In the name of God

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Academic Ph.D. Dissertation in:
Pharmaceutics

Formulation of a multiparticulate (pellet) drug delivery system intended for bimodal (sigmoidal) drug release and formula optimization based on artificial neural networks (ANNs)

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Dedication

To my dear parents:

For giving me the thirst for answers and the tools to find them.

To my dear wife, Shabnam:

For your unconditional love, patience and support.

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Abstract

Multiple-unit dosage forms are based on subunits such as granules, pellets, or minitablets and they are usually delivered in hard gelatin capsules. The recent interest in multiple-unit dosage forms is a result of the advantages they offer over the single-unit systems (e.g., tablets). The pelletization by extrusion-spheronization is a well-known technique for production of multiple-unit or multiparticulate dosage form (pellet).

Bimodal drug release profiles, where release is slow in the initial stages and increases to a faster release rate at some later stages, may be of significant therapeutic benefit. In disease states such as nocturnal asthma, increased drug release rates may help prevent the exacerbation of symptoms caused by circadian rhythms.

The first part of this study (chapter 2) demonstrated the feasibility of producing extruded and spheronized pellets with inclusion of binary formulations, i.e., microcrystalline cellulose (MCC) as an extrusion-spheronization aid and theophylline as a model drug. Such pellets exhibited the necessary physicomechanical characteristics as a drug core for further pharmaceutical processing, i.e., film coating. The factors, which mostly affect the preparation of theophylline pellets, were of theophylline content, amount of water, spheronization speed, and spheronization load. Consequently, a central composite experimental design (CCD) was used to investigate systemically the effect of two critical formulation variables (i.e., amounts of theophylline and water) and two important process variables (i.e., spheronization speed and load) on the mean diameter of pellets and their sphericity (as responses).

Two approaches, namely response surface methodology (RSM) and artificial neural network (ANN) were used as modeling tools for finding the relationships between independent variables and responses and subsequently applied as optimization techniques. Based on optimization by using RSM, optimum pellet production was predicted to occur with a high theophylline content and relatively low amount of water at fixed highest levels of spheronization speed and spheronization load. ANN showed less prediction error (or higher accuracy in prediction) compared to RSM. However, both ANN and RSM visualized acceptable results and their predictions regarding responses coincided relatively well. Moreover, the effects of formulation and processing variables on mechanical strength, density

(bulk, tapped, and apparent), and porosity of pellets were evaluated. The amount of water (as granulating liquid) exhibited significant effects on the extrudates' and/or pellets' morphology.

Natural or modified polysaccharides such as gelatin, dextran, chondroitin sulphate, calcium pectinate, pectin and chitosan have been used as potential carriers for drug delivery as they are safe, biodegradable and widely available. Among these polymers, the use of pectin and chitosan has shown particular promise, as they are able to form polyelectrolyte complex (PEC). Complexation of pectin with chitosan in the form of a PEC allows control over drug release while maintaining the ability of the pectin to be degraded by colonic bacteria; thus, potentially achieving bimodal drug delivery. The major problem encountered with polysaccharides such as pectin and chitosan is their high solubility and swelling properties in aqueous media. Film coatings consisting of pectin and/or chitosan are unable to prevent the release of drugs during the transit through the stomach and the small intestine. However, the incorporation of hydrophilic degradable polysaccharides in water-insoluble film forming polymers such as cellulosic or acrylic polymers could provide a promising alternative. The integrity of such mixed-film coating could be better controlled by preventing fast swelling and solubilization of pectin and/or chitosan during the transit from mouth to caecum.

The second part of this study (chapter 3) was carried out to develop a bimodal drug delivery system based on the pectin/chitosan/Eudragit® RS mixed-film coating. The theophylline pellets were coated with Eudragit® RS aqueous dispersions, containing various amounts of pectin-chitosan complex and different coating weight gains, using a fluidized-bed apparatus. Drug release studies were conducted using the USP apparatus I (basket) in dissolution media, mimicking the conditions prevailing in the stomach, small intestine or colon. Studies have shown that the drug release rate and pattern were dependent on both of the two mentioned factors. Some formulations showed bimodal and burst drug release, being triggered in the colonic medium by the action of pectinolytic enzymes. In formulations with 15 or 20% w/w of coating weight gain and 5 or 10% w/w of pectin-chitosan, the burst drug release was eliminated and replaced by the lag phase of drug release. In the viewpoint of burst drug release in the colonic medium, formulation with 20% w/w of coating weight gain and 15 or 20% w/w of pectin-chitosan were found to be better than the other formulations.

Besides pectin/chitosan/Eudragit® RS, other formulations based on pectin/chitosan and pectin/Eudragit® RS mixed-films were also prepared. Pectin/chitosan film was unable to

provide the protecting effect on the drug release from the pellet and its drug release rate was extremely high. It was clearly appeared that due to the leaching of pectin from pectin/Eudragit® RS mixed-film, a fast drug release at the early stage of dissolution could be observed. As expected, the drug release from pellets coated with pectin and Eudragit® RS was faster than those coated with mentioned ternary mixed-film were.

It was found that pectin/chitosan/Eudragit® RS mixed-film were not capable of demonstrating a bimodal drug delivery when they were getting in contact with acidic medium, thus, those formulations should be further coated with an enteric polymer. It was shown that the presence of pectinolytic enzymes in the dissolution medium resulted in an increase of the drug release rate. The SEM evaluation of the uncoated and coated pellets showed that after coating, pellets' surfaces became smoother and their exposure to the pectinolytic enzymes might be attributed to surface erosion of the film coating.

The mechanism of drug release associated with pectin/chitosan/Eudragit® RS mixed-film system was described in the third part of our study (chapter 4). For this purpose, drug release kinetics was characterized using mathematical fitting of release data into four distinct models: zero-order, first-order, Higuchi, and Korsmeyer-Peppas model. Zero-order kinetics was found as the better fitting model for all formulations in the simulated small intestinal medium. In the colonic medium, for the majority of formulations, an anomalous transport was found and both zero-order and Higuchi model characterized good quality adjustment.

We have mentioned that at the end of phase two (small intestine), some of drug molecules have already diffused and trapped within the whole coating volume and the mesh space of the film network. After the film exposure to pectinolytic enzymes, pectin degraded and leached from the coating and therefore a sudden (burst) drug release was occurred. In contact to enzyme, due to pectin degradation and removal from the film, the porosity of film increased and the drug that has been diffused to the surface of the core released immediately. After the enzymatic breakdown and leaching of pectin, the mixed-film could restructure, plugged up the possible pores and reduced the free volume between polymer chains, and therefore, slow down the drug release.

There should be a balance between coating weight gain and pectin-chitosan amount for creating the bimodal drug release. The inadequate amount of pectin-chitosan might be responsible for low or no burst drug release. On the other hand, at high coating weight gains,

i.e., 15 or 20% w/w and insufficient amount of pectin-chitosan, i.e., 5 or 10% w/w; film barrier predominately governs drug release because all pectin-chitosan aqueous channels were blocked.

The major objective of fourth study (chapter 5) was to model the relationship between two factors, i.e., coating weight gain and amount of pectin-chitosan and *in vitro* drug release profile by using neural network methodology. ANN as a multilayer perceptron feedforward network was incorporated for developing a predictive model of the formulations. Five different training algorithms belonging to three classes: gradient descent, quasi-Newton (Levenberg-Marquardt, LM) and genetic algorithm (GA) were used to train ANN containing a single hidden layer of four nodes. The next objective of that study was to compare the performance of aforementioned algorithms with regard to predicting ability. The precision of predictive ability was measured for each training algorithm and their performances were in the order of: IBP, BBP > LM > QP (quick propagation) > GA. According to BBP-ANN implementation, an increasing in coating levels and decreasing in the amount of pectin-chitosan generally retarded the drug release. Moreover, the latter causal factor played slightly more dominant role in determining the dissolution profiles.

In the fifth part of our study (chapter 6), pectin as an anionic polymer was complexed with chitosan as a cationic species and subsequently free (isolated) film was prepared. Besides pectin/chitosan film, Eudragit® RS, pectin/Eudragit® RS and pectin/chitosan/Eudragit® RS films were also prepared by solvent casting method. In mixed-film formulations, a fixed weight ratio of 1/5 of pectin or pectin-chitosan complex to Eudragit® RS was used. Characterizations of pectin-chitosan interaction in solution were investigated by turbidity and viscosity measurement and in the solid state by Fourier transform infrared (FTIR) spectroscopy, wide angle X-ray diffraction (WAXRD) and thermogravimetric analysis (TGA). It was observed that the swelling profile of pectin/chitosan film was pH-dependent and its swelling ratio in phosphate buffer solution (PBS) pH 7.4 was ≈ 2.5-fold higher than that of PBS pH 6.0. The formation of PEC between pectin and chitosan resulted in a decrease in the crystallinity and thermal stability caused by the interactions between polyions. Drug permeation or diffusion studies were carried out using a horizontal diffusion cell consisting of donor and acceptor compartments. Theophylline was chosen as a model drug to measure permeability coefficient. Drug permeation through pectin/chitosan/Eudragit® RS showed a bimodal pattern,