Journal of Pharmaceutical Sciences xxx (2017) 1-13

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Development and Characterization of Chitosan Cross-Linked With Tripolyphosphate as a Sustained Release Agent in Tablets, Part I: Design of Experiments and Optimization

Colin A. Pinto [1], Kalyan K. Saripella [2], Nikhil C. Loka [3], Steven H. Neau [1,*]

[1] The Philadelphia College of Pharmacy, University of the Sciences, Philadelphia, Pennsylvania 19104
[2] Formulation R&D, Douglas Pharma US Inc., Warminster, Pennsylvania 18974
[3] Product Development, Ascent Pharmaceuticals, Central Islip, New York 11722

ARTICLE INFO

Article history:
Received 13 July 2017
Revised 4 November 2017
Accepted 7 November 2017

Keywords:
chitosan
factorial design
tablet
dissolution
complexation
controlled release
oral drug delivery
particle size

ABSTRACT

Certain issues with the use of particles of chitosan (Ch) cross-linked with tripolyphosphate (TPP) in sustained release formulations include inefficient drug loading, burst drug release, and incomplete drug release. Acetaminophen was added to Ch:TPP particles to test for advantages of drug addition extragranularly over drug addition made during cross-linking. The influences of Ch concentration, Ch:TPP ratio, temperature, ionic strength, and pH were assessed. Design of experiments allowed identification of factors and 2-factor interactions that have significant effects on average particle size and size distribution, yield, zeta potential, and true density of the particles, as well as drug release from the directly compressed tablets. Statistical model equations directed production of a control batch that minimized span, maximized yield, and targeted a t_{50} of 90 min (sample A); sample B that differed by targeting a t_{50} of 240-300 min to provide sustained release; and sample C that differed from sample B by maximizing span. Sample B maximized yield and provided its targeted t_{50} and the smallest average particle size, with the higher zeta potential and the lower span of samples B and C. Extragranular addition of a drug to Ch:TPP particles achieved 100% drug loading, eliminated a burst drug release, and can accomplish complete drug release.

Introduction

The trend in the pharmaceutical industry is to generate sustained release formulations for those drugs requiring multiple daily dosing to improve patient compliance and avoid the peaks and troughs in the drug plasma concentration often observed with frequent dosing of immediate-release formulations.[1] Particularly in the area of over-the-counter drugs that represent the majority of pharmaceutical tablets consumed in the United States, typical dosing is required every 4-6 h, which is easily forgotten over the course of a busy day. Furthermore, terminally ill patients may require drug plasma levels maintained within the therapeutic window to avoid severe pain or side effects that would prohibit them from sleeping through the night in the absence of a sustained release form.[2]

Chitosan (Ch) has long been considered appropriate for use in pharmaceutical dosage forms due to its documented safety and low toxicity[3,4] as well as the abundance of the polymer from which it is derived, chitin, the second most common polysaccharide on earth,[5] second only to cellulose. Ch has been included in dosage forms suitable for oral, injectable, nasal, ophthalmic, and transdermal delivery.[6,7] Specific to oral solid dosage forms, claims have been made that, depending on its concentration in the formulation, Ch can act as a binder, lubricant, or even disintegrant.[8]

Multiple examples in the literature demonstrate the ability to generate drug-loaded Ch-tripolyphosphate (Ch-TPP) ionically cross-linked particles and films with various sustained release profiles.[9-18] Ionic gelation, the process most commonly used to cross-link Ch-TPP, is a technique based on the ability of polyelectrolytes to cross-link (i.e., form a complex) in the presence of counter ions, resulting in the formation of a hydrogel.[19] "Maximum cross-linking" for 1 of the 2 components occurs when that component is maximally involved in cross-linking. For Ch-TPP particles, this is significantly influenced by the charge state of the

* *Correspondence to:* Steven H. Neau (Telephone: 1-215-596-8825; Fax: 1-215-895-1161).
E-mail address: stevenneau@yahoo.com (S.H. Neau).

https://doi.org/10.1016/j.xphs.2017.11.018
0022-3549/

polyion (TPP) as well as the extent of protonation of Ch free amines, both of the sites where the cross-linking will occur. The locations of these interactions, probability, and associated energies are well described by Koukaras et al.[20] These charges can be influenced by both processing and formulation variables such as pH, ionic strength, and Ch:TPP, among many others. The extent of interaction and characteristics of the final Ch-TPP complex can be assessed by measuring outputs such as yield, zeta potential, and particle size.

As it relates to previous Ch-TPP studies, high and precise drug entrapment efficiencies are difficult to obtain,[21-24] incomplete drug release is typically observed,[10,12,22,23,25-30] and these formulations are not ideal for patient administration. However, if the integrity of the product and mechanism of sustained release found in these Ch-TPP particles and films can be maintained after its incorporation into a tablet dosage form, the product would represent a means to achieve reproducible production and performance.

Contributing to incomplete drug release is the incorporation of drug into the Ch-TPP particles during cross-linking[16,24,31,32] while high Ch concentrations, a high molecular weight of Ch, and a low Ch-TPP ratio have shown to each contribute to a slower release rate and the potential for incomplete release.[26] Relatively low drug entrapment efficiency is reported[16,24,33] with some improvement with an increase in the Ch-TPP ratio to provide free amine groups for hydrogen bonding, ion-dipole, or ionic interactions with the drug molecules.[27,34] Perhaps more importantly, a burst release of drugs is observed in simulated intestinal fluid[32,35-37] even when a protein is incorporated.[22] With acetaminophen as the active, 43-66% of the drug was released in 30 min.[10] This is expected due to the drug found at the surface of the Ch-TPP particles as a result of the manufacturing method and the tremendous surface area due to the small particle size.[32]

The present studies investigate the preparation of Ch-TPP ionically cross-linked nanoparticles for use as a matrix-forming excipient to impart sustained release properties to tablets. Instead of incorporating the drug during cross-linking, the drug is added to the nanoparticles just before compression of the tablets. Using this approach, there is 100% loading of the drug in the Ch-TPP matrix. Complete drug release is expected because the drug should not be found entrapped in the nanoparticles. It is extragranular addition of the drug and not the polymer. It is unusual if the granules for tablet compression do not include a drug.

High shear wet granulation has become the processing choice for high drug load granule formulations; yet loads in excess of 70% w/w of drugs with low solubility, poor wettability, and small size often result in poor granule properties.[38,39] Polymer addition to granules that include a drug before tablet compression is not uncommon, however. For example, Missaghi et al.[40] considered the effect of intragranular versus extragranular addition of hydroxypropyl methylcellulose and Starch 1500. An increase in tablet hardness but no change in drug release was observed with the extragranular addition of hydroxypropyl methylcellulose and Starch 1500. Durrani et al.[41] reported the novel extragranular addition of Carbopol to drug-containing particles produced by a wet granulation method because wetting of Carbopol results in a sticky material into which it is difficult to mix other components of the granulation. Manish Chawla, Rajeev Singh Raghuvanshi, and Ashok Rampal of Ranbaxy Laboratories Limited were granted a World Patent entitled “Stable sustained-release oral dosage forms of gabapentin and process for preparation thereof”[42] that describes “stable sustained-release tablets of gabapentin comprising an intragranular component, which comprises gabapentin and optionally one or more rate-controlling polymers and an extragranular component, which comprises one or more rate-controlling polymers.” Therefore, options are indeed available to the formulation scientist with intragranular and extragranular application of polymeric materials. Several production conditions from the literature[15,43,44] were investigated using design of experiments, including the Ch concentration and the Ch-TPP ratio, as well as the pH, temperature, and the ionic strength of the production medium.

Experimental Section

Materials

Powdered Ch, purchased from DCV BioNutritionals (Wilmington, DE), with a 92% degree of deacetylation and an average molecular weight of 470 kD[45] was used for all experiments. Sodium tripolyphosphate (NaTPP) was purchased from Sigma-Aldrich (St. Louis, MO). Acetaminophen purchased from Mallinckrodt Pharmaceuticals (St. Louis, MO) was used as a model active pharmaceutical ingredient (API) for dissolution testing. Hydrochloric acid, 37%; glacial acetic acid, $\geq$ 99.7%; and sodium hydroxide were all purchased from Fisher Scientific (Fair Lawn, NJ). Sodium chloride was purchased from Sigma-Aldrich.

Methods

Statistical Design—Initial Design of Experiments

A 5-factor, 2-level, half-fractional factorial design with 3 center points was generated using Design Expert® software version 10.0 (Stat-Ease, Minneapolis, MN). The design was subsequently expanded to a face-centered cube central composite design with an additional 2 center points using the Design Expert® software based on a statistically significant curvature observed during analysis of the initial half fractional factorial design for several of the responses. The 5 factors included the Ch concentration in solution, the mass ratio of Ch to tripolyphosphate (Ch:TPP) in the final solution, the pH of the solution just prior to initiation of cross-linking, the temperature of the solution, and the concentration of NaCl added to the solution. The levels used for each factor in the experimental design are presented in Table 1. ANOVA was performed using backwards hierarchical regression and strictly following the Design Expert® software guidance and recommendations.

Statistical Design—Optimization

Using the previously established statistically significant models generated by completion of the design of experiments, the optimization node in Design Expert® software was used to suggest factor levels to produce material with a predefined set of desired outputs or responses. First, criteria are defined for each applicable factor and/or response and an importance factor, weighted 1-5, is assigned to each defined criterion. When no criterion is defined for a specific factor or response, that specific attribute is allowed to “float” to best achieve the defined criteria; this is designated as “in range” for factors and “none” for responses. For factors, “in range” indicates that the value must be within the design space already explored.

Table 1
Experimental Design Factor Levels for Ch-TPP Cross-Linking

	Factors	Levels		
		Low (−1)	Center Point (0)	High (1)
A	Chitosan concentration (mg/mL)	1	3	5
B	Ch:TPP ratio	1	3	5
C	Temperature (°C)	25	45	65
D	pH	3	4	5
E	NaCl concentration (mM)	0.00	0.01	0.02