Development and characterisation of polymeric nanocapsules containing macromolecules

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Oral drug delivery systems are the most common route of administration. However, development oral delivery system containing macromolecules is still challenging due to different hurdles, including, digestive enzymes degradation and physiochemical properties of the molecules. Currently, several techniques have been applied to deliver the macromolecules orally e.g. polymer conjugates, excipients such as cyclodextrin, and entrapment inside carriers, such as liposomes, and nanocapsule systems. Accordingly, the aim of this study is to overcome these challenges by encapsulating macromolecule inside polymeric nanocapsules, trypsin as a protein was used as a model macromolecule.

The polymeric nanocapsules were prepared by double emulsion method s/o/w or w/o/w based on the quality by design (QbD) concepts. Critical quality attributes (CQA), were determined in order to achieve the quality target product profile (QTPP). The formulations were developed by using Poly(DL-lactide-co-caprolactone) copolymers in two different ratios (86:14, and 40:60) for lactide and Ɛ-caprolactone blocks, respectively. Trehalose was encapsulated with some formulations. Table1 shows the full experimental design consisting of eight formulations. Nanocapsules morphology and particle size were investigated by Transmission Electron Microscope, and Dynamic Light Scattering, respectively. The entrapment efficiency of nanocapsules, the effect of the polymer and preparation procedures on trypsin activity and the release profile in simulated gastric fluid SGF and simulated intestinal fluid SIF were assessed.

Table1: Design of experiment combining different factors at different levels to prepare eight different formulations containing trypin.

Formulation	Ɛ- Caprolactone ratio	Core physical state	Trehalose mM
F1	**14%**	**Liquid**	**0**
F2	**60%**	**Liquid**	**0**
F3	**14%**	**Solid**	**0**
F4	**60%**	**Solid**	**0**
F5	**14%**	**Liquid**	**10**
F6	**60%**	**Liquid**	**10**
F7	**14%**	**Solid**	**10**
F8	**60%**	**Solid**	**10**

Applying QbD saved the resources, and provided huge useful results within short time. Nanocapsules were spherical with no distortion, Figure 1. The encapsulation efficiency has reached up to 80.7%, and it has been affected significantly (P 0.005) by the copolymer blocks ratio. Moreover, the drug release profile in SIF over 24 hours was affected by the copolymer ratios, with released drug up to 64.01% in a triphasic pattern concluded in the following three steps; the first burst phase with 8% release within 15 minutes, then a plateau for 8 – 10 hours, finally trypsin started to release in a sustained rate over the rest of 24 hours, whilst the release in SGF reached 8% in average; which can protect the macromolecules from the gastric enzymes degradation. Trypsin biological activity was affected by the materials and the process parameters and retained only 18% of the original activity. However, adding trehalose and encapsulation of solid protein helped the protein to retain up to 84.65% of the original activity.

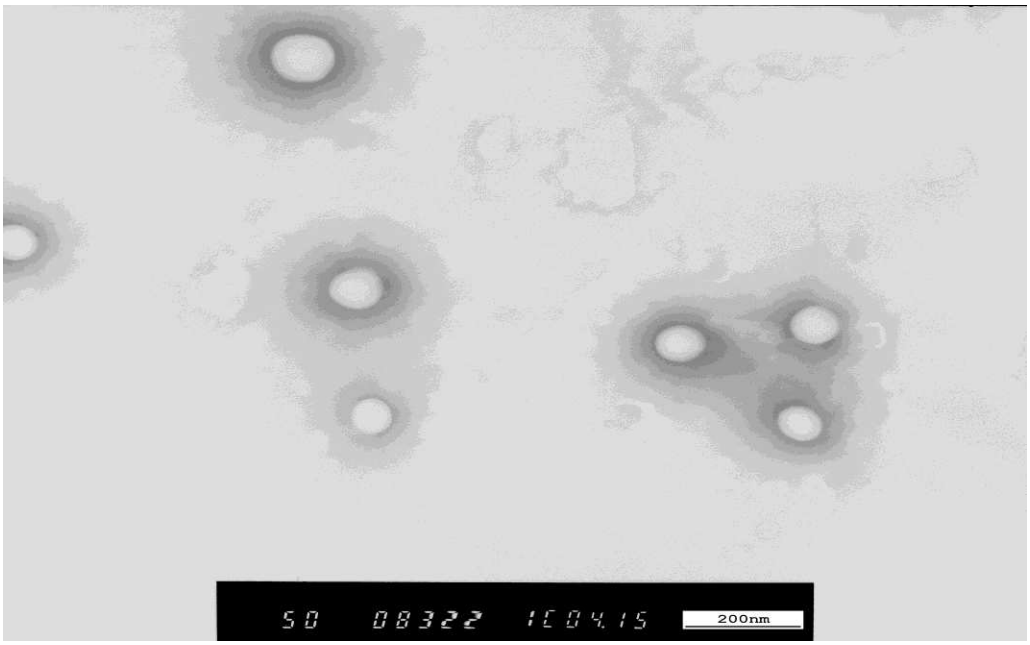

Figure 1: TEM image of one of nanocapsules formulations.

In conclusion, polymeric nanocapsules showed promising results to potentially deliver active protein orally in the presence of trehalose especially when it was prepared by s/o/w, and when the copolymer blocks ratio was optimised. The applied rationale could be applicable to further macromolecules including monoclonal antibodies, genes, and cells, in order to obtain close quality attributes.