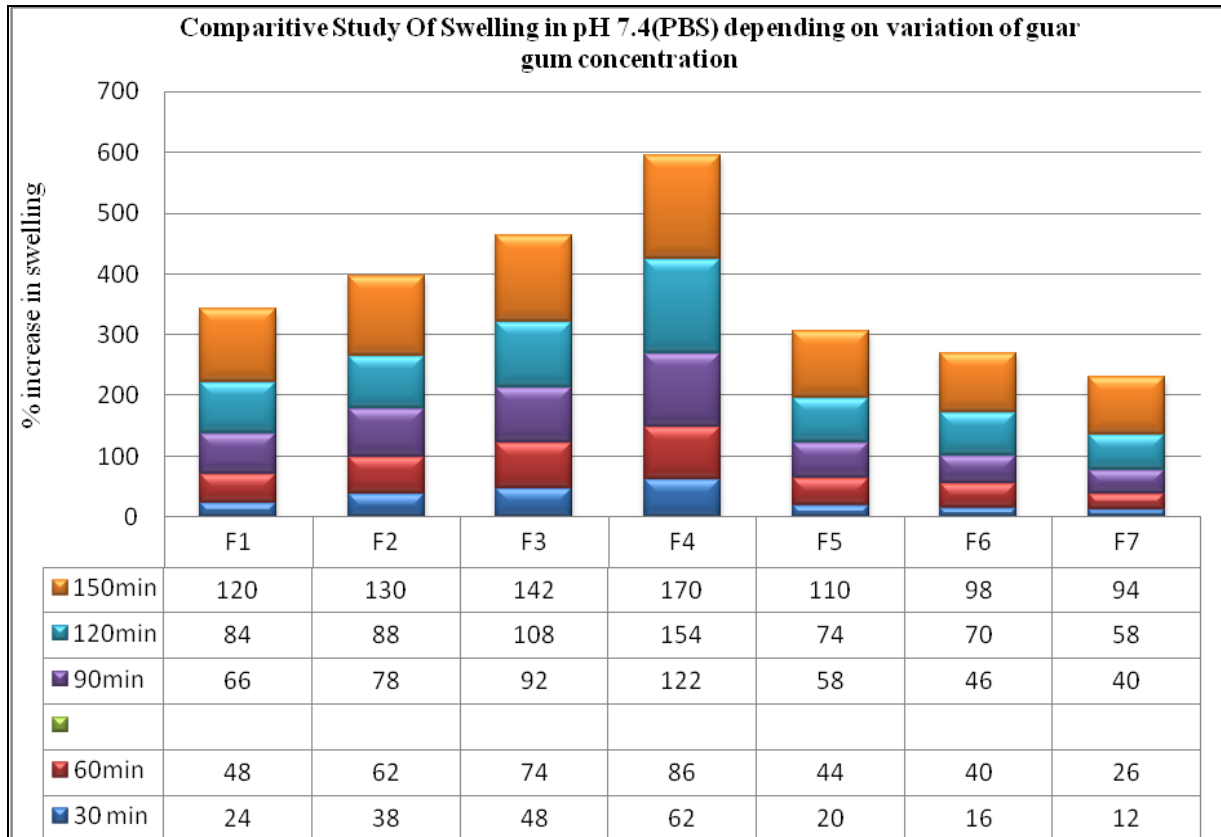


FIG. 16: COMPARATIVE STUDY OF SWELLING % OF ALL BATCHES DEPENDING ON VARIATION OF GUAR GUM CONC. IN PH 7.4 (PBS)

**Scanning Electron Microscopy:** Morphological characterization of the microspheres was done by taking scanning electron microscope in FEI Quanta-200 MK2, Netherlands. Cross sectional view were obtained by cutting the microspheres with a razor blade. The samples were coated to 200 A ° thickness with gold palladium using Pelco model 3 sputter coater prior to microscopy. A working distance of 20nm, a tilt of 0° and accelerating voltage of 15 kv were the operating parameters. Microspheres before and after dissolution were subjected to SEM study. Photographs were taken within a range of 50 – 500 magnifications (Fig. 17, Fig. 18 and Fig. 19).

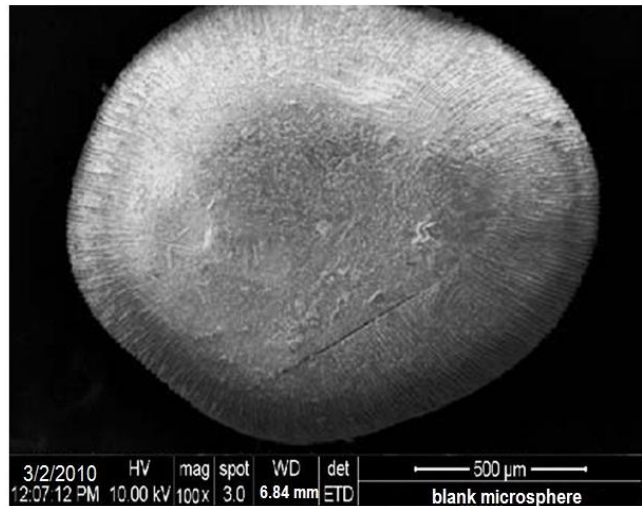


FIG. 17: SEM OF BLANK MICROSPHERE

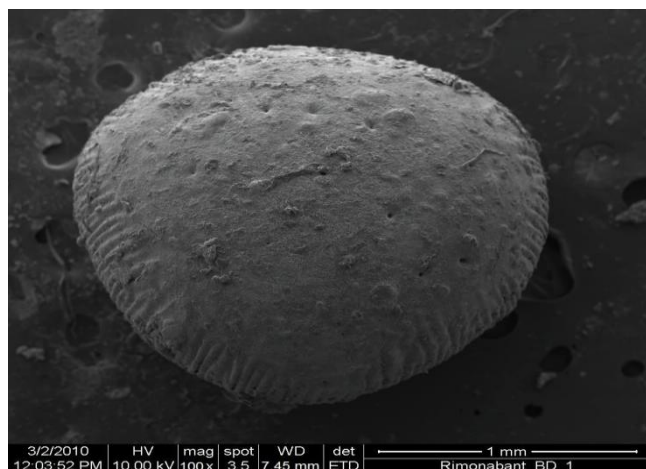


FIG. 18: SEM OF RIMONABANT MICROSPHERE BEFORE DISSOLUTION

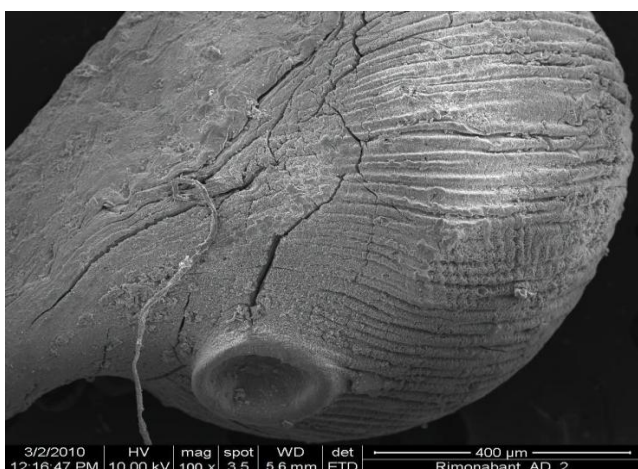


FIG. 19: SEM OF RIMONABANT MICROSPHERE AFTER DISSOLUTION

**Micromeritic Study:** To determine the rheological effects of the microspheres, the angle of repose of all the samples were measured using funnel method. Bulk density<sup>31, 32</sup> was determined by taking known quantity of microspheres in 100ml measuring cylinder and tapping it 3 times from a height of 1 inch at 2 seconds interval. The bulk density was calculated by dividing sample weight by final bulk volume<sup>4</sup> (Table 6).

**Surface Accumulation Study (SA):** This study<sup>9</sup> was conducted to estimate the amount of drug present on the surface of the microspheres which may show immediate release in the dissolution media. 100mg of microspheres (#22 sizes) were suspended in 100ml of phosphate buffer (pH 7.4), simulating the dissolution media. The samples were shaken vigorously for 15 minutes in a mechanical shaker. The amount of drug leached out from the surface was analyzed by UV spectrophotometer Shimadzu- 1700, Japan at 230nm. Percentage of drug released with respect to entrapped drug in the sample was recorded (Table 6).

TABLE 6: BULK DENSITY, SA, ANGLE OF REPOSE

Formulation code	Bulk Density ( $\rho_b$ ) (g/cm <sup>3</sup> ) $\pm$ S.D.*	Tapped Density ( $\rho_t$ ) (g/cm <sup>3</sup> ) $\pm$ S.D.*	Compressibility Index (Carr) (%) $\pm$ S.D.*	Hausner's Ratio $\pm$ S.D.*	Angle of Repose ( $^\circ$ ) $\pm$ S.D.*	SA with respect to Entrapped drug (%) $\pm$ S.D.*
F1	0.46 $\pm$ 0.02	0.51 $\pm$ 0.03	10.77 $\pm$ 2.08	1.11 $\pm$ 0.02	28.17 $\pm$ 0.08	4.11 $\pm$ 0.10
F2	0.44 $\pm$ 0.004	0.53 $\pm$ 0.01	17.74 $\pm$ 1.71	1.20 $\pm$ 0.01	35.73 $\pm$ 1.11	3.11 $\pm$ 0.14
F3	0.45 $\pm$ 0.01	0.46 $\pm$ 0.01	2.89 $\pm$ 1.02	1.02 $\pm$ 0.009	27.75 $\pm$ 6.72	4.38 $\pm$ 0.21
F4	0.41 $\pm$ 0.01	0.43 $\pm$ 0.016	4.16 $\pm$ 0.13	1.03 $\pm$ 0.009	25.63 $\pm$ 0.37	1.61 $\pm$ 0.21
F5	0.56 $\pm$ 0.009	0.60 $\pm$ 0.018	5.68 $\pm$ 1.42	1.05 $\pm$ 0.014	24.22 $\pm$ 0.678	4.61 $\pm$ 0.16
F6	0.51 $\pm$ 0.008	0.57 $\pm$ 0.024	0.111 $\pm$ 0.025	1.12 $\pm$ 0.029	1.12 $\pm$ 0.029	29.17 $\pm$ 0.38
F7	0.44 $\pm$ 0.008	0.47 $\pm$ 0.021	5.87 $\pm$ 3.80	1.06 $\pm$ 0.04	26.09 $\pm$ 0.755	3.05 $\pm$ 0.215

**RESULTS AND DISCUSSIONS:** A total number of seven batches of the drug Rimonabant were prepared in the form of microspheres by optimizing the proportion of Guar gum, Sodium alginate and stirring speed. Out of seven batches batch no. F4 showed best optimized result in respect of drug entrapment efficiency, cumulative percentage drug release, particle size, yield value, swelling property and flow property. DSC studies showed no interaction between drug and polymer. SEM studies confirmed smooth topographical nature of microsphere. Statistical interpretation of release rate confirmed Higuchi matrix model and non-fickian super case II for all the batches. According to the above mentioned data, the Cannabinoid-1 receptor antagonist. The results for process variables and optimization, particle size analysis, drug entrapment efficiency, drug loading yield%, Differential scanning colorimetry, SEM, micromeritic study, In vitro drug release kinetic study, comparative swelling study, time versus cumulative% drug release study is given in tabular and in figure form.

**CONCLUSION:** In the present study, in-vitro characterization of Guar gum- Sodium alginate based Rimonabant microspheres were prepared for gastrointestinal drug delivery, where Guar gum acts as a natural polymer<sup>15</sup> based carrier which is inexpensive and naturally occurring and also having hydrophilic and swelling properties. These properties and the viscous nature of the Guar gum retards release of the drug from the dosage form, making it more likely that degradation will occur in the gastrointestinal tract. Sodium alginate helps in uniform release of the drug over a longer duration of time and also acts as a biodegradable carrier. The natural polymers are also appealing for use in drug delivery for a wide range of molecular weights, varying chemical compositions, low toxicity and

biodegradability. Moreover, they are selectively degraded in the gastrointestinal tract.

Therefore, more research is necessary to be focused on the specificity of drug uptake in the gastrointestinal site. Sodium Alginate in the formulations degrades<sup>16</sup> slowly resulting in sustained release of drug from the microspheres. Rimonabant can be successfully formulated in microsphere form by optimizing the proportion of Guar gum and Sodium alginate as polymers and can be encapsulated for therapeutic purpose to reduce dose related side effects.

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#### REFERENCES:

1. Chakraborty M.; International Journal Of Pharmacy and Pharmaceutical Sciences, Nov – Dec. 2009, 1:1.
2. Bhaumik U, Development and validation of HPLC methods for bioanalytical applications with Rimonabant. J. Pharm. And Biomed. Anal.2009; 49(4): 1009-1013.
3. Croci T, Effect of Cannabinoid CB1 Receptor antagonist Rimonabant on non ciceptive responses and adjuvant induce arthritis in obese and lean rats. British J. Pharmacol. 2007; 150:559 -566.
4. *Indian Pharmacopoeia* 5<sup>th</sup> edition Controller of Publication. 1996:328-329,393-395
5. Mazumder Rana, Formulation and in vitro evaluation of natural polymers based microspheres for colonic drug delivery. International Journal Of Pharmacy and Pharmaceutical Sciences,2010 , 2: 1,
6. Wang J., Microencapsulation of Drugs with Aqueous Colloidal dispersion. J. Pharm. Sci. 1993:82(2):191-194

7. Abu IK., Preparation and evaluation of Zidovudine-loaded sustained release microspheres. *J. Pharm. Sci.* 1996;85(6):575-7=576
8. Higuchi, T. Rate of release of medicaments from ointment bases containing drug in suspension. *J.Pharm.Sci.*1961, 50(10),874-875.
9. Higuchi, T. Mechanism of sustained action medication. Theoretical analysis of rate of release of solid drug dispersed in solid matrix. *J.Pharm.Sci.*1963, 52(12), 1145-1149.
10. Korsmeyer, R.W.; Gurny ,R.; Doelker, E.M. ; Buri, P; Peppas, N.A. Mechanism of solute release from porous hydrophilic polymer. *nt.J.Pharm.* 1983, 15(1), 25-35.
11. Donbrow, M.; Samuelov,Y. Zero order drug delivery from double layered porous films : release rate profile from ethyl cellulose, hydroxyl propyl cellulose and polyethylene glycol mixture. *J. Pharm. Pharmacol.* 1980, 32(7), 463-470.
12. Vayas SP and Khar RK. Controlled drug delivery concepts and advances.Ed. Jain MK, 1<sup>st</sup> Edn. Ed.Jain MK, Vallabh Prakasan, Delhi, 2005; 218-219
13. Chourasia MK and Jain SK. Potential of guar gum microspheres for target specific drug release to colon. *J.Drug Targeting* 2004; 12(7): 435-442.
14. Schröder K, Influence of Bulk and tapped density on the determination of the thermal conductivity of powders and blends. *AAPS, PharmSciTech.* 2007; 8(3): 78.
15. Sheehan C. Expert committee: (EGC05) Excipient General Chapters USP 29 – NF 24 Page 2638 *Pharmacopeial Forum*; 31(3) pg 909.
16. R.L. Carr, *Chem Eng.* 1965 72, 163-168.
17. Kanig,et al. . *The Theory and Practice of Industrial Pharmacy* ,3 Ed., 1986..
18. H.H. Hausner, *Int J Powder Metall.* 1967; 3: 7-13
19. R.O. Grey "On the Hausner Ratio and its relationship to some properties of metal powders" *Powder Technology*, 1969, 2:6, 323-326.
20. JC Brown & G Livesey. "Energy balance and expenditure while consuming guar gum at various fat intakes and ambient temperatures". *Am J Clin Nutr.* 1994. 60(6):956-64
21. Pittler MH, "Ernst E. Guar gum for body weight reduction: meta-analysis of randomized trials". *Am J Med.* 2001; 110(9):724-730.
22. Uzunkaya, G. In vitro drug liberation and kinetics of sustained release indomethacin suppository II. *Farmaco.*, 58, 509-512, 2003.
23. Wu, P-C. Design and evaluation of sustained release microspheres of potassium chloride prepared by Eudragit®. *Eur. J.Pharm.Sci.*,2003, 19(2-3), 115-122,
24. Stavchansky, S.A., *Dissolution: Theory and Practice.* In: *Pharmaceutical Dosage Forms: Tablets*, Eds: H.A. Lieberman, L. Lachman, J. B. Schwartz, 2,393-403, 2<sup>nd</sup> edition, Revised and Expanded, Marcel Dekker, Inc, New York, 1990.
25. Meral YÜCE , Indomethacin loaded microsphere: preparation, characterization and in vitro evaluation regarding ethyl cellulose matrix material, *Turk J. Pharm. Sci.*2008, 5(3)129-142,
26. Birkeland, P.W., 1984, *Soils and Geomorphology*: Oxford University Press, New York, 14-15  
Blake, G.R., Bulk Density, in A. Klute, ed., *Methods of Soil Analysis, Part I. Physical and Mineralogical Methods*: Agronomy Monograph, 2<sup>nd</sup> ed.,2009:363-375.