

A Multiple Unit Abuse-deterrent Dosage Form Based on Sodium Alginate

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Abstract There are several approaches for the formulation of abuse-deterrent, tamper-resistant, or alcohol-resistant dosage forms. This work is specifically focused on the formulation of microforms and multiple unit dosage forms with the mentioned resistant features. We prepared microcapsules based on sodium alginate by Ca^{2+} -induced gelation, containing caffeine as a model drug. The prepared microcapsules were dried either by hot air or freeze-dried and the resistance in an alcoholic environment and the resistance against mechanical stress were observed. Subsequently, swelling studies were conducted to predict the behavior of prepared microcapsules during dissolution testing. Differences in the behavior of microcapsules during dissolution testing were strongly related to the different abilities of Ca^{2+} -alginate microcapsules to swell in an acidic and alkaline environment. Alginate microcapsules exhibited gastro-resistant properties due to excellent swelling in an alkaline environment and poor swelling in a gastric environment. The addition of ethanol did not influence the swelling behavior of alginate microcapsules in the gastric fluid; rather, it showed the opposite effect, where swelling was slightly suppressed. Therefore, we conclude that alginate microcapsules are alcohol resistant. Also, they showed high mechanical strength, and therefore, grinding the microcapsules into a powder was impossible.

Keywords Multiple unit dosage form – Abuse deterrent dosage form – Microcapsules – Microbeads – Sodium alginate

INTRODUCTION

Abuse-deterrent dosage forms are intended for the active pharmaceutical ingredients (APIs), which are susceptible to abuse and have properties that can lead to addiction. Some examples are analgesics (mainly opioids), antianxiety medication, sedatives, sedative-hypnotics, stimulants, antidepressants, narcolepsy-treating actives, attention-deficit treating actives, and psychoactive drugs (Tian et al., 2019). Abusers often manipulate (e.g., cut, crush, or dissolve) extended-release formulations to more rapidly released ones, most, if not all, of the drug (Gudin, 2016). More types of resistant dosage forms are distinguished: abuse resistant/deterrent, tamper resistant/deterrent, and alcohol resistant/deterrent. The word abuse can be defined as the intentional self-administration of a medication for a nonmedical purpose such as altering one's state of consciousness. Tampering is defined as a chemical or physical manipulation that alters or damages the integrity of a dosage form, often done to enhance a pharmacological effect upon administration. One of the tampering methods is to reduce particles, which

will allow faster dissolution, and make nasal insufflation and intravenous administration possible. The coingestion of alcohol with prescription drugs can alter a slow-release delivery system causing "dose dumping" of the drug into the bloodstream (Mastropietro & Omidian, 2013). Most of the formulations designed to deter abuse belong to one of the four groups according to the formulation approach. In the first group, there are dosage forms containing physical barriers providing resistance to physical manipulation or dosage forms swelling fast in the solution, which are not suitable for injection. The second formulation group is based on the combination of agonist/antagonist (e.g., buprenorphine HCl + naloxone HCl). Crushing or chewing releases sequestered naloxone and blocks euphoric effects. The third group utilizes the addition of aversive agents such as niacin, which causes flushing, or sodium lauryl sulfate, which irritates the nasal mucosa. Dosage forms with more deterring mechanisms belong to the fourth and last group (Walter et al., 2016).

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A multiple-unit dosage form contains a plurality of units, for example, pellets or beads, each containing release-controlling excipients, in a gelatine capsule or compressed in a tablet (European Medicines Agency, 2013). Few abuse-deterrent products are formulated as multiple unit dosage forms on the market. One of them is Oxycodone DETERx[®], a microsphere-in-capsule formulation, with each individual microsphere acting as its own drug delivery system and maintaining its extended-release pharmacokinetic profile even after chewing and crushing. The microspheres consist of oxycodone dispersed in a hydrophobic matrix of fatty acid and waxes; the oxycodone is present as a salt with myristic acid. A big advantage of this dosage form is the administration of microspheres by sprinkling directly into the mouth, onto soft foods, or through nasogastric tubes, providing dosing options for patients who have difficulty swallowing (Gudin, 2016). Jedinger et al. developed a multiple unit pellet system with a prolonged drug release, drug abuse deterrence, and minimal risk of alcohol-induced dose dumping. Deformable pellets based on matrix systems (cornstarch, gum arabic, xanthan) were prepared by hot-melt extrusion, with model drugs antipyrine and codeine phosphate. Formulations based on xanthan and gum arabic showed immediate drug release, but cornstarch-based pellets retarded the drug release for up to 3 h. To prolong the drug release and to provide resistance against alcohol-induced dose dumping, cornstarch pellets were additionally coated with Aquacoat[®] ARC. It was shown that processing cornstarch via hot-melt extrusion increased its resistance to common tampering practices (Jedinger et al., 2016). Hot-melt extrusion process was selected as a viable technique for the preparation of tamper-resistant formulations by Maddineni et al. also. They used a combination of excipients; high-molecular-weight grade polyethylene oxide was used as a tamper-resistant matrix, while hydroxypropyl methylcellulose (HPMC K15M), in combination with Carbopol 71G, improved the gelling characteristics in water and alcohol to limit the extraction of a drug (Maddineni, 2014). We can claim that pelletization techniques are already established processes in the manufacture of multiple unit dosage forms deterrent against abuse and dose dumping in the alcoholic environment. On the other side, there is a lack of studies focusing on the preparation of polymeric microspheres, microbeads, or microcapsules with abuse-deterrent features. One study focused on the formulation of smoking deterrent microspheres containing a model prescription opioid drug, thebaine. Microspheres were made by the single emulsion solvent evaporation technique comprising polylactic acid and polycaprolactone (Vasiukhina, 2022).

METHODS

Materials

The main excipient used in this work was sodium alginate, which is a polysaccharide formed by α -l-glucuronic acid (G) and β -d-mannuronic acid (M) linked by 1–4 glycosidic bonds.

It is a biodegradable polymer obtained from brown algae. It is “Generally Recognized as Safe” (GRAS) by the US Food and Drug Administration (FDA), and the European Commission has authorized it as a food additive (Niño-Vásquez, 2022). Sodium alginate was purchased from Sigma Aldrich (Darmstadt, Germany).

Artificial intestinal fluid was prepared by dissolving 6.8 g of monobasic potassium phosphate in 250 ml of water. Subsequently, 77 ml of 0.2 N sodium hydroxide and 500 ml of water were added. The resulting solution was adjusted with 0.2 N sodium hydroxide or 0.2 N hydrochloric acid to a pH of 6.8 ± 0.1 and finally diluted to 1000 ml. Artificial gastric fluid was prepared by dissolving 2.0 g of sodium chloride in 7.0 ml of hydrochloric acid and water up to 1000 ml. The final test solution had a pH value 1.2 ± 0.1 . Monobasic potassium phosphate, sodium hydroxide, hydrochloric acid, sodium chloride, calcium chloride, and ethanol 96% were all purchased from Centralchem (Bratislava, Slovakia).

Preparation of microcapsules

One hundred and fifty milliliters of aqueous sodium alginate solution (1.6% w/w) was prepared at laboratory temperature, followed by dispersing 0.1 g of caffeine in this solution. The prepared caffeine-containing alginate solution was extruded through a 21G needle (needle diameter 0.8 mm) into 300 ml calcium chloride solution (2% w/w), which was continuously stirred with a magnetic stirrer. After the extrusion was completed, the microcapsules were stirred for 20 more minutes. Finally, the excess liquid was decanted and the microcapsules were washed twice with distilled water. They were dried at 60°C for 6 h or freeze-dried at -50°C and 0.097 mbar.

Evaluation of microcapsules

The morphology of the microcapsules was characterized by scanning electron microscopy at a magnification of 77 $\times$ and 100 $\times$. The microcapsule samples were fixed on a metal holder using double-sided carbon tape. The fixed samples were subsequently coated with an approximately 6-nm-thick layer of gold in an ion sputter coater MCM-100P (SEC Co., Ltd, Suwon-si, South Korea). Microscopic images of the samples were taken using a scanning electron microscope SNE-4500M Plus (SEC Co., Ltd, Suwon-si, South Korea) under a high vacuum using secondary electron detection mode with an accelerating voltage of 15 kV.

The swelling test was performed with dried Ca²⁺-alginate microcapsules in artificial gastric (pH 1.2) and intestinal juice (pH 6.8). We also used a mixture of artificial gastric fluid (pH 1.2) with ethanol 40% (w/w) (pH 1.2 + EtOH) to simulate coingestion of alcohol with prescription drugs. Accurately weighed microcapsule samples were immersed in 50 ml of each medium. Samples were taken after 24 h; excess liquid was dried using filter paper and samples were weighed

accurately again. The weight change of the microcapsules was calculated according to the formula

$$\% \text{ weight change} = (W_s - W_i) / W_i \times 100$$

where W_s is the weight of the microcapsules in the swollen state and W_i is the initial weight of the microcapsules (Pasparakis & Bouropoulos, 2006).

Manipulation by milling was tested by a household coffee grinder for 5 min. Manipulation by grinding was performed manually in a mortar with the pestle.

RESULTS

In the acidic environment, the hot air-dried Ca^{2+} -alginate microcapsules were able to absorb 269% of water and, while the freeze-dried Ca^{2+} -alginate microcapsules absorbed 550% of their initial weight in the acidic environment. In the alkaline intestinal fluid, these values were much higher; hot-air dried Ca^{2+} -alginate microcapsules absorbed 9982% and freeze-dried Ca^{2+} -alginate microcapsules absorbed 9908% of water. The addition of ethanol did not influence the swelling behavior of alginate microcapsules in the gastric fluid; hot air-dried Ca^{2+} -alginate microcapsules absorbed 131% of water and freeze-dried Ca^{2+} -alginate microcapsules absorbed 305% of water. So, basically, it had an opposite effect. The swelling was even slightly suppressed in comparison to the gastric fluid alone.

All formulations were tamper resistant and had high compression strength; grinding the microcapsules into powder was impossible.

DISCUSSION

There are many reasons which led us to the formulation of a multiple unit abuse-deterrent dosage form based on sodium alginate. First of all, abuse-deterrent dosage forms are often formulated as monolithic tablets and with excipients that can swell when exposed to water, making the tablet sticky and difficult to swallow. More authors are pointing out this problem, and the formulation of microforms seems to be a convenient solution (Gudin, 2016). The development of abuse-deterrent dosage forms is focused on the use of polymeric excipients, which act as a barrier in the formulation and increase their resistance to crushing, chewing, and drug extraction (Vasiukhina, 2022). Several polymers (e.g., natural – cornstarch, semisynthetic – HPMC, synthetic – polyethylene oxide, Carbopol) are already established as excipients in abuse-deterrent, tamper-resistant, or alcohol-resistant dosage forms. To our knowledge, sodium alginate has not yet been studied for this purpose.

Alginate microcapsules were prepared by Ca^{2+} -induced gelation, which is a highly reproducible method, with high encapsulation efficiency ($\pm 90\%$), resulting in microcapsules of uniform morphology. One batch of prepared microcapsules

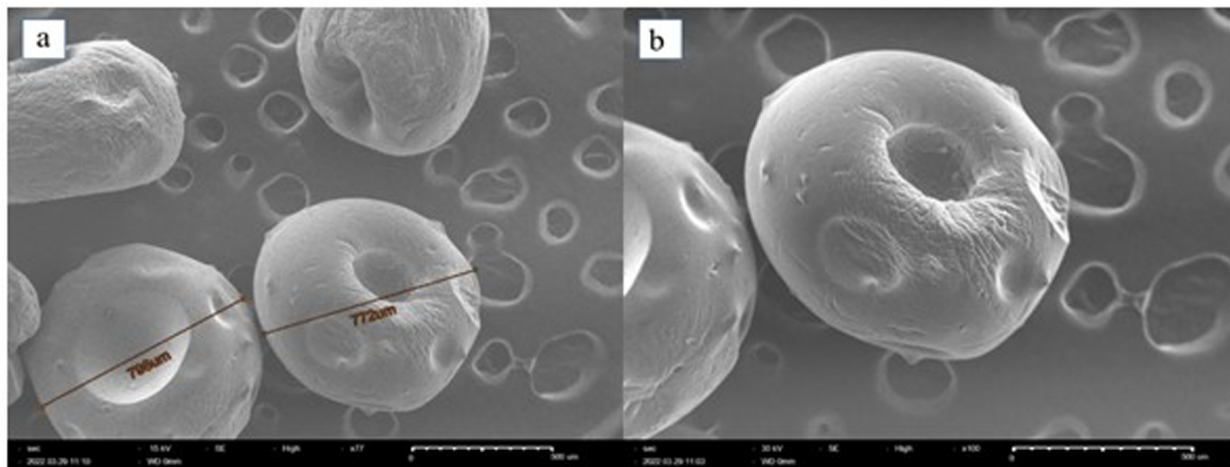


Figure 1. Hot dried Ca^{2+} -alginate microcapsules at 77 $\times$ and 100 $\times$ magnification.

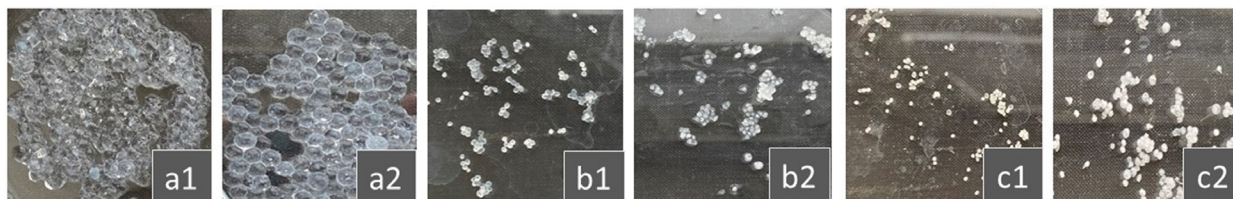


Figure 2. Ca^{2+} -alginate microcapsules taken after 24 h in artificial intestinal fluid pH 6.8 (a1 – hot dried, a2 – freeze-dried), artificial gastric fluid pH 1.2 (b1 – hot dried, b2 – freeze-dried), and artificial gastric fluid with ethanol 40% (w/w) (c1 – hot dried, c2 – freeze-dried)

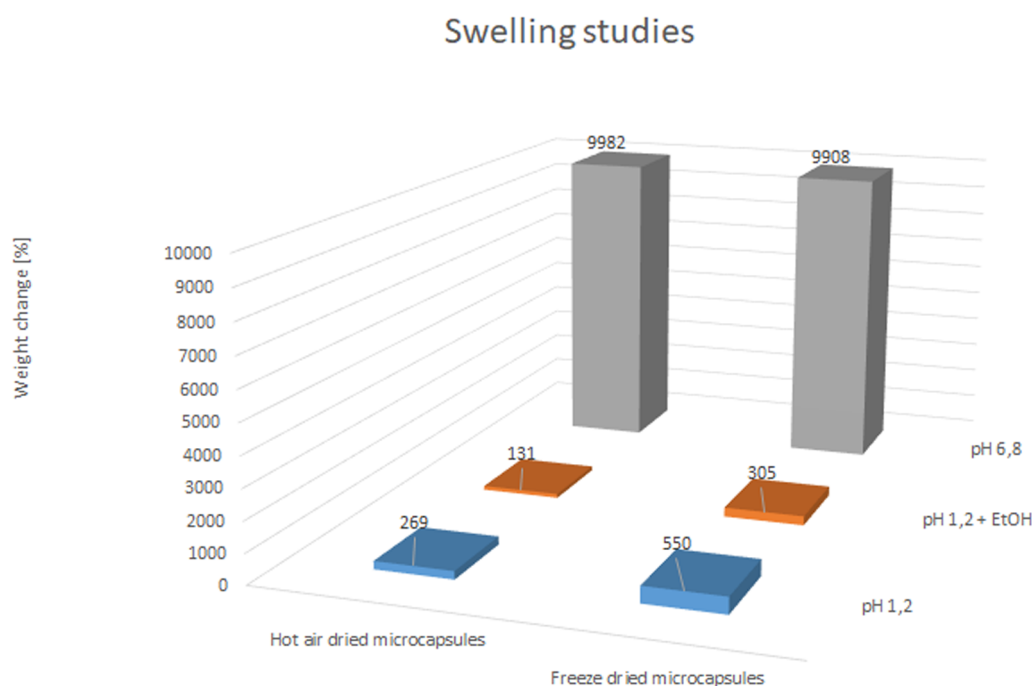


Figure 3. The swelling ability of Ca^{2+} -alginate microcapsules in artificial gastric fluid (pH 1.2), artificial gastric fluid with 40% (w/w) ethanol (pH 1.2 + EtOH), and artificial intestinal fluid (pH 6.8).

was dried by hot air and another batch was freeze-dried. Ca^{2+} -alginate microcapsules dried by hot air were microscopically observed. They had lost their ideally spherical shape to some extent. Fine wrinkling and a few cracks caused by dehydration of the polymer structure could be observed (Figure 1). Therefore, some authors (Pasparakis, 2006) prefer to dry microcapsules with ethanol. The mentioned process provides the microcapsules with an ideally spherical shape without cracks and wrinkles. Nevertheless, the prepared microcapsules retained a high degree of sphericity, and their size varied in the range of 750–800 μm .

A swelling test was performed since the release of the drug from alginate microcapsules depends on the degree of penetration of the dissolution liquid into the microcapsule and the alginate matrix's swelling rate. At the same time, the drug is dissolved by a dissolution liquid and can diffuse outward through the swollen matrix (Aldawsari, 2021). Ca^{2+} -alginate microcapsules exhibit a remarkable sensitivity to external pH stimuli. It is caused by the presence of carboxylic groups in the alginate structure. For a pH below its pK_a (pH < 3.4), the carboxylic acid groups are in the nonionized form, leading to an insoluble structure. At pH > 4.4, the carboxylic group became ionized, resulting in an increase of electrostatic repulsion of these negative charges, causing polymer chain expansion and swelling of the hydrophilic matrix, being highest around pH 7.4 (Agüero, 2017). The ability of alginate capsules to swell is shown in Figures 2 and 3. It was observed whether the method of drying (hot air drying/

freeze-drying) would affect the rate of swelling, but we were mainly interested to see if alcohol coingestion would modify the ability to swell. The drying process did not influence the swelling properties in the alkaline environment, but we could observe a small impact in an acidic environment. Hot dried microcapsules absorbed less water, thus they are a more reliable option for gastro-resistant dosage forms. The addition of ethanol 40% (w/w) to the gastric fluid slightly suppressed the swelling ability. So, we can conclude that Ca^{2+} -alginate microcapsules might be an option in the formulation process of alcohol-resistant dosage forms.

The extent to which a solid oral drug product can be physically manipulated is a function of several factors including tampering skills, time, and tampering resources available (U. S. Department of Health and Human Services, 2017). Despite existing approaches to make effective abuse-deterrent formulations, tampering with drugs can never be eliminated entirely. Rather, formulators should focus on reducing the abuse potential by making tampering difficult and time-consuming (Jedinger et al., 2016). We have proved that Ca^{2+} -alginate microcapsule powdering is practically impossible, they dispose of a superior hardness. We have proved that Ca^{2+} -alginate microcapsule powdering is practically impossible, their hardness was excellent. Drug extraction is possible, but time-consuming because microcapsules have to swell in the suitable liquid for hours, while the drug slowly diffuses through the matrix.

CONCLUSION

The formulation of alginate microcapsules by the ionotropic gelation process is a potential way to produce resistant dosage forms. Ca^{2+} -alginate microcapsules can be defined as being resistant to alcohol, thus preventing dose dumping in the case of alcohol coingestion with a drug. Also, they are tamper resistant to a certain extent. Alginate microforms are suitable for drugs that are absorbed mainly in the small intestine because they exhibit gastro-resistant characteristics. Our future studies will be focused on dissolution studies of Ca^{2+} -alginate microcapsules containing particular drugs susceptible to abuse.

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