UNIVERSITI TEKNOLOGI MARA

SUSTAINING DRUG RELEASE OF CHITOSAN SPHEROIDS PRODUCED BY AN EXTRUSION-SPHERONIZATION TECHNIQUE

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ABSTRACT

The sustained-release chitosan-alginate spheroids have lately been designed by means of melt pelletization technique. The melt pelletization operates via heating and melting a binder to agglomerate chitosan and alginate into spheroids. Different from melt pelletization, the extrusion-spheronization processes are operated at room temperature and are envisaged to bring about a lower level of material degradation. The study examined the formulation and drug release aspects of chitosan spheroids as a function of crosslinking and coacervation reactions between chitosan, tripolyphosphate and alginate. It identifies useful polymer reaction mode and evaluates its applicability in sustained-release chitosan spheroid formulation. Microwave was employed as drying tool to solidify the formed crosslinkages at a rapid rate prior to their dissociation. Seven types of spheroids were prepared using the extrusion-spheronization technique. Sodium tripolyphosphate was used as a crosslinker and chlorphenamine maleate as a model drug. Chitosan spheroids demonstrated a fast drug dissolution profile with more than 60 % drug released within 2 h of dissolution. Crosslinking of chitosan in matrix by tripolyphosphate ions was accompanied by channeling effect in matrix thus promoting fast drug release. Spheroids produced using deionized water as granulating liquid had better drug release retardation property than those produced using solutions of acetic acid and citric acid. Use of organic acid did not promote drug release retardation through enhancing chitosan-tripolyphosphate crosslinkage in acid milieu. The treatment of tripolyphosphate crosslinked-chitosan spheroids by microwave only reduced the extent of drug release by a small extent. The tripolyphosphate-crosslinked chitosan spheroids exhibited a higher extent of drug release than the untreated spheroids following matrix acidification and microwave drying of spheroids as a result of pore formation. The chitosan spheroids were characterized by fast drug release when both sodium tripolyphosphate and sodium alginate were embedded in the same matrix. Formulation of chitosan with alginate per se decreased the disintegration capacity of chitosan spheroids thereby lowering their drug release at the initial phase of dissolution. Different from alginate spheroids which underwent matrix erosion to a large extent, the availability of chitosan and alginate in the same matrix retained the microstructure of spheroids. Both chitosan and alginate were coacervated into patches of membrane covering the surfaces and inner core of spheroids during the process of dissolution.

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CHAPTER ONE
INTRODUCTION

1.1 OVERVIEW

1.1.1 Chitosan

Chitosan is a polysaccharide derived from deacetylation of chitin, a by-product of the seafood industry. It is natural biopolymer that can be found from the waste of crustacean shell and fungi [1- 4]. Chitosan receives much attention because of its extraordinary properties and for its inexpensive abundant resources [1]. It is a copolymer of glucosamine and N-acetyl glucosamine linked by β 1-4 glucosidic bonds obtained by N-deacetylation of chitin. It has a unique cationic feature that can interact with anionic moiety of drug or excipients. This interaction between anionic and cationic components is deemed useful in drug release modulation. Chitosan is useful in a wide range of biomedical and industrial applications due to its biocompatibility, biodegradability, non-toxic property and ability to interact with different hydrophilic or hydrophobic substances. The interest in chitosan and its derivatives as excipients in drug delivery has increased in recent years. Chitosan is commonly processed into drug delivery system by means of emulsion crosslinking, coacervation/ precipitation, spray drying, emulsion droplet coalescence and ionic gelation methods [6-8].

Over the past years, the drug release property of chitosan based dosage form has been modulated through the use of crosslinking agents such as tripolyphosphate, pyrophosphate or glutaraldehyde [9]. Alternatively, it is modified via coacervating the chitosan with oppositely charged polymers namely pectin, alginate, carboxymethycellulose and xanthan [10]. Microwave is used to induce crosslinkage or coacervate in chitosan based matrix with the aim to sustain drug release [11-18].

Spheroids are a multiparticulate system that receives an increasing application in oral drug delivery due to less risks of dose dumping, reduced plasma drug concentration fluctuation and increased flexibility in dosage management [2,18]. Formulation of spheroids has thus far not accompanied with a significant success in sustaining drug release [19-20]. The chitosan itself appears to possess a disintegrant