Oral delivery of unstable bioactive components sourced from food: formulation and assessment

In association with

Oral delivery is the preferred route for bioactive components sourced from food. Researchers at University College Dublin are working on formulating bioactive components, which are currently unstable and poorly absorbed to unlock their desired physiological effects

Dr Sinéad Ryan

Sinéad Ryan is an assistant professor of Bioscience in the School of Veterinary Medicine in UCD. Her research area is multidisciplinary, involving the design and assessment of formulations for peptide and food derived peptide (nutraceutical) oral delivery.

Bioactive components are natural food-derived non-essential nutrients with the potential for exerting health-protective or disease-preventive properties beyond their nutritive value. There are numerous food-derived bioactive compounds, many of them understudied, that work differently, presenting a wide range of biological properties, namely: antioxidants, anti-inflammatories, anti-microbials, anti-hypertensive activities and DNA-protective compounds and so on. Oral delivery is the preferred route for bioactive delivery due to high levels of patient acceptance, long-term compliance and ease of administration. However, in order for the bioactive component to elicit the desired physiological effects via the oral route, a number of challenges for oral administration must be overcome. These include insufficient gastric residence time, low permeability and/or solubility within the gut, instability under food processing conditions (temperature, oxygen, light) or in the gastrointestinal tract (pH, enzymes, presence of other nutrients), all of which may limit the activity and potential health benefits of bioactive molecules. To address these challenges, it is necessary to construct an appropriate formulation that will protect and maintain the active ingredient in the relevant location for it to deliver its physiological/therapeutic effect within the required time frame.

CHALLENGES

Our research group works on formulating unstable and poorly absorbed bioactive components sourced from food. One of the methods we use to enhance their delivery is nanotechnology. Currently, we are working on a set of interesting bioactives, which are selenium-based. Selenium is an essential micronutrient in both human and animal nutrition that exists in a wide array of different forms, both organic and inorganic. Selenomethionine, the selenium analogue of methionine, is the predominant form of organic selenium. It is present in foods from both the *Brassica* and *Allium* families. It has reported health benefits of cancer prevention, increased fertility and improved immunological status. However, it is readily oxidised and, even though it is less toxic than inorganic selenium, it still has a low therapeutic index. Oral delivery formulations of selenomethionine, therefore, need to consider the balance between doses that exert beneficial effects and those which may potentially be toxic.

PROCESS

To address this, selenomethionine was encapsulated into nanoparticles consisting of chitosan and zein.[1] Chitosan (a derivative of chitin isolated from mushroom) and zein (prolamine-rich protein derived from maize) are both biocompatible and biodegradable materials found in food, which are also generally regarded as safe (GRAS). By using GRAS-approved materials, the nanoparticle formulation has the potential to be approved by regulatory bodies faster than alternative compounds. We used the ionotropic gelation method to produce the nanoparticles. Ionotropic gelation involves using the cationic polyelectrolyte chitosan crosslinked with the polyanion tripolyphosphate as depicted in Figure 1. The formulation was optimised using a three-factor Box-Behnken experimental design methodology. This is a Response Surface Methodology designed for process optimisation with minimal experimental requirement. It is a more efficient approach to formulation experimentation than one factor at a time experiments. The chitosan:tripolyphosphate ratio, chitosan solvent pH, and drug-load concentration were independently varied. The dependent variables studied were encapsulation efficiency, particle size, polydispersity index and zeta potential. The optimum nanoparticles for oral delivery of selenomethionine were 187±58nm in size, polydispersity index 0.24±0.01 and zeta potential 36±6mV. However, it resulted in a low encapsulation efficiency of 39±3%. We managed to greatly increase this to 80±1.5% by varying the pH of the

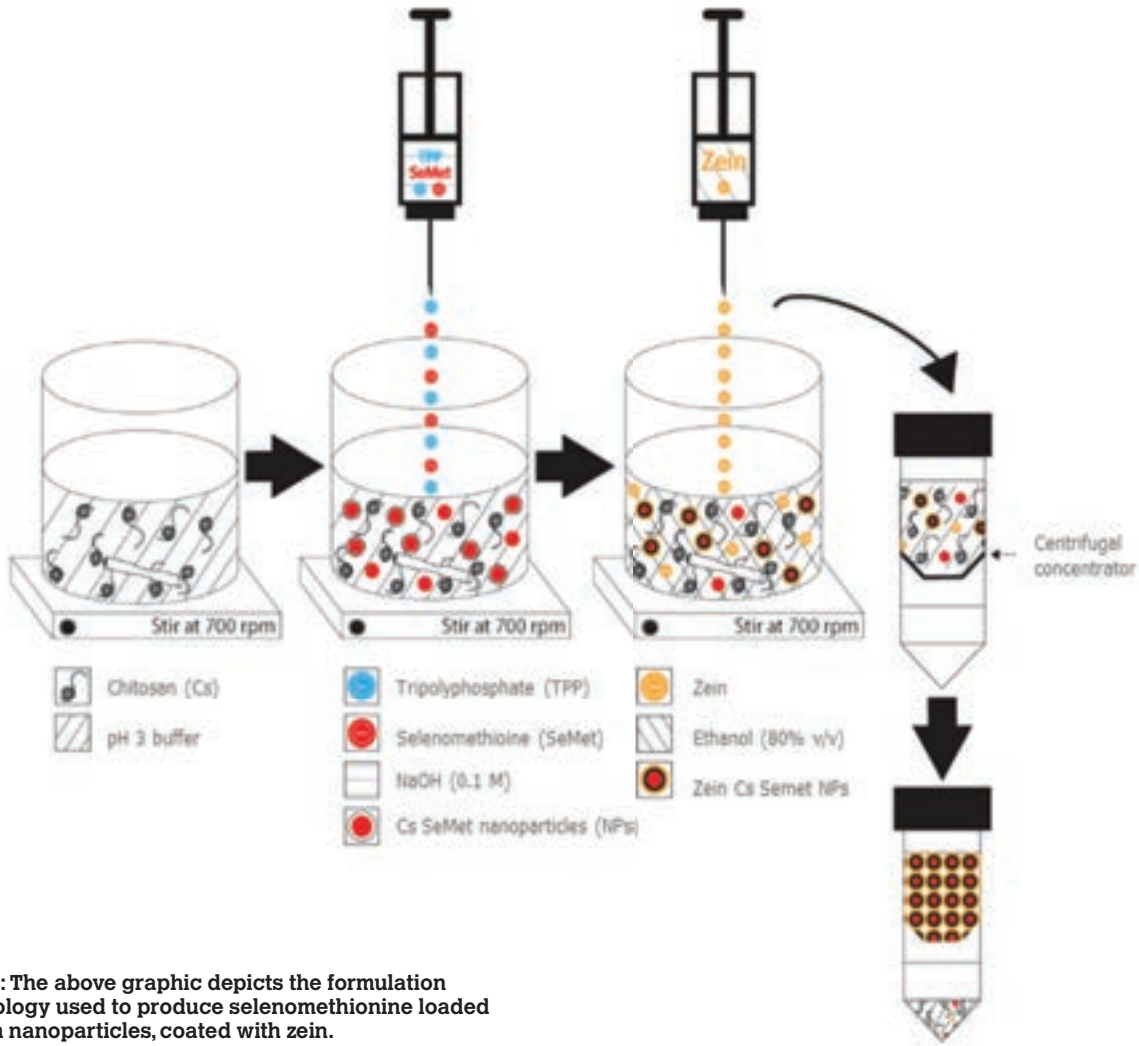

Figure 1: The above graphic depicts the formulation methodology used to produce selenomethionine loaded chitosan nanoparticles, coated with zein.

ionotropic solution components and, importantly, coating the nanoparticles with zein. This increased the nanoparticle diameter to 377±47nm, which is still within range for oral delivery, while retaining polydispersity index and zeta potential values.

ANALYSIS

Assessment analysis of the selenomethionine-entrapped nanoparticles showed they were not cytotoxic in relevant cell lines. Accelerated thermal stability studies indicated good stability of the nanoparticles under normal storage conditions (23°C). In simulated gastrointestinal and intestinal fluid conditions, 60% cumulative release of selenomethionine was obtained over six hours. We assessed its transport across isolated rat jejunum and colonic mucosae using an adapted Ussing chamber model and found that selenomethionine loaded into a nanoparticle formulation can deliver increased amounts across the intestinal barrier compared to its native form. In-vivo studies using intra-jejunal injection of selenomethionine in native and nanoparticle forms found similar indications as Ussing chamber results, with increased plasma selenomethionine levels detected in the selenomethionine-nanoparticle test group compared to native selenomethionine treatment. We also encapsulated other bioactive peptides with an anti-hypertensive effect, using the same formulations that have shown promising results.[2]

REFERENCES

1. Vozza G, Danish M, Byrne HJ, Frías JM, Ryan SM. Application of Box-Behnken experimental design for the formulation and optimisation of selenomethionine-loaded chitosan nanoparticles coated with zein for oral delivery. Int J Pharm. 2018 Nov 15;551(1-2):257-269. doi: 10.1016/j.ijpharm.2018.08.050. Epub 2018 Aug 25
2. Danish MK, Vozza G, Byrne HJ, Frias JM, Ryan SM. Formulation, Characterization and Stability Assessment of a Food-Derived Tripeptide, Leucine-Lysine-Proline Loaded Chitosan Nanoparticles. J Food Sci. 2017 Sep;82(9):2094-2104. doi: 10.1111/1750-3841.13824. Epub 2017 Aug 10

This research was funded by the Department of Agriculture, Food and the Marine.