MODA N2B-PATCH

Gel Attachment and Film Formation

Drug Release and Penetration to the Mucosa

Last updated 2016.09.07

			OVERVIEW of the simulation		
1	USER CASE		*Drug delivery to olfactory mucos.*		
2	CHAIN OF MODELS	MODEL A1	*CFD and chemistry models for flow and mixing of a viscoelastic fluid in an applicator tube (4.2 & 4.5)*		
		MODEL A2	*CFD and chemistry models for extrusion of a viscoelastic fluid from an applicator tube (4.2 & 4.5)*		
		MODEL A3	*CFD and chemistry models for film formation of a viscoelastic fluid on a mucous layer (4.2 & 4.5)*		
		MODEL B1	*Mass transfer and chemistry (mass balance and reaction kinetics) models for hydrogel matrix biodegradation (4.2 & 4.5)*		
		MODEL B2	*Mass transfer and chemistry (mass balance and reaction kinetics) models for drug release from biodegradable particles (4.2 & 4.5)*		
		MODEL B3	*CFD (mass transfer) for drug diffusion through a gel matrix (4.2 & 4.5)*		
3	PUBLICATION ON THIS ONE SIMULATION				
4	ACCESS CONDITIONS		*Model and data are not free* *Commercial (ANSYS) and in-house software (BEM)*		
5	WORKFLOW AND ITS RATIONALE		*The user case involves phenomena with different physics and the modellers choose to separate the case into two parts:* *A) Fast gelling hydrogel being extruded from an applicator tube. After extrusion the gel comes into contact with an overlying mucosal surface. The extruding gel expands and covers the mucosa.* *B) Release of drug from biodegrading microparticles - embedded in a hydrogel matrix attached to the olfactory mucosa – and diffusion to the Olfactory mucosa* *Part A* *The diagram above presents the key processes underlying the gel application and film formation.* *In A1 we have inertial constrained flow of a mostly viscous fluid* *In A2 we have extrusion and Stokes free-surface flow of a viscoelastic fluid* *In A3 we have free-surface Stokes flow of a mostly elastic fluid.* *The CFD and chemistry (Navier-Stokes, Laplace-Young equation and reaction kinetics + mass balances) model form a tightly coupled system. The models chosen (PE and MR) are the same for*		

all three processes.

Part B

The materials have been selected to be biodegraded within the treatment window, e.g., one month. Consequently drug release and transfer to the mucosa must occur during this time. Therefore the time scales for drug release, transfer and particle degradation are similar and as these processes are also coupled (see workflow below) they must be modelled together. The geometry of the hydrogel film will be defined from the output of the N2B-patch applicator simulations (i.e., MODA-A).

In B1 we have hydrogel matrix biodegradation
In B2 we have drug release from biodegradable particles
In B3 we have drug diffusion through a gel matrix

- *Degradation of hydrogel matrix affects diffusion of water and drug.*
- *Degradation of particles influence drug release rate from particles.*

The models chosen (mass transfer, mass balance, reaction kinetics) are the same for all three parts and are solved in a tightly coupled way.

The initial geometry input to Model B1 is obtained from the output of Model A3.

Kommentar [AdB1]: See comment 2

Workflow
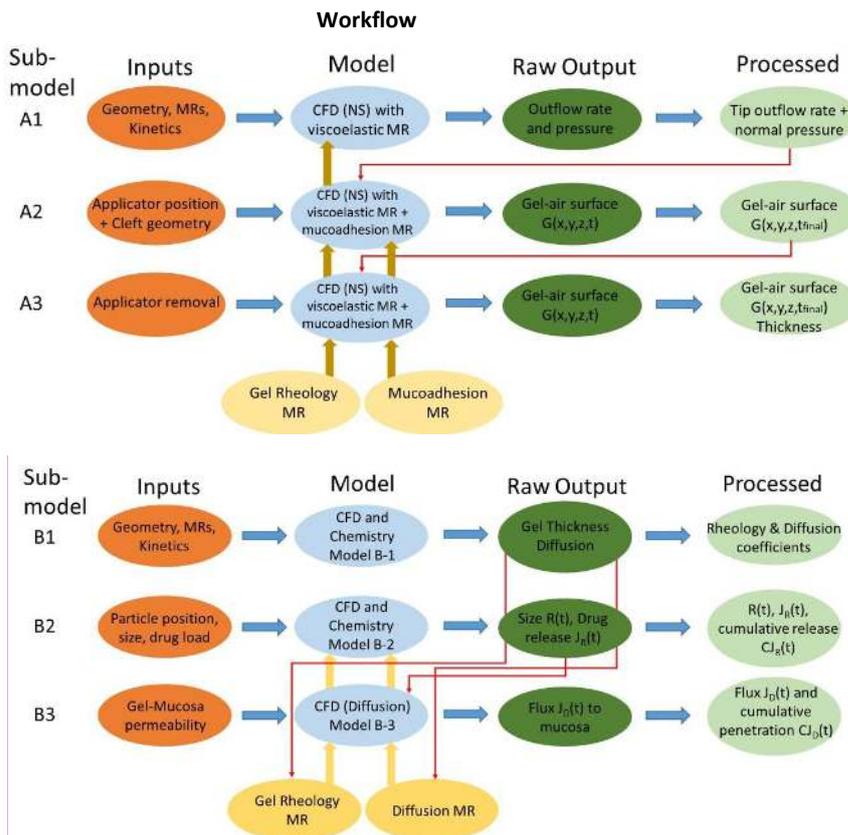
Kommentar [AdB2]: Can you insert a blue arrow indicating the output/input relation between part A and part B?

Note that both the gel rheology and the mucoadhesion are materials relations that can be described by corresponding equations or/and experimental data provided by the consortium.

Elements in materials modelling: from data to metadata

PART A Gel Attachment and Film Formation

1	**ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED**	
1.1	ASPECT OF THE USER CASE TO BE SIMULATED	*Fast gelling system, containing the drug loaded polymeric microparticles, based on hyaluronic acid mixed with a gelling agent in an applicator tube and then extruded from the applicator tube into the olfactory cleft region adjacent to the olfactory mucosa. After extrusion the gel comes into contact with the overlying mucosal surface, expands and forms a film that covers the mucosa.*
1.2	MATERIAL	*Tyramine derivative of Hyaluronic acid, hydrogen peroxide as crosslinking agent, water and chitosan coated polymeric microparticles.*
1.3	GEOMETRY	 Figure 1: (A) Simplified geometric representation for a computational model to describe the hydrogel application process at the olfactory cleft. (B) Problem description and assumptions for numerical simulation of the extrusion process, catheter detachment, matrix stability and degradation.
1.4	TIME LAPSE	*A few seconds for the HA extrusion and minutes for the hydrogel film formation*
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	*Body temperature, atmospheric pressure, 100% humidity*
1.6	PUBLICATION ON THIS ONE SIMULATION	

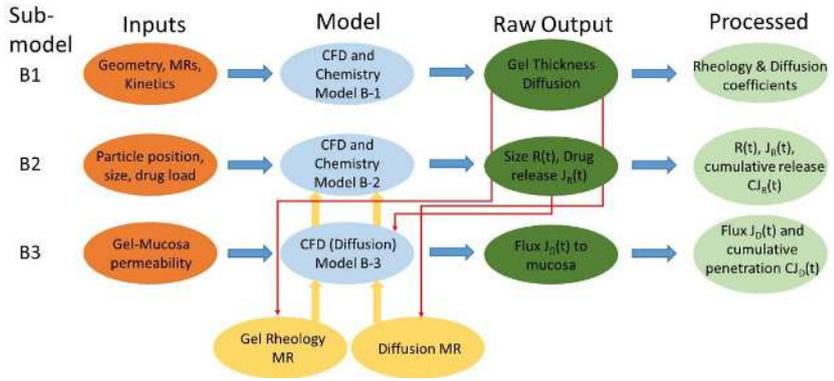| 2	**GENERIC PHYSICS OF THE MODEL EQUATION**		
2.0	MODEL TYPE AND NAME	4.2 & 4.5 Gel Attachment and Film Formation	
2.1	MODEL ENTITY	Finite volumes/surfaces	
2.2	MODEL PHYSICS/ CHEMISTRY EQUATION PE	Equation	PE1 - Navier-Stokes equations (NS) PE2 - Laplace-Young equation (LY) PE3 Chemistry model (reaction kinetics + mass balances) These form a tightly coupled system
		Physical quantities	Velocity Pressure

			Interface and contact line positions Concentrations Reaction rate constants
2.3	**MATERIALS RELATIONS**	**Relation**	*MR1* - Linear-viscoelastic "materials relation" completes NS and LY models *MR2* - Mucoadhesion "materials relation" completes NS and LY models MR3 – Reaction rate coefficients
		Physical quantities/ descriptors for each MR	*MR1 - In general, viscosity and elasticity quantities. Parameters number and values are dependent on the MR selected relation* *MR2 - Specific adhesion normal and tangential forces. Parameters number and values are dependent on the MR selected relation* *MR3 – Reaction rate coefficients.*
2.4	**SIMULATED INPUT**		As shown in the Workflow sub-models A2 and A3 employ as input results from the preceding sub-models, A1 and A2, respectively.

3	**SOLVER AND COMPUTATIONAL TRANSLATION OF THE SPECIFICATIONS**		
3.1	**NUMERICAL SOLVER**		*Finite volumes and boundary element methods (BEM)*
3.2	**SOFTWARE TOOL**		*ANSYS commercial fluid flow solver* *In-house BEM solver, cannot be shared, no website/publication.*
3.3	**TIME STEP**		*1ms< Dt <1s*
3.4	**COMPUTATIONAL REPRESENTATION** ,	**PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL**	*NS (A1: inertial, A2 and A3: Stokes) and LY (A2 and A3)* *MR1 is time-dependent due to the crosslinking reaction.* *MR2 is time-dependent due to the crosslinking reaction.* *Hyaluronic acid hydrogel*
3.5	**COMPUTATIONAL BOUNDARY CONDITIONS**		*Moving free-surface boundary between the extruded hydrogel and air.* *Hydrogel/mucous layer/air contact line follows a stick-slip boundary condition that is described by a mucoadhesion model* *Stick boundary conditions for the applicator tube with parabolic inflow conditions*
3.6	**ADDITIONAL SOLVER PARAMETERS**		*A1: 3D tetrahedral grid, ~10^6 cells to describe static mixer, explicit solver, 10^{-4} residuals* *A2 & A3: 1D (curve in 2D) with 10^1 -10^3 adaptive elements or 2D (surface in 3D) with 10^2 - 10^6 adaptive elements, explicit solver.*

Post processing

4	**POST PROCESSING**	
4.1	**THE PROCESSED OUTPUT**	Final hydrogel film thickness over the mucosa Percent mucosa coverage Mechanical stability to normal and shear forces.
4.2	**METHODOLOGIES**	Local thickness and percent coverage are obtained from the final position of the gel and the geometry of the olfactory mucosa. Normal distances from the olfactory mucosa are employed to determine thickness. Mechanical stability is determined based on minimal normal and shear forces necessary to displace the region of the gel in contact with the mucosa.
4.3	**MARGIN OF ERROR**	Local thickness and Mechanical stability need to be determined as accurately as possible, i.e., better than 10%.

Part B: Drug Release and Penetration to the Mucosa

		OVERVIEW of the simulation	
1	USER CASE	*Release of drug from biodegrading microparticles - embedded in a hydrogel matrix attached to the olfactory mucosa – and diffusion to the Olfactory mucosa.*	
2	CHAIN OF MODELS	MODEL B1	*Mass transfer and chemistry (mass balance and reaction kinetics) models for hydrogel matrix biodegradation*
		MODEL B2	*Mass transfer and chemistry (mass balance and reaction kinetics) models for drug release from biodegradable particles*
		MODEL B3	*CFD (mass transfer) for drug diffusion through a gel matrix*
3	PUBLICATION ON THIS ONE SIMULATION		
4	ACCESS CONDITIONS	*Restricted*	
5	WORKFLOW AND ITS RATIONALE	*The materials have been selected to be biodegraded within the treatment window, e.g., one month. Consequently drug release and transfer to the mucosa must occur during this time. Therefore the time scales for drug release, transfer and particle degradation are similar and as these processes are also coupled (see workflow below) they must be modelled together. The geometry of the hydrogel film will be defined from the output of the N2B-patch applicator simulations (i.e., MODA-A).*	

- *Note: Degradation of hydrogel matrix affects diffusion of water and drug.*
- *Degradation of particles influence drug release rate from particles.*
- *Sub-models B1, B2, and B3 are coupled and must be solved simultaneously.*
- *The initial geometry input to Model B1 is obtained from the output of Model A3.*

MODEL

1	**ASPECT OF THE USER CASE/SYSTEM TO BE SIMULATED**	
1.1	ASPECT OF THE USER CASE TO BE SIMULATED	*Release of drug from biodegrading polymeric microparticles (embedded in a biodegrading hydrogel matrix based on hyaluronic acid attached to the olfactory mucosa) and diffusion to the Olfactory mucosa.*
1.2	MATERIAL	*Hydrogel based on tyramine-derivative of hyaluronic acid, coated chitosan polymeric microparticles, and water.*
1.3	GEOMETRY	 Figure 1: Specific delivery of API at olfactory mucosa to ensure maximal CNS delivery.
1.4	TIME LAPSE	*One month*
1.5	MANUFACTURING PROCESS OR IN-SERVICE CONDITIONS	*Body temperature, atmospheric pressure, 100% humidity*
1.6	PUBLICATION ON THIS ONE SIMULATION	

2	**GENERIC PHYSICS OF THE MODEL EQUATION**		
2.0	MODEL TYPE AND NAME	*CFD(Diffusion) (4.2) and Chemistry (4.5)* *Drug Release and Transfer*	
2.1	MODEL ENTITY	*Finite volumes*	
2.2	MODEL PHYSICS/ CHEMISTRY EQUATION PE	**Equation**	*PE1 – Mass-transfer equations (Diffusion)* *PE2 – Chemistry model (reaction kinetics + mass balances)* These form a tightly coupled system
		Physical quantities	*Drug concentration* *Particle size, volume, mass, position* *Hydrogel matrix size, volume, mass* *Reaction rate constants*
2.3	MATERIALS RELATIONS	**Relation**	1. *MR1 - Viscoelastic materials relation completes PE1* 2. *MR2 - Drug diffusion coefficient MR affects PE1* 3. *MR3 – Hydrogel swelling MR affects PE1* 4. *MR4 – Degradation kinetic rate constants MRs affect PE2* 5. *MR5 – Drug solubility and partitioning MR affects PE1*
		Physical quantities/ descriptors for each MR	*MR1 - Viscosity and elasticity quantities. Parameters number and values are dependent on the MR selected relation* *MR2 - Drug flux and drug release rate. Parameters number and values are dependent on the MR selected relation* *MR3 – Thermodynamic degree of swelling in terms of environmental conditions (e.g., water content, gel crosslinking density). Parameters number and values are dependent on the MR selected relation* *MR4 – Degradation kinetic rate constants in terms of materials properties (e.g., molecular weight) and environmental conditions (e.g., moisture,*

			temperature).). Parameters number and values are dependent on the MR selected relation MR5 – Drug concentrations in the hydrogel and particle phases in terms of the environmental conditions and materials properties
2.4	SIMULATED INPUT		*Key input is the geometry of the applied hydrogel matrix. This is determined from the Applicator Model (MODA-A). As shown in the workflow figure, models B1, B2, B3 are tightly coupled.*

3	**SOLVER AND COMPUTATIONAL TRANSLATION OF THE SPECIFICATIONS**		
3.1	NUMERICAL SOLVER		*Finite Element Method (FEM), Finite Differences (FD), Collocation methods*
3.2	SOFTWARE TOOL		*FEM, FD, Collocation solvers, sharing will be decided, website will be set up later.*
3.3	TIME STEP		*1ms< Dt <1s*
3.4	COMPUTATIONAL REPRESENTATION ,	PHYSICS EQUATION, MATERIAL RELATIONS, MATERIAL	*Diffusion equation (B1,B2,B3).* *Mass balances and degradation kinetic models (for hydrogel – B1 and embedded microparticles – B2)* *MR1 is time-dependent due to hydrogel degradation.* *MR2 is time-dependent due to the degradation reactions.* *Hyaluronic acid Hydrogel* *Chitosan coated polymeric microparticles*
3.5	COMPUTATIONAL BOUNDARY CONDITIONS		*Key assumption is a zero drug concentration at the hydrogel/mucosa interface. This provides an upper limit to the drug mass flux. Alternatively finite constant values can be used based on experimental evidence.*
3.6	ADDITIONAL SOLVER PARAMETERS		*Explicit solver* *Tolerance =10^{-6}*

Post processing

4	**POST PROCESSING**	
4.1	THE PROCESSED OUTPUT	Drug flux as a function with time assuming a zero drug concentration at the mucosa. Drug delivery effectiveness as a % of drug load. Particles and drug loss due to degradation of the gel matrix.
4.2	METHODOLOGIES	Drug flux will vary with time but also position. A surface averaged flux will be obtained but also local averaged values, e.g., for the proximal olfactory region. Total drug delivery will be determined as a percentage of the drug load. Particles and drug lost will depend on the matrix degradation mechanism.
4.3	MARGIN OF ERROR	The total drug delivery will be calculated very accurately, i.e., <1%, excluding the percentage of drug loss due to matrix degradation.