

Manuscript Title: **Optimization of Gabapentin Release and Targeting Absorption, Through Incorporation into Alginate Beads**

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I think the idea of manuscript is a good one but its implementation is very bad as well as the use of calcium alginate for gabapentin was an unfortunate choice.

Authors Feedback:-

Thanks a lot for the reviewer valuable comments and pleas kindly find our details answers for each point.

1-Alginate is well known that it is suitable as drug delivery system for insoluble or high molecular weight drugs (in our case gabapentin is very water soluble and low molecular weight 171.14)

Authors Feedback:-

a) Alginate was used by many authors to control the release of water soluble drugs with low molecular weight.

Ref.

- (1) Taha et al., used Alginate to control the release of chlorpheniramine maleate – M. Wt. 274.788 and aq. Solubility 0.55 g/100 ml – (Taha, M.O., Nasser, W., Ardakani, A., and AlKhatib, H.S., 2008. Sodium Lauryl Sulfate Impedes Drug Release from Zinc-Crosslinked Alginate Beads: Switching from Enteric Coating Release Into Biphasic Profiles. *Int. J. Pharm.* 350, 291-300.).

(2) Das and Maurya also used Alginate beads to control the release of Diltiazem hydrochloride Das, M.K., and Maurya, D.P., 2008. Evaluation of Diltiazem Hydrochloride-Loaded Mucoadhesive Microspheres Prepared by Emulsification and Internal Gelation Technique. *Acta Poloniae Pharmaceutica - Drug Res.* 65(2), 249-259.

(3) During investigation of the nifedipine HCl- alginate beads, Takka et al., reported that alginate succeeded to retard the release of nifedipine HCl Takka, S., Ocak, Ö.H., and Acartürk, F., 1998. Formulation and Investigation of Nifedipine HCl–Alginate Gel Beads with Factorial Design-Based Studies. *Eur. J. Pharm. Sci.* 6, 241–246.

b) Alginate system alone (with no modification) could do nothing for controlling the release of gabapentin, however the use of solid dispersion instead of free gabapentin was the modification to alginate system that helped controlling the release of gabapentin from alginate system

2- In preparing calcium alginate we need some time for complete curing of beads (in case of the manuscript, not less than 30 min), most of the drug will escape during that time.

Authors Feedback:-

Solubility of gabapentin in water is 4490 mg/L and the volume used to cure beads was only 20 ml (maximum amount of drug to be leached out from the beads can be calculated to be 89.8 mg – supposing complete and highly efficient process - , after that saturation occurs in external phase and no further leaching of the drug from beads could take place)

3-Alginate was not characterized regarding the ratio of mannuronic acid (M) and guluronic acid, M blocks, G blocks, MG blocks or its molecular weight, viscosity (these criteria is very important for behavior of the beads prepared)

Authors Feedback:-

The substance was purchased from Aldrich® chemicals and the stated viscosity is 5-40 cp (1% solution).

4- The mucoadhesion experiment was performed using pig intestine but the medium used was simulated gastric fluid.

Authors Feedback:-

a) The evaluation of mucoadhesive behavior of diltiazem HCl-loaded alginate microspheres done by Das and Maurya was performed using intestinal pieces of goat at both simulated gastric fluid (0.1 M HCl, pH 1.2) and simulated intestinal fluid (phosphate buffer, pH 7.4). (Das, M.K., and Maurya, D.P., 2008. Evaluation of Diltiazem Hydrochloride-Loaded Mucoadhesive Microspheres Prepared by Emulsification and Internal Gelation Technique. *Acta Poloniae Pharmaceutica - Drug Res.* 65(2), 249-259.

b) In a study done by Prajapati et al., the determination of mucoadhesion of gliclazide-loaded alginate particles was done utilizing rat intestinal mucosa and using both simulated gastric fluid (0.1 M HCl, pH 1.2) and simulated intestinal fluid (phosphate buffer, pH 7.4) as the media (Prajapati, S.K., Tripathi, P., Ubaidulla, U., and Anand, V., 2008. Design and Development of Gliclazide Mucoadhesive Microcapsules: In Vitro and In Vivo Evaluation. *AAPS PharmSciTech* 9(1), 224-230.

5- No reference for mucoadhesion experiment

Authors Feedback:-

Ref. no 12

Prajapati, S.K., Tripathi, P., Ubaidulla, U., and Anand, V., 2008. Design and Development of Gliclazide Mucoadhesive Microcapsules: In Vitro and In Vivo Evaluation. AAPS PharmSciTech 9(1), 224-230.

6-The swelling of calcium alginate normally does not occur in gastric because alginate will not be in ionized form at acidic pH.

Authors Feedback:-

- a) Results of studying swelling of alginate beads done by Takka et al., showed that “Alginate beads swelled at pH:1.2–4.5, but underwent erosion at pH:7–7.5.” (Takka, S., Ocak, Ö.H., and Acartürk, F., 1998. Formulation and Investigation of Nicardipine HCl–Alginate Gel Beads with Factorial Design-Based Studies. Eur. J. Pharm. Sci. 6, 241–246.)
- b) In another study, dry alginate beads showed swelling in simulated gastric fluid (SGF) to – at most - 150% of their initial weight after that they got a plateau. This resembles the results we have got for the swelling of the majority of the prepared alginate beads. The study was done by Pasparakis and Bouropoulos (Pasparakis, G., and Bouropoulos, N., 2006. Swelling Studies and In Vitro Release of Verapamil from Calcium Alginate and Calcium Alginate–Chitosan Beads. . Int. J. Pharm. 323, 34-42).

7-We did not what is the size of beads before and after drying.

Authors Feedback:-

We didn't find previous papers measure this character and we don't know the importance and significance of this measurement on the beads characters.

8- Drying at ambient temperature overnight (The temperature used allowed the alginate beads to keep high amount of moisture that affect drug stability).

Authors Feedback:-

Gabapentin was shown to be highly stable in aqueous solutions since $t_{99.5\%}$ for gabapentin was shown to be 58 and 29 months at pH 6 and 7, respectively. (Zour, E., Lodfi, S.A., Nusbett, R.U., Silbering, S.B., and Shaturvedi, P.R., 1992. Stability Studies of Gabapentin in Aqueous Solutions. Pharm. Res. 9(5), 595-600).

9-No rationality in using surfactant to decrease the release of the drug from alginate.

Authors Feedback:-

a) Please check the following reference (Taha, M.O., Nasser, W., Ardakani, A., and AlKhatib, H.S., 2008. Sodium Lauryl Sulfate Impedes Drug Release from Zinc-Crosslinked Alginate Beads: Switching from Enteric Coating Release Into Biphasic Profiles. Int. J. Pharm. 350, 291-300).

b) Alginate polymer is an ionic one as well as the sodium lauryl sulfate. For this reason it is suggested that the effect of sodium lauryl sulfate on the release properties from alginate beads was not because of its nature as a surfactant but rather because of its ionic nature.

c) Despite the mentioned justifications, sodium lauryl sulfate was shown not to be effective in controlling the release of gabapentin from alginate – as it did in the study done by Taha et al., - and the negative results were included as they are in the manuscript for the benefit of others.

10-No mention for ethylcellulose in material or how was solid dispersion prepared in methods.

Authors Feedback:-

Ethylcellulose 100 cps

Aqualon, Wilmington, DE, USA

Ethylcellulose was dissolved in absolute ethyl alcohol and then the clear solution was levigated with the proper amount of the drug. The formed paste was then continued to be stirred using a pestle till all alcohol used was evaporated leaving fine and ground powder of Gabapentin-ethylcellulose solid dispersion. The powder was then left for drying over night to assure the complete evaporation of alcohol and dryness of the solid dispersion powder.

11- Still many linguistic mistakes present.

Authors Feedback:-

We made another revision and we are very happy to respond to definite mistakes