

A Novel Manufacturing Method for Sustained Release Products and Modelling Dissolution

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Abstract

A novel processing method for the manufacturing of slow-release particles is proposed. The method is based on the wet milling of active compounds and the selected biodegradable polymers combined with subsequent drying. In the proposed method the dissolution barrier is processed in one step compared to traditional methods consisting of several steps. The experimental dissolution curves of natural polymer (native potato starch and lignin) coated salts were compared with unmilled and milled salts. The dissolution process model was developed in order to characterize and to design sustained release particles. Models were verified with the existing dissolution data. Verified models combined with SEM-images could support the proposed dissolution mechanisms for different polymers. Estimates of effective surface area and diffusion layer thickness (active surface model) and effective diffusivity and gelling layer thickness (constant gel radius model) is achieved.

Keywords: Sustained release; Wet milling; Dissolution model

Introduction

In chemical industry there is a trend to increase process efficiencies and to reduce substantially equipment size, energy consumption and amount of produced waste thus aiming at sustainable processes. These developments share a common focus named as Process Intensification. The increase in efficiency can be achieved, for example, by accelerating chemical reactions or creating high mass and energy transfer rates. Efficiency can be also increased by combining several unit operations in one equipment thus reducing the amount of required processing steps and reducing throughput times [1]. On the other hand, also the reduction of speed of rate-based processes like slow-release dissolution enables to achieve products that use less material, are cheaper and safer and environmentally friendly. Recent reviews of slow-release technologies have been published by Azeem *et al.*, Wu and Liu, Zhan *et al.*, Han *et al.*, Hanafi *et al.*, Swarbrick, Wolny *et al.*, Ching *et al.*, Madene *et al.*, Lu *et al.* to name a few [2-11]. In pharmaceuticals the goal is to minimize the number of drug uptakes and to keep a controlled amount of pharmaceutical ingredients in the body system using sustained release products. In case of foods and nutrients the active compound is covered with a protective wall material to impart valuable compounds against evaporation, reaction or migration. In addition, *e.g.*, vitamins can be masked to hide bad taste. In cosmetics, the extra skin irritation can be eliminated using slow-release particles in ointments and in creams [12].

Production of slow-release particles is typically based on coating, spray-drying or melt extrusion. Those methods include either separate dissolution, heating or granulation processes [2]. In the chemical processing polymer derivatization and crosslinking are involved [4,13]. So there is a potential to increase efficiency by reducing amount of processing steps and by utilizing as barrier material biodegradable cheap polymers achieve the goal of sustainability as well.

To allow design of slow release products a model of dissolution is required. These models can be divided roughly into two groups: empirical models implemented as empirical or semi-empirical equations describing dissolved amount as function of time and mechanistic models based on material balance between dissolving spherical particle and solution and where the dissolution rate is determined by solute diffusion [14]. Several type of dissolution models,

both empirical and mechanistic models, are introduced in literature [14-18] and details of the models depends on the mechanism of the dissolution process and how the model will be applied. Mechanism of dissolution process consists of two steps: the first is surface reaction of molecules from solid into liquid at solid-liquid interface and the second step is diffusion across a thin diffusion layer from solid-liquid interface into bulk solution. It is assumed that the detachment of solute molecules from crystal is fast compared to diffusion step which is the rate determining step [19]. Also it is assumed that concentration at solid-liquid interface is saturation concentration and concentration in bulk is small compared to saturation concentration (=sink condition).

An example of the mechanistic model is the general solution of diffusion layer model for a mono dispersed spherical particle by Wang and Flanagan [19]. They have solved the mass balance expression for a spherical particle by applying pseudo steady state diffusion over constant thickness diffusion layer. Diffusion layer thickness is assumed to prevail during the whole dissolution. According to their study Wang and Flanagan [20] reached the conclusion that this is a valid assumption if mixing conditions do not change during the dissolution.

The general diffusion model assumes spherical particles and dissolution rate is homogeneous over the whole particle area and that the dissolving particle is in direct contact with solvent via the stagnant diffusion layer. In practice the dissolution may be hindered by a fully coating layer of another material or material attached on particle surface thus partly blanking the area and the general model has to be modified in order to take into account these inhibiting effects. Two common mechanisms for coated particles are the shrinking core-

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constant particle size model and the shrinking core-shrinking particle size model [17,18]. In the constant particle size model it is assumed that the coating layer diameter stays constant meanwhile the core inside shrinks. In the shrinking particle size model the particle size decreases and the coating layer thickness stays constant [18]. Safari *et al.* [18] have studied leaching of zinc ore containing silica and they have verified by experiments the validity of constant thickness gel layer model in their application. Partly blanked model, also named as active surface model, is the plain general diffusion model where the dissolution area is a fraction of full particle area.

Equations of empirical models are mostly n-th order reaction kinetic type functions, either analytical functions (like zero order, first order, Weibull) or a certain release parameter is used to characterize dissolution [14]. Costa and Lobo have evaluated several empirical equations with drug dissolution experiment data [14,15].

In this study the novel one step processing method based on wet milling and subsequent drying for the manufacturing sustained release particles is presented. The product particles have been manufactured as well as the dissolution tests have been done in lab-scale to demonstrate the method feasibility. The dissolution rates of the product particles were compared using the dissolution times for equal amounts of the dissolved salt. The dissolution was modelled by using three different mass transfer kinetics, and the models were fitted with the experimental data in order to verify dissolution mechanism. SEM=(scanning electronic microscope) image of coated and dried particles were taken and used to verify mechanism. Estimates of the effective surface area and diffusion layer thickness for the active surface model and effective diffusivity and gelling layer thickness for the constant gel radius model were determined for extracting coating parameters.

Governing equations

Three dissolution models were selected to fit experimental results: first order model, active surface model and constant gel radius model.

First order model: Here it is assumed that dissolution rate dc_p/dt is analogous compared to first order reaction:

$$dc_p/dt = -k_R c_p \quad (1)$$

where c_p is particle concentration in solution and k_R apparent dissolution rate constant. When (1) is solved and particle concentration changed into liquid concentration the expression is

$$(c_f - c)/(c_f - c_0) = \exp(k_R t) \quad (2)$$

where c is liquid concentration, c_f final concentration and c_0 initial concentration.

Active surface model: It is assumed that only a certain part of the surface is active and rest is covered by the coating material. Dissolution model is based on general diffusion model [19]. Liquid phase concentration change due to diffusion across layer having thickness h is

$$dc/dt = (Z/V) A k_c \Delta c \quad (3)$$

where, Z/V is particle number concentration, A sphere area, k_c mass transfer coefficient and Δc concentration difference over the layer. Concentration at the layer inner boundary is saturated concentration c_s and it is assumed that $c_s \gg c$ so $\Delta c \approx c_s$. Expression for concentration can be found also by integrating concentration gradient over the layer [19] and the result is

$$dc/dt = A(Z/V) D_{ab} c_s (1/r + 1/h) \quad (4)$$

Equating (3) and (4), the expression of mass transfer coefficient is

$$k_c = D_{ab} (1/r + 1/h) \quad (5)$$

Solution concentration change is

$$dc/dt = -dc_p/dt = -(Z/V) \rho_p A dr/dt \quad (6)$$

where ρ_p is particle density. It is assumed that the amount of particles does not change during dissolution so the number concentration Z/V can be calculated using initial particle concentration

$$Z/V = c_{p,0} / \left(\rho_p \frac{4}{3} \pi r_0^3 \right) \quad (7)$$

where, $c_{p,0}$ is initial particle concentration and r_0 initial particle diameter. Because only a certain fraction of particle surface is active solution concentration change is

$$dc/dt = a(Z/V) A k_c c_s \quad (8)$$

where a is surface activity factor between 0 and 1.

Constant gel radius model: Here it is assumed that there is a constant radius gel layer over the particle which slows down diffusion. A model for mass transfer coefficient is [17]

$$k_c = D_{eff} / (R_g - r) = e D_{AB} / (R_g - r) \quad (9)$$

where $D_{eff} = e D_{AB}$ is effective diffusion coefficient. e is effectiveness factor related to KCl diffusivity and it has values from 0 to 1 and R_g constant gel radius. Otherwise concentration change is modelled using equations (4) and (6).

Experimental

Materials

Model compound was potassium chloride KCl (Riedel-Haën, CAS 7447-40-7). Non-toxic, relatively inexpensive and biodegradable coating materials in this study were neutral unmodified potato starch (ChemGate Oy, CAS 9005-25-8) and Kraft lignin (Sigma-Aldrich, CAS 8068-05-01). De-ionized water and ethanol (purity >99.5 wt%) were the solvents.

Experimental set-up

Potassium chloride, polymer and solvent were milled in the mortar. The compositions of the polymer mixes in the experiments are shown in Table 1. In case of potato starch the mix was preheated to 65°C due to starch swelling [21] before milling, and in case of lignin the mix was heated to 40°C for the partial lignin dissolution [22]. The grinding time was 10 minutes in each experiment during which the solvent was evaporated. The drying completion was assured by weighing the material before and after the processing.

The dissolution of product particles were measured in a well-mixed laboratory-size vessel (200 ml volume, mixer speed 0.8 m/s) at constant temperature 25°C. The initial KCl liquid concentration in the dissolution experiments was 0.27 mol/L. The electric conductivity (Consort C3310) was calibrated to molar KCl concentrations in advance, as well as the electric conductivity effect of polymers were also measured. According to the pure polymer measurements, the measurement error was max 2% to the electric conductivity.

Results

Experimental results

SEM images of the particles (Figures 1 and 2) and the particle size

Test number	Initial KCl concentration (mol/L)	KCl amount (g)	Polymer	Amount of polymer (g)	Solvent	Amount of solvent (g)
1	0.27	7.7	-	0		0
2	0.27	7.7	-	0	30	0
3	0.27	7.7	Starch	0.77		0.77
4	0.27	7.7	Starch	1.54	4.1	1.54
5	0.27	7.7	Lignin	0.77	1.9	0.77
6	0.27	7.7	Lignin	1.54		1.54

Table 1: Composition of biodegradable polymer mixes. Polymer amounts 10% and 20% of the salt. Tests 1 and 2: grinded and ungrinded KCl samples.

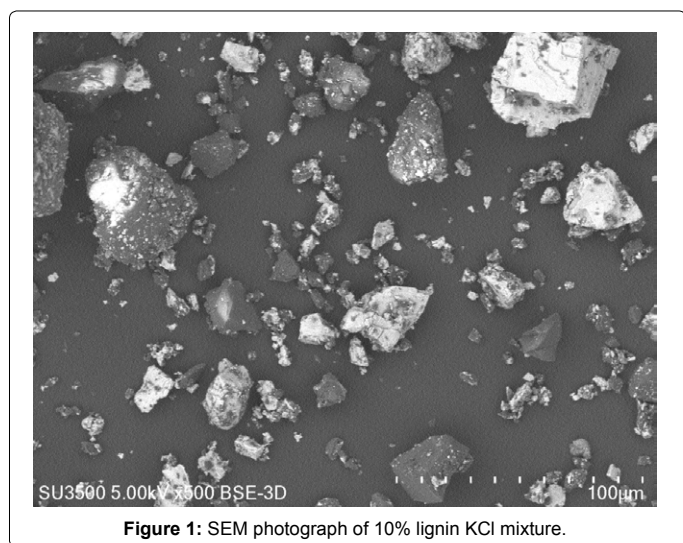


Figure 1: SEM photograph of 10% lignin KCl mixture.

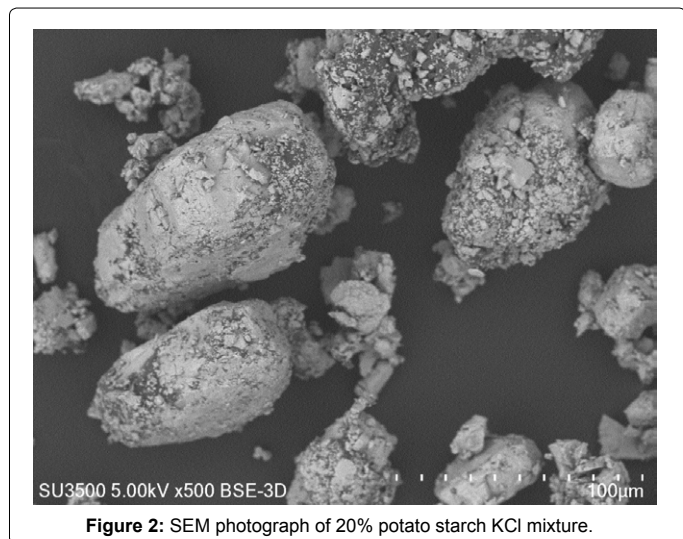


Figure 2: SEM photograph of 20% potato starch KCl mixture.

distributions (Figure 3) for the highest polymer loadings are presented. The crystallinity and the purity of KCl in starch coated particles were verified by X-ray powder diffraction (Figure 4). The dissolution times and profiles for 10 w% and 20 w% load of polymers are presented in Table 2 and in Figures 5 and 6.

Dissolution modeling

Three dissolution models were used to fit experimental data: first order reaction model, active surface model and constant gel radius

model. KCl physical properties used in the models are shown in Table 3. Models were implemented and solved with MATLAB [25].

Calculated model parameters for each case are in Table 4. Goodness of fit was evaluated by calculating coefficient of determination R^2 :

$$R^2 = 1 - SSR/SST \quad (10)$$

$$SSR = \sum (c_i - c_{i,est})^2 \quad (11)$$

$$c = \sum c_i / n \quad (12)$$

$$\bar{c} = \sum c_i / n \quad (13)$$

Where, c_i is measured value, $c_{i,est}$ value estimated from model and n amount of experiment points. R^2 values are shown in Table 5. For three different models experimental and fitted dissolution curves for each test is shown in Figures 7-9.

Discussion

The novel and straightforward manufacturing method was developed which comprised of: charging of starting materials, heating, wet milling and product drying. The lignin and the potato starch were selected due to their biodegradability and the low harmfulness in the environment/health issues. The reference particles were ungrinded and grinded salt, and the KCl was selected for the salt due to the easy correlation and validation of electric conductivity values to molar concentrations. The dissolution tests were done under a vigorous mixing in order to obtain maximum homogenous suspension.

According to the SEM photographs the surface is covered with separate lignin particles (Figure 1), but the coverage of the starch on the KCl surface is more thorough due to the starch swelling during particle processing (Figure 2). With equal amounts of polymers the particle size distributions were similar and comparable to the grinded KCl particles (Figure 3). According to the dissolution data the dissolution time (90% dissolved) was doubled with the lignin coated particles and was 5.5 times longer with the starch coated particles (Table 2 and Figure 6) compared to the reference KCl particles.

Experimental first order model was successful in approximating dissolution and the model parameter k_r can be used in comparisons between dissolution rates of different spheres. This is also reflected in Table 2, where to different particles are tabulated from smallest to largest 90% dissolution times which is same order if sorting were done from largest to smallest k_r (Table 4).

The dissolution of the ungrinded and grinded particles was unexpectedly best modelled by the gel radius model. The effective diffusivities were 19.2% and 100% for the pure KCl particles (grinded and ungrinded). The poor wettability may have been the cause for the small diffusivity for the grinded KCl particles. During the dissolution tests the pure KCl particles may have formed aggregates, which may

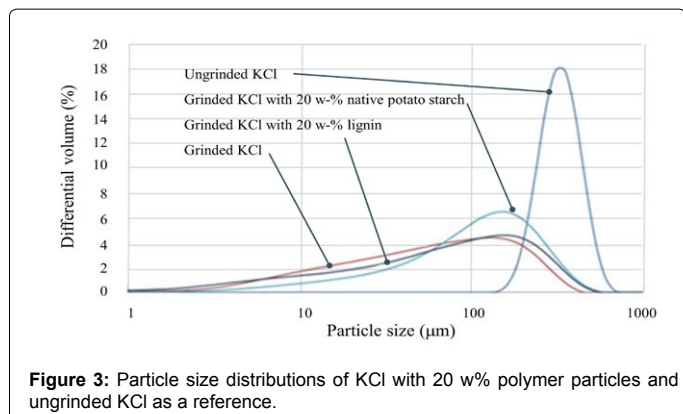


Figure 3: Particle size distributions of KCl with 20 w% polymer particles and ungrinded KCl as a reference.

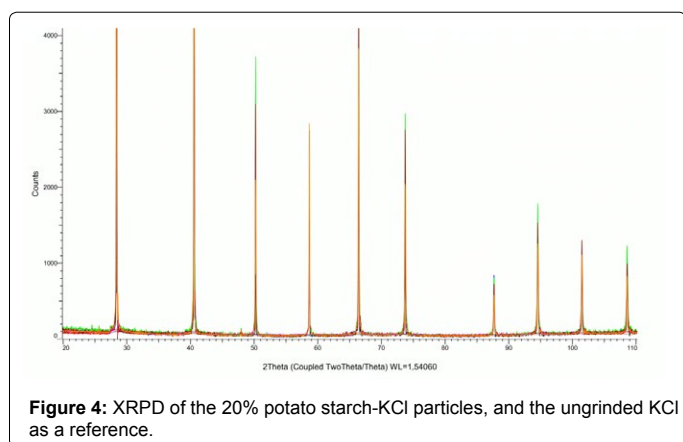


Figure 4: XRPD of the 20% potato starch-KCl particles, and the ungrinded KCl as a reference.

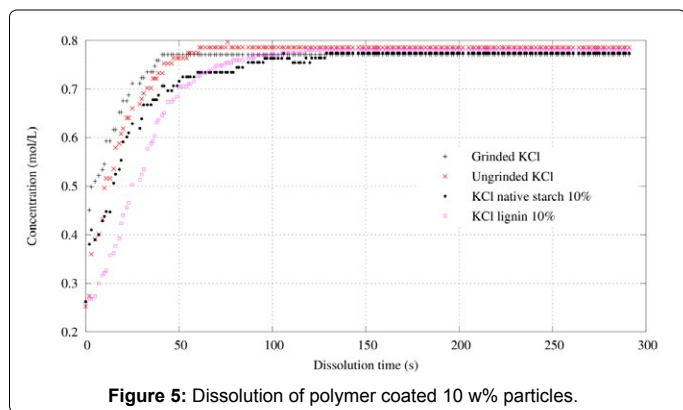


Figure 5: Dissolution of polymer coated 10 w% particles.

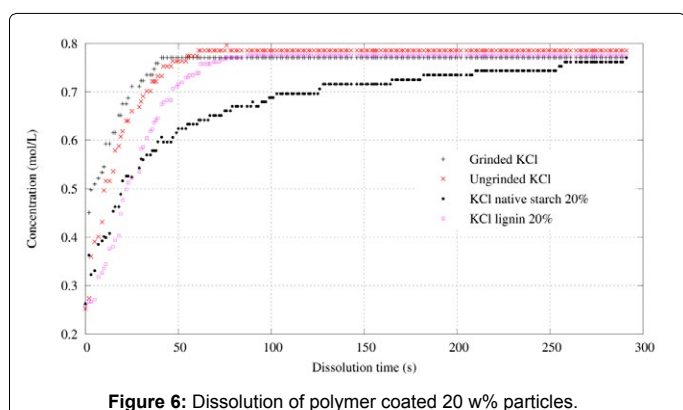


Figure 6: Dissolution of polymer coated 20 w% particles.

	Dissolution times, s					
	G	U	NS10	L10	L20	NS20
10% dissolved	1	2	1	7	9	3
50% dissolved	7	1	16	23	30	20
90% dissolved	30	39	52	52	61	164

Table 2: Dissolution times for 10%, 50% and 90% dissolutions from dissolution measurements (Figures 5 and 6). G=Grinded KCl, U=Ungrinded KCl, NS10=Native Starch 10%, L10=Lignin 10%, L20=Lignin 20%, NS20=Native Starch 20%.

Property	Value	Source
Density ρ_p	1998 kg/m ³	[23]
solubility c_s	355 kg/m ³	[23]
diffusivity D_{AB}	1.99×10^{-9} m ² /s	[24]

Table 3: KCl physical properties.

Model	Experiments					
	G	U	NS10	L10	L20	NS20
First order model						
$k_R/10^{-3} s^{-1}$	89	57	44	34	30	21
Active surface model						
$\alpha/\%$	4.0	4.0	5.4	5.7	5.1	4.0
$z=hlr_0$	0.38	0.027	0.50	3.6	3.6	0.97
Gel layer model						
$e/\%$	19.2	100	26.9	32.3	30.3	12.9
$D_0/\mu m$	96	530	170	222	222	141

Table 4: Estimated model parameters. G=Grinded KCl; U=Ungrinded KCl; NS10=Native Starch 10%; L10=Lignin 10%; L20=Lignin 20%; NS20=Native Starch 20%.

Model	Experiments					
	G	U	NS10	L10	L20	NS20
First order model	0.9165	0.9916	0.9768	0.9451	0.9547	0.9093
Active surface model	0.8313	0.9873	0.9363	0.9859	0.9841	0.7710
Gel layer model	0.9660	0.9905	0.9779	0.9542	0.9621	0.9844

Table 5: Goodness of fit: R^2 value. G=Grinded KCl; U=Ungrinded KCl; NS10=Native Starch 10%; L10=Lignin 10%; L20=Lignin 20%; NS20=Native Starch 20%.

explain the gel radius model suitability.

The dissolution data of lignin coated particles was best fitted for the effective surface model, although the data fit to the gel radius model was also good. The effective surface areas for the 10% and 20% lignin loadings were 5.7% and 5.1%. According to the SEM photographs (Figure 2) the lignin was partly coating the KCl particle surfaces which explains the suitability of this model. Additionally, the lignin is not dissolved into water and therefore gelling surface is not formed.

According to the results the gel radius model can also be used to model predicts especially well the dissolution from the data of the starch coated particles. The estimated effective diffusivity ratios e were 26.9% and 12.9% in the case of 10% and 20% starch coated KCl particles which correspond to the starch loadings. Estimated gel diameters D_0 were 170 and 141 μm .

Conclusions

Dissolution data of polymer coated KCl particles has been presented. Particles were manufactured by wet milling salt and polymers. They were dried during the milling stage which can be considered an energy efficient solution due to the fact that milling energy turns itself into

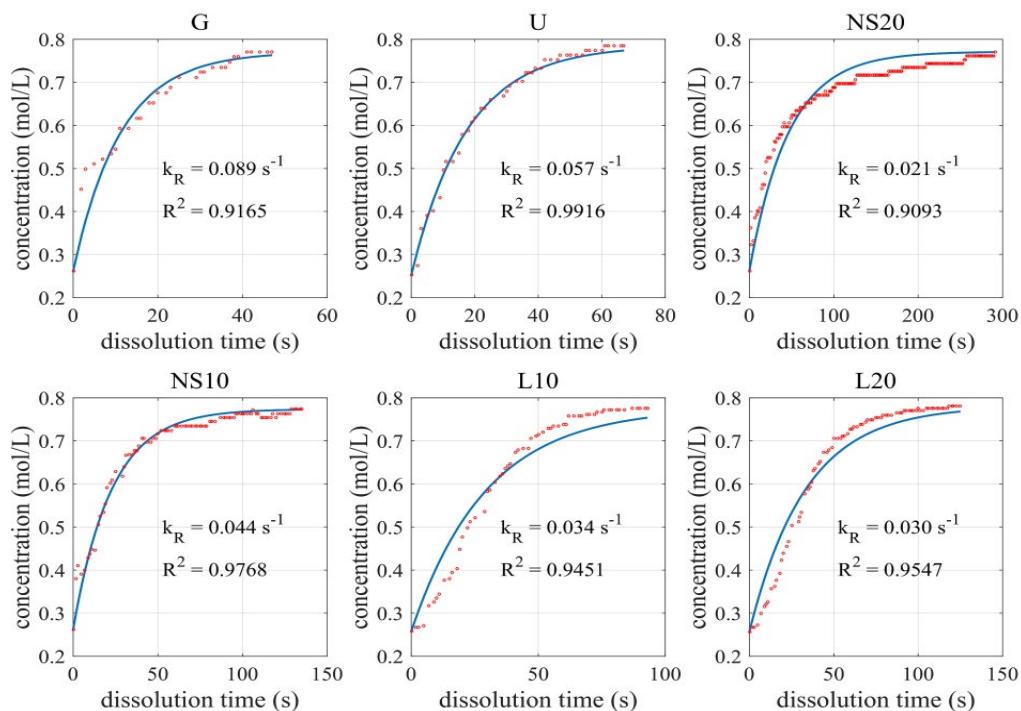


Figure 7: First order model: measurements (dots), fitted model (continuous) and model parameters: k_R : Apparent dissolution rate constant; R^2 : goodness of fit; G=Grinded KCl; U=Ungrinded KCl; NS10=Native Starch 10%; L10=Lignin 10%; L20=Lignin 20%; NS20=Native Starch 20%.

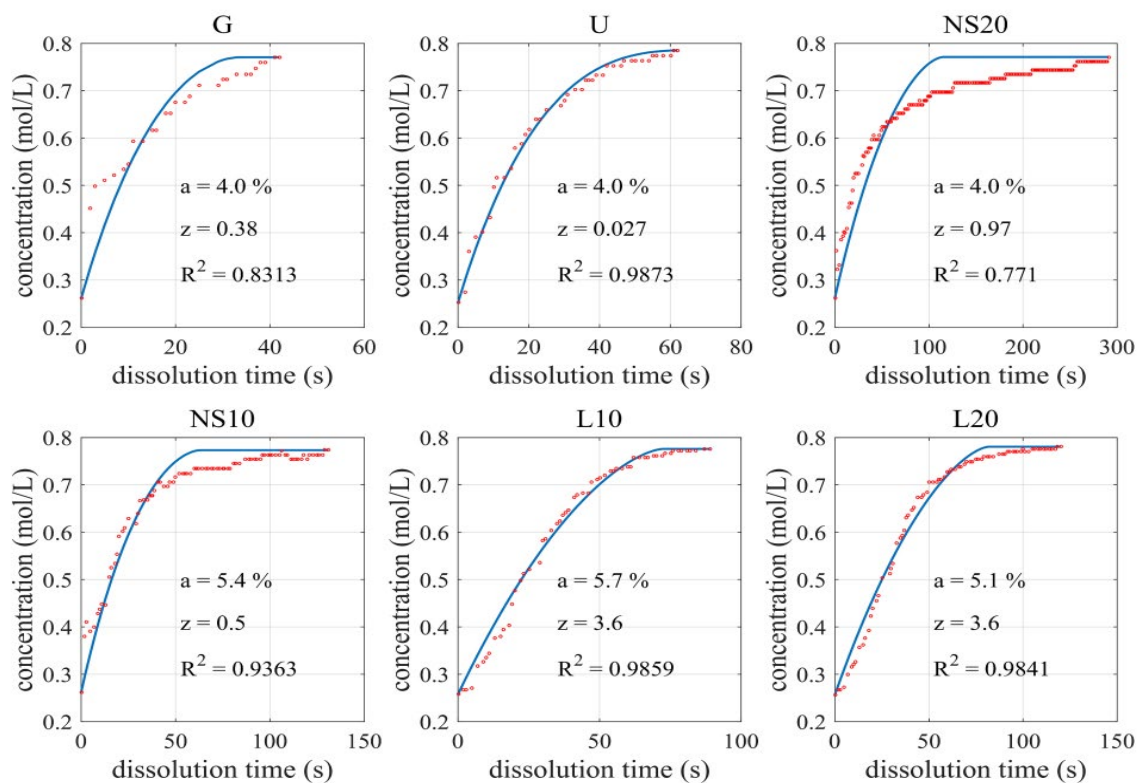


Figure 8: Active surface model: measurements (dots), fitted model (continuous) and model parameters: a : active surface; z : ratio between diffusion layer thickness and initial particle radius; R^2 : goodness of fit; G=Grinded KCl; U=Ungrinded KCl; NS10=Native Starch 10%; L10=Lignin 10%; L20=Lignin 20%; NS20=Native Starch 20%.

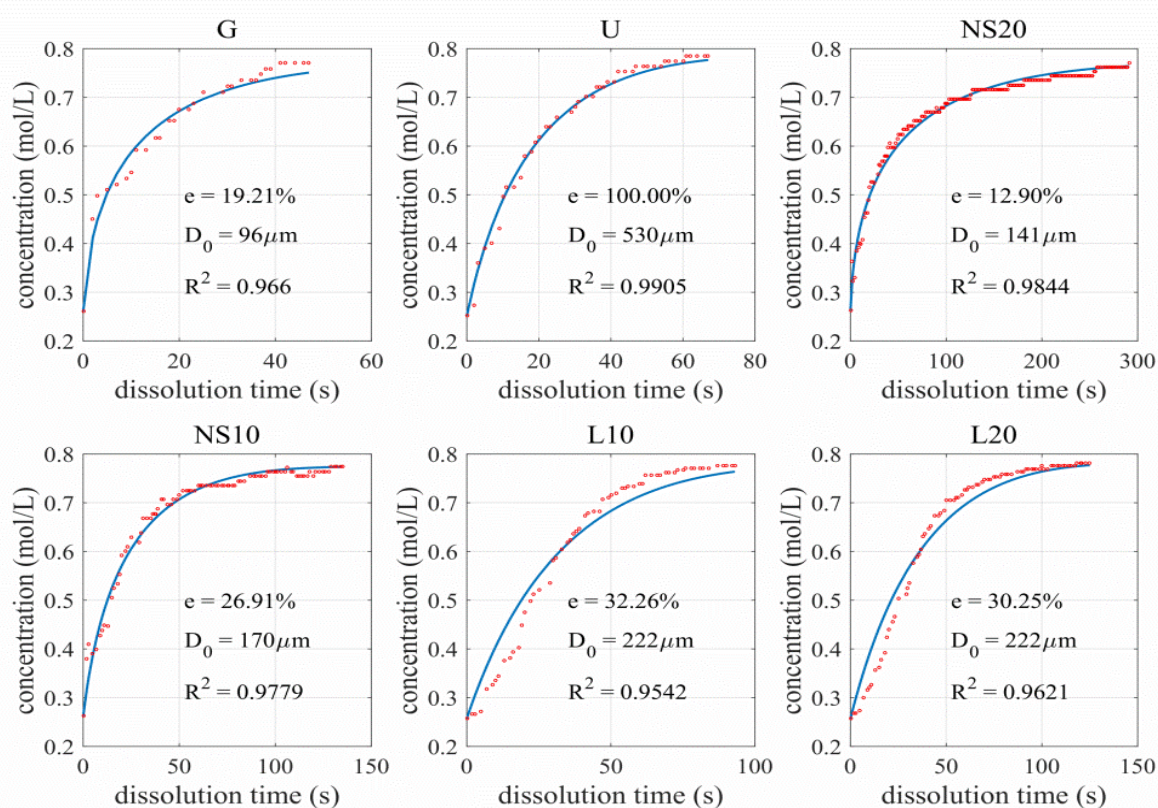


Figure 9: Constant gel layer model: measurements (dots), fitted model (continuous) and model parameters: Diffusivity ratio $e=D_{\text{eff}}/D_{AB}$; D_0 constant gel diameter; R^2 : goodness of fit; G=Grinded KCl; U=Ungrinded KCl; NS10=Native Starch 10%; L10=Lignin 10%; L20=Lignin 20%; NS20=Native Starch 20%.

heat. The produced polymer coated particles had almost six time longer dissolution times compared to the pure KCl particles under vigorous mixing conditions. The dissolution profiles were simulated using the traditional first order reaction kinetics model, the active surface model, and the constant gel radius model. The active surface model was well suited for the lignin coated particles due to the active surface reduction of the attached lignin particles. On the other hand, a very good data fit was obtained for the starch coated particles using the constant gel radius model. This result was expected because of the gelling nature of the native starch.

The potential of the wet grinding and the simultaneous drying of particles as a manufacturing method in coating of dissolvable compounds has been demonstrated. In the production of different coatings the developed models were used for explaining gel formation or active surface of particles in dissolution processes.

Notations

α	Surface activity factor in active surface model, 0...1
A	Particle area, m^2
c	KCl concentration, mol/L
c_0	KCl initial concentration, mol/L
c_f	KCl final concentration, mol/L
c_i	i :th experimental concentration
$c_{i,est}$	i :th estimated concentration
c_p	KCl particle concentration, g/L
c_s	KCl solubility in water, kg/m^3

D_{eff}	Effective diffusivity in gel layer model, m^2/s
D_{AB}	KCl diffusivity in water, m^2/s
D_0	Constant gel diameter in gel layer model, m
e	Diffusivity effectiveness factor in gel layer model, 0...1
h	Diffusion layer thickness, m
k_c	Mass transfer coefficient, m/s
k_R	First order model apparent dissolution rate constant, 1/s
n	Amount of experimental points
r	Particle radius, m
r_0	Particle initial radius, m
R_0	Gel radius in gel layer model, m
t	Time, s
V	Liquid volume, L
Z	KCl particle count
Z/V	Particle number concentration, 1/L

Greek alphabet

ρ_p	KCl particle density, kg/m^3
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