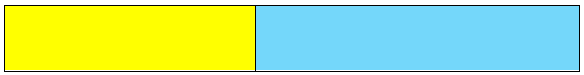
Author's feedback Editor comm.



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

Manuscript number: **2012_BJPR_3020**

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 chloropheneramine 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 nicardepine HCl- alginate beads, Takka et al., reported that alginate succeeded to retard the release of nicardepine HCl 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) 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

1-The authors mentioned some references used different alginate, different procedure as cross linker, time of curing, nozzles so they produced alginate with different characteristics.

2-The authors mentioned that “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”

So, in my opinion , It was the first priority to be focusing on the modification not on alginate alone but you did not include in the manuscript the method of preparation, drug:polymer ratio characterization, particle size, drug content of the solid dispersion.

1- We modified the paper and added the method of preparation of the solid dispersion as the reviewer suggested

2- We thank the reviewer for getting our attention to that great point of view.

3- The scheme of the research was done to evaluate the effect of different formulation variables on the rate of gabapentin release. Alginate, despite being the main focus in our research, couldn't reach the goal of the research – which is controlling the release of gabapentin efficiently - so the research was conducted in the field of modifying alginate system to reach the goal. For that reason, alginate was the main focus in the research paper because it was the main focus in the research activity.

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)

2-The authors insisted not to mention the quantity and the volume along the manuscript so the judgment on the validity of the method is difficult as the escaping of drug during curing time hence the encapsulation efficiency, the dispersion of the drug despite its high solubility…….etc

Example 1: In preparing the beads:

-What is the volume of CaCl2 used? 10 ml

-What is the amount of water drug dispersed in it? 2 ml

Example 2: Determination of drug load percentage

Specific weight (???) of beads was taken and crushed. The crushed beads were then placed in a vial and a proper amount (???) of deionized water was added to it. The vials containing crushed beads and water were shaken for 15 minutes for complete extraction of drug.

Example 3: **Determination of in-vitro release profile**

An accurately weighed amount of the beads (????) was placed in vials each containing 15 mL of dissolution media pre-warmed up in a shaking water bath at 37±0.5°C. The speed of shaking was adjusted to be 50 rpm. Samples (????) of the dissolution media were withdrawn

Mentioning "proper amount of the drug" means that the amount of the beads was not constant all over the experiment rather it was varying according to the amount of the drug required to be present in the beads to be evaluated. The proper amount of the drug was chosen to so that at lease 10% of that amount would be detected easily by HPLC.

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).

3- The stated viscosity is 5-40 cp (1% solution).

Because it is so low and I think the prepared beads had low mechanical strength which affect the integrity and the release pattern.

This was the case and alginate – as we had mentioned previously – could do nothing to control the release of gabapentin

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.

b) Evaluation of Diltiazem Hydrochloride-Loaded Mucoadhesive Microspheres Prepared by Emulsification and Internal Gelation Technique. Acta Poloniae Pharmaceutica - Drug Res. 65(2), 249-259.

c) 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.

4-Both references used both simulated gastric and simulated intestinal fluid. Why the author did not use the two fluids?

d) In the field of our research, we were interested more in performing the mucoadhesion study on pig's intestine because once gabapentin has passed the duodenum; it will not be absorbed from the intestine. So, the two papers were used as a guide for the validity of performing the test on intestinal piece using stomach pH.

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.

4- Ref. no 12 as it was mentioned in manuscript is Ref. No. 20

Thanks a lot for this accurate notice; we considered it in the modified paper version 5.

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 know 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.

7-The author should check any research of calcium alginate , he will find measurement of size of dry or/ and wet beads.

Unfortunately, we have used the paper of “Das and Maurya” as a guide for us and this paper didn’t mention the size of particles before and after drying.

This important notice will be considered in the future work of our lab team.

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).

6- How we prepare beads containing moisture and we do not know the amount of this moisture. How about the crystallization of the drug when evaporation occurred. Rapid evaporation or slow one could affect the porosity of the beads. How about the stability of solid dispersion!!!!!!!!!!!!!!!

Unfortunately, we have used the paper of "Das and Maurya" as a guide for us and this paper didn't mention the moisture content.

Also, this important notice will be considered in the future work of our lab team.

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.

I checked the reference: M.O. Taha et al. / International Journal of Pharmaceutics 350 (2008) 291–300, I found

1-Chlorpheniramine loading is inversely proportional to SLS levels

2-Calcium cross-linking in presence of SLS failed to retard the release of chlorpheniramine

That means SLS was not useful as retardant but in contrast increase the escaping of the drug during curing time. In addition,

- The result in the manuscript "sodium lauryl sulfate was shown not to be effective in controlling the release of gabapentin from alginate"

- No more research tried to explore the effect of sodium lauryl sulfate on the drug-releasing profiles of ionotropically crosslinked alginate.

a) we have used SLS with calcium cross linked alginate – despite being ineffective with calcium cross linked alginate beads and effective with the zinc cross linked ones in the previously mentioned research – because changing Chlorpheniramine (which is cationic) with alginate (which is amphoteric) could affect the properties of SLS (which is anionic)-loaded alginate beads.

b) we have mentioned that SLS could do nothing with alginate beads as it was stated in the research published by Taha et al., despite changing the drug. This was stated in the research for scientific honesty and for others who could think that changing the cationic drug with amphoteric one would affect the properties conferred by the anionic SLS to alginate.

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.

- It should be included in manuscript.

Thanks a lot for that notice, it was included in the manuscript.

-**2.2.3 Determination of encapsulation efficiency**

The content of gabapentin in certain weight of the beads was first determined by extraction then by HPLC quantification as previously mentioned (c.f. section 2.1.2 determination of percentage drug load).

No need for the above paragraph because it is not a separate step than Determination of drug load percentage

This notice was considered and it was modified in the new version of paper.