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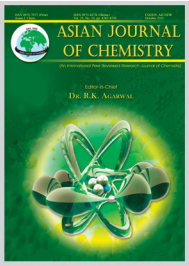

Preparation and Statistical Optimization of Alginate Based Stomach Specific Floating Microcapsules of an Antihypertensive Agent

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The present study involves preparation and characterization of floating microcapsules with Simvastatin as model drug for prolongation of gastric residence time. The main objective of this work is to improve solubility of simvastatin β-cyclodextrin complex (1:2) by co-precipitation method and then to deliver the same in sustained release dosage form. Sustained-release simvastatin microcapsules were prepared by the ionic gelation technique, using carbopol-941 as swellable floating polymer. A 3^3 full factorial design was used to study the effect of polymer concentration, drug complex and sodium alginate. The formed microcapsules were subjected to various evaluation tests such as drug encapsulation efficiency, *in vitro* drug release and surface morphology was studies using SEM. Powdered X-ray diffractometer and FTIR were used to investigate the complexation of simvastatin in the microcapsules. As the carbopol 941 is self swellable polymer, immediate floating was observed. The *in vitro* release studies and floating behaviour were performed in HCl buffer pH 1.2. The best fit release kinetics was achieved with first order release. It was concluded from the present investigation that porous carbopol 941 microcapsules are promising sustained release as well as stomach specific carriers for delivery of simvastatin.

Key Words: Floating microcapsules, Simvastatin, *In vitro* release, Sustained drug release, Main effect plot, Counter plots.

INTRODUCTION

Microcapsules are small particles that contain an active agent or core material surrounded by a coating or shell. At present, there is no universally accepted size range that particles must have in order to be classified as microcapsules. However, many workers classify capsules smaller than 1 μm as nanocapsules and capsules larger than 1000 μm as microcapsules. Commercial microcapsules typically have a diameter between 3 and 800 μm and contain 10-90 wt. percent core[1].

Floating drug delivery systems or hydrodynamically balanced systems are among the several approaches that have been developed in order to increase the gastric residence time of dosage forms[2-4].

Ionic gelation method is dropping or spraying a sodium alginate solution into a calcium chloride solution producing microcapsules. The divalent calcium ions cross-link the alginate, forming gelled droplets. These gel droplets can be permanently cross-linked by addition to a polylysine solution. Variations on this method with different polymers have been developed[5-8].

The purpose of present study is to improve the bioavailability of simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor with a very low aqueous solubility, which is enhanced by Simvastatin β-cyclodextrin complex, in addition release retarding polymer was also incorporated in to the microspheres to achieve a prolonged action.

EXPERIMENTAL

Simvastatin was a gift sample from Ranbaxy labs, Gurgaov. Carbopol-941 (Lubrizol Lab. Pvt. Ltd., Mumbai). Sodium alginate (Cental Drug House, New Delhi) and calcium chloride (Cental Drug House, New Delhi) were procured from commercial sources. All other reagents used were of analytical grade.

Preparation of inclusion complex by co-precipitation: Simvastatin and β-cyclodextrins with 1:2 molar ratio were accurately weighed. Saturated β-cyclodextrin solutions were prepared with β-cyclodextrin and water. Then, Simvastatin solution in methanol was added slowly and a suspension was formed. The suspension was stirred at 40 ºC for 30 min and kept stirring at room temperature for 24 h. The obtained masses were filtered through 0.45 μm membrane filter and dried at 40 ºC in an oven for 24 h. The dried complexes were ground to fine powder and screened through 80-mesh sieve[9].

Preparation of microcapsules: Microcapsules containing simvastatin were prepared employing sodium alginate in carbopol-941 as coat material. Ionic gelation process[10,11] that has been extensively used to prepare large alginate beads was employed to prepare the microcapsules.

X-ray diffractometry: The X-ray diffraction patterns were recorded at room temperature using a Scintag diffractometer (XGEN-4000, Scintag Corp., USA). The samples were irradiated with Ni-filtered CuK_α radiation, at 45 kV voltage and 40 mA current. The scanning rate employed was 2 º/min over a diffraction angle of 2 h.

Ionic gelation method: Different proportion of sodium alginate and the polymer carbopol-941 were taken (Table-1) dissolved in 200 mL of purified water to form a homogeneous polymer solution. The active substance, simvastatin β-cyclodextrin complex was added to the polymer solution and mixed thoroughly to form a viscous dispersion. The resulting dispersion was then added manually dropwise into calcium chloride (10 % wt/vol) solution through a syringe with a needle of 18 gauge maintaining gentle stirring rate of 300-400 rpm. The added droplets were retained in the calcium chloride solution for 1 h to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules were collected and the product thus separated was washed repeatedly with water and dried at 45 ºC for 12 h.

TABLE-1
FORMULATION BATCHES OF FLOATING MICROCAPSULES

S. No.	Batch code	Carbopol (g)	Sod. alginate (g)	Simvastatin complex (g)	Drug encapsulation efficiency (%)
1	F1	6	2	2	59.09 ± 2.98
2	F2	6	3	6	65.65 ± 2.21
3	F3	6	3	2	49.65 ± 3.87
4	F4	4	4	6	53.33 ± 2.35
5	F5	4	3	2	47.56 ± 1.96
6	F6	6	4	2	54.67 ± 3.87
7	F7	2	3	6	46.62 ± 2.74
8	F8	4	2	6	51.12 ± 2.77
9	F9	2	2	2	47.50 ± 2.63
10	F10	2	3	4	50.04 ± 2.54
11	F11	2	4	6	48.56 ± 2.67
12	F12	4	4	2	45.67 ± 3.94
13	F13	6	2	6	57.80 ± 2.74
14	F14	6	4	6	45.22 ± 3.91
15	F15	4	2	4	56.54 ± 3.53
16	F16	4	3	6	46.76 ± 3.06
17	F17	2	4	2	58.65 ± 3.47
18	F18	2	2	4	50.55 ± 2.53
19	F19	6	4	4	46.65 ± 2.97
20	F20	4	3	4	50.61 ± 3.76
21	F21	2	4	4	49.88 ± 3.87
22	F22	4	4	4	51.32 ± 2.76
23	F23	6	3	4	47.65 ± 3.17
24	F24	4	2	2	47.54 ± 3.76
25	F25	2	3	2	57.87 ± 3.24
26	F26	2	2	6	55.61 ± 3.07
27	F27	6	2	4	49.09 ± 3.62

± Indicates; n = 3

Characterization of microcapsules

Estimation of simvastatin: Spectrophotometric method based on the measurement of absorbance at 238 nm in HCl acid buffer (pH 1.2). The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range 5 to 30 µg/mL.

Microencapsulation efficiency: Sample of 10 mg of microspheres were taken crushed and dissolved in 10 mL methanol. Solution was shaken vigorously for 10 min. It was then filtered. Equivalent mL of filtrate diluted to 10 mL with 1.2 pH HCl buffer. The absorbance was measured at 238 nm.

Microencapsulation efficiency was calculated using the following formula[12]: microencapsulation efficiency = (estimated percentage drug content/theoretical percentage drug content) × 100.

Scanning electron microscopy: In order to access surface morphology the scanning electron microscopy was performed and it was noted that the surface is somewhat irregular with slightly hollowness present in between the crevices, which helps the microcapsules to immediately float on the solvent surface.

Drug release study: The drug release study was performed using USP XXIV paddle apparatus (Electrolab, TDT-06T, Mumbai, India) at 37 ºC 6 ± 0.5 ºC and at 50 rpm using 900 mL of HCl buffer (pH 1.2) as a dissolution medium. Microcapsules equivalent to 45 mg of Simvastatin were used for the test. Five milliliters of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 mm membrane filter, diluted suitably and analyzed spectrophotometrically. An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug dissolved at different time intervals was calculated using the Lambert-Beer's equation. The average values of % drug release for batches F1 to F27 are mentioned in Table-2.

Floating time: Ten floating microcapsules were placed in 100 mL of the HCl acid Buffer (pH 1.2). Microcapsules exhibits floating behaviour of microsphere was observed up to 12 h in all batches.

Factorial design: A statistical model incorporating interactive and polynomial terms was used to evaluate the responses:

$$Y = \beta_o + \beta_1 X_1 + \beta_o X_2 + \beta_o X_3 + \beta_{12} X_1 X_2 + \beta_{13} X_1 X_3 + \beta_{23} X_2 X_3 + \beta_{123} X_1 X_2 X_3$$

where, Y is the dependent variable, β_0 is the arithmetic mean response of the 27 runs and β_i is the estimated coefficient for the factor X_i. The main effects (X_1, X_2 and X_3) represent the average result of changing one factor at a time from its low to high value. The interaction terms ($X_1X_2X_3$) show how the response changes when 3 factors are simultaneously changed. The polynomial terms ($X_1X_2X_3$) are included to investigate nonlinearity.

The above quadratic equation for % release and % drug encapsulation efficiency can be rewritten as:

$$\% \text{ release} = 41.26 - 13.93 X_1 + 15.12 X_2 + 17.58 X_3 + 7.53 X_1X_2 + 10.76 X_1X_3 - 47.64 X_2X_3 + 41.26 X_1X_2X_3$$

$$\% \text{ DEE} = 12.27 - 17.59 X_1 + 11.01 X_2 + 17.03 X_3 + 11.85 X_1X_2 + 47.31 X_1X_3 - 36.02 X_2X_3 + 58.57 X_1X_2X_3$$

Stability studies: For any formulation coming to market must exhibit desired shelf life so that it can withstand the stress conditions. The main objective of stability studies is to assure that formulated product will remain within its therapeutic limits. ICH has proposed various conditions for performing stability studies (ref). Out of all formulated batches F1, F2, F3 and F4 batches were subjected to accelerated stability studies

TABLE-2
PERCENTAGE DRUG RELEASE BATCHES F1-F27

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	8.97 ± 1.23	10.98 ± 2.97	11.05 ± 0.98	11.87 ± 3.09	2.97 ± 2.56	8.84 ± 3.09	5.06 ± 3.98	6.97 ± 2.98	4.12 ± 2.09
2	17.09 ± 1.09	20.89 ± 1.07	19.05 ± 1.97	16.54 ± 0.97	8.09 ± 3.77	14.08 ± 2.92	12.95 ± 1.09	14.44 ± 1.08	10.87 ± 0.31
3	29.66 ± 2.86	33.98 ± 1.77	28.85 ± 2.09	23.43 ± 1.09	17.96 ± 3.78	20.98 ± 1.98	19.54 ± 0.89	21.83 ± 2.75	18.06 ± 0.99
4	38.96 ± 2.06	42.09 ± 2.07	36.95 ± 1.88	31.84 ± 2.98	23.87 ± 1.89	27.96 ± 2.89	26.09 ± 0.41	28.73 ± 3.5	25.98 ± 2.08
5	50.87 ± 1.97	53.98 ± 1.08	45.96 ± 2.78	37.93 ± 1.98	33.06 ± 0.95	34.09 ± 1.12	34.91 ± 2.09	37.98 ± 4.09	30.76 ± 3.96
6	58.67 ± 3.08	63.21 ± 2.08	53.92 ± 2.02	46.43 ± 3.87	40.87 ± 4.98	42.23 ± 2.93	40.63 ± 1.43	43.23 ± 1.09	37.07 ± 1.24
7	65.09 ± 1.07	73.45 ± 2.23	58.76 ± 0.78	58.52 ± 0.76	50.84 ± 2.45	50.87 ± 1.09	45.87 ± 2.98	49.06 ± 2.76	45.92 ± 2.98
8	70.77 ± 2.07	81.98 ± 1.09	65.06 ± 0.87	62.14 ± 0.67	57.99 ± 1.97	58.67 ± 1.89	51.07 ± 1.43	56.07 ± 1.43	50.62 ± 1.04
9	74.98 ± 1.09	86.23 ± 0.93	70.65 ± 3.98	69.05 ± 2.98	62.07 ± 2.56	65.93 ± 3.98	59.56 ± 2.88	60.54 ± 2.32	56.07 ± 1.27
10	79.88 ± 2.08	88.06 ± 0.89	78.96 ± 1.09	74.85 ± 1.76	68.43 ± 2.09	70.63 ± 2.65	64.06 ± 1.09	66.67 ± 1.43	63.32 ± 2.01
11	82.09 ± 1.45	90.85 ± 2.09	84.97 ± 3.89	79.52 ± 2.89	73.97 ± 3.89	76.07 ± 1.88	69.87 ± 2.94	72.56 ± 1.98	68.31 ± 2.78
12	84.12 ± 2.78	92.89 ± 2.87	88.05 ± 1.02	85.63 ± 2.88	75.71 ± 2.34	80.56 ± 1.98	72.76 ± 0.42	77.23 ± 2.56	72.82 ± 3.97
	F10	F11	F12	F13	F14	F15	F16	F17	F18
1	6.07 ± 2.07	5.94 ± 2.98	4.21 ± 2.08	10.04 ± 1.98	3.07 ± 2.87	11.89 ± 2.97	5.07 ± 1.76	12.97 ± 1.98	7.07 ± 3.98
2	11.98 ± 3.06	10.43 ± 1.96	9.06 ± 1.45	23.96 ± 2.86	8.78 ± 0.65	26.97 ± 0.87	11.97 ± 2.32	28.06 ± 3.97	16.43 ± 1.95
3	20.87 ± 1.45	18.52 ± 2.08	16.96 ± 2.09	30.34 ± 2.42	15.05 ± 0.42	35.87 ± 2.85	20.76 ± 1.19	38.44 ± 1.07	28.06 ± 0.65
4	29.96 ± 0.89	26.08 ± 1.43	25.05 ± 3.88	38.05 ± 0.95	22.52 ± 1.09	44.05 ± 3.97	28.52 ± 1.76	48.06 ± 2.98	37.95 ± 1.95
5	37.05 ± 0.64	34.86 ± 2.91	32.98 ± 1.09	45.07 ± 0.39	29.76 ± 3.98	52.23 ± 1.32	35.97 ± 2.06	55.98 ± 1.07	45.07 ± 1.97
6	42.88 ± 2.61	41.96 ± 1.43	40.88 ± 0.96	50.84 ± 2.07	36.54 ± 1.08	60.65 ± 1.08	41.07 ± 1.75	62.07 ± 0.98	53.76 ± 4.08
7	49.06 ± 2.97	47.65 ± 1.15	46.92 ± 0.81	56.04 ± 2.93	41.73 ± 3.67	65.97 ± 2.97	49.76 ± 1.89	67.62 ± 1.07	59.67 ± 1.95
8	54.76 ± 4.65	52.09 ± 2.16	51.85 ± 1.97	60.73 ± 1.86	46.02 ± 2.06	69.06 ± 1.06	57.88 ± 2.97	72.86 ± 1.58	64.99 ± 1.34
9	60.96 ± 3.98	59.96 ± 1.86	60.99 ± 2.43	65.12 ± 2.95	53.71 ± 1.96	73.95 ± 1.67	64.76 ± 0.91	75.99 ± 2.65	69.07 ± 1.53
10	66.07 ± 1.78	64.02 ± 2.64	64.92 ± 2.98	72.08 ± 3.08	59.88 ± 3.95	76.76 ± 3.98	67.07 ± 0.88	78.07 ± 1.96	73.04 ± 2.29
11	72.93 ± 3.98	69.06 ± 1.04	67.53 ± 1.41	75.33 ± 2.95	65.93 ± 1.53	78.87 ± 1.45	70.45 ± 2.95	79.03 ± 0.97	75.56 ± 3.07
12	76.04 ± 0.98	72.42 ± 1.88	70.95 ± 1.53	78.84 ± 1.67	70.52 ± 2.65	79.83 ± 2.19	72.03 ± 2.02	80.42 ± 1.25	78.51 ± 2.86
	F19	F20	F21	F22	F23	F24	F25	F26	F27
1	6.89 ± 1.87	9.65 ± 2.95	5.95 ± 3.96	9.56 ± 2.86	3.03 ± 1.75	4.94 ± 2.08	10.43 ± 1.96	9.65 ± 2.84	4.07 ± 1.99
2	14.76 ± 1.84	18.88 ± 2.94	12.05 ± 1.07	19.65 ± 2.95	9.05 ± 3.85	8.95 ± 3.96	19.56 ± 3.97	17.04 ± 0.23	10.06 ± 0.65
3	22.81 ± 2.04	29.03 ± 1.05	20.95 ± 2.67	25.92 ± 1.96	16.83 ± 4.05	18.06 ± 4.97	30.96 ± 0.88	26.74 ± 3.94	17.33 ± 2.85
4	33.79 ± 2.11	38.94 ± 2.77	29.37 ± 1.08	33.05 ± 0.88	21.04 ± 2.04	22.97 ± 1.86	40.03 ± 1.87	36.04 ± 1.84	26.85 ± 1.89
5	40.64 ± 3.88	48.03 ± 1.98	36.65 ± 2.88	40.83 ± 0.52	29.45 ± 2.87	28.03 ± 2.95	49.04 ± 0.43	45.62 ± 3.95	32.98 ± 3.43
6	46.92 ± 3.06	55.41 ± 2.56	47.04 ± 3.98	47.32 ± 1.89	38.04 ± 1.78	37.04 ± 1.97	58.78 ± 4.94	53.88 ± 0.98	37.81 ± 2.89
7	52.16 ± 1.07	63.81 ± 2.67	52.93 ± 2.76	54.51 ± 2.64	46.94 ± 4.87	43.12 ± 1.53	66.06 ± 2.83	60.95 ± 0.99	43.88 ± 1.76
8	58.72 ± 0.88	69.03 ± 4.87	57.04 ± 1.67	59.03 ± 3.98	51.73 ± 3.75	50.94 ± 1.99	70.75 ± 2.85	65.06 ± 2.98	50.31 ± 1.78
9	65.82 ± 2.96	72.18 ± 2.95	63.23 ± 2.31	64.21 ± 1.77	59.04 ± 1.08	55.73 ± 0.87	74.98 ± 1.76	70.65 ± 1.94	57.98 ± 2.23
10	68.92 ± 1.03	74.94 ± 1.85	67.03 ± 1.98	68.72 ± 3.87	64.22 ± 2.78	60.03 ± 2.97	77.09 ± 2.65	74.96 ± 3.89	62.93 ± 1.98
11	71.08 ± 2.93	75.88 ± 2.06	70.94 ± 2.89	71.92 ± 2.76	67.52 ± 1.09	65.06 ± 1.07	78.45 ± 1.85	77.96 ± 3.95	67.72 ± 1.86
12	73.06 ± 1.97	76.52 ± 2.64	71.95 ± 1.76	74.96 ± 1.87	70.63 ± 2.98	69.95 ± 2.45	80.42 ± 0.66	79.56 ± 1.34	71.06 ± 2.08

± Indicates, n = 3

TABLE-3
ACCELERATED STABILITY STUDIES *IN VITRO* RELEASE PROFILE

Batch/Time	F1 2nd Month	F1 4th Month	F1 6th Month	F2 2nd Month	F2 4th Month	F2 6th Month
1	8.12 ± 1.32	7.98 ± 1.42	7.88 ± 1.32	10.05 ± 2.12	9.22 ± 1.21	8.76 ± 1.06
2	16.56 ± 2.75	16.22 ± 2.64	15.98 ± 1.10	19.34 ± 2.85	18.43 ± 2.54	17.05 ± 0.78
3	27.06 ± 2.12	26.88 ± 1.84	26.45 ± 1.43	32.86 ± 1.84	30.94 ± 1.64	29.05 ± 2.41
4	37.94 ± 1.45	37.11 ± 1.54	36.67 ± 2.95	41.52 ± 1.72	40.42 ± 2.69	39.88 ± 1.66
5	48.33 ± 0.96	47.95 ± 0.65	47.31 ± 0.96	52.74 ± 0.97	51.32 ± 1.26	50.04 ± 2.85
6	56.87 ± 2.09	55.84 ± 0.85	55.12 ± 2.11	62.73 ± 0.78	60.52 ± 1.17	59.84 ± 3.02
7	64.93 ± 2.64	63.06 ± 1.43	62.76 ± 3.05	71.96 ± 2.89	69.04 ± 2.41	68.94 ± 1.32
8	69.54 ± 1.43	68.03 ± 2.54	67.73 ± 2.65	80.65 ± 0.64	79.06 ± 2.71	78.06 ± 1.08
9	73.67 ± 3.42	72.94 ± 1.32	71.06 ± 2.14	84.23 ± 0.39	83.97 ± 0.78	82.06 ± 2.74
10	77.93 ± 1.42	76.92 ± 1.53	76.42 ± 1.06	87.41 ± 2.34	86.03 ± 1.28	85.77 ± 1.16
11	81.07 ± 0.94	80.42 ± 0.86	79.52 ± 2.51	88.08 ± 2.43	87.43 ± 1.95	86.94 ± 1.95
12	83.88 ± 0.31	83.22 ± 0.78	82.05 ± 1.45	91.05 ± 1.53	90.16 ± 2.05	89.07 ± 2.81

for a period of six months at 400c and 75 % RH in thermo labs stability chamber. The *in-vitro* release profile after every two months was performed. The release profile after re-test period is shown in Tables 3 and 4 and dissolution kinetic factors are shown in Table-5.

RESULTS AND DISCUSSION

The formed drug complex (1:2) exhibit nine folds increase in solubility of Simvastatin. The XRD studies confirmed the formation of stable complex between drug and β-cyclodextrin (Fig. 1).

TABLE-4
ACCELERATED STABILITY STUDIES *IN-VITRO* RELEASE PROFILE

Batch/Time	F3 2nd Month	F3 4th Month	F3 6th Month	F4 2nd Month	F4 4th Month	F4 6th Month
1	9.03 ± 2.43	8.82 ± 1.73	7.54 ± 1.32	11.87 ± 1.32	10.04 ± 2.54	9.84 ± 1.32
2	18.42 ± 0.78	16.31 ± 1.82	15.53 ± 1.97	16.54 ± 2.43	16.45 ± 1.74	14.43 ± 2.84
3	26.21 ± 1.31	24.39 ± 0.93	22.63 ± 1.32	23.43 ± 1.93	22.92 ± 1.09	20.62 ± 1.99
4	35.03 ± 1.87	32.12 ± 0.84	30.92 ± 0.85	31.84 ± 2.75	28.21 ± 2.82	26.41 ± 2.43
5	42.34 ± 1.43	40.03 ± 1.37	38.54 ± 2.83	37.93 ± 1.54	35.81 ± 0.78	34.96 ± 1.83
6	50.03 ± 2.61	48.63 ± 1.92	47.91 ± 1.93	46.43 ± 0.92	44.84 ± 1.42	41.07 ± 2.74
7	55.83 ± 0.95	53.93 ± 0.94	52.76 ± 2.43	58.52 ± 0.63	57.53 ± 2.85	55.93 ± 0.78
8	63.81 ± 0.63	62.31 ± 1.81	61.65 ± 1.23	62.14 ± 2.65	61.34 ± 1.94	60.32 ± 1.73
9	68.96 ± 2.94	65.21 ± 1.28	63.23 ± 1.94	69.05 ± 1.84	67.18 ± 0.42	65.43 ± 1.32
10	75.43 ± 1.83	72.84 ± 2.83	71.42 ± 0.64	74.85 ± 2.54	73.02 ± 0.92	71.61 ± 0.98
11	81.23 ± 2.02	79.31 ± 0.94	78.64 ± 0.84	79.52 ± 2.03	77.03 ± 1.95	76.31 ± 0.54
12	86.06 ± 1.92	84.94 ± 0.89	83.86 ± 1.23	85.63 ± 1.17	84.852.93	83.24 ± 1.87

TABLE-5
RELEASE KINETICS OF VARIOUS FORMULATED BATCHES

Batch	Best fit model	r^2	n	k
F1	Higuchi	0.978	0.122	6.837
F2	Zero order	0.978	0.136	7.978
F3	Zero order	0.994	0.122	5.492
F4	Zero order	0.996	0.119	3.014
F5	Zero order	0.994	0.116	-2.155
F6	Zero order	0.998	0.115	0.880
F7	Zero Order	0.998	0.105	0.863
F8	Zero order	0.997	0.108	2.206
F9	Zero Order	0.999	0.105	-0.560
F10	Zero order	0.997	0.109	1.473
F11	Higuchi	0.966	0.304	5.656
F12	Zero order	0.994	0.107	-0.550
F13	Higuchi	0.990	0.309	3.034
F14	Zero order	0.999	0.102	-1.931
F15	Higuchi	0.990	0.292	2.252
F16	Zero order	0.991	0.108	1.376
F17	Higuchi	0.989	0.289	1.864
F18	Higuchi	0.981	0.285	4.092
F19	Zero order	0.987	0.107	4.285
F20	Higuchi	0.980	0.284	3.611
F21	Zero order	0.988	0.108	2.427
F22	Zero order	0.989	0.104	6.294
F23	Zero Order	0.995	0.107	-1.919
F24	Zero Order	0.998	0.102	-0.794
F25	Higuchi	0.981	0.275	3.536
F26	Higuchi	0.980	0.280	4.112
F27	Zero order	0.997	0.104	-0.294

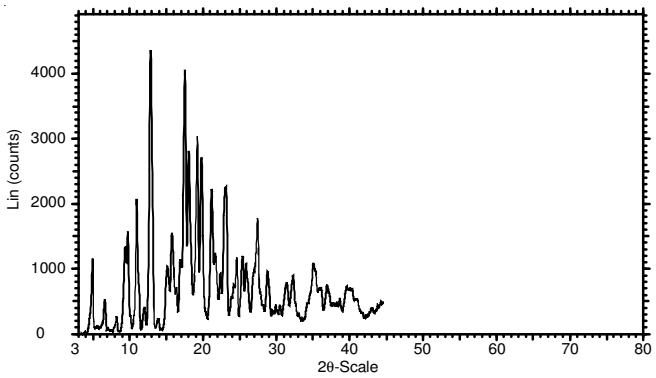

Fig. 1. XRD Simvastatin β-cyclodextrin complex (1:2)

As carbopol 941 is self swellable polymer the immediate floating of microcapsules was observed. All the batches exhibited immediate floating when placed in distilled water. The full factorial design was set up to access the effect of excipient composition on the % DEE and % release. Ionic orifice gelation method because of its simplicity and versatility was selected for formulation of floating microcapsules.

The microcapsules were found to be discrete, spherical and free-flowing. The microcapsules were uniform in size. The SEM photographs indicated that the microcapsules were spherical and completely covered with the coat polymer (Figs. 2 and 3). The microencapsulation efficiency was in the range of 45-65 %. Microcapsules with a coat consisting of alginate and a floating polymer exhibited good floating properties. Simvastatin release from the microcapsules was studied in HCl buffer (pH 1.2) for 12 h. Simvastatin release from the microcapsules was slow and depended on the composition of the coat

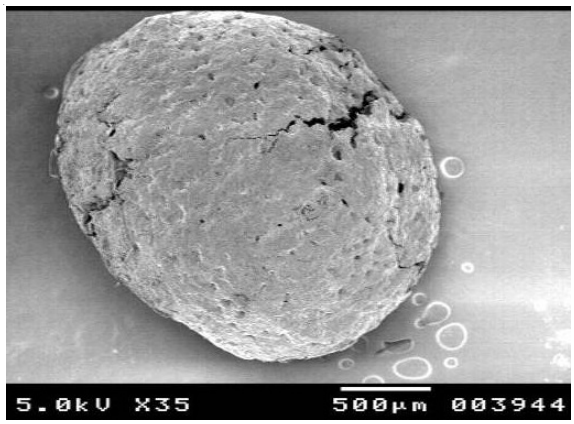

Fig. 2. SEM of optimized batch F2

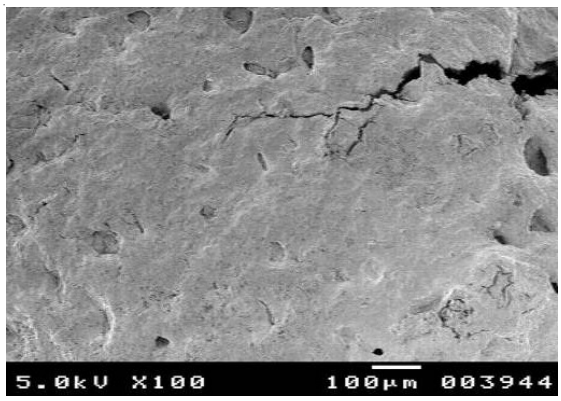

Fig. 3. SEM of optimized batch F2 (surface view)

Conclusion

Microcapsules containing drug complex with a surrounding coat consisting of alginate and a floating polymer carbopol-941 was prepared by an ionic gelation method. The microcapsules exhibited good floating properties *in vitro* test. Simvastatin release from prepared microcapsules was slow and extended over longer periods of time and depended on composition of the coat. From main effect plot it was concluded that high concentration of sodium alginate hampers both drug encapsulation efficiency and % release, however improvement in % drug release was seen with intermediate concentration whereas high concentration of carbopol and drug complex provides good encapsulation efficiency and high release too. These microcapsules are thus, suitable for oral sustained release of simvastatin.

REFERENCES

1. S. Benita, Microencapsulation-Methods and Industrial Applications, Marcel Dekker, Inc. New York, Basel, Hong Kong, pp. 1-20 (1980).
2. P.R. Seth and J. Tossounian, *Drug Dev. Ind. Pharm*., **10**, 313 (1984).
3. F.J. Ahmad, S. Drabu, H. Dureja and S. Khatri, *Asian J. Chem.*, **21**, 4603 (2009).
4. A.A. Deshpande, C.T. Rhodes, N.H. Shah and A.W. Malick, *Drug Dev. Ind. Pharm*., **22**, 531 (1996).
5. V.K. Sharma and A. Bhattacharya, *Asian J. Chem.*, **22**, 7661 (2010).
6. K.P.R. Chowdary and D.V. Ramanjaneyulu, *Asian J. Chem.*, **23**, 3529 (2011).
7. J.K. Patel, R.P. Patel, A.F. Amin and M.M. Patel, *AAPS Pharm. Sci. Tech.,* **6**, E49 (2005).
8. R.F. Hu, J.B. Zhua, G.L. Chen, Y.L. Sun, K.K. Mei and S. Li, *Asian J. Pharmaceut. Sci.*, **1**, 47 (2006).
9. L.X. Liu and S.Y. Zhu, *J. Pharm. Biomed. Anal.*, **40**, 122 (2006).
10. C.K. Kim and E.J. Lee, *Int. J. Pharm.*, **79**, 11 (2006).
11. P.C. Hari, T. Chandy and C.P. Sharma, *J. Microen.-Capsul.*, **13**, 319 (1996).
12. S.P. Vyas and R.K. Khar, Microspheres-In Targeted and Controlled Drug Delivery, Novel Carrier Systems, CBS Publication; edn. 1, pp. 417-457 (2007).