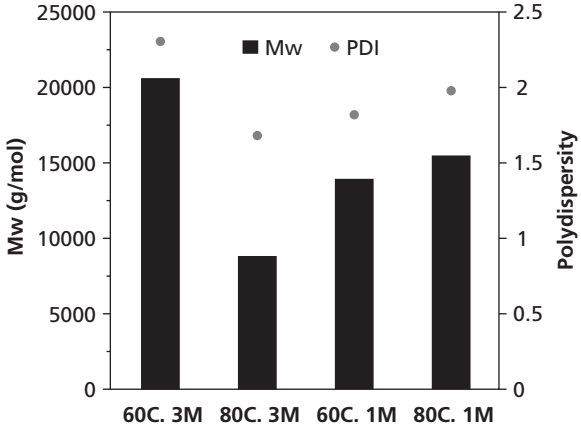

Figure 1 Synthesis of ISA23 by microwave-assisted polymerization. Molecular weight (Mw) and polydispersity (PD) of the reaction mixtures were determined at 30 min.

Conclusion

Gene delivery has been the preferred method to deliver proteins into cells. Although some successes have been achieved, no treatment has been approved by the Federal Drug Administration (FDA) yet. In past years, novel strategies to deliver proteins into cells have emerged and poly(amidoamine)s have been successfully used. Synthesis of a platform of novel poly(amidoamine)s using microwave-assisted polymerization will expand the tools to deliver functionally active proteins into cells. This could lead to the development of novel therapeutics with intracellular target and could also help scientists to investigate protein function.

New Scientists Session

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Assessing drug release and dissolution in the stomach by means of Dynamic Gastric Model: a biorelevant approach

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Introduction and Objectives

Drug dissolution within the gastrointestinal tract is a critical step in achieving optimum drug bioavailability. For Biopharmaceutics Classification System class II and IV drugs, great variability in solubility/bioavailability can be observed in fasted/fed states. Solubility within the gastrointestinal fluids can be measured in human gastric aspirates in the fasted and fed states, using physiological media such as fasted-state simulating gastric fluid or recreating digestion 'snapshots'.[1] In this study, we used a new in-vitro system, the Dynamic Gastric Model (DGM) (Institute of Food Research, Norwich, UK), to assess the release of nifedipine from two different controlled release tablets.

Method

DGM was primed with 20 ml acid and salt solution to simulate the residual gastric juice in fasted conditions; one 60 mg nifedipine tablet was coadministered with 150 ml of water ($n = 4$). Physiological acid and enzymatic gastric secretions were added following variations in pH and calorific content as *in vivo*. Dissolved nifedipine and added internal standard (nimodipine) *in digesta* leaving the DGM was extracted into n-pentane : ethyl acetate (70 : 30 v/v) and quantified using reverse-phase high-performance liquid chromatography (Kromasil C-18 (4.6×250 mm) column, mobile-phase methanol : water 80 : 20 v/v and detection at 350 nm).

Results

The drug release from two commercially available tablets (a push-and-pull osmotic pump, Adalat LA from Bayer, and an erodible matrix, Coral from So.Se.PHARM), was measured using the DGM, which is able to reproduce the hydrodynamics and gastric secretions of the human stomach. During fasted digestion, the release of nifedipine from the two formulations was different. The drug started to appear within the gastric fluids after 11 min from Adalat LA, 0.003 μg/ml (SE $\pm$ 0.003), while the release was immediate (at 3 min) from Coral, 0.259 μg/ml (SE $\pm$ 0.156). At the end of digestion (13 min), the nifedipine release was 0.056 μg/ml (SE $\pm$ 0.044) and 3.77 μg/ml (SE $\pm$ 1.83) from Adalat LA and Coral, respectively. These results are consistent with in-vivo data[2] from which a lag time of 1 h was found in the fasted state for Adalat LA but not for Coral tablets.

Conclusion

The release of poorly water-soluble drug nifedipine in the fasted stomach mimicked by the DGM was found to be dependent on the type of formulation tested, and the results were consistent with in-vivo data. The study, therefore, supports the hypothesis that the DGM may provide a realistic temporal and dynamic model for stomach activity.

References

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Development and evaluation of a novel floating in-situ gelling system for stomach-specific drug delivery of balcofen

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Introduction and Objectives

Baclofen has absorption window in stomach or proximal part of intestine. Often display low bioavailability. Baclofen is difficult to formulate into sustained release product because on arrival to colon, its absorption is low or nonexistent. Therefore, in present investigation afford have been made to improve absorption by preparing floating in-situ gelling system for stomach-specific delivery of baclofen.

Method

Gelling systems were prepared by dissolving various concentration of sodium alginate in deionised water, to which varying concentrations of drug and calcium bicarbonate were added. A 3^2 full factorial design was used for optimisation. The concentration of sodium alginate (X_1) and concentration of calcium bicarbonate (X_2) were selected as independent variables. Drug released at 1 h (Q_1), 10 h (Q_{10}) and viscosity of solution were selected as dependent variables. Gel was evaluated for in-vitro buoyancy and in-vitro drug release. Contour plot drawn for each dependent variables, and check point batch was prepared. Drug-release data were fitted into different kinetic models.

Results and Discussion

The floating lag time and floating time were found to be 2 min and 12 h, respectively. Decreasing trend in drug release was observed with an increase in concentration of $CaCO_3$ because gelation occur due to presence of Ca++ ions, increasing concentration of Ca++ ions leads to stronger gel formation and release of drug from these gel is decreased. The release of drug from this gel was characterised by initial phase of high release (burst effect). However, as gelation processed, the remaining drug was released at a slower rate followed by second phase of moderate release.[1] This bi-phasic pattern of release is a characteristic feature of matrix diffusion kinetics. The initial burst effect was considerably reduced with increase in polymer concentration. The computed and experimental values for Q_1 and Q_{10} for check point batch were 25 and 86%, and 27.1 and 88.34%, respectively. Similarity factor (f_2) for check point batch was 80.25. Therefore, it was concluded that the two dissolution profiles were similar. Kinetics of drug release from in-situ gel follows higuchi model, i.e. diffusion-controlled release.

Conclusion

This study has shown the feasibility of forming gel in the in-vitro condition with aqueous solutions of sodium alginate containing Ca++ ions in complexed form. Furthermore, it was observed that gel remained buoyant for 12 h and releases balcofen till 12 h.

Reference

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9
A quantum-dot based probe for the simultaneous detection of sodium and protons

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Introduction and Objectives

The aim of this study was to develop a fluorescent probe based on quantum-dot (QD) capable of simultaneously detecting both Na+ and H+ ions. Sodium is an important blood electrolyte, and fluctuations in its concentration can have deleterious effects on human health. Cancerous tissue has also been shown to have a higher sodium concentration and lower pH compared to normal tissue. Therefore, sensors that can identify situations when Na+ and H+ are present at high concentrations have obvious benefits. The QDs are fluorescent semiconductor nanocrystals with all three dimensions in the 2–10 nm range. They have impressive optical properties compared to traditional organic dyes. We have developed the first QD-based probe that only switches fluorescence "on" when sodium and protons bind at particular concentrations.

Methods

We obtained 560-nm-emitting CdSe/ZnS QDs from Evident Technologies, USA. The surface trioctylphosphine oxide (TOPO) ligands were exchanged with 2-mercaptoaniline. The sodium receptor was prepared in three steps. o-Anisidine was first dialkylated with 2-chloroethanol and then reacted with triethylene glycol ditosylate and NaH in refluxing THF to afford the N-(o-methoxyphenyl)aza-

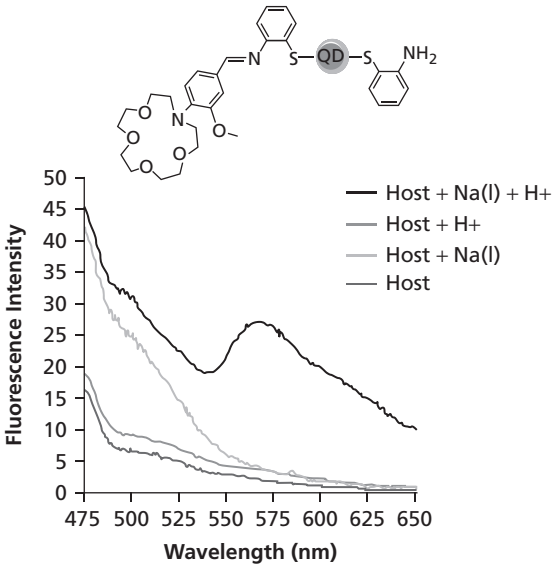

Figure 1 AND logic behaviour of probe.

15-crown-5 receptor. This was then subjected to a Vilsmeir formylation reaction and the resulting aldehyde attached to the QD through a facile Schiff base reaction. The extent of attachment was determined to be 20% by 1H NMR spectroscopy. Therefore, the QD possesses two receptors, the crown ether selective for sodium and the aniline selective for protons. Fluorescence measurements were conducted in aqueous-based samples buffered at 7.0 with HEPES buffer and recorded on a Perkin-Elmer LS55 spectrophotometer.

Results and Discussion

The QD emission of the probe (λ_{MAX} = 560 nm) was quenched in the absence of Na+ or H+ when excited at 370 nm due to photo-induced electron transfer (PET) from the receptors to the excited QD. Upon the simultaneous addition of Na+ (10-3 M) and H+ ions (10-6.2 M), QD fluorescence was recovered due to the PET process being cancelled when the receptors bind their ions (Figure 1). However the independent addition of Na+ or H + resulted in no recovery of QD fluorescence. Thus, the probe functions as a two-input AND molecular logic gate with Na+ and H+ as inputs and λ_{MAX} = 560-nm fluorescence as the output.

Conclusions

A QD-based molecular probe that enables the detection of Na+ and H+ only when both are present over a threshold value has been synthesised. Thus, the conditions of a two-input AND logic gate are satisfied. This is the first example of a QD-based AND molecular logic gate for H+ and Na+ and benefits from the improved photophysical properties QDs offer.

Short Papers in Medicinal Chemistry

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Design, synthesis and evaluation of iron chelators to identify a prospective prophylactic agent for Alzheimer's disease

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Introduction and Objectives

The contribution of metal ions, especially iron, in mediating neurotoxicity either by favouring beta-amyloid plaque formation or by redox cycling in Alzheimer's disease (AD) brain has already been established.[1] Hence, the selective chelation of beta-amyloid-associated iron is a prospective therapeutic approach for the prophylaxis of AD. Ideally, an iron chelator should be able to cross the blood–brain barrier (BBB) and exhibit neuroprotective efficacy against oxidative stress in AD brain to act prophylactically. The present work aims to identify a lead compound with such properties from a library of bidentate iron chelators.

Method

Several bidentate iron chelators (3-hydroxypyridin-4-ones) were synthesised based on the structure of deferiprone, a chelator used in the treatment of iron-overloaded thalassemia major. Structural considerations to assist BBB permeability were observed in designing these chelators. In-situ brain perfusion was carried out on guinea pigs using these chelators and deferiprone. High-performance liquid chromatography of extracts from guinea pig brains was used to quantify the BBB influx efficiency of each chelator. Chelators with a higher BBB influx efficiency than that of deferiprone have been selected for neuronal cell culture studies in order to evaluate their neuroprotective efficacy against various oxidative insults.

Results and Discussion

Total synthesis of ten 3-hydroxypyridin-4-ones was carried out; their molecular weights varied from 157 to 207, and their log $D_{7.4}$ values fell in the range of −1 to 1. All animal experiments were performed in accordance with the Animals (Scientific Procedures) Act 1986. A steady state of in-situ brain perfusion was determined at a flow rate of 6 ml/min of brain perfusate for 15–20 min with an 800 μM chelator concentration. The BBB influx efficiency of the chelators was calculated using a conventional calculation protocol.[2,3] Deferiprone measured 0.04 on the BBB influx efficiency index, indicating a moderate BBB influx efficiency. Four out of the ten 3-hydroxypyridin-4-ones fared better than deferiprone on the BBB influx index. Some chelators failed to cross the BBB. The molecular weight, lipophilicity,