

Optimization of Gabapentin Release and Targeting Absorption, Through Incorporation into Alginate Beads

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ABSTRACT

Aims: 1) To study the effect of some formulation variables on drug load, encapsulation efficiency, swelling ratio, mucoadhesion and drug release.
2) Optimize the mucoadhesion capabilities for targeting drug absorption and release-controlling capabilities of alginate beads.

Methodology: alginate beads were prepared by dripping sodium alginate gel into calcium chloride solution and then dried overnight at ambient temperature. The effects of alginate concentration, cross linker concentration, cross linking time, volume of cross linking solution and drug/polymer ratio on drug load, encapsulation efficiency, swelling ratio, mucoadhesion and drug release were investigated. Formulae containing sodium lauryl sulfate (SLS), gabapentin-ethylcellulose solid dispersion, mixture of free drug and solid dispersion were prepared for modifying the drug release rate.

Results: Mucoadhesion of alginate beads was shown to be decreased upon adding SLS (30% after 8 hrs). Drug release was so fast (92.46% after 2 hrs). The incorporation of solid dispersion has led to well accepted mucoadhesion (74.44% after 8 hrs) as well as release properties (93.35% after 10 hrs) Beads containing mixtures of drug and ethylcellulose-drug solid dispersion showed acceptable mucoadhesion (74.44% after 8 hrs) and control of gabapentin release (93.35% after 10 hrs). Statistical analysis of variance between groups was performed using the one-way layout ANOVA with duplication. Significant differences in mean values were evaluated by Student's unpaired t test ($p < 0.05$).

Conclusion: A finally optimized formula was suggested by incorporating a combination of solid dispersion and free gabapentin in alginate system to achieve burst release of gabapentin and hence fast effect (33.417% was released during the first 30 minutes in fasting-simulated conditions) and controlled release (91.217% after 6 hrs).

Keywords: Alginate, Control release, Targeting, Gabapentin, Sodium lauryl sulfate, Ethylcellulose, Solid dispersion.

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22 **1. INTRODUCTION**

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24 Alginic acid is a natural polysaccharide found in all species of brown algae. It exists as a
25 linear polymer consisting of β -D-(1 \rightarrow 4) mannuronic acid (M) and α -L-(1 \rightarrow 4) guluronic acid
26 (G) in varying proportions and sequential arrangement [1]. The homopolymer regions
27 composed of M blocks and G blocks are interspersed with MG heteropolymeric regions.
28 Alginic acid is a hydrophilic polymer that swells in the presence of water. Sodium alginate,
29 which is the sodium salt of alginic acid, is soluble in water and can be cross-linked with
30 divalent cations such as Ca^{2+} and Zn^{2+} and polyvalent ones to form an insoluble alginate.
31 Calcium ion was found to bind selectively guluronic acid residues (GG) in a planar two-
32 dimensional structure producing the so-called "egg box" structure [2]. The ratio of G to M
33 residues was found to affect the release of drugs from calcium-cross-linked alginate systems
34 [3].

35 Alginate systems were found to have a number of properties that are used to deliver DNA
36 [4], locally deliver enzymes [5], immobilize enzymes [6], oral immunization [7], and to act as
37 adenovirus vector [8].

38 The mucoadhesive properties of alginate emphasized its use as an efficient tool to improve
39 oral mucoadhesion for increasing bioavailability of drugs [9] such as nifedipine HCl [10],
40 glimepiride [11,12], and diltiazem HCl [13] and to control systemic absorption of some narrow
41 absorption window (NAW) drugs.

42 Gabapentin is an orally available γ -aminobutyric acid analog which is used to control partial
43 seizures in combination with other antiepileptic drugs [14]. It is one of the NAW drugs **since it**
44 **is** actively absorbed from upper duodenal region via L-amino acid transporters [15].

45 The aim of this study was to evaluate the effect of formulation variables on alginate beads
46 properties and **optimizing their drug targeting properties as well as release control profile**
47 using gabapentin as a hydrophilic model drug.

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49

50 **2. MATERIAL AND METHODS**

51

52 **2.1 Materials**

53 Sodium alginate was purchased from Sigma Aldrich, St. Louis, USA. Gabapentin was a gift
54 from Delta Pharm, 10th of Ramadan city, Egypt. Calcium chloride dihydrate from VWR
55 Scientific, West Chester, PA, USA. Sodium lauryl sulphate (SLS) from Aldrich, Milwaukee,
56 WI, USA. The other chemicals used were all of analytical and HPLC grade.

57

58 **2.2 Methods**

59

60 **2.2.1 Preparation of calcium alginate mucoadhesive beads**

61 **Calcium alginate beads were prepared by ionotropic gelation.** The amounts of sodium
62 alginate, concentration of calcium chloride solution and quantity of gabapentin used and the
63 formulation **variables** of the beads are listed in table 1. **A gel solution of sodium alginate was**
64 **made by hydrating** the proper amount of sodium alginate in deionized water and stirring till a
65 clear gel solution is formed. **In separate vial,** gabapentin was dispersed evenly in deionized
66 water and then added to the gel. A gentle and consistent mixing for about 5 **minutes.** **The**
67 **formed gel containing the drug was then placed in a syringe pump (model M362, Sage**
68 **Instruments, Orion Research Inc., Massachusetts, USA) then** introduced into calcium
69 chloride solution by dripping from a syringe pump. Beads were then strained, washed twice
70 by deionized water and then left to dry **at ambient** temperature overnight.

71

72

73

74 Table 1. Compositions and Variables of Formulation of Different formulae.

FORMULA CODE	SODIUM ALGINATE CONC. (% W/V)	CROSS- LINKER CONC. (% W/V)	CROSS- LINKING TIME (MIN)	CROSS- LINKER VOL. : GEL VOL. (ML)	DRUG : POLYMER RATIO
F1	5	1	30	2:1	1:1
F2	2.5	1	30	2:1	1:1
F3	1.67	1	30	2:1	1:1
F4	1	0.5	30	2:1	1:1
F5	1	1	30	2:1	1:1
F6	1	2	30	2:1	1:1
F7	1	1	10	2:1	1:1
F8	1	1	20	2:1	1:1
F9	1	1	60	2:1	1:1
F10	1	1	120	2:1	1:1
F11	1	1	30	1:1	1:1
F12	1	1	30	3:1	1:1
F13	1	1	30	2:1	1:2
F14	1	1	30	2:1	2:1

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80 **2.2.2 Determination of drug load percentage**

81 The process of determining percentage of drug loaded was done utilizing extraction of the
82 drug from beads as mentioned by Reis and co-workers with little modification [16]. Specific
83 weight of beads was taken and crushed. The crushed beads were then placed in a vial and a
84 proper amount of deionized water was added to it. The vials containing crushed beads and
85 water were shaken for 15 minutes for complete extraction of drug. The aliquot containing the
86 drug was then analyzed for gabapentin using the method published by Zour et al. [17], The
87 mobile phase was prepared in the ratio of 55:35:10 (water:methanol:acetonitrile). The flow
88 was 1 mL/minute; the injected volume of all samples was 20 µL; and The UV detector was
89 set to detect samples at 210 nm.

90 The percentage drug load was given by the formula:

91
$$\text{Percentage Drug load} = (W_{t_{Dg}} / W_{t_{Bd}}) \times 100$$

92 where, $W_{t_{Dg}}$ is the amount of drug loaded in beads and $W_{t_{Bd}}$ is the weight of beads

93

94 **2.2.3 Determination of encapsulation efficiency**

95 The content of gabapentin in certain weight of the beads was first determined by extraction
96 then by HPLC quantification as previously mentioned (c.f. section 2.1.2 determination of
97 percentage drug load). Encapsulation efficiency of the drug was given by the formula:

98
$$\text{Percent encapsulation efficiency (EE)} = (W_{t_{Dg}} / W_{t_{Th}}) \times 100$$

99 Where, $W_{t_{Dg}}$ is the amount of drug loaded in beads $W_{t_{Th}}$ is the amount of the drug assumed
100 to be present theoretically in the weight of beads used.

101

102 **2.2.4 Determination of swelling index**

103 Swelling index of beads was determined according to the method described by
104 Pongjanyakul and Puttipipatkachorn [18]. A weight of approximately 100 mg of beads was
105 taken and placed in a vessel. 14 ml of testing medium were added to the beads. After
106 predetermined time intervals, all beads were withdrawn from the vessel, carefully and quickly
107 dried and then weighed. The swelling index was then calculated using the following formula:

108
$$\text{Swelling index (S.I.)} = [(W_t - W_o) / W_o] \times 100$$

109 Where, W_t is the weight of beads determined at time t and W_o is the weight of beads
110 determined before immersion of beads in testing medium.

111 Two testing media were used in this test, 0.1 N HCl solution; and 0.01 N HCl solution
112 containing 0.2% of NaCl and 0.25% SLS to simulate gastric fluid without enzymes in fasting
113 state and in fed state, respectively [19].

114

115 **2.2.5 Determination of mucoadhesive properties**

116 The mucoadhesive properties of the beads were evaluated employing the method described
117 by Lehr et al. [20] with modification. The apparatus used was disintegration tester.

118

119 **2.1.5.1 Tissue Preparation:**

120

121 A pig's intestine excised freshly within the first hour of slaughtering was cut longitudinally
122 and evacuated from its contents. The empty and flattened intestine was then washed
123 carefully with water and divided into several segments. Tissue segments were then put in zip
124 bags and are kept frozen at -15 °c. When needed, tissue segment(s) was/were taken out of

125 the freezer and kept in the refrigerator 24 hrs prior to performing the mucoadhesive
126 properties testing.

127

128 **2.1.5.2 Apparatus Preparation**

129 A piece of the pig's intestine was cut to be as long as a microscopic slide. This piece was
130 then made to be fixed tightly to the microscopic slide using paper clips, the microscopic slide
131 was designed to be hanged in a disintegration apparatus and during the test it was set to go
132 up and down in the test solution.

133 The water bath of the disintegration apparatus was filled with testing solution and the
134 temperature was adjusted to be 37°C. The volume of the solution in the water bath was
135 adjusted so that at highest point of movement of the apparatus, slide didn't get out of the
136 testing solution and at lowest point, it didn't touch the bottom. This was done to make the
137 movement of the test solution in relation to the slide smooth and not turbulent.

138 As in testing the swelling index of the beads, two test media were used in this experiment,
139 0.1 N HCl solution; and 0.01 N HCl solution containing 0.2% of NaCl and 0.25% SLS to
140 simulate gastric fluid without enzymes in fasting state and in fed state, respectively [19].

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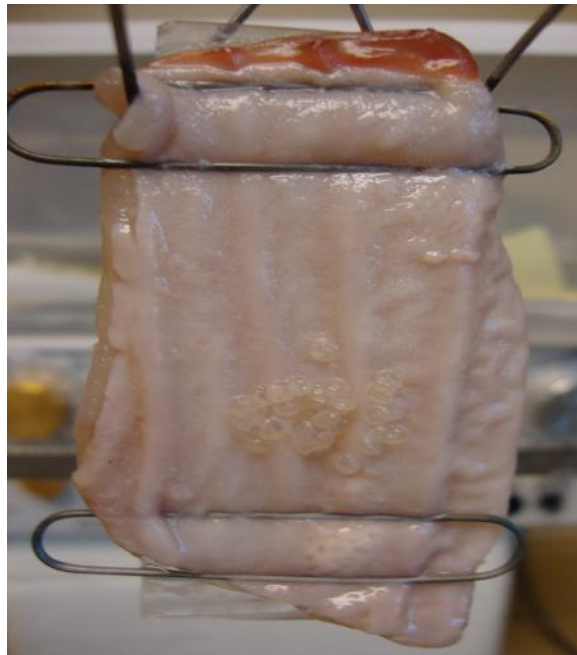
142 **2.1.5.3 Performing Test:**

143 The mucosal surface of the intestinal piece was irrigated with some of the test media to
144 simulate the real conditions. 30 beads were then put randomly on the mucosal surface of the
145 pig's intestine piece. A weight of 50 grams was put on the beads for 30 seconds, then the
146 load was removed and the slide containing the intestinal piece loaded with the beads was
147 hanged on the disintegration apparatus as shown in figure 1.

148 The apparatus was turned on and the piece of pig's intestine, bearing the beads, was
149 allowed to go in and out of the test media freely.

150 At each time point, the number of beads remaining adhering to the mucosal surface of the
151 hanged piece of pig's intestine was counted and the number is expressed as a percentage
152 of the total number of the beads loaded on the intestinal piece.

153



154

155 **Fig. 1. Mucoadhesion testing showing pig's intestine fixed to a slide and beads**
156 **adhering to it.**

157

158 **2.2.6 Determination of in-vitro release profile**

159 In-vitro drug release study was performed in a simulated acidic environment in fasting and
160 fed conditions of the stomach [19].

161 The release of gabapentin from alginate beads was done using the procedure published by
162 Pasparakis and Bouropoulos [21]. An accurately weighed amount of the beads was placed
163 in vials each containing 15 mL of dissolution media **pre-warmed** up in a shaking water bath
164 at $37\pm 0.5^{\circ}\text{C}$. The speed of shaking was adjusted to be 50 rpm. Samples of the dissolution
165 media were withdrawn from each vial and replaced by equivalent amount of fresh dissolution
166 media pre-warmed to $37\pm 0.5^{\circ}\text{C}$. Samples withdrawn **were** analyzed using HPLC method
167 previously mentioned above [17].

168
169 **2.2.7 Statistical analysis**

170 Data are presented as means \pm SE. For group comparisons, the one-way layout ANOVA with
171 duplication was applied. Significant differences in mean values were evaluated by Student's
172 unpaired t test. A p value of <0.05 was considered statistically significant.

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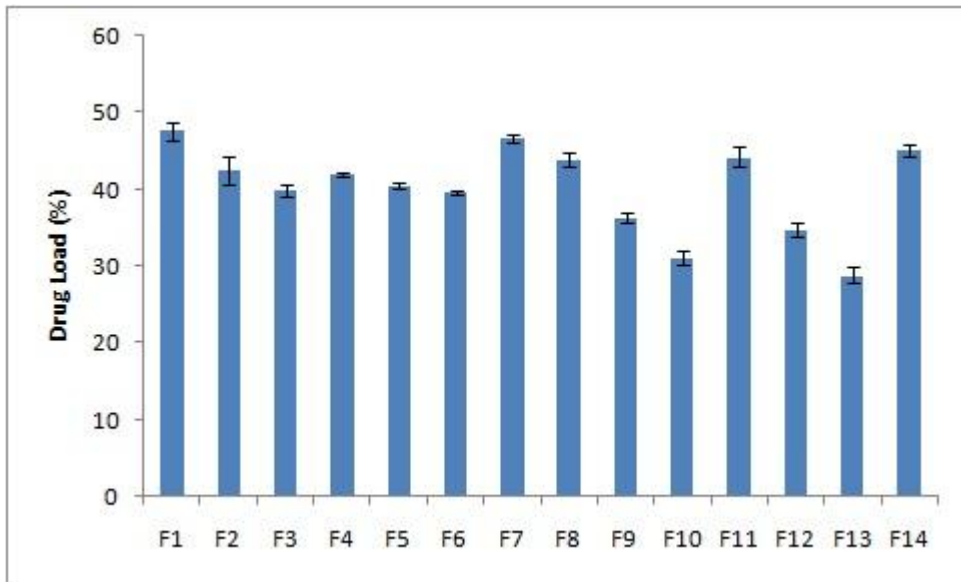
175 **3. RESULTS AND DISCUSSION**

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177 **3.1 Drug load and encapsulation efficiency (EE)**

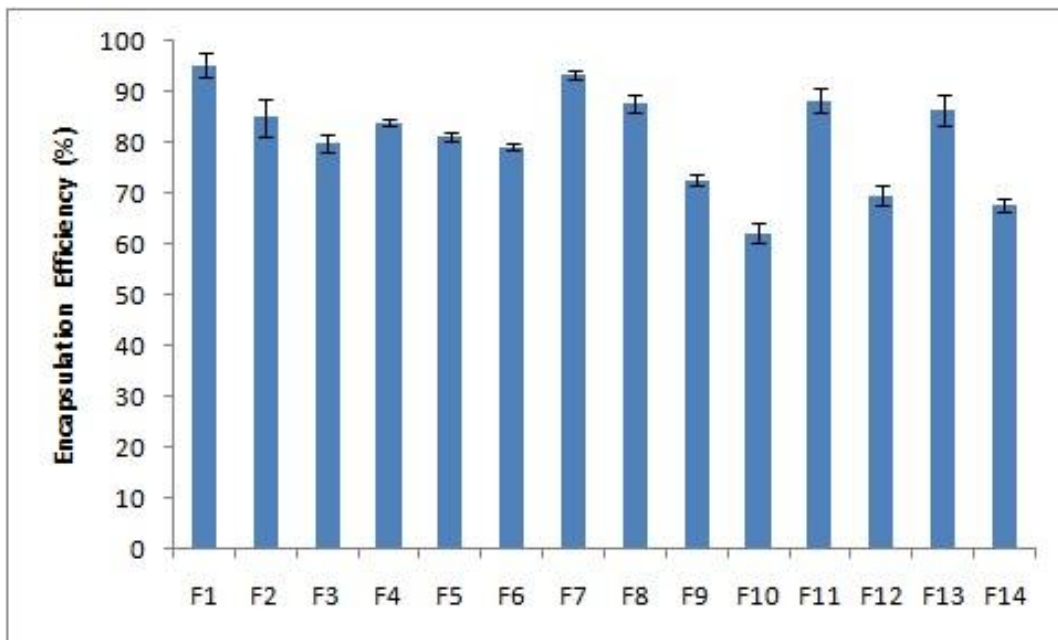
178 Figures 2 and 3 show the percentage drug load and encapsulation efficiency (EE) of the
179 prepared alginate formulae. It was shown that, regarding drug loading capacity, increasing
180 gel concentration, increasing drug/polymer ratio resulted in increasing percent drug load.
181 Decreasing concentration of cross linker, decreasing time of cross linking and/or reducing
182 volume of cross linking solution also resulted in increasing percent drug load. **This agreed to
183 results mentioned by Silva and co-workers showing that** increasing alginate concentration
184 lead to a consequent increase in EE [22]. Das and Maurya mentioned the same results in
185 previous study [13]. **This might be attributed to reduced amount of drug that is lost from
186 beads during cross linking** [23,24]. Encapsulation efficiency also depended on the amount of
187 drug lost during cross linking, therefore, the effect of the gel concentration, concentration of
188 cross linker, time of cross linking, volume of cross linking solution on EE would resemble that
189 on drug load. However, regarding drug/polymer ratio, the amount of drug lost during cross
190 linking is not the only determining factor. A comparison between formulae F13, F5, F14
191 revealed that increasing drug/polymer ratio resulted in increasing percent drug load and
192 decreasing EE. **These results agreed to results published by Belgamwar et al.** [25]. This is
193 suggested to be attributed to the fact that increasing drug/polymer ratio result in increasing
194 the amount of drug in the beads (drug load) and at the same time increasing the amount of
195 drug lost during cross linking (thus reducing the amount of drug existing in beads as
196 compared to the originally incorporated amount, i.e., reducing EE).

197



198

199 **Fig. 2. Percentage drug load of formulae F1 – F14. Each data point represents mean \pm**
 200 **S.E. (n=3).**
 201



202

203 **Fig. 3. Encapsulation efficiency of formulae F1 – F14. Each data point represents**
 204 **mean \pm S.E. (n=3).**

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206 **3.2 Swelling index**

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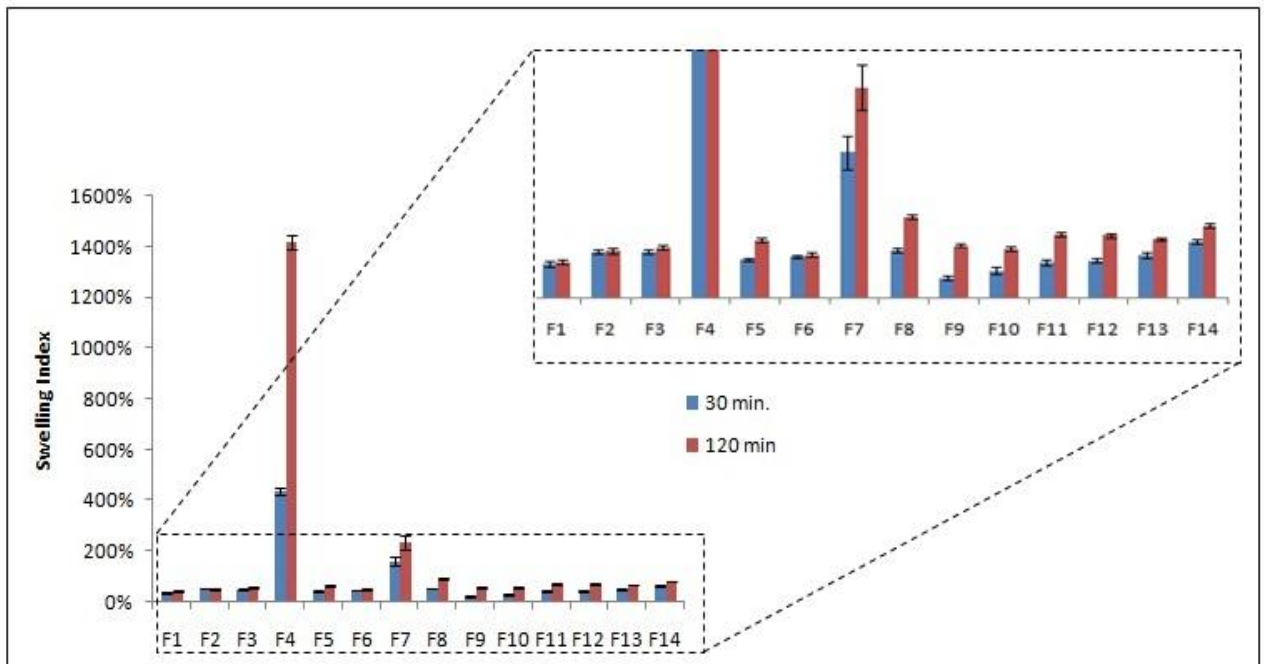
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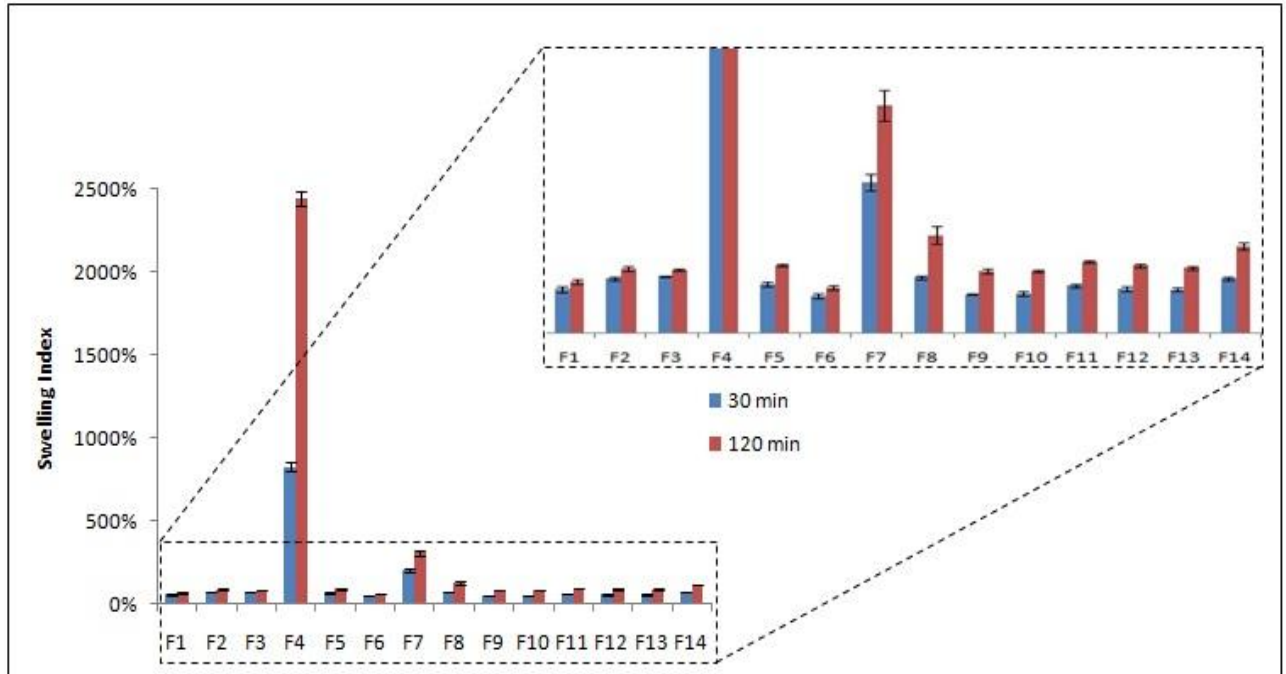
Figures 4 and 5 show swelling index of the prepared alginate formulae after 30 minutes and 120 minutes in fasting and fed-simulated conditions. It was shown that swelling ratio of beads increases as alginate gel concentration decreases, drug/polymer ratio increases, cross linker concentration decreases and/or time of cross linking decreases. **These results**

211 agreed to a previous study done by Roy et al. [26]. It was also shown by Ramesh Babu and
 212 co-workers that increasing the concentration of cross linker solution has led to a decrease in
 213 the water uptake by sodium alginate–methylcellulose blend microspheres [27]. This
 214 observation may be attributed to the fact that increasing calcium ions concentration in the
 215 cross linking solution leads to formation of the “egg-box” structure of calcium alginate [2] with
 216 smaller cavities which accommodate less amount of water and hence decreasing water
 217 retained by alginate and SI of beads. This can be also explained on the basis of Flory’s
 218 theory of swelling [28]. According to this theory, the swelling ratio of a network (Q) can be
 219 described by the following equation:
 220
$$Q^{5/3} = \left\{ \left[\frac{i}{2VN} \cdot S^{3/2} \right] + \left(\frac{1}{2} - X_i \right) / V_i \right\} / V_e / V_o$$

 221 where i/VN is the concentration of the fixed charges referred to unswollen network, S is the
 222 ionic concentration in the external solution, $(1/2 - X_i)/V_i$ is the affinity of matrix for water, and
 223 V_e/V_o is the cross link density of network.
 224 Volume of cross linking solution had no effect on the swelling of alginate beads. Swelling of
 225 beads in fed-simulated conditions was shown to be higher than in fasting-simulated ones,
 226 which was also reported in many cases [10,29].
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228
 229 **Fig. 4. Swelling indices of formulae F1 – F14 after 30 and 120 minutes in fasting-**
 230 **simulated conditions. Each data represent mean ± S.E. (n=3).**
 231

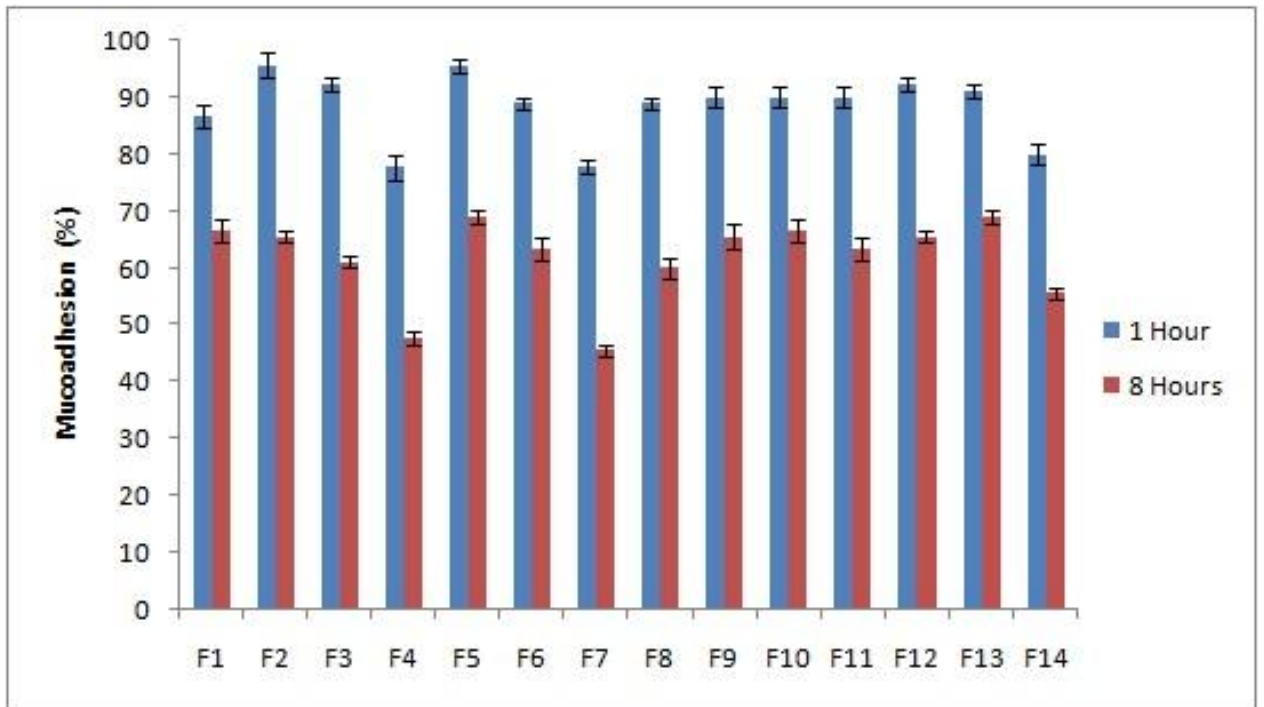


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Fig. 5. Swelling indices of formulae F1 – F14 after 30 and 120 minutes in fed-simulated conditions. Each data represent mean \pm S.E. (n=3).

236 3.3 Mucoadhesion properties

237 Figures 6 and 7 show mucoadhesion of the prepared alginate formulae after 1 and 8 hrs in
 238 fasting and fed-simulated conditions, respectively. It was shown that mucoadhesion of beads
 239 decreases as alginate gel concentration decreases, drug/polymer ratio increases, cross
 240 linker concentration decreases and/or time of cross linking decreases. It has been reported
 241 by Chickering and Mathiowitz that surface charge density plays an important role in
 242 mucoadhesion. They also reported that polyanionic polymers, such as alginate, are more
 243 efficient than polycationic or nonionic polymers in mucoadhesion [30]. Increasing degree of
 244 cross linking resulted in reducing the surface negative charge on the alginate beads resulting
 245 in decreasing efficiency of mucoadhesion. It was shown also that volume of cross linking
 246 solution had no effect on the swelling of alginate beads. Formula F4 (corresponding to cross
 247 linker concentration of 0.5 %) and formula F7 (corresponding to cross linking time of 10
 248 minutes) showed a way less mucoadhesion after 8 hrs as compared to other formulae. This
 249 is attributed to the increase in weight of beads prepared according to these formulae to a
 250 high extent as compared to other formulae. This is shown in SI study (c.f. figures 4 and 5).
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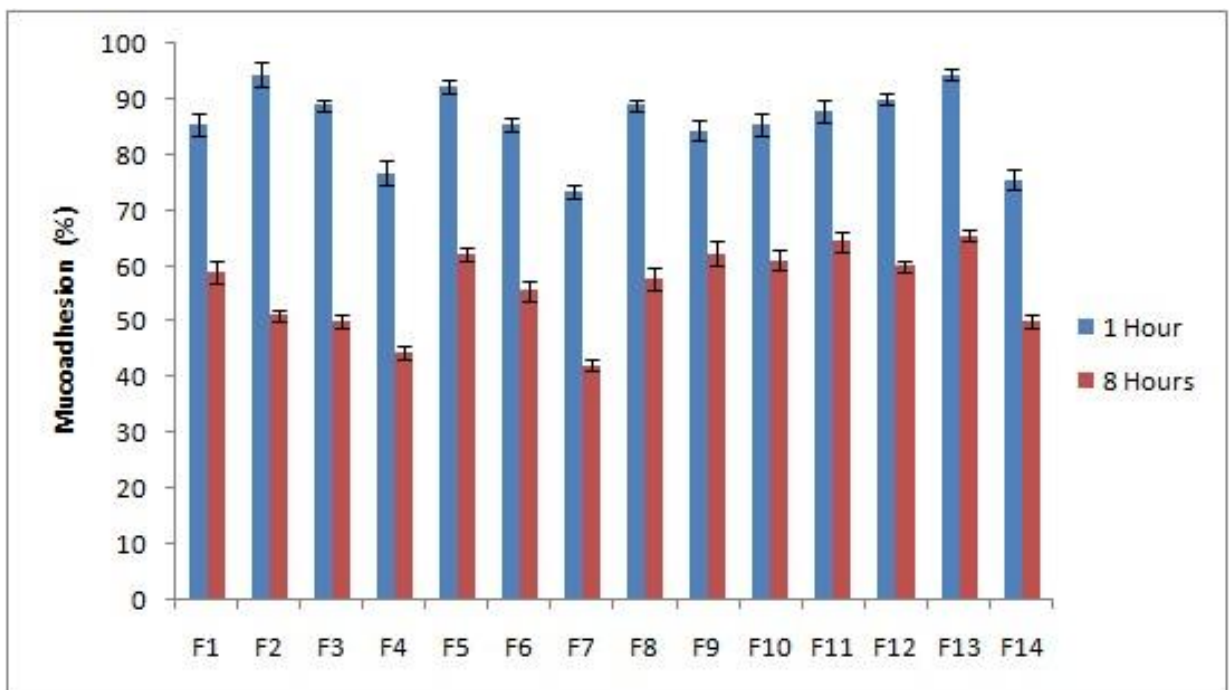


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253 Fig. 6. Mucoadhesion of formulae F1 – F14 after 1 and 8 hrs in fasting-simulated
 254 conditions. Each data represents mean \pm S.E. (n=3).

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257

258 Fig. 7. Mucoadhesion of formulae F1 – F14 after 1 and 8 hrs in fed-simulated
 259 conditions. Each data represents mean \pm S.E. (n=3).

260

261 **3.4 Drug release profile**

262 Table 2 shows the time at which alginate formulae released 50% and 90% of their drug
 263 content. It was shown that the rate of drug release from alginate system was retarded as the
 264 concentration of alginate gel was increased; the drug/polymer ratio was reduced, cross linker
 265 concentration was increased and/or cross linking time was increased. This is suggested to
 266 be attributed to the increased viscosity of alginate [31] and/or increased degree of cross
 267 linking [32]. Rokhade and co-workers studied polymer network microspheres and reported
 268 that increasing drug/polymer ratio resulted in faster drug release from the microspheres [33].
 269 It was shown also that release in fed-simulated conditions was faster than that in fasting-
 270 simulated ones. Formulae showing high swelling index showed also a fast release of the
 271 drug and vice versa. This is attributed to the fact that swelling index of beads is indicative for
 272 the interaction between beads and media. The more the interaction between beads and
 273 media is, the more the beads swell.
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 275
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Table 2. T₅₀ and T₉₀ of drug release from alginate formulae

	Fasting Conditions		Fed Conditions	
	T ₅₀ * (min)	T ₉₀ ** (min)	T ₅₀ * (min)	T ₉₀ ** (min)
F1	98.63 ± 2.38	211.00 ± 7.56	89.38 ± 2.38	198.33 ± 12.76
F2	81.73 ± 2.08	180.20 ± 14.57	76.75 ± 2.30	162.90 ± 14.20
F3	63.67 ± 2.71	129.50 ± 3.35	50.00 ± 1.85	102.41 ± 6.68
F4	17.63 ± 0.57	37.41 ± 1.89	16.91 ± 0.85	33.28 ± 1.22
F5	42.47 ± 1.81	100.18 ± 4.04	35.01 ± 1.73	85.02 ± 2.71
F6	66.48 ± 2.31	121.30 ± 3.77	49.30 ± 1.70	118.65 ± 6.54
F7	20.32 ± 0.52	49.38 ± 3.80	20.50 ± 1.80	44.88 ± 2.07
F8	33.82 ± 1.86	78.70 ± 3.66	30.60 ± 1.51	71.87 ± 3.43
F9	61.74 ± 2.38	121.35 ± 3.99	49.28 ± 2.32	98.58 ± 5.90
F10	65.62 ± 1.61	117.95 ± 4.51	53.73 ± 3.36	108.03 ± 2.89
F11	45.59 ± 0.95	86.03 ± 2.13	35.75 ± 1.37	79.48 ± 3.05
F12	51.95 ± 1.56	92.73 ± 3.78	31.87 ± 1.96	78.68 ± 2.57
F13	40.20 ± 1.62	122.09 ± 1.70	39.94 ± 1.82	103.50 ± 1.49
F14	27.13 ± 2.42	73.90 ± 2.21	51.67 ± 15.37	66.63 ± 3.20

* T₅₀ is the time at which 50% of the drug was released from the beads

** T₉₀ is the time at which 90% of the drug was released from the beads

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3.5 Seeking for an optimal formulation

281 Table 3 shows a summary of the studied factors and their effect on the properties of alginate
 282 beads. An optimized formula (OF) was suggested so that the effects of formulation factors
 283 can be compensated. It was shown from figures 8-12 that the percent drug load, EE, SI and
 284 mucoadhesion of OF formula were accepted for targeting and delivering gabapentin to the
 285 upper duodenal region. However, OF formula showed fast release that is not suitable for
 286 sustaining the release of the drug as shown in figures 13,14. Controlling drug release from
 287 alginate beads was attempted using SDS [33] and solid dispersion [34]. The compositions of
 288 OF, SDSF, SDF and FSF formulae are shown by table 4. SDSF formula showed inferior
 289 properties as compared to all other formulae. It was shown that incorporating SDS into gel
 290 beads has facilitated the release of drug during both cross linking process and drug release

291 study. This resulted in reduction of the percent drug load and encapsulation efficiency; and
 292 improper sustained release drug delivery system profile. The use of solid dispersion for
 293 sustain the release of the drug had no effect on the targeting properties of alginate beads but
 294 sustained the release of the drug to a great degree. To obtain a very fast release and a
 295 sustained one, the drug incorporated into beads was divided into two portions, the first
 296 portion (1/3 of the total amount) is free drug to produce a fast release and the second portion
 297 (2/3 of the total amount) was solid dispersion to sustain the release of the drug. The release
 298 of this system, as shown in figure 10, exhibited a fast release (almost 33% during the first
 299 half an hour) and sustained release during the rest of the 10 hrs.

300
 301 **Table 3. summary of the studied factors and their effect on the properties of alginate**
 302 **system.**

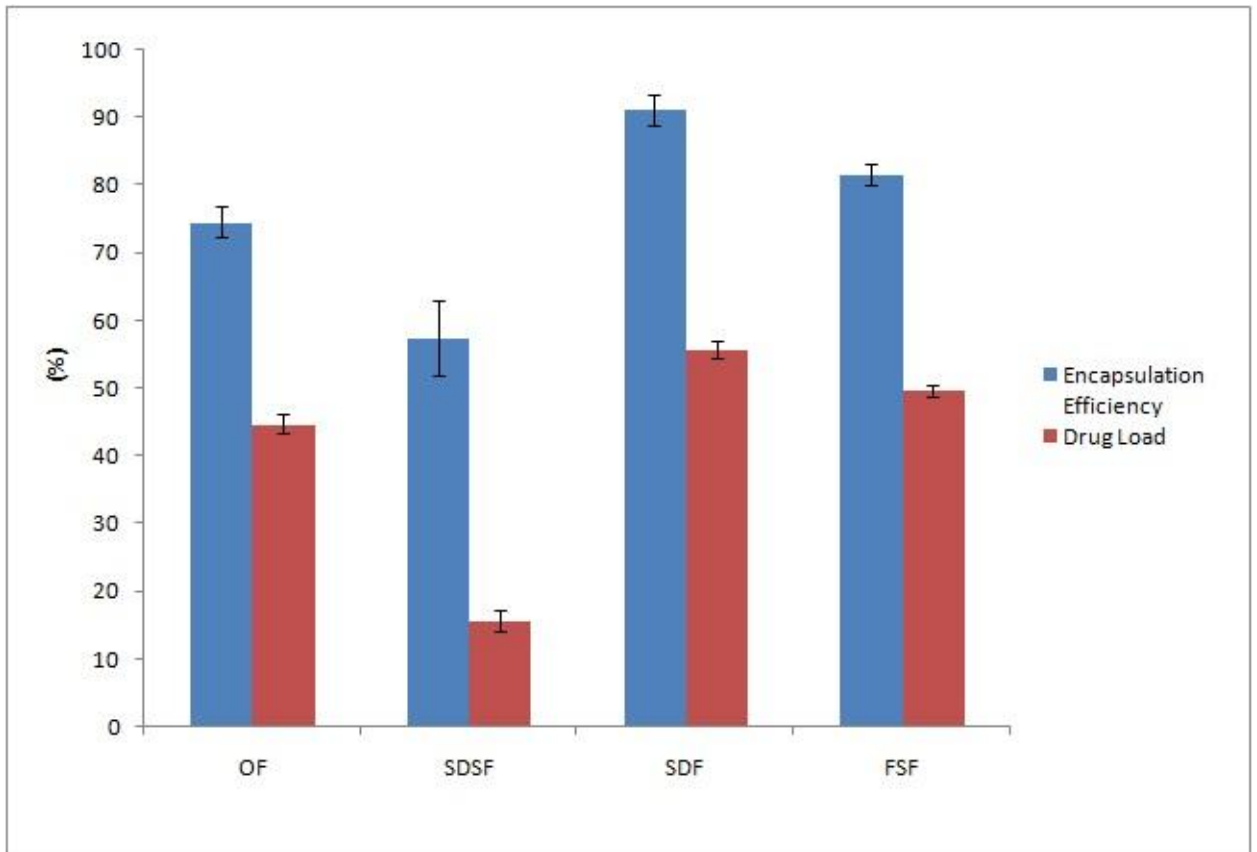
	Drug Load	Encapsulation Efficiency	Swelling Index	Mucoadhesion		Release Rate
				1st	2nd	
Conc. Of Alginate	+ *	+	- **	-	+	-
Conc. Of CaCl2	-	-	-	-	+	-
Time of Cross Linking	-	-	-	-	+	-
VDps : VCLS	-	-	N †	N	N	N
Drug:Polymer Ratio	+	-	± ‡	±	±	+

303
 304 * Inversely Related
 305 ** Directly Related
 306 † Not Related
 307 ‡ Increase to certain Limit or beyond Certain Limit
 308

309 **Table 4. Compositons and Formulation Variables of Modified Alginate Formulae**

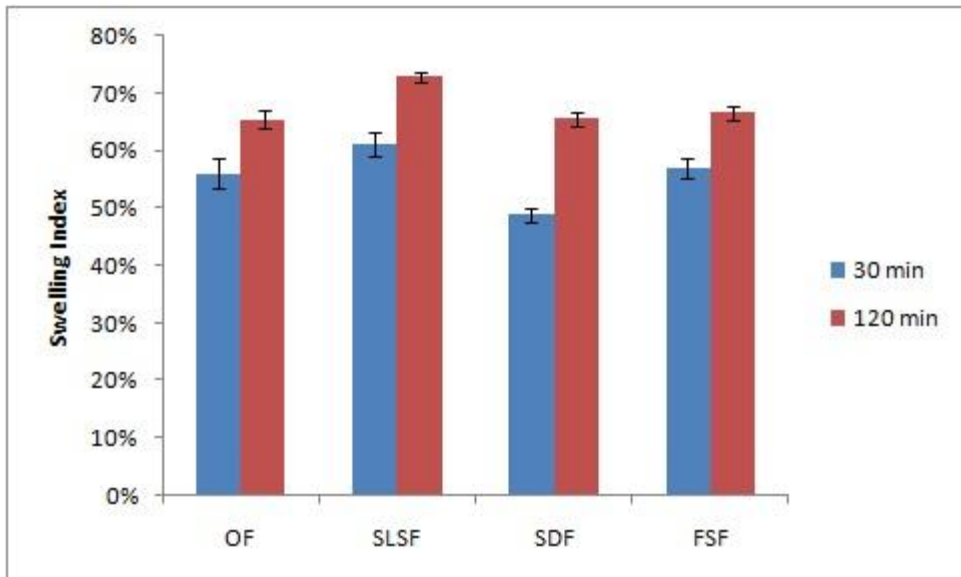
Formula Code	Sodium Alginate Concentration (% W/V)	Cross Linking Solution Concentration (% W/V)	Cross Linking Time (min)	Cross-Linking solution Volume : Gel Volume	Drug : polymer Ratio	SDS (g)	Free Drug (% of the Total Amount of Drug Added)	Drug-EC Solid Dispersion (% of the Total Amount of Drug Added)
OF *	2	1	30	1:1	3:2	-	-	-
SDSF **	2	1	30	1 : 1	3 : 2	3	100	0
SDF †	2	1	30	1 : 1	3 : 2	-	0	100
FSF ‡	2	1	30	1 : 1	3 : 2	-	33.33	66.67

310 * Optimized formula
 311 ** SDSF sodium dodecyl sulfata formula
 312 † solid dispersion formula
 313 ‡ finally suggested formula



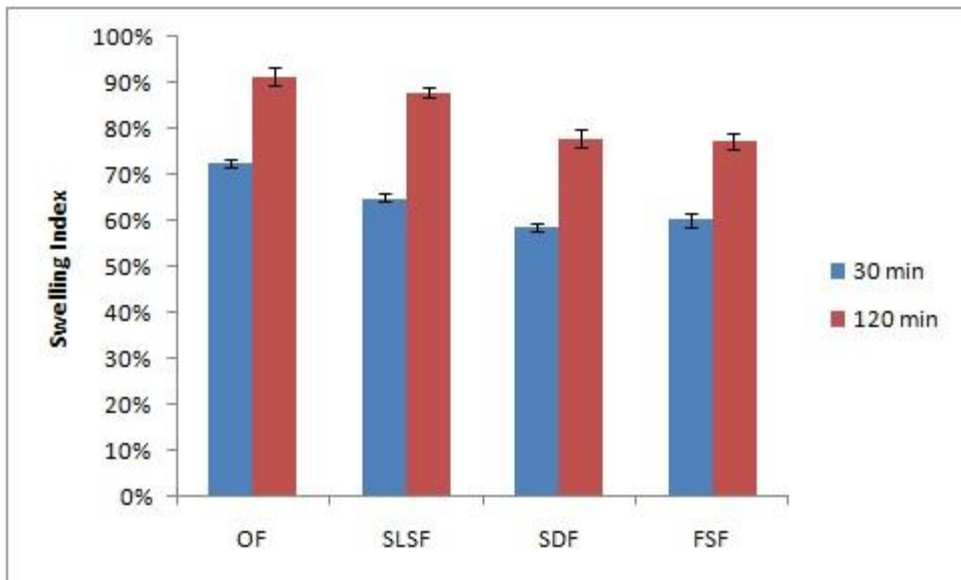
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Fig. 8. Drug load and encapsulation efficiency of formulae OF, SDSF, SDF and FSF. Each data represents mean \pm S.E. (n=3).



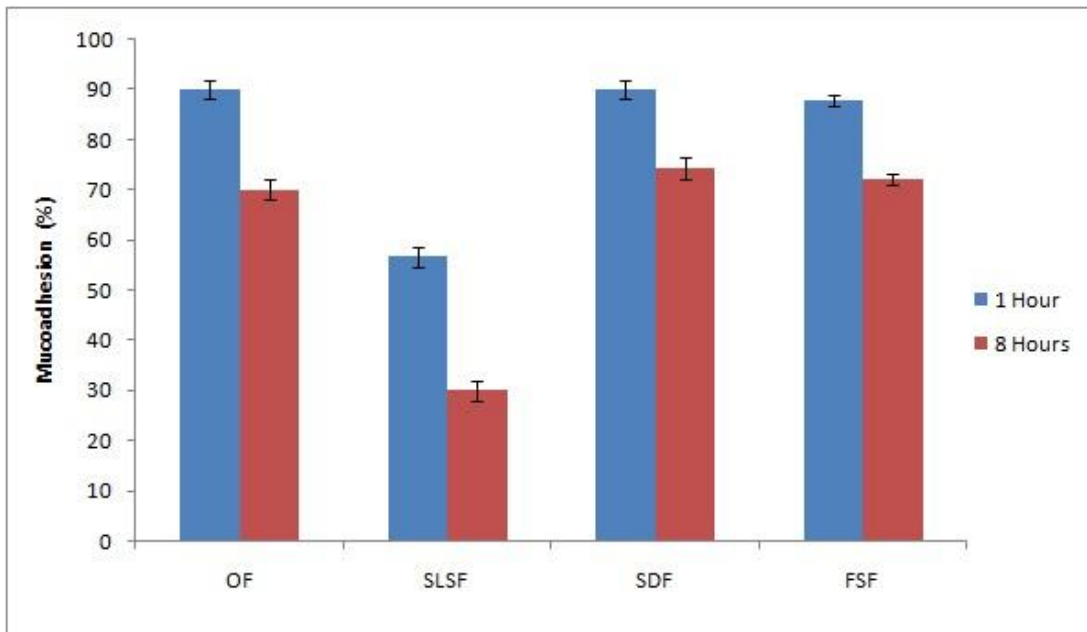
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Fig. 9. Swelling ratio of formulae OF, SDSF, SDF and FSF after 30 and 120 minutes in fasting-simulated conditions. Each data represents mean \pm S.E. (n=3).



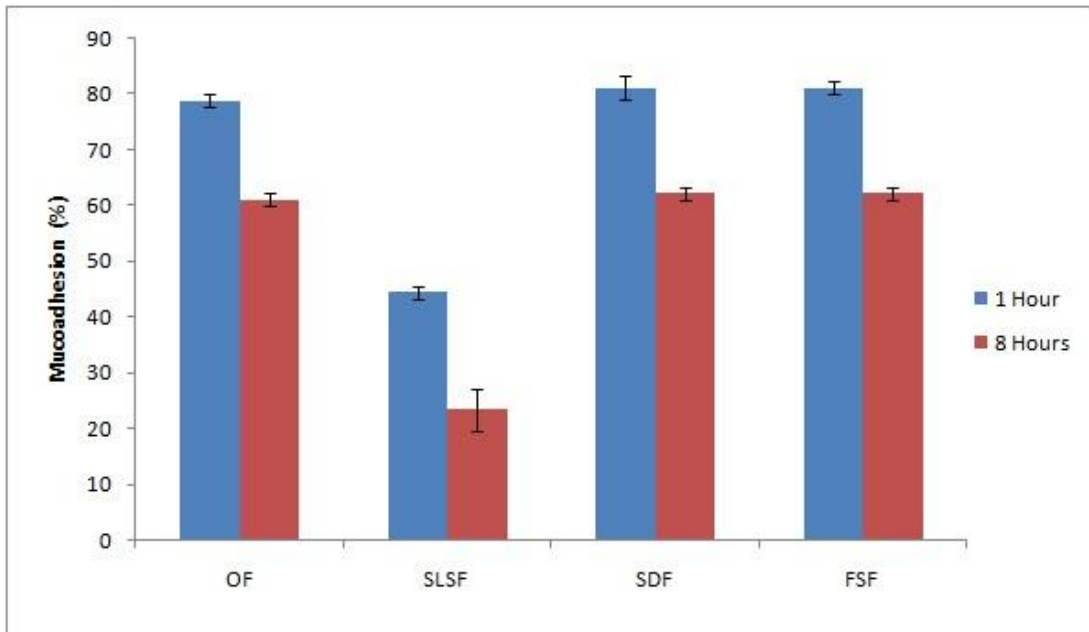
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Fig. 10. Swelling ratio of formulae OF, SDSF, SDF and FSF after 30 and 120 minutes in fed-simulated conditions. Each data represents mean \pm S.E. (n=3).



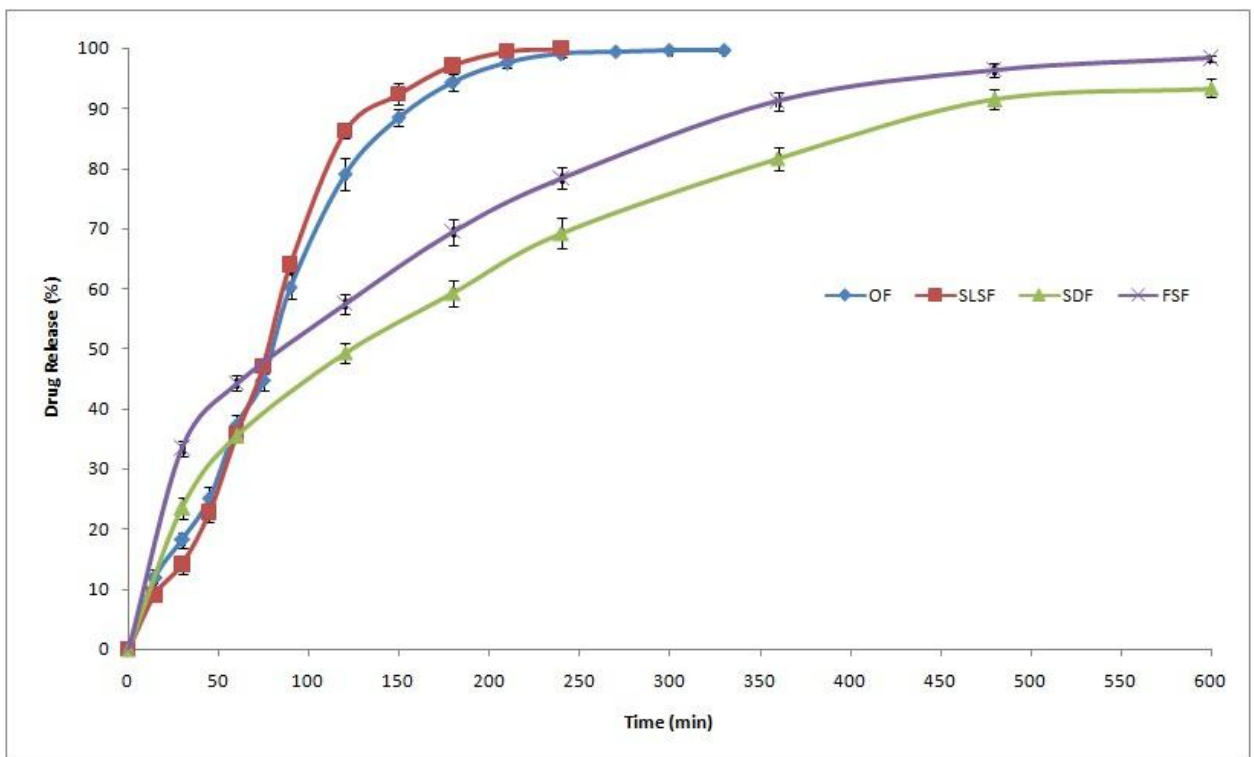
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Fig. 11. Mucoadhesion of formulae OF, SDSF, SDF and FSF after 1 and 8 hrs in fasting-simulated conditions. Each data represents mean \pm S.E. (n=3).



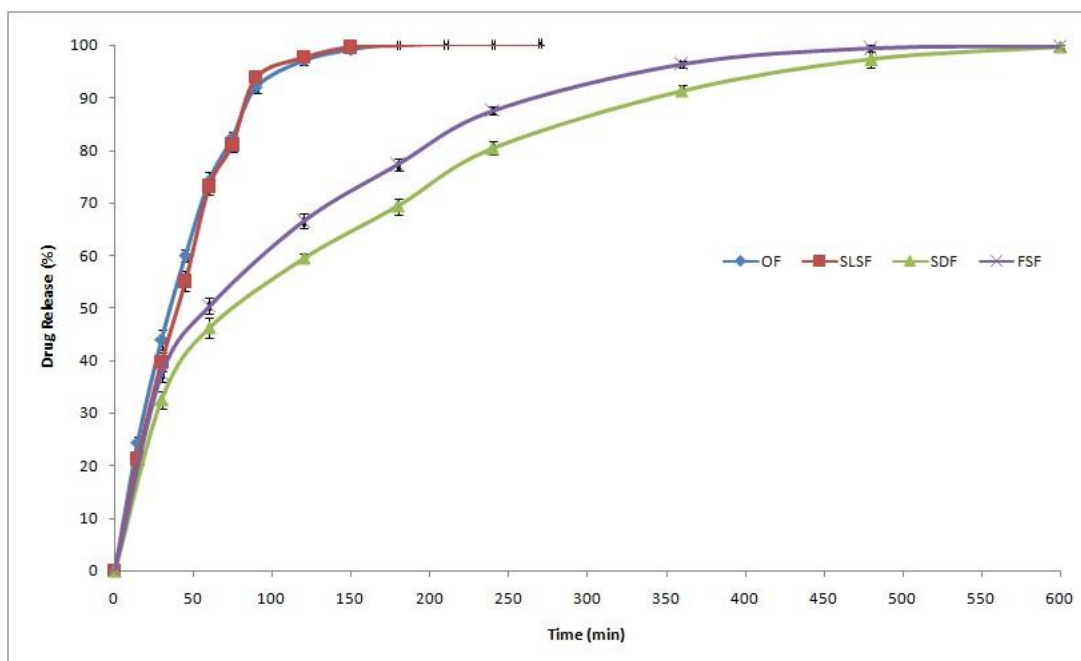
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Fig. 12. Mucoadhesion of formulae OF, SDSF, SDF and FSF after 1 and 8 hrs in fed-simulated conditions. Each data represents mean \pm S.E. (n=3).



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Fig. 13. Drug release profiles of formulae OF, SDSF, SDF and FSF in fasting-simulated conditions. Each data represents mean \pm S.E. (n=3).



341
 342 **Fig. 14. Drug release profiles of formulae OF, SDSF, SDF and FSF in fed-simulated**
 343 **conditions. Each data represents mean ± S.E. (n=3).**
 344

345 The dissolution efficiency (D.E.), which is a suitable comparative parameter for the
 346 quantification of dissolution data, was utilized to assess the effect of alginate modification on
 347 the dissolution rate of the drug [35]. It was calculated according to the equation mentioned
 348 by Khan and Rhodes [35] as follows,

349
 350 Dissolution Efficiency (D.E.) = $\frac{\int_0^t y \cdot dt}{y_{100} \cdot t}$
 351

352 Dissolution efficiencies of optimized formulae are given by table 5. The DE0-60min for OF,
 353 SLSF, SDF and FSF formulae were shown to be 265.68, 258.54, 7.06 and 8.48,
 354 respectively. It was shown from the values of DE of OF, SDSF, SDF and FSF formulae that
 355 incorporating SDS into alginate beads had insignificant effect on retarding drug release.
 356 However, the use of EC solid dispersion retarded the release of gabapentin from alginate
 357 beads significantly.

358
 359 **Table 5. Dissolution efficiency of modified formulae.**
 360

	Fasting-Simulated Conditions				
	0.5 h	1 h	2 h	3 h	4 h
OF	135.28	256.68	1047.02	1200.02	1241.19
SDSF	114.71	258.64	1117.11	1228.84	1249.87
SDF	2.45	7.06	9.04	10.71	25.15
FSF	3.23	8.48	10.57	12.31	28.26
	Fed-Simulated Conditions				
	0.5 h	1 h	2 h	3 h	4 h

OF	324.77	489.75	1227.81	1252.57	1254.92
SDSF	296.03	481.47	1233.39	1250.96	1252.11
SDF	3.28	8.81	10.74	12.48	28.64
FSF	3.66	9.74	11.98	13.74	30.67

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4. CONCLUSION

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The optimized formula, OF formula, has shown acceptable drug load, encapsulation efficiency, swelling index and mucoadhesion but not sustained gabapentin release profile ,i.e. alginate system is not capable of fulfilling requirements of producing gabapentin sustained release dosage form (spatial placement and temporal delivery) by just adjusting formulation variables.

368

Incorporating SDS released gabapentin even faster than OF formula. It also reduced targeting capabilities of alginate system as indicated by fast detachment of beads from intestine piece during mucoadhesion testing.

371

Incorporating solid dispersion of EC with gabapentin in alginate beads instead of free drug retarded the release of gabapentin from alginate beads successfully. Ethylcellulose - gabapentin solid dispersion also increased the drug load and EE with minor positive impact on the mucoadhesion capabilities of alginate beads.

375

A finally optimized formula has been suggested by incorporating a combination of solid dispersion and free gabapentin in the ratio of 1:2 in alginate system to achieve burst release of gabapentin and hence fast effect (33.417% \pm 2.087 of gabapentin was released during the first 30 minutes in fasting-simulated conditions) and sustained release and hence maintained effect (after 6 hrs, only 91.217% \pm 2.523 of gabapentin was released).

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AUTHORS' CONTRIBUTIONS

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"All authors read and approved the final manuscript."

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