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Short communication

Evaluation of influence of viscosity as main CQA on raft properties of alginate based anti-reflux suspension using DoE

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Introduction

Alginate-based anti-reflux suspensions are used for symptomatic relief of gastroesophageal reflux disease (GERD) by forming a floating raft on the acidic content of the stomach. Alginates are natural polysaccharide block co-polymers of L-guluronic and D-mannuronic acid which relative proportions are species dependent and can be influenced by growth conditions. The strength of the gel is dependent on various factors. Molecular weight and the ratio of D-mannuronic and L-guluronic acid residues are intrinsic properties that influence raft strength. Extrinsic factors, which influence the raft strength, include presence or absence of specific cations and also excipients like viscosity building agents which are an important part of the formulation development of alginate suspensions, due to their natural origin.

Studies revealed that calcium ions increase the raft strength, while the addition of aluminum ions, reduce the raft strength in alginate–based systems. The ability of calcium ions to increase raft strength is attributed to its ability to crosslink alginic acid polymers, allowing the gel to form an “egg-box” structure which has great inherent strength. Generally, alginate suspensions are formulated to include bicarbonate, which acts as a gas generating system. The carbon dioxide bubbles, which are formed in the presence of gastric acid, become entrapped within the gel matrix, converting it into foam and providing buoyancy, which allows the gel to float on the surface of the gastric contents (Kapadia et al., 2007).

Literature findings show that there is relation between viscosity of suspension and raft properties. Namely, high viscosity can retard the escape of generated carbon dioxide within the polymer matrices and prolong raft duration (Awasthi et al., 2021).

The purpose of this study was to formulate raft-forming alginate-based anti-reflux suspension and to evaluate influence of viscosity on final product quality – influence on raft properties using DoE (Design of Experiments) approach.

Materials and methods

Active pharmaceutical ingredients (APIs, Alginate, AL and Antacid, AN) were provided by DuPont, US and Merck, DE, accordingly.). Calcium carbonate ($CaCO_3$, Magnesia, DE), Carbopol 974P (CP, Lubrizol, BE), Sodium Hydroxide (NaOH, Kaustik, NE), Methyl Para hydroxybenzoate and Propyl Para hydroxybenzoate (MP, PP Merck, DE), Sodium Saccharin (SS, JMC, CH) Flavor Peppermint (FP, Symrise, DE).

Laboratory trials were carried out in a glass with 400 ml aqua purificata with 1 min steering time between all materials added in the given order AN, $CaCO_3$, NaOH and AL. AL was added in 3 equal parts with 15 min steering between parts. In second glass with 200 ml aqua purificata CP is dissolved and pH of solution is adjusted until pH 7.00, using 10% NaOH solution. In separate glass solution of MP and PP is prepared, according well-known procedure. Contents of both glasses are added to the glass containing APIs with addition of FP (mixing time: 15min; after adjusting to final volume mixing time 30 min).

Experimental design approach (MODDE, Umetrics, SE) was performed in order to evaluate influence of viscosity on raft properties. For that purpose (23) full factorial design with 2 center points and without replicates was applied with varying two factors/independent variables- amount (%) of $CaCO_3$ and amount (%) of CP in formulation, whereas raft strength; raft speed, raft thickness, raft volume, raft weight, pH and viscosity were

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selected as dependent variables (responses). Composition of laboratory trials is shown on Table 1.

Table 1. Qualitative and quantitative composition of trials

Material	AL	AN	Na OH	MP	PP	SS	FP
w/w %	10.00	2.00	0.14	0.40	0.06	0.10	0.07

Prepared suspensions were fully characterized of their raft properties. Raft speed was measured as time required for raft forming. Raft strength (CT3 Texture analyzer-1000, Brookfield Amtek, US;1 kg load-cell (5 mm/s; 100 points/s), Raft weight - by weighing the formed raft on analytical balance (in pre-tarred petri dish), after letting it drain for 30-60 s (until the free flow of acid from the raft is stopped). Raft thickness was measured after formation using transparent ruler, by measuring the thinnest and thickest regions of the raft. The average raft thickness was calculated by dividing the raft volume with the surface area of the beaker used for formation. Raft volume was measured using the water displacement method. The formed raft was transferred into a 250 ml graduated cylinder, filled with exactly 200 ml of distilled water. The rise in the water level after complete submersion of the raft was used for determination of the raft volume.

Results and discussion

Identifying the influencing parameters at beginning of every formulation development is from crucial importance, since these will affect the properties of the final dosage form. The experimental design method analyzes the influence of different variables on the properties of the drug delivery system.

A 2^3 full factorial design was used to describe the relation between the response under question and the variables studied. Each response was individually analyzed. Summary statistic for R2, Q2, reproducibility in relation to concerned response variables: raft strength, raft speed, raft thickness, raft volume and raft weight (R2> 0.9; Q2> 0.4, reproducibility> 0.8) has shown that the model is significant and fits the data. Model validity was low (<0.25) for all responses except raft thickness, this is due to the fact that generally models have high sensitivity and high variability in results within responses can result with low model validity.

Results from DoE evaluation have shown that generally raft properties are not related just to viscosity i.e., % of viscosity building agent (CP) in formulation, but are directly correlated with appropriate ratio of $CaCO_3$ and CP in formulation. Formulations where CP is not present and $CaCO_3$ is in higher % than 2.0 (w/w) gave very high raft strength (greater than 30.0 g; acceptance criteria: 9.0-20.0 g) which after formation can be easily broken and gives unsatisfactory quality of the final raft. Viscosity (% of CP) was evaluated as not critical for parameter raft strength. Raft speed for all trials was very different in general, especially when mechanism of raft formation was compared. Raft speed was generally linked with higher % of CP and $CaCO_3$ in formulation. Higher viscosity (0.4% CP) had shown slower raft formation. Raft speed can be viscosity related and has to be optimized during development process. Raft thickness gave satisfactory values for all laboratory trials regardless the viscosity (% of CP) of final product. Regarding raft volume and raft weight DoE results have shown that these parameters are directly influenced by % of $CaCO_3$, meaning bigger the % of $CaCO_3$ was, bigger raft volume and raft thickness are observed. Viscosity as crucial parameter for liquid floating raft forming system was related with CP % but also with % of CaCO3. High levels of both factors ($CaCO_3$ 3.5%; CP 0.4%) gave highest results for viscosity (4600 cP).

Conclusion

According to the obtained results from this study, raft properties of final product are directly related not only to the viscosity (i.e., % of viscosity building agent in formulation) of suspension but also to the % of $CaCO_3$ in the formulation.

It can be concluded that the formulations with bigger % of Calcium Carbonate (≥ 2.0 % w/w) had better raft properties compared to other trials. This study support literature regarding $CaCO_3$ importance in raft formation and strengthening the raft through the interaction of calcium ions with alginate polymer chains.

Optimization of % $CaCO_3$ in formulation and ratio between % of $CaCO_3$ and Carbopol will be from crucial manner in order to obtain satisfactory final product quality.

References

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