Chapter 8

An Engineering Point of View on the Use of the Hydrogels for Pharmaceutical and Biomedical Applications

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Abstract

In this chapter, the modern uses of hydrogels in pharmaceutical and biomedical applications are revised following an engineering point of view, i.e. focusing the attention on material properties and process conditions. The chapter discusses the applications following the increase in scale-size. First, the nanoscale systems, i.e. hydrogel nanoparticles (HNPs), are analysed in terms of preparative approaches (polymerization methods and uses of preformed polymers) and with a brief mention of the future trends in the field. Secondly, systems based on hydrogel microparticles (HMPs) are examined following the same scheme (polymerization methods, uses of preformed polymers, a mention of novel and future trends). Thirdly, and last but not the least, the hydrogel-based drug delivery systems (macroscopic HB-DDSs) are presented, focusing in particular on tablets made of hydrogels, discussing the characterization methods and on the modelling approaches used to describe their behaviour. Other macroscopic systems are also discussed in brief. Even if the vastness of the field makes its discussion impossible in a single chapter, the presented material can be a good starting point to study the uses of hydrogels in pharmaceutical and biomedical sciences.

Keywords: nano-hydrogels, micro-hydrogels, macro-hydrogels, drug release, modelling

1. Introduction

Hydrogels are hydrophilic polymer networks, which are able to absorb and retain large amounts of water. Networks can be composed of homopolymers or copolymers, and their network

structure and physical integrity are due to the presence of cross-links of chemical (tie-points, junctions) or physical (entanglements, crystallites) nature. Based on the stability/strength of these cross-links, hydrogels can either withstand exposure to water or they can degrade and dissolve in water, after a given exposure time [1]. Because of the wide spectrum of chemical and mechanical properties as well as their excellent biocompatibility, hydrogels have been extensively investigated for pharmaceutical and biomedical applications [2–6]. In particular, hydrogels are the main component in controlled drug delivery systems (DDSs), as described in reviews by Kamath and Park [7], Peppas [8], Peppas et al. [4] and Hoare and Kohane [9]. For some drugs difficult to be administered, such as the protein, the hydrogels are one of the most important ways to delivery [10–15]. Hydrogels are also interesting because they can be prepared *in situ* [16–20], and their degradation times can be tailored by the used building blocks, the chemical nature of cross-links and the cross-link density [21]. Importantly, because of their high water content and soft nature, hydrogels are well tolerated by cells and tissues and therefore they possess a good biocompatibility [22]. Hydrogels are also under investigation in the form of nanogels as delivery systems for NABDs (nucleic acid-based drugs, such as pDNA, siRNA and mRNA) [23,24].

This chapter is intended to give an overview of the hydrogels in pharmaceutical applications, with a particular—even if not exclusive—focus on the research activities carried out at the University of Salerno by Transport Phenomena and Processes Group (http://gruppotpp.unisa.it). The chapter is organized following the size of the described systems: first of all, the applications of nanoscale hydrogels are discussed, then the micro-scale hydrogels are analysed and, last but not the least, macroscopic drug delivery systems based on hydrogels are presented. Of course, since this is a huge topic, the chapter cannot be exhaustive but it has to be considered as a guiding path to explore the active researches in the field.

2. Nano systems

Over the past few years, hydrogel nanoparticles (HNPs) or nanogels have been investigated as carrier systems for site-specific and/or time-controlled drug delivery. The reason for this interest is because of the combination of the features of a hydrogel, i.e. hydrophilicity, high water content and swelling ability, useful for controlled release [25] with those of a nanoparticle, especially the small size [26]. Both synthetic and natural polymers can be used in hydrogel nanoparticles production for their different surface properties or bulk erosion rates to control the release rate of active molecules. The former (synthetic polymers) include especially block copolymers consisting of two or more segments of simple polymers (blocks) joined in some arrangement, such as the biodegradable and biocompatible poly(D,L lactic acid) (PLA), poly(glycolic acid) (PGA) and their copolymer poly(D,L-lactic-co-glycolic acid) (PLGA)polyvinyl alcohol and polyethylene oxide [27]. The latter (natural polymers) are characterized by a variety of functional groups, a wide range of molecular weights and variable chemical composition. Among them, polysaccharides are the more often used: they are carbohydrate-based polymers formed of repeating units (monosaccharides) joined together by glycosidic bonds and can be of algal (alginate), plant (cellulose, starch) and animal (chitosan) sources [28]. Therefore, hydrogel nanoparticles are ideal drug-delivery systems due to their

excellent drug loading capacity, high stability, biologic consistence, flexibility, versatility, biocompatibility and response to a wide variety of environmental stimuli (such as ionic strength, pH and temperature) [29]. The techniques for preparing hydrogel nanoparticles can be divided into two main categories: methods exploiting the direct polymerization of monomers (based on chemical cross-links) and methods based on the use of preformed polymers (based on physical interactions) [30].

2.1. Polymerization methods

The preparation of HNPs via monomer polymerization includes two simultaneous steps, polymerization and formation of nanostructures, that can be accomplished by interfacial polymerization, by emulsion polymerization or by controlled radical polymerization [31]. For example, an inverse emulsion polymerization method was used for poly(ethylene glycol) (PEG) cross-linked acrylic nanoparticles for the controlled release of curcumin, a hydrophobic molecule that inhibits proliferation and induces apoptotic cell death in numerous cell lines established from malignancies such as leukaemia, breast, lung, prostate and colon tumours [32]. In particular, emulsification was obtained by dispersing the aqueous phase, made of 10% acrylic acid, 5% sodium hydroxide and 15% water, in a continuous lipophilic phase consisting of liquid paraffin (68%) and emulsifiers (2%): Span 80 and Tween 80 (75:25 ratio). To the mixture, first a PEG diacrylate (1%) as cross-linker and then the initiator, ammonium persulphate, were added. The polymerization was performed at 60°C for 6 h. The obtained particles were centrifuged, washed and finally freeze-dried. Curcumin was loaded in polymer nanoparticles after polymerization: a nanoparticle/water solution was placed in contact with a solution of curcumin dissolved in chloroform under constant stirring (by vortex) and sonication. The curcumin-loaded nanoparticles were then lyophilized. They showed a higher entrapment efficiency and lower particle size with the decrease of the cross-linking degree, and a release rate dependent on the pH of the releasing medium, in particular, a high swelling at pH 7.4 than at pH 2.2. However, a higher cross-linking degree caused a reduction of the HNPs swelling at pH 7.4, thus a more controlled increase in mesh size that allowed a lower initial burst release followed by a sustained release. Moreover, curcumin HNPs showed *in vitro* a cellular uptake similar to their free counterpart confirming their ability to overcome the barrier of curcumin's aqueous dispersibility, facilitating the *in vivo* administration. Again, they showed more cytotoxicity and apoptotic effects towards cancer cells than free curcumin, thanks to both nanoparticulate form and the use of hydrophilic polymers for minimizing the opsonization and prolonging the *in vivo* circulation of HNPs. A different polymerization technique was the PRINT (particle replication in non-wetting templates) particle fabrication technique, which is characterized by a higher degree of difficulty, but by complete, orthogonal control over particle characteristics, and an easiness of scaling up [33]. Ma et al. proposed a PRINT particle fabrication technique for the production of hydrogel nanoparticles conjugated with siRNA (short interfering RNA, highly used for gene therapy) [34]. The same technique was used by Kai et al. for the nano-encapsulation of cisplatin, a cytotoxic drug used in therapy against a wide variety of cancers [33]. In both cases, a pre-particle solution was prepared by dissolving different percentages of reactive monomers in methanol, where the reactive monomers were: a cure-site monomer, the oligomeric poly(ethylene glycol) (PEG,

MM: 700 g/mol) with terminal acryloxy functionality; a hydrophilic monomer, tetraethylene glycol monoacrylate (HP4A); an amine containing monomer, 2-aminoethyl methacrylate hydrochloride (AEM), for providing the amine functionality needed to conjugate PEG onto the surface of the PRINT particles; a photoinitiator, diphenyl (2,4,6-trimethylbenzoyl)-phosphine oxide (TPO). A thin film was drawn onto polyethylene terephthalate (PET), laminated to the patterned side of the mould and delaminated at the laminator nip roll. Then particles were cured by passing the filled mould through a UV-LED; a polyvinyl alcohol harvesting sheet was hot laminated to the filled mould and cooled to room temperature and particles were removed from the mould by splitting the harvesting sheet from the mould. Particles were then harvested by dissolving the polyvinyl alcohol in water and passed through a filter. After centrifuge, the cisplatin-containing particles were also subjected to PEGylation and succinylation. Incubation of the active molecules for obtaining the conjugation with the HNPs followed. siRNA-conjugated HNPs were characterized by a loading efficiency of up to 29% and high transfection efficiency *in vitro* by efficiently controlling hydrogel composition, surface modification and siRNA loading ratio. For cisplatin HNPs, an inverse correlation between PEG density (conformation that surface-bound PEG chains achieve: 'mushroom conformation', with low density PEG coverage, i.e. PEG chains are not fully extended away from the nanoparticle surface, and 'brush conformation' with the PEG chains extending away from the nanoparticle surface, resulting in a thick layer) and drug loading, and an improved exposure in the blood (higher total amount of drug reaching circulation) and tumour accumulation (due to both nanodimensions and PEG presence), with concurrent renal protection were observed.

2.2. Preformed polymers: physical and chemical interactions

Chemically cross-linked nanogels need the presence of reactive sites along the polymer chains. Some polymers possess inherent reactive sites, such as polyethyleneimine (PEI) with a high density of amine functional groups, or natural polymers containing amine or carboxylic acid groups. Chemical cross-linking provides nanogels with a great structural stability owing to irreversible inter- or intra-molecular covalent bonding formations. The chemical networks in the core inhibit the simple diffusion of hydrophobic drug molecules, giving enhanced encapsulation efficiency. However, some drawbacks can arise—sometimes the desired functionality requires complex chemical modifications of cross-linkers causing the loss of nanogel versatility; also, small chemicals for the cross-linking reaction can be toxic for medical uses [35].

2.3. Novel and future trends

Physically cross-linked HNPs, usually obtained in aqueous media with mild conditions, can be modified in size by changing some parameters, such as the pH value, ionic strength and temperature [29]. In particular, amphiphilic polymers can self-assemble into micelles with core–shell structure: the hydrophilic outer shell allows a prolonged circulation, i.e. it is a barrier against recognition and opsonization, and the hydrophobic core increases the drug loading via hydrophobic or electrostatic interactions [36]**.** Physical interactions are of two typologies:

amphiphilic association, based on Van der Waals links, including hydrogen bond and hydrophobic interaction, and electrostatic interaction. Used preformed polymers can be consequently divided into amphiphilic or triblock copolymers that form self-aggregates in water by undergoing intra- and/or inter-molecular association between hydrophobic moieties due to the minimization of interfacial free energy, and polymers modified with the aim to have reactive sites to form physical cross-links via electrostatic interaction [37]. To obtain physical cross-linking by self-association, hydrophobic polymers chains, such as poly(lactic acid), were grafted on a backbone of dextran in order to obtain water-soluble biodegradable graft copolymers of dextrose and PLA able to form nanometric aggregates in an aqueous solution [38]. The nanogel was prepared by the solvent exchange method: the copolymer was first dissolved in dimethyl sulphoxide (solvent for both PLA and dextran); then distilled water was added at a rate of 1 drop every 10 s under high shear stirring until a water content of about 30–50 wt% was reached; the resulting solution was dialyzed for organic solvent removal, after that the solution turned slightly opaque because of an aggregate formation with the hydrophobic PLA cores and the hydrophilic dextran skeleton. The mean diameters of the aggregates ranged from 16 to 73 nm with narrow size distribution. Moreover, copolymers showed low critical aggregation concentration values, further decreasing by increasing the amount of hydrophobic PLA, indicating a strong tendency of the copolymers towards formation of stable nanogels.

Recent trends in preparation of HNPs exploit the use of a hydrogel core in liposome nanoparticles to obtain lipogels. Liposomes are vesicular structures consisting of an aqueous core enclosed in one or more phospholipid layers which possess low intrinsic toxicity and immunogenicity, capability to incorporate hydrophilic and hydrophobic drugs and good biocompatibility [39]. Wang et al. demonstrated for the first time the possibility to form a poly(acrylic acid) (PAA) hydrogel core in liposomes for the encapsulation of an anticancer drug 17-DMAPG, a geldanamycin (GA) derivative [40]. In particular, a PAA hydrogel core was formed inside liposomes (already produced by the thin film hydration method) through UV-initiated activation and polymerization of acrylic acid (AA) and N,N'-methylenebis(acrylamide) (BA). An optimized pH gradient and electrostatic/hydrophobic interactions between cationic drug and anionic gel in the liposomal core were used to obtain about 90% of loading efficiency of the active molecule and its sustained release independently of the external solution pH, confirming that the lipid bilayer was intact in the presence of the gel core. Moreover, lipogels did not exert cytotoxicity to cells *in vitro* neither at the highest concentration tested (about 0.4 mg/ml of material).

These few examples showed how polymeric hydrogel nanoparticles are particularly attractive, thanks to their easiness of production, affordability and ability of incorporating a variety of active molecules, including proteins, peptides and oligosaccharides, anti-tumour agents and vaccines. However, the development of these systems still require a more comprehensive characterization, especially about the structure of the HNPs, the application of novel materials with targeting and environmental sensitivity, the toxicology effect and the interaction with cells and tissues *in vivo*, before their full potential can be exploited.

3. Micro systems

When hydrogels are in the form of macroscopic links confined to micrometric dimensions, they are termed as microgels or hydrogel microparticles (HMPs), which are different in size from the sub-micrometrc HNPs (nanogels) [41]. The size of the particles is a crucial factor in determining their properties: the specific surface area of a spherical particle, as well as the diffusion rate, is inversely proportional to the diameter, and the time required for a stimulus to reach the centre of a gel particle is proportional to the square of the particle's diameter. Thus, a smaller particle is a much quicker and more serviceable tool; however, if the particles are too small, they sometimes can cause problems such as difficulty in handling, difficulty in recovery, unavoidable dissipation and so on. Due to their size and environmentally sensitive nature, microhydrogels can be used as smart micro-containers, micro-reactors, building block for intelligent materials and for optically functionalized devices [42]. Microgels show unique advantages in comparison with other polymer systems: in particular, a fast response rate to external stimuli; suitability for subcutaneous administration; high biocompatibility for the large amount of water in the swollen state; a large surface area for multivalent bioconjugation; an internal network for the incorporation of several active molecules, thus large drug loading capacities; and adjustable chemical and mechanical properties, and soft architecture enabling them to flatten onto vascular surfaces, thus simultaneously anchoring in multiple points [43]. As already seen for HNPs, hydrogel microparticles can be formed from both natural and synthetic polymers and produced by essentially two methods: particle-forming polymerization, including inverse emulsion polymerization and precipitation polymerization, and molecular assembly of existing polymer molecules in aqueous solutions, aided by the external stimuli, such as temperature, pH and/or the presence of polivalent ions [44]. In particular, microgels of synthetic polymers are usually obtained starting from a monomer, such as acrylic acid, methyl methacrylate, acrylamide and ethylene glycol. Some examples are pH-sensitive hydrogel P(MAA-co-EGMA) microparticles obtained by dispersion photopolymerization by using MAA and ethylene glycol (EG) as monomers [45] and pH-sensitive microhydrogels prepared from N-vinylcaprolactam and methacrylic acid monomers by free radical polymerization [46]. Instead, biopolymer microgels are obtained either by the polymer itself, for example, alginate or chitosan that is gelled in a microparticle, or by a macro-gel, which is mechanically comminuted for producing anisotropic and irregularly shaped microgels, of high interest for tissue replacement applications [47], for biosensor, diagnostics and targeted drug delivery [48]. Methods for producing HMPs are shown in **Table 1**.

Particle properties which can be manipulated to obtain good entrapment and release properties are: the degree of crosslinking; particle size and size distribution; polymer type (controlling their responsiveness to the environment pH, temperature or enzymatic response); particle surface charge; and particle shape from spherical to elongated rods and fibres. HMPs can also be designed to shrink or swell by creating an imbalance in the osmotic pressure between their inside and outside via alteration of pH, temperature or ions in the suspension [49]. Moreover, existing microhydrogels can be modified to improve their properties or functions by using post-treatments such as surface modification, that is, surface grafting or

surface graft polymerization, and composite formation by inclusion in HMPs of functional nanoparticles, such as colloidal metals, semiconductor nanocrystals and magnetic nanoparticles.

Polymerization methods	Molecular assembly
Dispersion photopolymerization: It involves the mixing of monomers with the addition of cross-linker, UV-initiator and dispersion stabilizer followed by ultraviolet light irradiation	**Emulsion technique:** Uniform-sized droplets (obtained by microfluidics or membrane method) are dispersed into a continuous phase resulting in oil in water, water in oil or multiple emulsions. After the formation of emulsion, the cross-linking agent is incorporated to harden the final product.
Free radical precipiation polymerization: It is a heterogeneous polymerization that involves a continuous phase in which monomer and initiator are completely soluble. When the reaction starts, the yielded polymer remains insoluble and precipitates.	**Physical gelation:** Uniform-sized droplets (obtained by atomization by different ways, such as twin nozzle or ultrasonic atomization) of biopolymer form a network structure through non-covalent bonds, such as hydrogen bonding, electrostatic (ionic) interactions and hydrophobic interactions, under specific conditions (for example, temperature or pH).
Free radical polymerization: It involves a repeated addition of free radicals building blocks and requires polymer, monomer, initiator, and cross-linker. In most cases, the HMPs are obtained by passing hydrogel through a sieve of desired size, using an anti-solvent, or by stirring at a high rate.	**Chemical gelation:** Uniform-sized droplets (obtained by atomization by different ways, such as twin nozzle or ultrasonic atomization) of biopolymer form a network structure via covalent bonds with a chemical cross-linking agent.
Inverse emulsion polymerization: It involves the water in oil polymerization method: water-soluble droplets are uniformly dispersed by mechanical stirring in a continuous organic phase with the help of oil-soluble surfactants. Polymerization is initiated in aqueous droplets upon addition of a radical initiator.	**Macro-gelation:** It involves the comminution of a macro-gel during its gelation in microgel by shearing the gel to form uniform droplets or, for proteins, by interrupting the aggregation process of random coil proteins with shearing or denaturing the protein, followed by cooling to form a network gel structure.
Ionic gelation method: A solution containing the monomer–cross-linker and a solution with the polymer and an initiator are mixed, and the reaction is carried out at a given temperature for a specific time.	

Table 1. Methods for producing HMPs.

3.1. Polymerization methods

As shown in **Table 1**, the production of HMPs via polymerization can be accomplished by several methods, that is, photopolymerization, precipitation polymerization, free radical polymerization, inverse emulsion polymerization and ionic gelation polymerization. Han et

al. produced hollow-structured poly(vinyl amine) (PVAm) hydrogel particles, which are able to encapsulate macromolecules, by using the *in situ* hydrolysis/cross-linking reaction on poly(N-vinylformamide) (PNVF) particles, previously obtained by using dispersion polymerization [50]. PNVF particles were produced by performing the polymerization at 70°C for 24 h of a mixture of 19 g of *N*-vinyl formamide and 1 g of *N*,*N*'-methylene-bisacrylamide (MBA) in 170 g of methanol containing an initiator, 2,2'-azobis(isobutyronitrile) (AIBN) and a stabilizer, poly(2-ethyl-2-oxazoline) (PETOZO). After polymerization, all unreacted monomers and additives were completely removed by repeated centrifugation with an ethanol. The PNVF particles (about 1 g) were then re-dispersed in an ethanol solution containing glutaraldehyde, GA (76 ml, conc. GA: 0.1 mol/l). Then, 40 g of a 2 N sodium hydroxide aqueous solution was slowly added and the reaction was carried out at 80°C for 12 h. After washing away by-products, PVAm hydrogel particles were obtained. They were generated by competition between the partial disconnection of the cross-linked network in the centre part of PNVF particles and the secondary cross-linking induced by additional reaction of glutaraldehyde with primary amine groups in the PVAm chains located at the periphery of the particles (the secondary cross-linking depended on the glutaraldehyde diffusion from the continuous phase). Particles were characterized by an average diameter of 2.3 μm and showed a discrete spherical hollow capsule structure. As the cross-linked hydrogel shell is formed by the diffusion-limited secondary cross-linking, the thickness of the shell was constant at approximately 250 nm (the cross-linking density could be tuned by changing the concentration of glutaraldehyde). Except the cases using a high amount of glutaraldehyde, all the particles were found to be non-toxic to the cells, that is, it is the glutaraldehyde moiety that affects the cell viability, and not the cationic moieties in PVAm chains. Moreover, regardless of the cross-linking density of the hydrogel phase, the HMPs were very adhesive to both the normal human keratinocyte cells and the normal human dermal fibroblast cells. Thus, the carrier system seemed to be applicable for macromolecule delivery into the cell.

Thermo-sensitive microgels useful as drug carriers were produced by precipitation copolymerization of N-isopropylacrylamide (NIPAM) and N-hydroxyethylacrylamide (HEAM) with various concentrations of a cross-linker in the presence of an anionic surfactant, sodium dodecylsulphate (SDS) [43]. In particular, the poly(NIPAM-co-HEAM) HMPs were synthesized by free radical precipitation polymerization: a water solution of NIPAM, HEAM, N,N'-methylene-bis-acrylamide (BIS) and SDS was first heated to 70°C under a gentle stream of nitrogen, after 1 h a solution of potassium persulphate (KPS) was inserted to start the reaction, that proceeded for 8 h. After cooling the product to room temperature, the obtained HMPs were purified by dialysis and then freeze-dried. The monomer ratio was defined by the knowledge that the linear copolymer poly(NIPAM-co-HEAM) at 10:2 molar ratio in the initial reaction mixture has a lower critical solution temperature (LCST) close to the physiological temperature of 37°C. The volume phase transition temperature (VPTT, a characteristic of all thermoresponsive gels) was evaluated by different methods and it approached very close to the human body temperature, thus confirming the applicability of these HMPs for biomedical and biological applications (requiring a sharp phase transition around the physiological temperature). In effect, the *in vitro* release rates of a model drug, propranolol, was strongly influenced by the temperature: below the VPTT, when HMPs were in a swollen state and no

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steric or hydrophobic interactions occurred, the drug was rapidly released, whereas above the VPTT, shrunk HMPs produce a reduced release rate.

3.2. Molecular assembly

Self-assembly methods are characterized by the use of amphiphilic polymers that spontaneously form self-aggregates in water (in this way the uses of solvents and harsh reaction conditions are avoided) by undergoing intra- and/or inter-molecular association between hydrophobic moieties due to the minimization of interfacial free energy. This process allow the production of both particles with a shell-core structure and good stability, depending on hydrophobic/hydrophilic constituents and polyelectrolytes complexes between two polymers having different charges, for example, polysaccharides of complementary charge. Moreover, polyelectrolytes can aggregate into microparticles by cross-linking with substances with opposite charge via electrostatic interaction by the ionotropic gelation [30]. For example, chitosan undergoes ionic gelation due to the complexation with oppositely charged species, such as tripolyphosphate (TPP). Barba et al. deeply studied the release kinetics and the influence of the structure of chitosan-TPP complexed particles on transport phenomena [51]. In particular, vitamin B12-loaded chitosan microparticles were produced by dripping or nebulizing via ultrasonic atomization in a water solution of 1% w/w chitosan (containing 0.2% w/w of B12) in the cross-linking solution of 1% w/w TPP (with defined reticulation time and stirring), as shown in **Figure 1**. Then particles were filtered, washed and finally stabilized by convective drying at 50°C. The concentration of chitosan was chosen taking into account that low values brought low encapsulation efficiency and poor particles consistence, instead, at

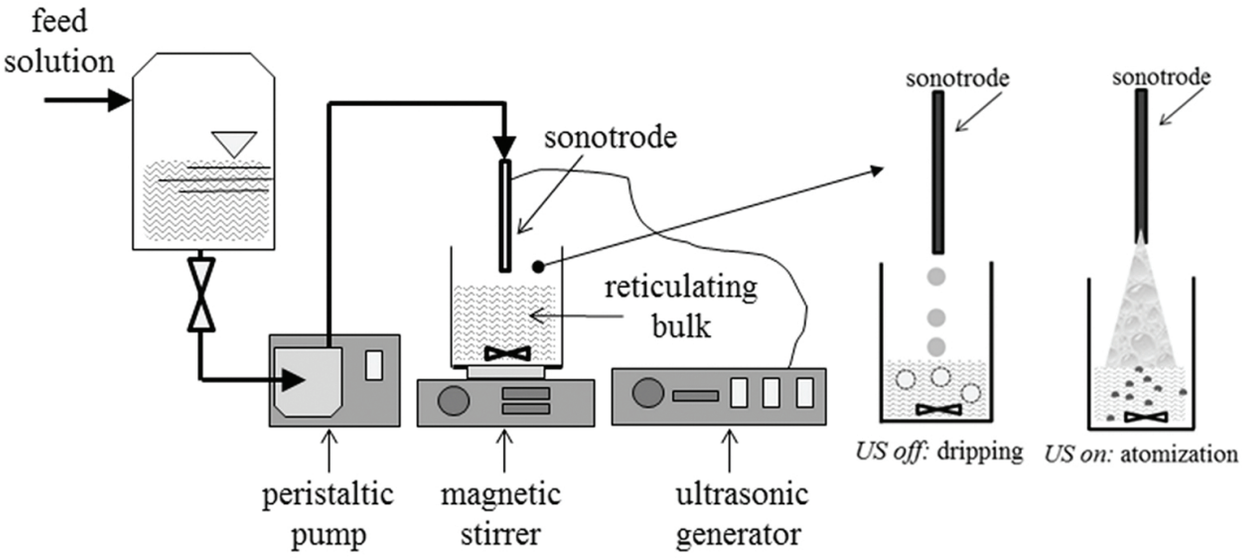

Figure 1. Sketch of the homemade apparatus assembled and used to produce chitosan and alginate cross-linked HMPs. From Barba et al. [51], Copyright © (2012) Croatian Society of Chemical Engineers.

large values, highly viscous solutions that are difficult to process are obtained. In a similar manner, the concentration of TPP was chosen, taking into account that chitosan cross-linked structure obtained at pH 3 had a higher density (and lower porosity) then those reticulated at pH 9. The milli- and micrometric particles (from dripping and ultrasonic atomization, respectively) presented an average diameter of 3.75 mm and 613 μm, respectively. High losses of B12 in the reticulating bulk, giving a low encapsulation efficiency, and a very fast B12 release rate were observed for both the particles: after 30 min more than of 70% of active molecule was transferred in the dissolution bulk. These phenomena suggested that diffusion was the dominant transport phenomenon, thus polymeric network mesh-size (PNMS) was placed under investigation. A simple model of the drug release was proposed, considering a drug-containing spherical particle inserted in a dissolution medium, to obtain the evolution of the drug concentration with time, in function of known or estimated parameters, such as number of particles, particles radius, volume of dissolution medium and initial drug loading concentration, and of the unknown parameter B12 diffusivity:

$$C_A^O(t) = N\frac{4\pi a^2}{V_2}\frac{D}{\delta}C_{A0}^I\tau\left[1-\exp\left(-\frac{t}{\tau}\right)\right] \tag{1}$$

In Eq. (1) the time constant τ is:

$$\tau = \left[\left(4\pi a^2\right)\frac{D}{\delta}\left(\frac{1}{NV_1}+\frac{1}{V_2}\right)\right]^{-1} \tag{2}$$

The fitting between experimental data and model data allowed to calculate the B12 diffusivity through the polymeric shell resulted in larger milli-metric particles because the kinetics (and the extent) of the reticulation may be affected by the size of the produced droplets and ultrasound can have an effect on gel network. These values were inserted in a relationship obtained starting from the volume free theory (proposed by Lustig and Peppas and tested by Amsden):

$$\frac{D}{D_0} = \left(1-\frac{r_s}{\xi}\right)\exp\left(-\gamma\frac{\varphi}{1-\varphi}\right) \tag{3}$$

In this way, they were able to calculate the mesh sizes of two kind of particles (2.3 nm for milli-particles and 1.2 nm for microparticles), that were shown to be larger than the B12 Stokes radius (0.86 nm, estimated by www.chemspider.com); thus, they were able to demonstrate that the hydrogel structure had to be modified (by physical protocols, for example, by microwaves curing, or by the use of reactive chemical agents) in order to keep the active molecule inside.

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The same relationship was already used for estimating the release of a little molecule, theophylline (TP), from calcium chloride-cross-linked alginate HMPs [52]. Production of particles was performed in the same plant used for chitosan (**Figure 1**). An alginate/TP aqueous solution was atomized into a beaker containing 80 ml of a stirred calcium chloride solution (concentration 8.9 g/l) in order to have a rigid network deriving from the coordination of alginate molecules by bivalent positive ions. Once reticulated, the alginate particles were separated by centrifugation or by filtration and dried. Also in this case, the mesh size of

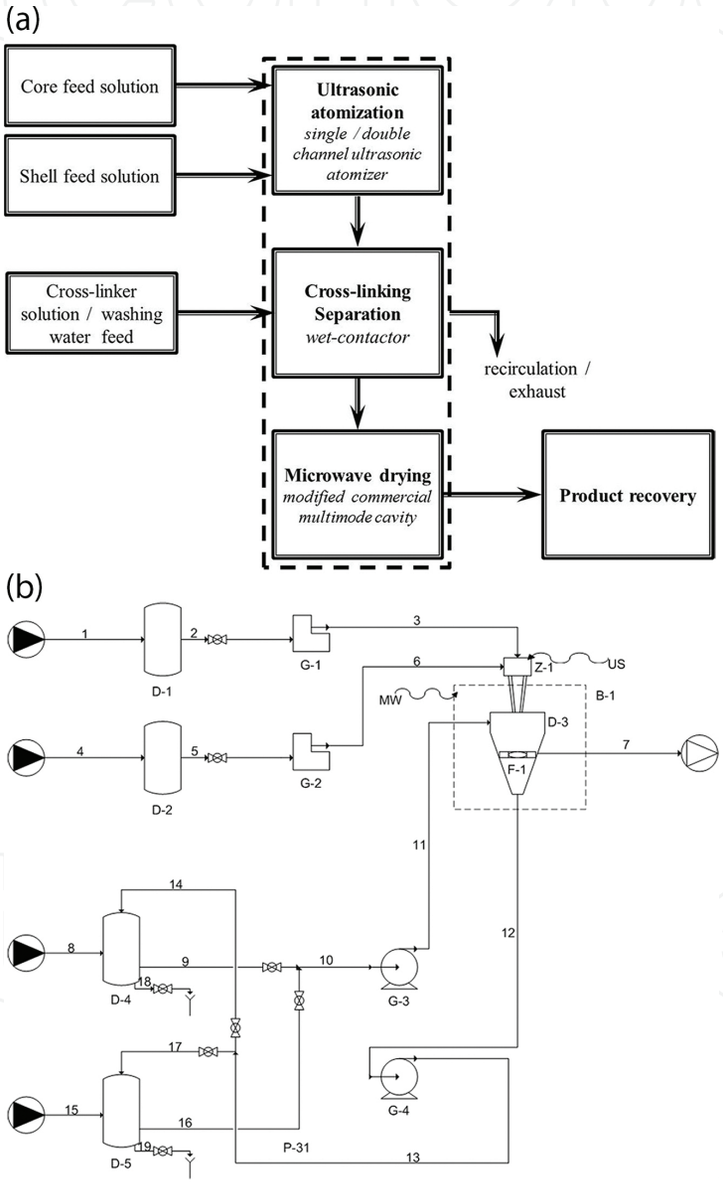

Figure 2. (A) Schematic diagram of the microparticles production. (B) Layout of the microencapsulation single-pot semi-continuous bench scale apparatus (Z-1, ultrasonic double channel atomizer; D-3, wet collector; B-1, microwave oven cavity; G-1/G-2, peristaltic pumps-core and shell feeding channels; G-3/G-4, centrifugal pumps-reticulation solution feeding and suspension recirculation; D-1/D-2, core and shell feeding tanks; D-4/D-5, reticulation solution tank, rinsewater tank; and F-1, filter; box with dashed line: MW cavity). Reprinted with permission from Dalmoro et al. [54], Copyright © (2014) American Chemical Society.

polymer network was not able to retain the small molecule: from the equation of the release kinetic by diffusion from a sphere, using the estimated TP diffusivity in sodium alginate membranes and the particles size (about 100 μm), a 99.9% release of the encapsulated drug after 2–3 s in a water medium (thus the cross-linking bulk) was estimated. To improve the entrapment of a model drug in cross-linked alginate particles, an external protection could be the right choice, thus shell-core particles were produced and compared to matrix (only core) system. Dalmoro et al. produced both shell-core and matrix beads of alginate encapsulating vitamin B12: the shell water solution (alginate 1.5% w/w) and the core water solution (alginate 1.5% w/w and B12 0.525 g/l and some drops of Tween 80) were separately pumped, under controlled conditions, into a stainless steel coaxial double-channel device (a variant of a typical drop generation systems, such as a syringe used to produce large drops) and dropped into a stirred water calcium solution (0.89% w/v) to promote alginate chains reticulation. For matrix particles production, only core channel was fed. After a given time of exposure to calcium ions, they were filtered, and washed by distilled water. Dissolution tests of B12-loaded particles showed that the presence of an additional thin layer of reticulated alginate (the shell-core structure) reduced losses during production, giving a loading B12 ratio of about 70% for shell-core systems, higher than that of matrix systems, of about 45% (same value theoretically estimated from the equation of the release by diffusion from a sphere), and allowed a delayed B12 release [53]. An evolution of shell-core dripping was the use of a double-channel ultrasonic nozzle for the production of shell-core HMPs. Dalmoro et al. proposed the design of a novel process to produce microparticles with a shell-core structure in a bench scale apparatus purposely realized, involving the coupling of atomization assisted by ultrasonic energy and microwave heating for stabilization (**Figure 2**) [54].

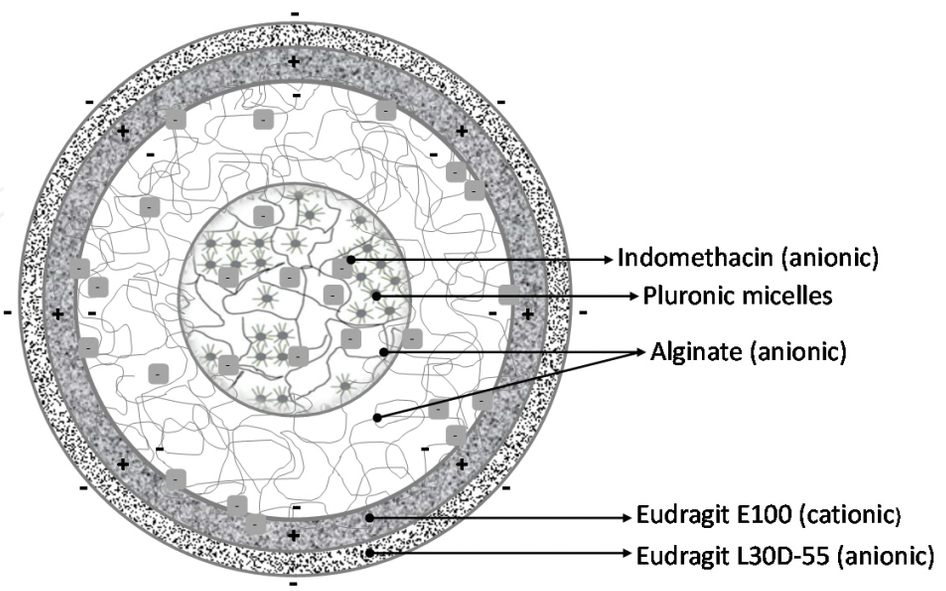

Figure 3. Structure of the HMPs produced by ultrasonic-atomization—two stage polyelectrolyte complexation. From Dalmoro et al. [59], Copyright © (2016).

A core feed aqueous solution, composed of 1% active principle, α-tocopherol, 1.5% alginate and a mesh size reducer, Tween 80 (as previously described in [53]), together with the shell feed solution, made of an aqueous solution of 1.5% alginate, were sent to the coaxial ultrasonic atomizer for the nebulization in the $CaCl_2$ cross-linking aqueous solution. Then they were filtered and stabilized in the same apparatus and finally recovered. Also in this case, the matrix system was obtained by atomizing only the core solution, containing the active molecule and alginate, in the inner channel leaving the external one empty. Both the kinds of HMPs (shell-core and matrix) showed an encapsulation efficiency of around 100% and globally good enteric release properties because α-tocopherol was negligibly released at simulated stomach pH 1, and completely released only at intestine simulated pH 6.8. Again, shell-core HMPs were preferable to matrix ones, confirming the functional role of the shell structure because they showed a better gastro-resistance, that is, a smaller amount of α-tocopherol released at acidic pH. Moreover, microwave treatments, used for stabilization, proved to be useful in controlled drug release since they caused a little delay in α-tocopherol release, especially for shell-core HMPs. The described production process not only gave alginate HMPs with good drug release and entrapment properties, but shown several other advantages [55], that is, it was simple, able to operate at room conditions and in absence of solvents, low energy consumption, thanks to the use of ultrasound compared to conventional techniques of atomization [56], with easily predictable and tuneable features (size) of the micro-droplets as function of process parameters [56,57]. The process proved to be versatile allowing the encapsulation of a molecule, ergocalciferol (vitamin D2), which is less lipophilic than α-tocopherol [58]. The alginate concentration and flow rates of shell and core solution were kept unchanged. The variations needed to encapsulate D2 were: vitamin D2 was first dissolved in ethanol and then emulsified with the aqueous core feeding solution in order to achieve a concentration of 0.2% (w/v) of D2; Tween 80 in core solution as stabilizer was replaced by Pluronic F127 for its amphiphilic properties, that is, for its ability to link to alginate with the hydrophilic moiety and to D2 with the hydrophobic one. Optimization of manufacturing parameters allowed to obtain high encapsulation efficiency (nearly 92%); good gastro-resistance properties (less than 10% release at pH of 1.0, nearly 100% release at pH of 6.8 and 240 min of dissolution); limited ergocalciferol degradation after 5 months of storage, reduction of D2 degradation during microwave-assisted stabilization process compared to the convective one. Another modification of the process, that is, the coupling of the ultrasonic atomization technique with the polyelectrolyte complexation, allowed to produce enteric shell-core HMPs encapsulating an anionic gastrolesive drug, indomethacin (**Figure 3**) [59]. Again, both the solutions, core and shell feed (with unchanged features), were sent to the coaxial ultrasonic atomizer where they were nebulized and placed in contact with the cross-linking solution. In this case, the cationic Eudragit® E 100 (E100) was used as a new complexing agent for the anionic alginate and also to interact with the anionic drug to raise encapsulation efficiency. However, E100 dissolves at pH < 5, thus particles obtained after cross-linking were filtered and put in a solution of the anionic Eudragit® L30D-55 (L30D) copolymer that interacted with the cationic E100 and formed an external gastro-resistant layer on the fine droplets (fresh shell-core microparticles). HMPs were then centrifuged and freeze-dried. The interaction of the cationic E100 with alginate first, and then E100 with L30D-55, obviously caused the formation of larger parti-

cles than the previous cases where there was the interaction of alginate with bivalent ions. Also, HMPs obtained by the double complexation method showed high encapsulation efficiency (about 74%) and good enteric release properties.

3.3. Novel and future trends

The methods used for HMPs production are numerous and their suitability depends on the polymer carrier as well as the functionality, particle size and particle size distribution required. Some methods are accessible at industrial scale, although methods producing HMPs with a mono-disperse size distribution are currently best suited to laboratory-scale manufacturing only [49]. Moreover, HMPs are sometimes very sensitive to the presence of contaminants, thus this feature must be improved for enlarging their application field. Therefore, the research must aim at the development of novel innovative matrices with controlling mechanical viscoelastic properties, versatile swelling performance, size and internal organization, triggered degradation behaviour and the enhancement of their biological interactions with body components. It will be also interesting to explore 'softness' for developing biomimetic particles (i.e. artificial cells), shape changing colloids or particles which evolve or move in time based on local chemical cues from each other or other entities (e.g. cells). Fundamental will be also the studies about the mechanisms of passive (traditional methods, i.e. polymerization or gelation) and driven (innovative methods, such as lithographic processing where hydrogel colloids are templated in a highly controlled and reproducible manner) self-assembly in HMPs. There are also still many opportunities not yet realized in the food industry, such as the possibility to use them for food preservation (thus, compatibility with foods), satiety control, encapsulation of phytonutrients and prebiotics and texture control for healthier food formulations.

4. Macro systems

4.1. Compressed tablets

Among the compressed systems used in oral administrations, the hydrogel-based tablets and matrices are the most diffused and, consequently, studied. The process of drug release from a hydrogel-based matrix is very complex and different transport phenomena have to be taken into account. For these reasons, during the years several experimental techniques and modelling approaches have been developed to describe the whole release process, starting from simplified systems (i.e. simple geometry, reduced number of components or 1D mass transport allowed), to more complex systems (i.e. complex geometry, pharmaceutical forms composed of several units, each with a specific behaviour).

4.1.1. Experimental approaches

The first step to characterize a hydrogel matrix behaviour is to measure the swelling phenomenon, which can be quantified by water uptake measurement [60], by evaluation of the swelling

ratio [61] or by rheological analyses [62]. Each of these measurements can be performed using several experimental techniques, ranging from the simple gravimetric technique to evaluate the weight gain after a certain dissolution time [60], to a colorimetric technique combined with the image analysis to identify the position of the swelling, the diffusion and the erosion fronts [63]. In general, to describe the swelling phenomenon, the use of a combination of experimental techniques, each with its pros and cons [64], is widely diffused [65] due to the plurality of the aspects involved.

From an engineering point of view, the experimental measurements that characterize the hydrogel behaviour inside a compressed pharmaceutical form can be divided into two groups: (i) the macroscopic measurements, which involve the changes of the whole matrix, how the entire system evolves during the time; and (ii) the microscopic measurements, which involve the changes inside the matrix, how a single part of the system is affected by the external conditions during the time.

Typical examples of macroscopic measurements on a tablet are the evaluation of the total water uptake of the polymer eroded and the drug released after a certain dissolution time. The water uptake and the polymer eroded can be easily obtained by a gravimetric technique, which allows to determine their amounts in the whole matrix during the dissolution time. Concerning the drug eventually contained into the matrix, using an analytical technique, such as a spectrometric or a HPLC method, the amount of drug released can be measured and, since the initial amount of drug in the tablet is usually a known quantity, the drug amount residual into the matrix can be calculated. Thus, by the use of simple techniques all the macroscopic profiles can be measured [66].

In order to understand which parameters and phenomena influence the hydrogel behaviour, a microscopic analysis can be of aid in evaluating what happens inside the polymeric matrix. As described above, when the water diffuses inside the matrix, the polymer starts to swell, leading to the formation of a gel layer, which modulates the rate of drug release. For this reason, evaluate the water distribution inside the matrix is a key topic in the pharmaceutical applications and it is the basis of a deeper knowledge of the swelling process, necessary to understand the tablet behaviour. One of the most used techniques to evaluate the water distribution inside a polymer matrix (i.e. for a cylindrical tablet along the radius of the matrix) is the image analysis technique. The basic principle of this method is that, during the hydration of a tablet inside a dissolution medium, a camera records several grey-scale pictures of the tablet, which has a different grey level, depending on the hydration level [67] (i.e. in the glassy white core of the tablet, where the water has not penetrated, the image remains white, whereas in the hydrated gel the image is darker). Based on this non-destructive technique, after a proper calibration, it is possible to determine the water mass fraction along the radius of a swelling matrix made of pure hydrogel in which the water uptake is allowed only in the radial direction [67]. This last hypothesis is fundamental to maintain the water content uniform in a given section of the matrix. Moreover, with the aid of the image analysis, the movements of the erosion, swelling and diffusion fronts can be evaluated [68]. The main drawback of this technique is that if a third component (i.e. a drug) is added to the polymer (and water) in the tablet, it may interfere with the light intensity and the correlation may fail.

Focused on the development of a non-invasive method to study the behaviour of hydrophilic matrices, a technique based on the nuclear magnetic resonance imaging (NMRI) to produce a two-dimensional map of the density of nuclei inside a complex object has been developed [69]. This technique is very useful to characterize the water content and the diffusion phenomena in a swollen hydrogel matrix, and the evolution of the matrix diameter during the swelling [70]. The extent of the swelling can be identified evaluating the position of the interface between the dry core of the tablet and the swollen region; the erosion front can be identified at the interface between the dissolution medium and the swollen region. By the coupling of a NMR micro-imaging analysis and of an *ad hoc* experimental apparatus [71], it is possible to study the water uptake and the swelling behaviour of extended release tablets of hydrogels [72]. Once a NMR image has been taken, at each pixel of the image can be associated a numerical value that can be put in relation with the proton T2 relaxation (due to the water protons). Once the proton relaxation has been associated with the amount of water inside the tablet with a calibration [73], the hydration level of the matrix during the dissolution can be evaluated both in the axial and in the radial direction, which is a great improvement compared with the simple image analysis technique.

A laborious but effective technique to determine all the mass fractions inside the matrix is the gravimetric technique [66], which can be used both for simplified systems, for example, a cylinder in which the water penetrates only by the radial surface, and in more complex ones, in which the water uptake is allowed both from radial and axial surface. After a certain dissolution time, the tablet is withdrawn from the dissolution medium and, using several punches of different diameters, a series of radial sections and a central core can be obtained. In each of these sections, measuring the water content (by weighting the hydrated tablet and drying until constant weight, and weighting once again), the drug content (by dissolving the section content and assaying the drug concentration in the solution) and the polymer content (by difference between the initial weight of the section material and the water and drug weights), it is possible to obtain the components' mass fractions. Repeating these evaluations for several dissolution times, it is possible not only to determine what happens during the time to the matrix, but even the mass evolution along the radius. These data are particularly useful to identify the most relevant transport phenomena involved in the dissolution and to build a predictive tool of the hydrogel-based matrices behaviour. The described method is very labour intensive and time consuming, but allows to gain a lot of information about the matrix behaviour. However, the main drawback of this technique is the fact that it is destructive for the samples. A combined approach could be used to compare the image analysis results with the gravimetric ones [74].

A recent approach to evaluate the degree of hydration of a hydrogel matrix is the use of texture analysis, which is a non-destructive method based on indentation or compression tests on the swollen matrix to evaluate the gel layer position and strength. It is based on the fact that the resistance of the swollen matrix to the penetration (in the indentation tests) is related to the water content. Indeed, the higher the water concentration inside the polymer matrix, the larger the amount of gel formed and the lower the resistance opposed by the matrix. Moreover, due to the difference between the strength of the glassy core and the gel layer, the position of the

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swelling front and the thickness of the gel layer formed can be easily evaluated during the swelling by measuring the force opposed to the penetration from the slope of the force-displacement diagram. The use of this technique alone does not allow to quantify the water amount into the matrix, but it gives qualitative indication. For this reason, a method based on the coupling of the texture analysis and the gravimetric technique has been developed to relate the water content to the penetration work resulting from an indentation test [75] for a simple system, in which the water uptake is allowed only by lateral surface. Then, this technique has been improved to correlate the slope of the force-displacement diagram to the water amount even for more complicate system in which the matrix swells both in radial and axial directions [76].

4.1.2. Modelling approaches

Once the mechanisms which affect the drug release from a hydrogel-based compressed system have been clarified and quantified using both the macro- and microscopic approaches, the final goal of the engineering applied to the study of such pharmaceutical systems is to develop a mathematical model. This model should be able to describe the observed phenomena and to predict the matrix behaviour, with the aim to reduce time and costs required by the development of novel dosage forms. During the years, several modelling approaches have been proposed, starting from the empirical to the mechanistic ones.

First of all, the empirical models have been used to describe the release profile, relating the fractional drug release from a thin film to the square root of time by Higuchi [77], an approach later generalized relating the release to a general *n*th-power of time, where '*n*' is a function of the drug transport regime [78]: generally, for a thin film, it is 0.5 for Fickian diffusive process (Higuchi's equation), 1 for the Case-II transport (swelling-controlled drug release) and takes intermediate values for anomalous transport. The hypotheses on which the model was founded are constant diffusivities and negligible swelling, thus it is not particularly suitable for hydrogel-based systems and, despite it is widely used to describe the experimental results, its use should be avoided to derive phenomenological interpretation.

Then, a more complex modelling approach, which takes into account the simultaneous presence of the solvent, polymer matrix and drug during the dissolution process, is the mechanistic approach. To proper describe the complex phenomena which take place during the dissolution, the mass balance equations, coupled with the momentum conservation equation, have to be used. Often these models obtain the constitutive equations from the mixing and elastic free energy of the hydrogel, following the theory of Flory-Huggins and the affine network theory, respectively [1]. Being the gel made of cross-linked polymer and water, the degree of hydration, which in turns is influenced by the gel elasticity, is crucial to the drug release purpose [79]. Indeed, the amount of water modifies the stretching of the polymer chains and tunes the mobility of the active ingredient. Another factor, which affects sensibly the drug release from such matrices, is the tortuosity of the diffusion path inside the hydrogel [2]. The tortuosity is an aspect usually difficult to be estimated and it depends on the pore size into the matrix, on the pore size distribution and it is influenced by the composition and cross-link density of the hydrogel polymer network. A recent trend in pharmaceutical application is to

produce superporous hydrogels, which are characterized by fast swelling and large swelling ratios [80].

The mechanistic models could be divided into two groups: (i) the multicomponent mixture models, in which the hydrogel is considered as a single phase constituted by several components; and (ii) the multiphasic models, in which the hydrogel is considered as constituted by different phases.

The *multiphasic* models have the advantages of using different phases for the solid (polymer) and liquid (solvent plus dissolved components) parts, that makes them theoretically easier to extend to very complex systems such as drug delivery matrices [81]. However, this approach has several drawbacks like the high numbers of non-linear partial differential equations (PDEs), that make the system numerically solvable under very limitative conditions, and the scarce physical meaning of some parameters. Instead, the *multicomponent* approach, with more rigorous thermodynamic bases, limits the numbers of PDEs and constrains the variables to physical quantities. However, the theoretical complexity, until now, has led to simplified approaches which take into account only the mass transport equations. One of the first multicomponent models for drug delivery systems was based on purely diffusive mass transport equations by Siepmann et al. [82]. Considering the matrix composed by water, polymer and drug, the water and drug mass transport equations were solved, coupled with their boundary conditions, in a 2D axisymmetric domain, under several hypotheses: (i) no volume contraction upon mixing, (ii) fast drug dissolution compared to drug diffusion, (iii) perfect sink condition for the drug, (iv) strong dependence of the diffusivities (of water and drug) on the hydration level and (v) affine deformations:

$$\begin{cases} \dfrac{\partial \rho_i}{\partial t} = \dfrac{1}{r}\dfrac{\partial}{\partial r}\left(D_i \dfrac{\partial \rho_i}{\partial r} \right) + \dfrac{\partial}{\partial z}\left(D_i \dfrac{\partial \rho_i}{\partial z} \right) \qquad i = 1,3 \\ @\, t = 0, \forall r, \forall z, \rho_i = \rho_{i,0} \\ @\, r = R(t), \forall t, \forall z \;\; \rho_i = \rho_{i,eq} \\ @\, z = Z(t), \forall t, \forall r \;\; \rho_i = \rho_{i,eq} \\ @\, r = 0, \forall t, \forall z \;\; \dfrac{\partial \rho_i}{\partial r} = 0 \\ @\, z = 0, \forall t, \forall r \;\; \dfrac{\partial \rho_i}{\partial z} = 0 \end{cases} \tag{4}$$

where ρ_i is the mass concentration of the ith species, $\rho_{i,eq}$ is the interface mass concentration of the ith species and D_i the diffusion coefficient of the ith species. $R(t)$ and $Z(t)$ represent the radius and the thickness, respectively, of the erosion boundaries. The diffusivity has been described by a Fujita-type equation [83] and the polymer mass release during the time (erosion) has been evaluated by the product of an erosion constant and the erosion surface area, which changes during the time due to the swelling:

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$$\begin{cases} \dfrac{dm_2}{dt} = -k_{er} A_{er}\left(t\right) \\ @\, t = 0 \; m_2 = m_{2,0} \end{cases} \tag{5}$$

where m_2 and $m_{2,0}$ are the polymer mass and the initial polymer mass, k_{er} is an erosion constant and A_{er} is the erosion surface, that is the surface exposed to the external medium. The model is able to describe the evolution of water, polymer and drug masses during the time for a given system. Based on this work, a 1D model to describe the hydration of pure HPMC tablet confined between glass slabs has been developed [67]. The system swelling has been described considering the variation of the total mass due to both the water inlet and the polymer erosion. The efficacy of this model has been proved by the authors comparing its results and the experimental data of water mass fraction profiles along the radial direction obtained by analysing the normalized light intensity of swollen tablet pictures for several dissolution times. The model has been later improved [84] to describe the drug release kinetics from different shaped matrices. These models are very useful to describe the behaviour of geometrically simple systems, but the hypothesis of affine deformation is a big limitation for more complex systems. For this reason, recently a 2D axisymmetric model was proposed [85] to overcome the affine deformation hypothesis. In this model, the transport equations for water and drug have been solved for the respective mass fractions with a finite element method, along with the proper initial and boundary conditions, and the constitutive equation for the system density has been obtained considering the summability of the specific volumes of the single species. The novelty of this model consists in the description of the swelling phenomenon: the inlet water flux has been divided into two components, the first one responsible for the tablet swelling ($j_{1,swe}$) and proportional to a swelling constant (k_{swe}), and the latter responsible for the inner layer hydration($j_{1,diff}$). The deformation rate of the hydrogel has been defined by a water mass balance on a boundary element ($A\delta$), where simultaneously the swelling and the erosion phenomena (the first leads to a volume increasing and the latter to a volume decreasing) happen:

$$\begin{gathered} \rho \frac{d}{dt}\left(A\delta\omega_{1,eq}\right) = \boldsymbol{A}\cdot\boldsymbol{j}_{1,\boldsymbol{diff}} - \boldsymbol{A}\cdot\boldsymbol{j}_1 \\ \boldsymbol{v}_{\boldsymbol{swe}} = \frac{d\delta}{dt} = -\frac{\boldsymbol{j}_{1,\boldsymbol{swe}}}{\rho\,\omega_{1,eq}} = -\frac{k_{swe}\boldsymbol{j}_{1,\boldsymbol{diff}}}{\rho\,\omega_{1,eq}} \\ \boldsymbol{v}_{\boldsymbol{eros}} = -k_{eros} \end{gathered} \tag{6}$$

The model has been proved to work in comparison with experimental macroscopic results. Recently, a mechanistic model based on water diffusion in concentrated systems has been proposed [86,87]. This model is based on the assumption that: (i) the swelling is due to the water uptake and to the translocation of polymer, thus the polymer flow at the interface between the tablet and the external medium causes the swelling and the shape change, without

polymer release; and (ii) the erosion phenomenon is due to interactions between the tablet surface and external fluid. Due to this new approach, the model has been found able to describe not only the macroscopic behaviour of a matrix, but even what happens inside the hydrogel matrix, and it is in good agreement with the experimental data.

4.2. Hydrogels for biomedical applications

During the years, biomedical applications of the hydrogels in the tissue engineering are gaining increasing interest, which aims to create biological body parts to replace harvested tissues and organs. In this application, the polymer plays a major role in the determination of the cell adhesion, in the formation and growth of a new 3D structured tissue in the human body; and its selection is governed by the physical, the mass transport properties and the biological interaction requirements. For these reasons, and due to their properties, the hydrogels have been explored as systems suitable for tissue engineering [88]. Despite the critical parameter in the selection of the hydrogel to be used in tissue engineering, the biocompatibility, the mechanism of gelling [89], the mechanical properties, the controlled degradation, the interaction with cells [90] and the gel structure are the most important design parameters to be taken into account [91]. That is, alginate hydrogels, already well exploited for biomedical applications like wound dressing and drug release, are receiving particular attention in tissue engineering applications, thanks to the property of forming macro-porous anisotropic structure with ordered capillaries [92]. This 3D structure can mimic the primary microstructural elements of some tissues (nerve, bone, microvasculature, etc.) and facilitate the cells growth processes. Recently, with a combined experimental and modelling approach, the variables that affect the capillaries formation and length, like ion and alginate sol concentration, have been investigated [93].

A consolidated biomedical application of the hydrogels is the development of patches based on water swellable polyacrylates for long-term transdermal drug delivery. One of the most relevant side effects of a conventional transdermal delivery system is the skin occlusion due to the long-term application. In fact, the conventional patches were based on hydrophobic polymer matrices, and therefore intrinsically occlusive; this drawback can be easily overcame with non-occlusive water swellable matrices as hydrogels. The ability of these polymers to exchange water with the skin increases their suitability for the transdermal applications [94]. Of great relevance for the hydrogels used in the development of transdermal patches are the mechanical properties, due to the high mechanical stresses experienced by these systems. In fact, the force exerted to promote the adhesion on skin surface and the continuous mechanical stimuli connected with the patient movements are a key parameter to be taken into account during the development of these delivery systems [95]. Among the various patches types, the muco-adhesive buccal patches are largely diffused due to large permeability of the mucus membranes that allow rapid uptake of a drug into the systemic circulation. Bio-adhesion, which is a phenomenon taking place between a biological material and another, usually a polymer, is the fundamental property in the designing of these systems [96]. The main factor promoting bio-adhesion is the presence of carboxyl and hydroxyl groups on the polymer backbone, to form hydrogen bonds. It was seen that anionic poly-

mers form stronger bonds with respect to neutral or cation polymers. Good polymer wettability is also required to expose the bond-forming sites. The polymer molecular weight should be kept within an optimum range so that the dry system can quickly uptake water (upper limit for the Mw) to form a gel, that should not be too weak (lower limit for the Mw) [97]. However, in mucoadhesive applications, although the formation of H-bonds remains crucial, the modification of the mucus layer beneath the mucoadhesive material becomes important. This step, needed to overcome the anti-adherent properties of mucus, can be attributed to the macromolecular interpenetration effect or to the dehydration effect [98]. To better understand the mechanisms that lead to the adhesion phenomenon and to develop a mathematical model able to describe the mechanical behaviour and the water uptake of the system, following the engineering point of view, the adhesion phenomenon has been studied between a water-rich agarose system (which simulates the biological membrane), and a Carbopol tablet (which simulates the patch) [99].

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