

Simulation and Mathematical modeling of controlled release of Ondansetron

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Abstract: - A mathematical model has been applied to predict the mass of dissolved drug and absorbed drug. This paper presents application of mathematical model to simulate of ondansetron release. Ondansetron hydrochloride is a highly selective 5 HT₃ receptor antagonist used in the treatment of nausea and vomiting. The data was collected from 12 healthy, fasted volunteers [2]. It is assumed that there are four particles with different radius, pH is 6.0 and drug solubility was adjusted around this pH. Data were used by Runge-Kutta method using Maple 6.0 software. A computer method has been devised to describe the theoretical dissolution rate of a polydisperse powder drug (ondansetron) under non sink condition. Its base is on particle size distribution and pH in GI tract. This is from a novel controlled release formulations. This program simulates from experimental data, and expresses the dissolution rate, mass of solid drug and absorbed drug. PH was affected on dissolved drug. This model predicts that with increasing PH (above 6.1), dissolution rate percent is decreased.

Key-Words: - Simulation, controlled release, Ondansetron, Drug delivery,

1- Introduction

Without controlled release technologies people need to take numerous doses of drugs, OTC products and nutritional supplements to realize the benefits. At times this results in undesirable spikes in serum levels, malabsorption and dumping of excessive ingredients and compromised bioavailability. Controlled delivery Technology (CDT®) addresses these concerns by optimizing bioavailability of active ingredients while diminishing adverse side effects, improving dosing compliance and maximizing overall product effectiveness [1].

CDT® technologies enable precise control over the timing and amount of active ingredients released. These technologies originated in the mid 1990s during extensive research in the pharmaceutical laboratories of Dr. Reza Fassihi, B. Pharm., Ph.D. at Temple

University School of Pharmacy. Since then, this research has led to the development of a wide platform of patented controlled delivery technologies. The CDT® platform is founded on the art of matrix erosion, changes in gel thickness, electrolyte ionization, and ionic interactions. These are self-correcting systems that lead to carefully controlled erosion as well as a predictable, programmable release of the active ingredient contained in the medicinal core. Previously, this has not been achievable with first-generation delivery systems [1].

Ondansetron hydrochloride is a highly selective 5 HT₃ receptor antagonist used in the treatment of nausea and vomiting. It is a weakly basic drug with a pK_a of 7.4 and has a pH dependent solubility profile being highly soluble around pH 1.5 and poorly soluble in alkaline pH. The solubilization of this drug within the hydrophilic matrix is a critical

issue given its low solubility in aqueous media around pH > 6. The release mechanism of the solubilized drug from the hydrated matrix is as yet unexplored.

Mathematical modeling of dissolution profiles has become a common tool employed in characterization of mechanism of drug release [3]. Efforts to use mathematical modeling for the purpose of predicting dissolution of oral delivery (Ondansertone) have been reported.

2- Model

The equations used to this model under non-sink conditions. Hintz modified these equations for poly-disperse powder [4].

These equations are:

$$\frac{dx_s}{dt} = -\frac{3Dx_0^{1/3}x_s^{2/3}}{\rho hr_0} \left(C_s - \frac{x_d}{V} \right) \quad (1)$$

$$\frac{dx_d}{dt} = -k_a x_d + \frac{3Dx_0^{1/3}x_s^{2/3}}{\rho hr_0} \left(C_s - \frac{x_d}{V} \right) \quad (2)$$

$$\frac{dx_a}{dt} = -k_a x_d \quad (3)$$

where

k_a (1/min)	absorption constant
x_s (mg)	mass of solid drug
t (min)	time
x_0 (mg)	the initial drug mass
ρ (mg/ml)	drug density
r_0 (cm)	initial particle radius
C_s (mg/ml)	drug solubility
x_d (mg)	mass of dissolved drug
V (ml)	volume of the dissolution media

h (cm) diffusion layer thickness

Particles were assumed spherical.

Dissolution from poly-disperse drug powder can be simulated using these equations.

Particle sizes are:

25 micron,	$i = 4$
45 micron,	$i = 3$
60 micron,	$i = 4$
120 micron,	$i = 2$

Dose was assumed 8mg and divided equally in particles.

The program calculates dissolution and absorption for each particle and then sum of particles and finally

$\sum x_{dR}$ and $\sum x_{da}$ are obtained.

The other data for calculations were collected from experimental studies [2]. The assumptions are:

$\rho = 1$ mg/ml

$h = 0.005$ cm (Constant for all particles)

$D = 0.0011$ cm²/min

$V = 200$ ml

$k_a = 0.0004$ 1/min

Vol. of distribution = 110 - 193 lit (based on Human weight)

By these assumptions, we have:

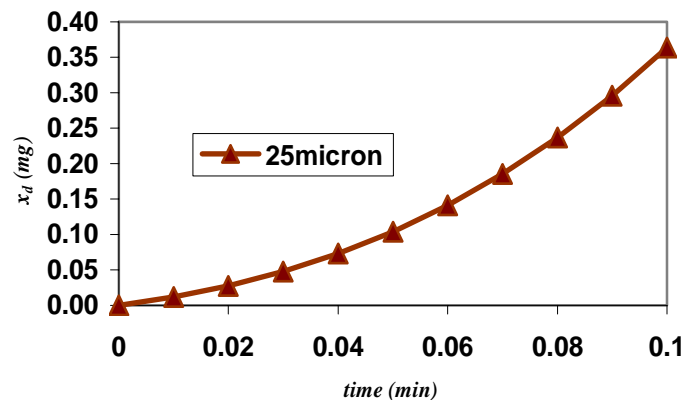


Fig.1 - dissolution of drug with 25micron particle size

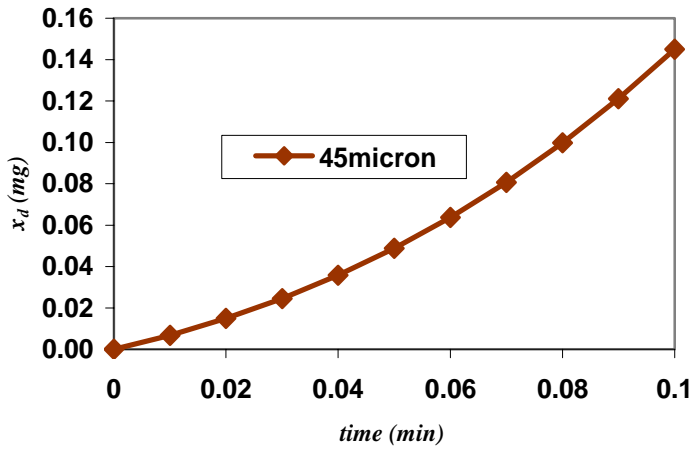


Fig.2 - dissolution of drug with 45micron particle size

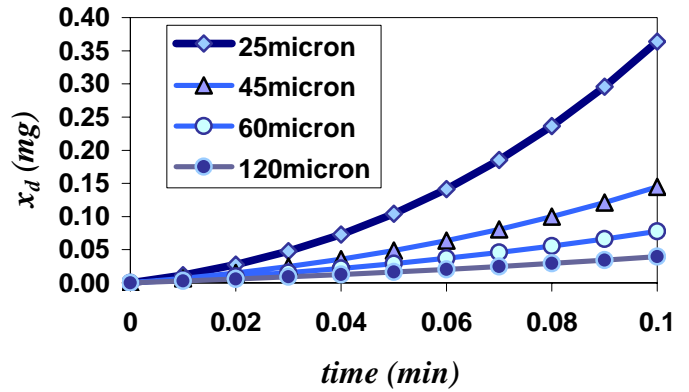


Fig.5 - Comparison of different particle sizes of dissolved drug

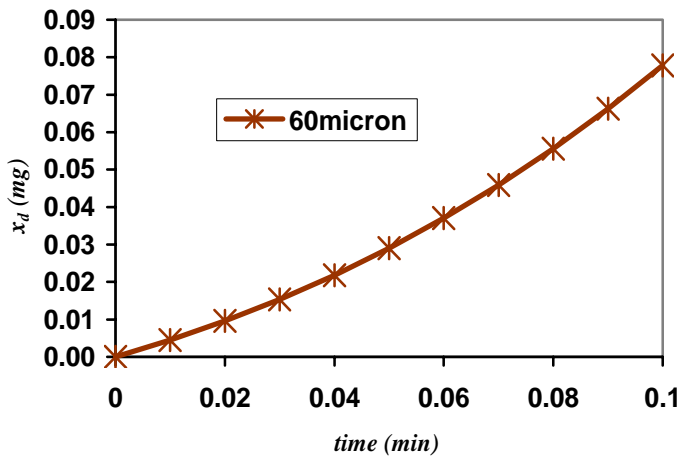


Fig.3 - dissolution of drug with 60 micron particle size

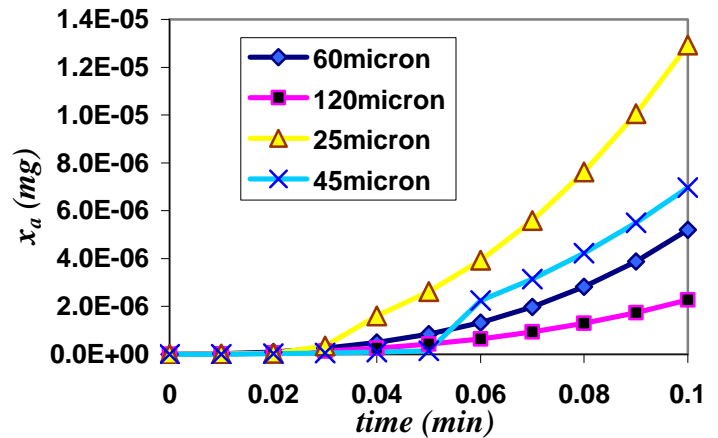


Fig.6 - Comparison of different particle sizes of absorbed drug

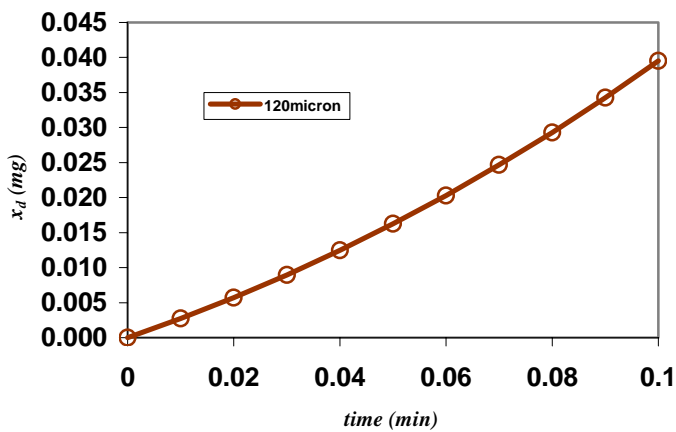


Fig.4 - dissolution of drug with 120 micron particle size

These curves indicate with decreasing particle size, dissolution rate and absorption rate will be increased.

Another simulation was by changes in pH at GI tract in unfasted state. By using equation 4, data collected [2] and some assumptions, we have:

$$\frac{dx_d}{dt} = -\frac{V_{Cl}}{V} k_s x_d + DR \times S_0 \left[\frac{1 - \frac{10^{-pH}}{C_s}}{1 - \frac{10^{-pH_0}}{C_s}} \right] \quad (4)$$

Where

pH_0 initial pH

DR a constant of dissolution rate = 0.025 mg/min

C_s solubility

$VC1$ Volume of distribution in central compartment (ml)

And $S_0 = 0.017$ mg/ml

PH is in GI tract.

These data collected from experimental studies [2]. We have obtained curves for unfasted states by analytical method and programming Maple 6.0

3- Discussion

In two studies, prediction of drug dissolved in unfasted state and particle size distribution by considering factors such as pH, solubility and changes in GI tract were simulated. When $pH > 5.4$, solubility of ondansetron drug is decreased, in $pH = 6.0$, although solubility is decreased, but drug dissolved is increased and by simulation in particle sizes, amount of dissolved drug is greater when the particle sizes are smaller.

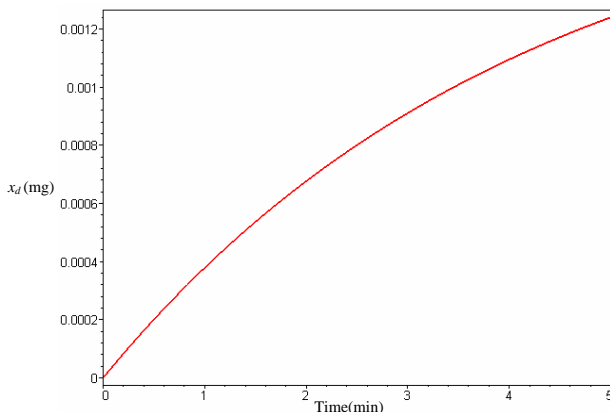


Fig.7 -Unfasted state - pH = 7.0

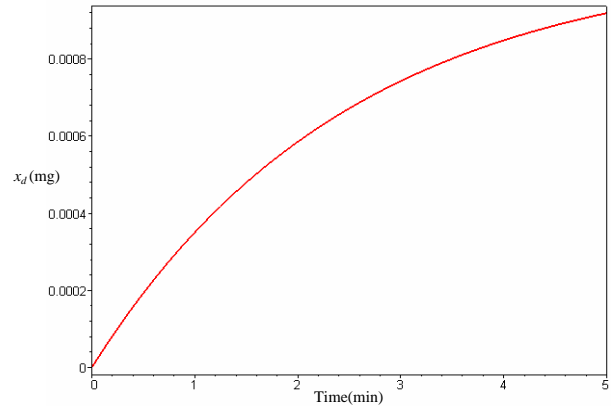


Fig.8 -Unfasted state - pH = 6.5

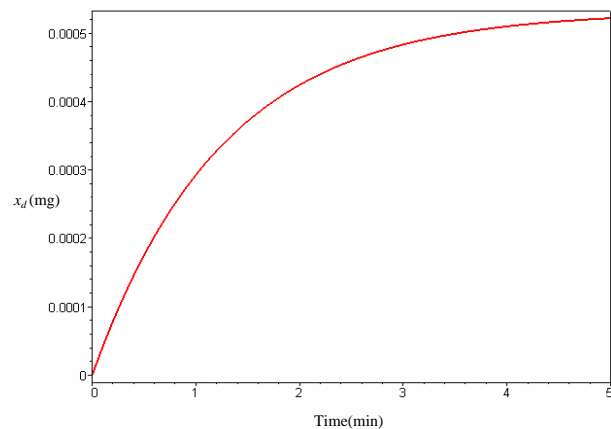


Fig.9 -Unfasted state - pH =6.0

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