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Modeling of *in vitro* drug release from polymeric microparticle carriers

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Abstract

Incorporation of active substances in polymeric microparticles (microencapsulation) is an important technological strategy used in the pharmaceutical industry to improve the functionality, quality, safety and/or therapeutic efficiency of pharmaceutical preparations for different routes of administration. The current focus of research in this field is on the encapsulation of small molecules and macromolecules into microparticles based on biocompatible synthetic polymers and biopolymers, such as polypeptides and polysaccharides, in order to achieve preferable drug release kinetics and many other advantages. Diversity in the structure and size of microparticles, choice of polymers, and manufacturing processes, allows for designing a multitude of microcarriers (e.g., monolithic matrix microspheres, hollow microcapsules, water- or oil-core microcapsules, stimulus-sensitive microcapsules), whereby their impact on biopharmaceutical profile of drugs can be manipulated. The results so far indicate that the *in vitro* drug release kinetics evaluation is one of the key aspects of the microparticle-type carrier characterization, where the application of the mathematical analysis (modeling) of the drug release profiles is an important tool for elucidating drug release mechanisms, as well as for evaluating the influence and optimization of formulation and process parameters in the microencapsulation procedure. The article reviews representative studies in which mathematical modeling of experimentally obtained release data was performed for microencapsulated model drugs with different physicochemical properties, as well as the relevance and potential limitations of this approach.

Key words: microencapsulation, polymer microparticles, *in vitro* drug release, mathematical modeling of drug release kinetics

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Introduction

Microencapsulation of drug substances into particles ranging in size from 1 to 1000 μm is a well-established formulation approach with a well-recognized potential to improve the quality, therapeutic efficacy and safety of pharmaceutical products. The main goals of microencapsulation are: 1) protection of bioactive substances from unfavorable environmental factors (e.g., oxidation, hydrolysis, light or heat) or against the biological environment (e.g., pH, enzymes, hydrolysis, proteolysis, endocytosis); 2) overcoming certain production challenges, including poor flowability of powders, incorporation of volatile and/or liquid ingredients into a solid dosage form, drug incompatibility, and unpleasant taste, odor or color of the drug substance; 3) increasing drug retention time on the skin or the mucous membranes; 4) localizing drug delivery and/or achievement of a prolonged drug release in order to enhance patient compliance and minimize risks of side effects (1-4). Among all microencapsulation carriers, polymer microparticles based on various synthetic and semi-synthetic polymers and/or natural macromolecules have the greatest potential to protect and deliver drugs in a controllable way (5-8). In recent years, biocompatible microparticles based on biodegradable polymers and biopolymers, including polypeptides and polysaccharides, have received widespread attention as carriers for controlled drug release (Table I). However, a common drawback of biopolymer based microparticles is an initial burst release phase causing a lack in the optimal control of drug loading and release, and a poor correlation between *in vitro* release profiles and *in vivo* therapeutical outcomes (5-8). In order to establish better control over drug release from such biocompatible polymer microparticles, various technological strategies are proposed, including the formation of polyelectrolyte complexes (9-11), layer-by-layer (LBL) self-assembly of nanofilms (12, 13), chemical cross-linking or introduction of molecules sensitive to environmental stimuli (14-21). In this way, complex carriers are created which, according to the internal morphology, can be classified as microspheres (i.e., monolithic polymer matrix-based microparticles) or microcapsules (i.e., core-shell microparticles comprising a reservoir surrounded by a polymer wall). The current approach in modeling *in vitro* drug release data in order to elucidate drug release mechanisms and evaluate the influence of various formulation and process variables on release kinetics is discussed in detail.

Table I Examples of mathematical modeling of the drug release kinetics of polymer microparticle drug delivery carriers

Tabela I Primeri matematičkog modelovanja kinetike oslobađanja lekovitih supstanci iz nosača tipa polimernih mikročestrica

Microparticle type	Administration route	Active substance	Active substance type	Polymer	Drug release pattern	Drug release kinetics	Drug release mechanism	Ref.
matrix	oral	ibuprofen	small molecule (hydrophobic)	PEC based on CH and XG	extended release during 12 h	*Korsmeyer-Peppas* kinetics (close to *zero-order* kinetics)	diffusion after the swelling of the carrier, relaxation of polymer chains and erosion	(10)
matrix	oral	ibuprofen	small molecule (hydrophobic)	PEC based on CH and XG	extended release during 12 h; pH-dependent release	*zero order* or *Korsmeyer-Peppas* kinetics	diffusion after the swelling of the carrier, relaxation of polymer chains and erosion	(11)
matrix	oral	meloxicam	small molecule (hydrophobic)	AGP and sodium alginate (crosslinked with $CaCl_2$)	pH-dependent, release; sustained release up to 24 h	*zero-order* kinetics	super case II transport drug release (diffusion from polymer and polymer erosion)	(27)
matrix	oral	celecoxib	small molecule (hydrophobic)	LBG and XG	sustained or controlled release during 24 h	*first-order* kinetics (optimum formulation)	super case II transport (optimum formulation)	(28)
matrix	oral	resveratrol	small molecule (hydrophobic)	calcium alginate	initial burst release (first 30 min), followed by prolonged release (from 30 min to the end)	*Peppas* kinetics	swelling (freeze-dried MPs)/ shrinkage (wet MPs) and drug diffusion (first 30 min) and diffusion-controlled release (from 30 min to the end)	(29)
matrix	oral	gliclazide	small molecule (hydrophobic)	mucilage of Isabgol husk (cross-linked with GA)	sustained release during 8 h; pH-dependent release	*Higuchi* kinetics (optimized formulation)	swelling-controlled release followed by drug diffusion	(30)
matrix	oral	*Eschweilera nana* extract – rutin	small molecule (hydrophobic)	mixture of Arabic gum and XG	prolonged release during 8 h	*second-order* kinetic	anomalous transport (non-Fickian) governed by diffusion and swelling of the polymer chains	(31)
matrix	oral	diclofenac sodium	small molecule (hydrophilic)	IPN of XG and PVA crosslinked with GA	pH-dependent release; prolonged release during 12 h	*Peppas* kinetics	swelling of IPN; Fickian transport phenomena	(32)
matrix	oral	acetaminophen	small molecule (hydrophilic)	CH crosslinked with TPP, FA, or GA	initial burst release (first 30 min), followed by sustained release during 6 h	*Higuchi* kinetics	drug dissolution from the surface (burst release) and Fickian diffusion (sustained release)	(33)
matrix	oral	ciprofloxacin hydrochloride	small molecule (hydrophilic)	IPN of XG-based SAP and PVA crosslinked with GA	sustained and controlled release during 8 h	*Korsmeyer-Peppas* kinetics	non-Fickian drug release	(34)
matrix	oral	escin	small molecule (amphiphilic)	PEC based on CH and XG	extended release during 12 h; pH-dependent release	*Korsmeyer-Peppas* or *Higuchi* kinetics	diffusion after the swelling of the carrier, relaxation of polymer chains and erosion	(35)
matrix	intranasal	metoclopramide hydrochloride	small molecule (hydrophilic)	gellan gum	moderately sustained release up to 5 h, without lag time	*Korsmeyer-Peppas* kinetics (optimum formulation)	anomalous (non-Fickian) transport (optimum formulation)	(36)

Microparticle type	Administration route	Active substance	Active substance type	Polymer	Drug release pattern	*Drug release kinetics*	Drug release mechanism	Ref.
matrix	ocular	atropine sulfate	small molecule (hydrophilic)	BSA and CH	initial burst release (first 5 h) followed by extended release up to 72 h	*Higuchi* kinetics	diffusion-controlled release (for the first 25 h)	(37)
matrix	pulmonar	resveratrol	small molecule (hydrophobic)	PCL	sustained release up to 24 h	*first-order* kinetics	concentration gradient pattern based on Fick's law	(38)
hollow structure microcapsules	oral	curcumin	small molecule (poorly soluble)	EC	sustained release; pH-dependent release	*zero order* or two-stage (quickly and then slowly) *Higuchi kinetics* (at pH 6.8) *first-order kinetics* (at pH 7.4)	Fickian diffusion (at pH 6.8); EC wall swelling and the non-Fickian drug diffusion though the enlarged pore in microcapsule wall (at pH 7.4)	(40)
aqueous core microcapsules	oral	5-ASA	small molecule (poorly soluble)	PEC based on NaCS-CHC	sustained release up to 12 h	*Ritger-Peppas kinetics*	Fickian diffusion or non-Fickian transport (drug release is governed by the swelling and erosion)	(44)
aqueous core microcapsules	a wide range of sustained drug delivery systems	fluorescein sodium	small molecule (hydrosoluble)	PLGA or PLA	sustained release over 7 days (PLGA-based wall) or 49 days (PLA-based wall)	*zero order kinetics* (PLGA/PLA1:3) *first order kinetics* (PLGA/PLA 3:1 and 1:1)	polymer erosion (degradation) and drug diffusion through the polymeric wall	(46)
aqueous core microcapsules	parenteral	human albumin	macromolecule (hydrosoluble)	Alg/PES	sustained release with plateau reached after 19 h	*first-order kinetics*	diffusion of protein desorbed from alginate hydrogel core through polymeric wall	(50)
aqueous core microcapsules	oral	BSA	macromolecule (hydrosoluble)	CH-FRA conjugates	sustained release	*Corrode kinetics*	drug diffusion of the outer and inner surface (in the initial release phase), slow drug diffusion through micropores formed as a result of polymer degradation (in the second phase), and fast erosion-controlled drug release (in the final phase)	(51)
oil core microcapsules	topical	α-tocopherol	liquid (lipophilic)	CH/SDS or CH/SLES coacervates, without and with cross-linking agent (FA or GA)	fast release (10 min)	*Korsmeyer-Peppas kinetics* (CH/SDS)	non-Fickian diffusion through the microcapsule wall (diffusion/swelling release mechanism) (CH/SDS coacervate microcapsules); desorption (rinsing from the wall surface) (CH/SLES coacervate microcapsules)	(52, 53)
oil core microcapsules	biological and medical applications	TTO	liquid (hydrophobic)	CH with crosslinking agent TPA	rapid release up to 10 h	*first-order kinetics*	Fickian diffusion (drug release rate correlates directly with the thickness of the capsule walls)	(55)

Microparticle type	Administration route	Active substance	Active substance type	Polymer	Drug release pattern	*Drug release kinetics*	Drug release mechanism	Ref.
pH-responsive microcapsules	drug delivery systems with bacteriostatic activity	PyTNH	small molecule (hydrophilic)	BGCS or CMCS cross-linked with GA	prolonged pH-dependent release	*Korsmeyer–Peppas kinetics*	Fickian diffusion (CMCS microcapsules); anomalous diffusion and polymer relaxation (BGCS microcapsules)	(43)
multi-stimuli responsive microcapsules	parenteral	green fluorescent dye Coumarin 6	small molecule (hydrophobic)	magnetic microcapsules with magnetic nanoparticles shell or with magnetic Fe_3O_4 nanoparticles core	magnetism-mediated targeted drug delivery and redox-responsive controlled drug release	*Ritger and Peppas equations*	anomalous transport (first release stage) and combination of the erosion and diffusion (second release stage)	(14)

Abbreviations: 5-ASA – 5-aminosalicylic acid; AGP – Aloe vera gel powder; Alg/PES – alginate-polyethersulfone; ALG - low viscosity sodium alginate; BGCS – biguanidino chitosan; BSA – bovine serum albumin; CH – chitosan; CMCS – O-carboxymethyl chitosan; EC – ethyl cellulose; FRA – ferulic acid; FA – formaldehyde; GA – glutaraldehyde; GAR – gum arabic; IPN – interpenetrating polymer network; LBG – Locust bean gum; MD – maltodextrin; MPs – microparticles; NaCS-CHC – sodium cellulose sulfate-chitosan hydrochloride; PCL – polycaprolactone; PEC – polyelectrolyte complex; PLA – poly(lactide); PLGA – poly(lactide-co-glycolide); PVA – poly(vinyl alcohol); PyTNH – 2,4-diamino-6-(2-pyridyl)-1,3,5-triazine; SAP – superabsorbent polymer; SLES – sodium lauryl ether sulfate; SDS – sodium dodecyl sulfate; TPA – terephthalaldehyde; TPP – tripolyphosphate; TTP – tea tree oil; WPC – whey protein concentrate; XG – xanthan gum

Skraćenice: 5-ASA – 5-aminosalicilna kiselina; AGP – Aloe vera gel prašak; Alg/PES – alginat-polietarsulfonat; ALG – natrijum alginat male molekulske mase; BGCS – bigvanido hitozan; BSA – goveđi serum albumin; CH – hitozan; CMCS – O-karboksimetil hitozan; EC – etil celuloza; FRA – ferulinska kiselina; FA – formaldehid; GA – glutaraldehid; GAR – arapska guma; IPN – interpenetrirajuća polimerna mreža; LBG – galaktomanan; MD – maltodekstrin; MPs – mikročestice; NaCS-CHC – natrijum celuloza sulfat-hitozan hidrohlorid; PCL – polikaprolakton; PEC – polielektrolitni kompleks; PLA – poli(laktid); PLGA – poli(laktid-ko-glikolid); PVA – poli(vinil alkohol); PyTNH – 2,4-diamino-6-(2-piridil)-1,3,5-triazin; SAP – superapsorbujući polimer; SLES – natrijum lauril etar sulfat; SDS – natrijum dodecil sulfat; TPA – terftalaldehid; TPP – tripolifosfat; TTP – ulje čajevca; WPC – koncentrat proteina surutke; XG – ksantan guma

Drug release from microspheres

Microspheres are usually spherically shaped matrix type particles with the drug homogeneously distributed (dissolved or dispersed) in a biodegradable or non-biodegradable polymeric matrix. The properties of the polymer significantly affect the site, mechanism and kinetics of drug release from the carrier. Two main mechanisms of drug release from the microspheres have been described: (a) the drug's diffusion and/or dissolution from the swellable or non-swellable polymer matrix, and (b) the drug's diffusion and/or dissolution governed by the erosion or dissolution of the polymer (22–26). The release of the drug substance from the biodegradable microspheres is a consequence of the gradual decomposition (bioerosion) of the polymer matrix, typically by hydrolysis or enzymatic degradation. Microspheres can be loaded with different types

of drugs, small molecules of different physicochemical and biopharmaceutical properties, as well as with peptides and proteins. Moreover, microspheres can be prepared by various methods, including spray drying, emulsion/solvent evaporation, and ionic gelation technique. Given the diversity in terms of the type of polymer, the preparation technique, and the properties of the incorporated drugs, these carriers can be formulated for different routes of drug administration (oral, ocular, intranasal, buccal, transdermal, topical, vaginal, rectal, etc.), as well as for gene therapy, vaccine delivery, and tissue engineering.

Microspheres are mainly developed as oral drug delivery carriers for controlled release of incorporated drugs. Ćirić et al. formulated matrix microparticles based on polyelectrolyte complexes (PECs) of chitosan (CHI) and xanthan gum (XG) as carriers for ibuprofen extended release. These microparticles differed in terms of pH (3.6, 4.6, or 5.6) and pH adjusting agent (hydrochloric acid or acetic acid) used for the preparation of PECs. The drug release properties of PECs obtained by ambient drying were affected significantly by acid type and pH value. Physical mixtures of PECs and ibuprofen at PEC-to-drug mass ratios 1:1 and 1:2 were evaluated. Ibuprofen release was immediate from the PECs prepared with hydrochloric acid at pH 3.6. The authors stated that, at the mass ratio of 1:1, drug release followed the *first-order* kinetics (Table II), depending on its concentration and the presence of the PEC. At a mass ratio of 1:2, ibuprofen release followed the *Korsmeyer-Peppas* kinetics (Table II) with the *n* value near zero, so the PEC had a low impact on drug release. Ibuprofen release from its mixtures with other PECs prepared with hydrochloric acid was extended during 10 h, with the amounts of drug released after 10 h up to 80%. Drug release from these mixtures followed the *Korsmeyer-Peppas* kinetics characteristic for drug carriers with high swelling ability. For ibuprofen mixtures with PECs comprising acetic acid, extended release of ibuprofen was achieved in all cases, except with PEC prepared at pH 3.6 and PEC-to-drug mass ratio of 1:2, where immediate release was observed. Amounts of drug released after 10 h from mixtures with other PECs were also up to 80%. In these mixtures, ibuprofen release followed the *Korsmeyer-Peppas* kinetics, while the mechanism was modified Fickian diffusion. Authors concluded that only PECs prepared with acetic acid at pH values of 4.6 and 5.6 could be considered extended release carriers for ibuprofen, since the drug release from these mixtures was controlled by PECs, even when the content of the drug was twice that of the carrier (9). In the continuation of the research, the same group of authors evaluated the impact of the entrapment procedure of ibuprofen on drug release performances of CH/XG-based PECs. The aim was to achieve controlled drug release. The PECs were prepared by two drug entrapment procedures (before or after the mixing of polymers) at pH 4.6 and 5.6 and three CH-to-XG mass ratios (1:1, 1:2 and 1:3). All ibuprofen release profiles were similar and showed their extended release, with 60–70% of the drug released after 12 h. The ibuprofen release from all PECs followed the *Korsmeyer-Peppas* kinetics (Table II). The main mechanism of drug release from all samples was considered to be diffusion after the swelling of the samples, but erosion and polymer chain relaxation were also included. Moreover, high values of determination coefficients for *zero-order*

kinetics (Table II) for all samples suggested that ibuprofen release did not depend on its concentration, so an almost constant amount of the drug was released per time unit.

Table II Mathematical models of *in vitro* release of drug substances (57, 58)

Tabela II Matematički modeli *in vitro* oslobađanja lekovitih supstanci (57, 58)

Model	**Equation**
Zero-order	$F = k_0 \cdot t$
First-order	$F = 100 \cdot (1 - e^{-k1 \cdot t})$
Quadratic (second-order)	$F = 100 \cdot (k_1' \cdot t^2 + k_2' \cdot t)$
Higuchi	$F = k_H \cdot t^{1/2}$
Peppas *Korsmeyer-Peppas* *Ritger-Peppas*	$F = k_{KP} \cdot t^n$
Peppas-Sahlin	$F = k_F \cdot t^m + k_C \cdot t^{2m}$
Hixson-Crowell (corrode) model	$F = 100 \cdot [1 - (1 - k_{HC} \cdot t)^3]$

F – amount (%) of drug released in time *t*
t – time
k0 – *zero-order* release constant
k1 – *first-order* release constant
k1' – constant in *quadratic* model denoting the relative contribution of t^2-dependent drug release
k2' – constant in *quadratic* model denoting the relative contribution of *t*-dependent drug release
kH – *Higuchi* release constant
kKP – release constant incorporating structural and geometric characteristics of the drug/dosage form
n – diffusional exponent indicating the drug release mechanism
kF – constant related to Fickian kinetics
kC – constant related to Case-II relaxation kinetics
m – diffusional exponent for a device of any geometric shape which inhibits controlled release
kHC – release constant in the *Hixson–Crowell* model

F – količina (%) oslobođene lekovite supstance u vremenu *t*
t – vreme
k0 – konstanta brzine oslobađanja kinetikom *nultog reda*
k1 – konstanta brzine oslobađanja kinetikom *prvog reda*
k1' – konstanta u *kvadratnom modelu* koja označava relativni doprinos t^2-zavisnog oslobađanja lekovite supstance
k2' – konstanta u *kvadratnom modelu* koja označava relativni doprinos *t*-zavisnog oslobađanja lekovite supstance
kH – konstanta brzine oslobađanja *Higuchi* kinetikom
kKP – konstanta brzine oslobađanja koja uzima u obzir strukturna i geometrijska svojstva lekovite supstance/farmaceutskog oblika
n – difuzioni eksponent koji ukazuje na mehanizam oslobađanja lekovite supstance
kF – konstanta za proces Fick-ove kinetike
kC – konstanta za proces Case-II relaksacione kinetike
m – difuzioni eksponent za tvorevinu bilo kog geometrijskog oblika koja inhibira kontrolisano oslobađanje lekovite supstance
k_{HC} – konstanta brzine oslobađanja *Hixson–Crowell*-ovom kinetikom

Controlled ibuprofen release closest to *zero-order* kinetics was achieved for PECs prepared at pH 4.6, as well as drug entrapped both before and after the complexation of polymers at their mass ratios of 1:1 and 1:2. Deviations from this model were observed for PECs prepared at pH 5.6, and at a CH-to-XG mass ratio of 1:3 at pH 4.6. For those reasons, the authors assumed that the pH and CH-to-XG mass ratio had a greater impact on drug release kinetics in comparison with the entrapment procedure. Finally, it was concluded that the PEC prepared at pH 4.6, with ibuprofen entrapped before the mixing of polymers at a CH-to-XG mass ratio 1:2, was optimal for providing controlled drug release closest to *zero-order* release kinetics (10). Very recently, Ćirić et al. also investigated the influence of the drying method (ambient drying and spray drying) on drug release performances of ibuprofen-loaded CH/XG-based PECs. *In vitro* drug release both from ambient-dried and spray-dried PECs was extended and almost constant during 12 h. Incomplete release of approximately 30% of the entrapped hydrophobic drug ibuprofen was observed within the mentioned time. Differences in released amounts of the drug from ambient-dried and spray-dried PEC after 12 h were negligible. A slightly faster release of ibuprofen from the spray-dried sample was noticed and related to the smaller particles of PECs obtained by the spray-drying procedure, due to an increase in the contact of the particles with dissolution media. Furthermore, pH-dependent ibuprofen release was achieved from both PECs. Significantly lower amounts of the drug were released in 0.1 M hydrochloric acid (pH 1.2) after 3 h compared to the phosphate buffer pH 7.4 during the next 9 h. The authors concluded that the entrapment of ibuprofen into CH/XG PEC-based carriers can enable its site-specific drug release in the small intestine. Moreover, the study showed that drug release from both ibuprofen-loaded PECs was approximately constant during 12 h. For the spray-dried PEC, ibuprofen release followed the *Korsmeyer-Peppas* kinetics (Table II), regardless of the pH of the medium. On the other hand, for the ambient-dried PEC, ibuprofen release during the first 3 h (in pH 1.2) followed the *Korsmeyer-Peppas* kinetics (typical for drug carriers with swelling ability), and during the next 9 h in phosphate buffer pH 7.4 the *first-order* kinetics (Table II) (drug release rate dependent on its concentration). The suggested mechanism of ibuprofen release was a combination of diffusion after the swelling of PECs, relaxation of polymer chains, and erosion (11). Other hydrophobic anti-inflammatory drugs were also incorporated into microspheres in order to achieve their controlled release. Abadi et al. prepared a colon-specific carrier for meloxicam (MLX) by the ionotropic gelation method, using calcium chloride as a crosslinking agent. Fourteen batches of mucoadhesive matrix microspheres (MLX-Na-AGP) based on sodium alginate and Aloe vera gel powder (AGP) as drug release modifiers were obtained at different polymer ratios and varying concentrations of the crosslinking agent. *In vitro* drug release of all batches of MLX-Na-AGP microspheres was investigated at increasing pH values using different buffers of pH 1.2, 4.5, 6.8, and 7.4 during 24 h. MLX release from all batches was slow and almost negligible at an acidic pH and increased progressively with an increase in pH. Maximum drug release was observed at pH 7.4 at the end of the 24th hour. The study also showed that drug release followed *zero-order* kinetics (Table II), with the anomalous

super case II transport release mechanism indicating that MLX release was controlled both by diffusion and polymer erosion (27). Moreover, celecoxib (CXB), a COX-2 inhibitor, was incorporated into polymeric-based matrix microparticles based on natural polymers, locust bean gum (LBG) and XG prepared by the emulsification method. These microspheres differed in the LBG-to-XG and drug-to-polymers weight ratios. Experimental design was implemented in order to define the optimized formulation with sustained drug release performances. Authors pointed out that drug release from sustained-release formulations followed the *first-order* kinetics (Table II), while the release from controlled-release dosage forms followed the *zero-order* kinetics. To be more precise, sustained dosage forms enable a prolonged period of drug release which is not constant per unit time. On the contrary, in controlled-release dosage forms, drug release is constant per unit of time. For those reasons, authors consider that sustained-release formulations can exhibit some advantages over the controlled-release ones, including higher bioavailability, slower degradation of the drug and its concentration dependent release. *In vitro* experiments on drug release were performed at pH 1.2 during 2 h, followed by 22-hour release testing at pH 7.4. At pH 1.2, low amounts of CXB were released (up to 9%), while at pH 7.4 drug release was fast in the initial stage and slow in the later stage, reaching the released amount of approximately 90% at the end of the study. The *in vitro* release studies also indicated an increase in drug release retardation, with increasing LBG and XG concentration at both pH values. CXB release followed the *Peppas* or *Higuchi* kinetics (Table II), depending on the formulation, whereas the release mechanism of the drug from all formulations was super case II transport (28). Resveratrol (RSV), a hydrophobic drug of natural origin, has been shown to prevent or slow the progression of many diseases, including cancer, cardiovascular diseases, ischemic injuries, and Alzheimer's disease. However, the medicinal use of RSV is still limited due to its short half-life, fast degradation, and rapid metabolism and elimination. That is why it can be used only when incorporated into a carrier that protects the drug from degradation, preserves its activity, and enhances bioavailability. RSV-loaded microspheres based on calcium alginate were prepared by ionic gelation of alginate with calcium chloride to obtain prolonged-release drug carrier. These microspheres differed in the concentrations of alginate (0.5 and 1 % *w/v*) and calcium chloride (0.5 and 1 M). The release behavior was evaluated both for wet and freeze-dried microspheres at pH 7.4 during 24 h. A slower initial burst release (during the first 30 min) was observed for freeze-dried microspheres in comparison with wet microspheres, regardless of alginate and calcium chloride concentrations. During this phase, two mechanisms (swelling and diffusion) controlled the release of the drug from the dry microspheres. However, for wet microspheres RSV release included two phenomena: i) shrinkage owing to the release of water and drug, ii) the diffusion of RSV from the microspheres. These differences in release mechanisms explained the slower release of the drug from freeze-dried microspheres. On the other hand, during the second phase (from 30 min to the end), the swelling of the microspheres was constant and did not affect the drug release. Moreover, an increase in alginate concentration resulted in slower release rate of RSV. In addition,

a higher concentration of calcium chloride slowed the initial burst of RSV release regardless of alginate concentration. Gelation of sodium alginate with calcium chloride is based on the tight junction between guluronic acid residues, so the number of crosslinking points increases with increasing their concentrations (29). Sharma et al. developed mucoadhesive microspheres based on mucilage of Isabgol husk crosslinked with glutaraldehyde (GA) by emulsification-crosslinking technique for sustained release of gliclazide. They differed in process temperature (25–80 °C), the concentration of GA (0.25–1% *v/v*) and Isabgol husk mucilage concentration (2–8% *w/v*). The *in vitro* testing of release properties of gliclazide from prepared microspheres was performed in distilled water, 0.1 N hydrochloric acid and phosphate buffer pH 7.4 during 8 h, and the release kinetics of the optimized formulation was evaluated. Drug release properties were expressed as the time needed to release 50% of the incorporated drug ($t_{50\%}$). The release of gliclazide from microspheres was affected by GA concentration, Isabgol husk mucilage concentration, gliclazide content, and the nature of dissolution media. Results indicated that, by increasing the concentration of GA from 0.25% to 1% *v/v*, the extent of crosslinking increased, which resulted in higher values of $t_{50\%}$. Highly swollen microspheres showed a faster drug release rate. At higher crosslinking density (higher GA concentrations), the swelling ability was lower, due to the slower relaxation of the polymer chains, which decreased drug release rate. The prolonged release from microspheres prepared at higher concentrations of GA could also be explained by the reduced free space available for the diffusion of dissolution media. Moreover, by an increase in the Isabgol husk mucilage concentration, a decrease in gliclazide release was observed, since its higher content in microspheres resulted in the formation of thicker matrix and slowed gliclazide diffusion through the swollen matrix. Similarly, higher drug content led to the release of greater amounts of the drug and authors suggested that higher drug content in crosslinked microspheres was a driving force for the uptake of dissolution media by the microspheres, resulting in the increase of the released amount of drug. pH of dissolution media also significantly influenced gliclazide release. Higher amounts of gliclazide were released in phosphate buffer pH 7.4 than distilled water and 0.1 N hydrochloric acid, probably due to the better solubility of the drug and swelling of matrix at higher pH values. Calculated *n* values for *Korsmeyer-Peppas* model (Table II) showed a non-Fickian drug diffusion mechanism, indicating the swelling-controlled diffusion of gliclazide from swellable matrix of microspheres (30).

There are examples of utilization of microspheres for the incorporation of herbal extracts in order to obtain the controlled release of the active ingredients and improve their bioavailability. Microparticles loaded with *Eschweilera nana* extract were prepared by spray drying technique using a mixture of arabic gum and XG. The main components of this extract are poorly water-soluble flavonoids, rutin and hyperoside. The prepared microspheres differed in extract-to-polymers ratios (1:3, 1:4, and 1:6). The *in vitro* test of rutin release was carried out in ultra-pure water during 8 h, and the results indicated that its release from the microparticles was slower in comparison with the pure extract. It was also observed that an increase in the proportion of polymers in microspheres decreased

rutin release, probably due to an increase in the size of particles. The size increase caused a reduction in the area exposed to the dissolution medium and decreased the dissolution rate. It was determined that rutin release from all microspheres followed the *second-order* kinetics (Table II). Calculated *n* values for the *Korsmeyer-Peppas* kinetic model (Table II) ($0.43<n<0.89$) indicated that the release mechanism was anomalous transport (non-Fickian), governed by the diffusion and swelling/relaxation of the polymer chains (31).

Microspheres can also be used as carriers for oral administration of hydrophilic drugs, in order to modify their release and improve bioavailability, efficacy, and patient compliance. For example, Ray et al. developed matrix microspheres based on the interpenetrating network (IPN) of XG/poly(vinyl alcohol) (PVA) for the pH-sensitive delivery of diclofenac sodium (DS) to the intestine. Microspheres were prepared by the emulsion-crosslinking method, with GA as a crosslinker, and dried at 50 °C. Many formulation factors were varied, including the XG-to-PVA ratio and extent of crosslinking, to obtain an optimized formulation in terms of drug release kinetics. An *in vitro* release study was performed at pH 1.2 (during 4 h) and 6.8 (during 12 h). First of all, it was noted that significantly lower amounts of DS were released at pH 1.2 in comparison with pH 6.8. The results of DS release study showed its slower release from the formulations prepared at higher amounts of GA, indicating the formation of a denser network structure in those samples, which resulted in the reduction of the swelling rate and consequently drug release rate from the matrix. With respect to the XG-to-PVA ratio, the *in vitro* release study indicated that an increase in the XG content in the matrix led to an increase in the swelling ability of microspheres due to the hydrophilic nature of XG. That resulted in higher release of DS from the carrier. The release data were then analyzed by the *Peppas* equation (Table II) to define the mechanism of DS release from the prepared matrix microspheres. The obtained *n* values (0.329–0.369) showed a Fickian trend of drug release from microspheres, which depended on the crosslinking extent and the XG-to-PVA ratio. The calculated *n* values increased with an increase in crosslinking density and a decrease in XG content in the IPN matrix. Lower *n* values were correlated with the formation of a loosely crosslinked polymer network, which resulted in increased swelling ability. Based on the obtained results, the authors concluded that the investigated IPN-based microspheres have a potential to enable controlled release of water-soluble DS after oral administration (32). Another group of authors developed CH-based microspheres crosslinked using different concentrations of tripolyphosphate (TPP), formaldehyde (FA) or GA (1% or 2% *w/w*) by spray drying, and evaluated the effect of the crosslinking agent on the release of acetaminophen from the prepared microspheres. The *in vitro* release studies were carried out in phosphate buffer solution (pH 7.4) during 6 h. The results indicated that drug release from microspheres depended on the nature of matrix and its rigidity, since a higher swelling ability of microspheres usually results in a higher amount of acetaminophen diffused from the matrix. Microspheres crosslinked with TPP showed a higher drug release rate at both concentrations of crosslinking agent when compared to those crosslinked with FA and GA. This may be due to higher swelling capacity, water uptake and erosion of CH-TPP compared to CH-FA and CH-GA

microspheres. In addition, the release rate of acetaminophen from microspheres decreased with an increase in crosslinking agent concentration from 1% to 2%, due to the decrease of water uptake, swelling ability, and relaxation of the polymer chains. Furthermore, the *in vitro* release data were analyzed using the *Higuchi* equation (Table II) to elucidate the mechanism of acetaminophen release from the prepared microspheres. It was revealed that the drug release from matrix involved initial swelling followed by drug diffusion. A biphasic release from all microspheres was also noted, with an initial burst release, followed by a subsequent slower release. That was explained by a quick release of 43–66% of acetaminophen which was located on the surface of microspheres in the first 30 min. Subsequently, the drug release rate after the swelling of the microspheres was sustained and mainly controlled by the Fickian diffusion of acetaminophen (33). Bhattacharya et al. formulated the IPN hydrogel microspheres of XG-based superabsorbent polymer (SAP) (i.e., superabsorbent poly(acrylic acid)/XG-modified bentonite) and PVA by water-in-oil emulsion-crosslinking method (GA was used as a crosslinking agent) for sustained release of ciprofloxacin hydrochloride (CIPRO) and by varying the hydrolyzed SAP-to-PVA ratios and the crosslinking density. The *in vitro* drug release study was carried out in acidic (pH 1.2 during 2 h) and alkaline (pH 7.4 during 8 h) media. Moreover, the drug release mechanism from the microspheres was evaluated by fitting the release data (up to 55% of released drug) in the *Korsmeyer-Peppas* equation (Table II). All batches of the prepared microspheres showed satisfactory *in vitro* release performances. The formulation prepared at a higher amount of GA exhibited a lower release rate due to the formation of a denser network and the reduction of the swelling rate. Moreover, the swelling of microspheres increased with the increase in the content of hydrolyzed SAP in the matrix. It was explained by the hydrophilic nature of polymer, which led to the higher release of CIPRO. The results of release kinetics evaluation indicated a non-Fickian trend of drug release from microspheres. The authors concluded that CIPRO-loaded IPN microspheres were suitable for sustained-release applications (34). Very recently, Ćirić et al. evaluated CH/XG-based PECs as carriers for amphiphilic and weakly acidic drug substance escin (35). The study aimed to investigate the impact of escin-to-polymers (CH and XG) mass ratio (EPMR) (1:1, 1:2, and 1:4) and drying method on the PECs drug release properties. An *in vitro* release test showed the extended release of escin during 12 h from all PECs. Up to 80% of the entrapped escin was released from spray-dried PECs compared to ambient-dried ones. In spray-dried PECs, escin could likely be rinsed from the microparticle surface, while in ambient-dried PECs it was entrapped within the polymer network and diffused from it after the network swelling and the polymers' chains relaxation. Among the PECs prepared by the same drying method, the highest released amount of escin was recorded at EPMR 1:1. The study showed the most pronounced pH-dependent profile of escin release for ambient-dried PEC prepared at EPMR 1:1, with lowest amount of drug released at pH 1.2, and the highest at pH 7.4. The *Korsmeyer-Peppas* escin release kinetics (Table II) was observed in most cases, except for spray-dried PECs at EPMR 1:2 and 1:4, where escin release best fit the *Higuchi* model (Table II). Moreover, escin release from the ambient-dried PEC at EPMR 1:1 was

controlled by the polymer network so that the high correlation coefficient for *zero-order* kinetics (Table II) was achieved, while from other PECs escin release followed a non-Fickian or Fickian diffusion mechanism.

In addition, microspheres have been investigated as carriers for other administration routes except oral, for example intranasal, ocular, pulmonary, etc. Mahajan and Gattani developed gellan gum-based matrix microparticles for intranasal delivery of a hydrophilic drug, metoclopramide hydrochloride, by the spray drying method. Five formulation batches were prepared by varying the drug-to-polymer ratio (1:1, 1:2, 1:3, 1:4, and 1:5). The *in vitro* drug release from microspheres was evaluated using Franz diffusion cells with dialysis membrane. The donor compartment contained the solution labeled as simulated nasal electrolytes (SNES), and the receiver compartment a phosphate buffer solution pH 6.6. The release of the drug from microspheres was moderately sustained for up to 5 h without lag time. The obtained release pattern was correlated to the formation of hydrogels by ionic gelation upon the contact of gellan gum with cations in SNES. The weakest gel was obtained at a drug-to-polymer ratio of 1:1, and the stiffest at a ratio of 1:5. Consequently, the release rate and the amount of metoclopramide released from microparticles significantly decreased with increasing gellan gum content in the formulation. After the evaluation of drug release data, the formulation with drug-to-polymer ratio of 1:3 was selected as optimum formulation. To define the drug release mechanism, the release data of the optimum formulation were analyzed using different kinetic models. The calculated *n* value of 0.4897 for the *Korsmeyer-Peppas* model (Table II) indicated the anomalous (non-Fickian) transport mechanism of drug release. The authors concluded that spray dried microspheres based on gellan gum could be a suitable nasal delivery system for the administration of metoclopramide (36). Bovine serum albumin (BSA)/CH-based microparticles crosslinked with GA were prepared by the spray drying technique for ocular delivery of atropine sulfate to sustain the drug release, improve efficacy, and minimize the side effects (37). *In vitro* release testing of atropine sulfate from the microspheres in natural tear fluid (pH 7.4) revealed a biphasic drug release, with an initial burst release of approximately 30% of the drug released during the first 5 h. Subsequently, a more controlled, extended release of the drug was noted, with approximately 72% released after 25 h and 85% at the end of the study. The drug release mechanism was defined by fitting the *in vitro* release data to various kinetic models (*zero-order*, *first-order*, and *Higuchi*) (Table II). The drug release data (for drug release up to 25 h) fitted best in the *Higuchi* model. The authors suggested dominantly diffusion-controlled release during that period. However, during the first 5 h of burst release of atropine sulfate, drug molecules located at the surface of particles were dissolved in a dissolution medium after a short period of incubation (37). Dimer et al. developed an inhalable RSV-loaded dry powder composed of polycaprolactone (PCL)-based microspheres for the treatment of pulmonary arterial hypertension. Microspheres were prepared by vibrational atomization spray drying. Due to the low density, adequate flowability, spherical shape, and irregular surface, the microspheres exhibited aerodynamic properties suitable for drug deposition in the aimed regions of the lungs and

showed the potential to achieve sustained drug release. The *in vitro* dissolution test of RSV (free and incorporated into microparticles) was performed in an aqueous medium containing 1% of polysorbate 80 (due to low aqueous solubility of RSV) for 24 h. After the first 30 min, more than 80% of free RSV was released. However, from RSV-loaded microparticles only 25% of the drug was released after the same time. RSV release was controlled for up to 720 min, with more than 85% of drug released in this period. The apparent kinetic rate constants (the *first-order* rate constant (K) and $t_{50\%}$), both for free RSV and RSV-loaded microparticles, were obtained when drug release data were fitted to the *first-order* kinetic model (Table II). For free RSV, the values of K and $t_{50\%}$ were 3.67 ± 0.67 h^{-1} and 0.19 ± 0.04 h, respectively, while for RSV-loaded microparticles these values were 0.30 ± 0.04 h^{-1} and 2.34 ± 0.35 h. Based on the obtained results, the authors concluded that a significant control of RSV release can be achieved by its incorporation into PCL-based microspheres (38).

Drug release from microcapsules

A microcapsule is a microparticle that has a spherical single or multilayer flexible polymeric wall which surrounds one core or multiple cores. Typically, the solid drug substance is embedded in a hollow cavity or it is dispersed (dissolved or suspended) in a core that is a solid polymer matrix, or the core of the microcapsule is an aqueous or oily solution or a suspension of the drug substance. Drug encapsulation inside the polymer wall of the microcapsule has attracted more and more attention as a way to improve the storage stability of vegetable and essential oils and vitamins, and overcome protein degradation. In addition, the availability of the microcapsule wall for the inclusion of target-specific molecules and stimuli-responsive moieties is of considerable importance when it comes to exerting a relevant therapeutic effect of cytotoxic substances by a selective delivery to the target site and eliminating side effects (14-21). The achievement of such goals requires an appropriate design, including particle size, size distribution, surface morphology and composition of the microcapsules, which allows for tuning the drug-release process (39). The drug release mechanisms and the factors relevant for the release kinetics of active substances with different physicochemical properties from hollow microcapsules, aqueous core microcapsules, oil core microcapsules and stimuli-responsive microcapsules are commented on in detail.

Drug release from hollow structure microcapsules

Hollow structure microcapsules consist of a polymer wall surrounding the drug encapsulated in an empty microcapsule cavity. Several studies have examined the influence of drug properties and drug-loading capacity, as well as the composition, thickness and design of the polymer wall, on drug release kinetics. Song et al. (40) considered the influence of the drug content embedded in the hollow structure ethyl cellulose (EC) microcapsules on the release kinetics of a poorly soluble model drug curcumin. An *in vitro* drug release study was performed in the phosphate buffered saline (PBS) with pH 6.8 and 7.4, containing 0.6% (w/v) sodium dodecyl sulfate, which simulate

the small intestine and colon environment, respectively, and release data were fitted to mathematical models, including *zero-order*, *first-order*, and *Higuchi* kinetics (Table II). High drug-loaded capacity microcapsules have a higher drug release rate than lower drug-loaded capacity microcapsules, likely due to the higher osmotic diffusion of curcumin through the polymer wall of EC microcapsule. At pH 6.8, microparticles with the highest drug-loaded capacity perform constant (*zero-order*) release profile, while the ones with lower drug-loaded capacity have a two-stage (quickly and then slowly) sustained-release (*Higuchi*) profile based on Fickian diffusion. However, in PBS pH 7.4, all types of curcumin-loaded EC microcapsules showed a non-constant sustained-release characteristics best described by the *first-order* equation, indicating that the drug release rate depended on both EC wall swelling and non-Fickian drug diffusion through the enlarged pore in microcapsule wall.

Drug release from microcapsules obtained by LBL self-assembly of polyelectrolytes

LBL self-assembly of polyelectrolytes has been proposed as a promising microencapsulation method for reducing the release rate, and particularly for suppressing the initial burst (12, 39). Zhang et al. (41) constructed the microcapsules by direct LBL self-assembly of the polycation poly(vinyl galactose esterco-methacryloxyethyl trimethylammonium chloride) (PGEDMC) and the polyanion poly(sodium 4-styrenesulfonate) (PSS) on the acyclovir crystals with an average length distribution of 20 μm. The release of acyclovir from suspensions of microcapsules coated with different multilayers was investigated in a vertical (Franz) diffusion cell, with a 0.45 μm cellulose acetate membrane and phosphate buffer or hydrochloric acid as receptor medium. For all of the samples, the initial burst release of at least 10% of the drug was observed during the first 30 min, likely due to the release of acyclovir intertwined with the polyelectrolyte layers during the polymer deposition process. After that, the drug release was in accordance with the Fick's diffusion law. A hollow PGEDMC/PSS multilayered network with nanoscale thickness was able to sustain the drug release, and the release rate decreased with the increase of coated layer number. In addition, a drying process enhanced the sustained drug release effect of a multilayer which shrank and tightened up, and the half release time ($t_{1/2}$) for the dried sample was 1.6 times longer than that for wet one. Although the direct deposition of polyelectrolyte multilayer films on drug microcrystals can reduce the drug release rate, in some cases (e.g., ibuprofen) no significant difference was observed between the coated and uncoated crystals (12). The deposition of polyelectrolyte multilayer films on the microparticles containing the drug substance into the solid polymer matrix turned out to be a more effective strategy to reduce the initial burst and prolong drug release. Wang et al. (12) reduced the initial burst release of ibuprofen by combining biodegradable drug-loaded poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) microparticles, fabricated by conventional solvent evaporation, with LBL self-assembly of polysaccharides CHI and sodium alginate (ALG) to produce microcapsule wall. An *in vitro* ibuprofen release evaluation in a dialysis bag

immersed in PBS (pH 7.4), pointed that the half release time ($t_{1/2}$) was prolonged from 1 h for the bare microparticles to 62 h for the CHI/ALG microcapsules. After 200 h, 95% of ibuprofen was released from bare microparticles, in contrast to 60% drug released from CHI/ALG microcapsules. This study indicated that polysaccharide multilayer films with a higher cross-linking density can form an effective barrier to the drug diffusion and the release rate can be tuned by varying the number of deposited layers. In contrast, the multilayer wall consisting of a different combination of polysaccharides (poly(diallyldimethylammonium chloride) (PD) and sodium poly(styrenesulfonate) (PSS)) had almost no restriction on the burst release. Moreover, the drug release rate depended on the size of microparticles, so the small ibuprofen-loaded microparticles were released faster than the big microparticles due to the large surface-to-volume ratio. Similar observations on the effect of the size and morphology of the microcapsule on the drug release kinetics were reported by Luo et al. (42) for the rifampicin-loaded PLGA microcapsules. The release parameters of Rhodamine 6G dye, as the small lipophilic model active substance, were also highly related to the size and morphology of the calcium alginate microcapsules size and polymer cross-linking density (4). Moreover, the effect of the microcapsule diameter and different concentrations of calcium chloride (polymer) and sodium alginate (crosslinking agent) solutions on the release kinetics responses (time of initial burst, release rate and percentage of initial burst) was statistically analyzed to identify favorable input parameters for controlled release behavior. The optimal combinations that provided the lowest and the highest percentage release in distilled water were with 0.3% (w/v) of polymer, 0.25 M of crosslinking agent, and the 30 m nozzle tip, and with 0.3% (w/v) of polymer, 0.1 M of crosslinking agent, and the 20 m nozzle tip, respectively. Faster release kinetics was observed for smaller microcapsules due to their higher surface-to-volume ratio, while higher concentrations of the polymer and crosslinking agent resulted in higher cross-linking of the microcapsules and reduced drug release rate.

Drug release from aqueous core microcapsules

Non-biodegradable and biodegradable polymer microcapsules with mononuclear aqueous core have been recognised as promising sustained release carriers for both small molecule hydrophilic drugs and proteins, and different release mechanisms have been proposed.

CHI, a cationic linear polysaccharide obtained from the extensive deacetylation of chitin, is a suitable microcapsule wall material due to its biocompatibility and biodegradability; however, they have the low encapsulation efficiency of a water-soluble core material and a significant burst effect (43). Cross-linking of the CHI-based capsule wall has been proposed as a strategy to overcome the burst drug release. Su et al. (44) investigated the importance of polyphosphates, namely, sodium tripolyphosphate (STPP), sodium pyrophosphate (SPPP) and sodium hexametaphosphate (SHPP), as cross-linking agents, on the kinetics of the release of 5-aminosalicylic acid (5-ASA) from microcapsules based on the PECs of sodium cellulose sulfate-CHI hydrochloride (NaCS-

CHIC). The molecular structure and charges of the polyphosphates significantly affected the interaction between the polymers and microstructure of the microcapsules, enabling sustained drug release profiles without the burst effects, in comparison with microcapsules without polyphosphates. SPPP microcapsules enabled a higher cumulative drug release rate of 5-ASA at the same time point and released completely at 12 h due to their larger specific surface area and a greater contact area with the receptor medium (SCF (pH 6.4)). The drug release mechanisms analysis by the *Ritger-Peppas* model (Table II) (R^2 0.984-0.997) indicated that the microcapsules without polyphosphates and SHPP microcapsules were mainly diffusion controlled (Fickian diffusion), while STPP and SHPP microcapsules followed the mechanism of non-Fickian transport, i.e., the drug release was governed by the swelling and erosion process. Heidari et al. (13) achieved sustained release of doxorubicin loaded at 53±1.9% by normal diffusion into the hollow cavity of CHI-bovine serum albumin (CHI-BSA) microcapsules, after 24 h incubation. The multilayered microcapsule wall was assembled with consecutive layering of a polycation (CHI) and a polyanion (BSA) solidified by crosslinking with GA. *In vitro* drug release experiments of the microcapsules as a lung targeted drug delivery system *via i.v.* injection were performed in the presoaked dialysis bag method in two acceptor media (PBS (pH 7.4) and 50% V/V fresh bovine serum in PBS solution). Although most of doxorubicin had been released from the microcapsules after 10 h in both media, the sustained drug release continued up to 85% for PBS and 92% for serum/PBS, at 70 h. Higher cumulative drug release in the presence of serum was related with slow enzymatic degradation of microcapsules by serum components.

The polyester polymers poly(lactide-co-glycolide) (PLGA) and poly(lactide) (PLA) are the most widely used synthetic biodegradable polymers for microencapsulation, with a great capacity to control the release of the encapsulated drugs (45). Abulateefeh et al. (46) demonstrated the *zero-order* drug release profiles over the first 90% release of fluorescein sodium as a model hydrosoluble drug from the mononuclear aqueous core surrounded by a biodegradable wall comprising PLGA or PLA. Both types of microcapsules exhibited similar sizes and drug loadings; however, the drug release in PBS (pH 7.4) was sustained over 7 days from microcapsules with a PLGA-based wall and 49 days from a PLA-based wall. The slower release from the PLGA microcapsule was related with the presence of additional methyl groups in PLA which increase steric hindrance for water infiltration and hydrophobicity, and thus reduce the degradation of PLA and the diffusion coefficient of the hydrophilic drug through the wall. The observed significantly different release rate enabled the achievement of the optimal zero order drug release by preparing microcapsules with a wall based on a mixture of PLGA and PLA at PLGA/PLA mixture ratio 1:3, while drug release from microcapsules comprising 3:1 and 1:1 PLGA/PLA mixtures was in accordance with the *first-order* release model (Table II). In contrast, the drug release from polynuclear microcapsules and monolithic matrix-based PLGA microspheres followed the *Higuchi* model (Table II), reflecting the drug release limited to diffusion through the internal walls and the polymer matrix, respectively (47). Such promising findings initiated a more

comprehensive investigation on the effect of polymer properties (e.g., molecular weights, monomer ratios, end functionalities) on the drug release behavior of the produced microcapsules (in PBS pH 7.4) for a model hydrophilic drug phenobarbital sodium. As expected, drug release was strongly connected to the minor variations of polymer properties. Increases in molecular weight and the lactide-to-glycolide ratio, as well as ester termination, resulted in increased hydrophobicity and decreased flexibility and the rate of degradation of the polymer, and thus slowed down the release of phenobarbital sodium up to a few days to several weeks (45). Such a mononuclear microcapsule represents a reservoir system and drug diffusion through a wall in accordance with the *zero-order* or *first-order* kinetics is expected (Table II) when the drug concentration in the core is kept nearly constant or decreases significantly during the release process, respectively (1, 48). The investigated microcapsules exhibited an initial fast drug release, followed by a slower release best fitted to the *first-order* kinetics (R^2 0.955 – 0.995). It must be taken into account that the drug release from polyester microparticles also takes place *via* a degradation of the wall matrix. In the early phase, drug release occurs mainly as a result of drug diffusion through the polymeric wall, while in the later phase polymeric hydrolysis allows the erosion of the wall, and hence the release becomes mediated by both diffusion through the polymeric wall and wall degradation (49).

Aqueous core microcapsules may provide a protecting polymeric wall for protein drugs. However, a common disadvantage of such carriers can be a burst initial release in aqueous release media due to rapid protein desorption from microparticle surface, incomplete release due to protein adsorption to microcapsule wall and clogging of its pores or protein adsorption to a polymer core or wall (e.g. microcapsules comprising alginate) (50). Kupikowska-Stobba et al. (50) evaluated human albumin (HA) release from alginate-polyethersulfone (Alg/PES) microcapsules obtained by electrostatic coextrusion method. PES forms a hydrophobic non-biodegradable wall; thus, HA release was gradual (did not display burst effect) and it was based solely on the diffusion of protein desorbed from Alg hydrogel in microcapsule core through membrane pores. HA release followed the first-order kinetics, with the highest release rate during the first 5 h, and with a plateau reached after 19 h. Nevertheless, this study also shows that actual concentration of HA released from the microcapsules equaled 60% of the theoretical value for microcapsules with 100% permeability, which could be related to protein adsorption to Alg core or PES membrane. Different release pattern of the microencapsulated protein was described in a study by Li et al. (51) for BSA loaded as a model protein drug on CHI-ferulic acid (CHI-FA) conjugates. The CHI-FA conjugate based microcapsules were prepared by the spray drying technique. They provide a high swelling ratio and sustained *in vitro* protein release, with the mechanism described by the *Hixson-Crowell* (*corrode*) model (Table II). Such drug release behaviour involves a combination of drug diffusion of the outer and inner surface (in the initial release phase), slow drug diffusion through micropores formed as a result of polymer degradation (in the second phase), and fast erosion-controlled drug release (in the final phase).

Drug release from oil core microcapsules

Oil core microcapsules comprise a fluid core encapsulated by a solid flexible wall, which can enhance storage stability and/or provide controlled release of the encapsulated fatty or essential oil. The release of microencapsulated liposoluble substances from the oil core through the polymer wall usually takes a few minutes (52-54). By combining polymers and chemical cross-linking, the mechanisms of controlled release of liposoluble substances from the oil core through the wall can be achieved. The ability of the wall to retain oil within the core is significantly affected by the wall material type. Milinković Budinčić et al. (52) investigated the release of a lipophilic active substance vitamin E (α-tocopherol) from CHI/anionic surfactant sodium dodecyl sulfate (SDS) or sodium lauryl ether sulfate (SLES) microcapsules, prepared without and with cross-linking agent (FA or GA) by spray drying of oil-in-water emulsion. Although the overall release was very fast, small variations in the chemical structure of anionic surfactants led to significant differences in mechanisms of vitamin E release in ethanol 80%. The *in vitro* release profiles from the microcapsules based on CHI/SDS coacervates fit with the *Korsmeyer-Peppas* model (Table II) ($R^2 > 0.9$), with fast release of vitamin E during the first 10 min, after which the plateau continued during the next 50 min. The results pointed out that the cross-linking agents had not established a strong bond with CHI molecules to significantly reduce the porosity of the microcapsule wall and the drug release rate. A consideration of the value of the diffusion exponent *n* showed that the release of vitamin E was based on non-Fickian diffusion through the microcapsule wall cross-linked with GA and without a cross-linking agent ($0.43 < n < 0.85$), while for FA cross-linked microcapsules it was near 0.43, indicating the release was mainly controlled by Fickian diffusion. A deviation from the Fickian diffusion was likely caused by a combined diffusion/swelling release mechanism within the microcapsule wall. For CH/SLES microcapsules without cross-linking agent and cross-linked with GA, $n < 0.43$ was determined, reflecting the low influence of the CH/SLES microcapsule wall on the release of vitamin E and rinsing from the wall surface as the main release mechanism. The observed difference in release mechanisms was attributed to predominantly hydrophobic interactions between CH and SLES; thus, their coacervate phase was less compact than the CH/SDS coacervate, where electrostatic interactions were dominant (53). Bajac et al. (54) aimed to encapsulate juniper berry essential oil (JBEO) by spray drying and to assess the influence of different wall materials (gum arabic (GAR), maltodextrin (MD), low viscosity sodium alginate (ALG) and whey protein concentrate (WPC)) on microcapsule properties, including JBEO release. The highest encapsulation efficiency (70.07%) and the best results in density properties, porosity, dissolution time and thermal properties were obtained by using GAR/MD (1:1) for microcapsule wall formation. The wall material also influenced the time needed for the complete JBEO release (15 – 45 min); thus, the formulations differed in surface oil retention efficiency. The GAR/MD microcapsules enable high oil retention efficiency (82.66%) and the complete release of the JBEO in 50% V/V ethanol. The *Peppas-Sahlin* model (Table II) ($R^2 > 0.99$) was found appropriate to explain release kinetic of JBEO. Considering the diffusion and erosion

constants k_1/k_2 ratio higher than 1 (9.06–17.84), diffusion was identified as the main release mechanism of JBEO. Furthermore, it was observed that the *Korsmeyer-Peppas* model (Table II) was not optimal to describe release behaviour ($0.67 \leq R^2 \leq 0.9$); however, the calculated values of *n* ($0.06 \leq n \leq 0.24$) were lower than 0.5, indicating Fickian diffusion as well. Mu et al. (55) demonstrated the direct dependence between tea tree oil (TTO) release rate from the CHI microcapsules and the thickness of capsule wall. CHI microcapsules with thin polymer wall for controlled release of TTO are prepared by a simple one-step microfluidic strategy from oil-in-water emulsion templates. Soybean oil containing TTO and crosslinking agent terephthalaldehyde (TPA) is used as the inner oil phase. The crosslinking of CHI by TPA takes place at the oil/water interface. Such ultrathin microcapsule walls allow a more significant increase of the loading capacity than ordinary microcapsules with an equal size, as well as lower mass transfer resistance and rapid penetration and release of the microencapsulated substance in comparison to the microcapsules with membrane thickness at microscale. The cumulative release rate of TTO from CHI microcapsules with polymer wall thickness of 3.1 nm and 4.3 nm reach 76.1% and 56.6% within 10 h, respectively. Both types of microcapsules fit with the *first-order* kinetics (Table II), with a typical initial period of rapid release and a subsequent period of equilibrium release. The drug release rates correlate directly with the thickness of the capsule walls, so drug release was achieved twice as fast with a thinner capsule wall.

Drug release from stimuli-responsive microcapsules

In recent years, biocompatible wall materials whose characteristics (wettability, adhesivity, porosity, etc.) relevant for the release of a microencapsulated drug could be tuned in response to variations in external conditions such as pH, temperature, magnetism, light, enzymes, or concentration of salts, glucose, or redox agents, have been of considerable importance. Such stimuli-responsive microcapsules may be used as drug carriers for site specific drug delivery, releasing their payload in response to internal or external triggers, and thus enhancing drug efficacy and reducing systemic side effects (17, 20). For such delivery systems, the modeling of drug release should also take into account the stimulus effect.

Drug release from osmotic-responsive microcapsules

Certain progress has been made in the last couple of years in the preparation of polyelectrolyte microcapsules for osmotic-responsive release. Jiang et al. (56) reported the example of microcapsules based on pectin- CHI -collagen (PCCM) PECs with sustained release capacity of the encapsulated model active biomacromolecule fluorescein isothiocyanate dextran (FITC-dextran) under different osmotic pressure and salt concentrations. The PCCM wall was stabilized *via* intermolecular electrostatic interactions and hydrogen bonds established between pectin (anionic polysaccharide), CHI (cationic polysaccharide), and collagen (protein) and had excellent mechanical strength and anti-swelling characteristics. A higher collagen concentration in the microcapsule wall improved the mechanical strength and resistance to water diffusion

and thus prolonged the FITC-dextran release in various media. The osmotic pressure-triggered and ionic strength-triggered release was determined by exposing the prepared microcapsules in solutions to different polyethylene glycol (PEG) concentrations (0-15%) and sodium chloride concentrations (1-500 mM), respectively. The release rate gradually increased as the PEG concentration, i.e., osmotic pressure decreased, or ionic strength increased. A higher ion concentration suppressed the electrostatic interaction within the pectin/CHI complex, causing an increase in stable microcapsule wall permeability and faster drug release.

Drug release from thermo-responsive microcapsules

Hollow microcapsules obtained by LBL self-assembly of oppositely charged polyelectrolytes with controllable physicochemical properties have also found their application as thermo-responsive carriers. In particular, thermo-responsive microcapsules based on biocompatible poly(Nisopropylacrylamide) (PNIPAAm) have obtained attention due to the crystal solution temperature (LCST) of 32 °C (18). Wang et al. (18) prepared environmentally sensitive (PNIPAAm/ALG)n microcapsules using $MnCO_3$ microparticles or melamine formaldehyde (MF) microparticles as removable templates. Sacrification of $MnCO_3$ cores releases Mn^{2+}, which can form complexes with ALG and PNIPAAm and thus improve the stability of the microcapsule wall. Therefore, the microcapsules from $MnCO_3$ cores were thermo-sensitive and pH-sensitive within a broad pH range. Microcapsules from MF particles were thermo-sensitive but unstable in basic solutions. Thermo-sensitivity of microcapsules is attributed to PNIPAAm. Moreover, ALG and PNIPAAm multilayer films were adsorbed on recrystallized taxol. The release of coated recrystallized taxol in 20% ethanol solution at 25 and 37 °C was much longer than that of uncoated recrystallized taxol at both temperatures. In addition, coating significantly prolonged the release time of taxol above the lower crystal solution temperature (LCST) of PNIPAAm, because it adopted a compact structure that reduced the permeability of the multilayer microcapsule wall.

Drug release from pH-responsive microcapsules

Huo et al. (43) explored the pH sensitivity of the microcapsule walls based on chitosan derivatives biguanidino chitosan (BGCS) or O-carboxymethyl chitosan (O-CMCS) cross-linking with GA, to achieve pH-dependent release of the hydrosoluble antibacterial agent 2,4-diamino-6-(2-pyridyl)-1,3,5-triazine (PyTNH) from the aqueous core. *In vitro* drug release was considered in phosphate buffer solutions of neutral, acidic, and basic pH using a dialysis bag method. The study pointed the pH-dependent drug-release of the hydrophilic drug from the CMCS microcapsules, which was related with the successive formation of H-bonds and repulsive forces within the wall under the variations of the pH of the release medium. Strong hydrogen bonds established in the acidic (pH 3.5 and pH 5.5) media, as well as in the neutral medium, contracted the wall and suppressed drug release. In the basic medium (pH 9), the ionization of carboxyl groups prevented the formation of hydrogen bonds and thus a large amount of drug was released over the time. BGCS microparticles reduced burst release and prolonged overall

drug release. Fitting the drug release data to the *Korsmeyer–Peppas* equation (Table II) showed that the release mechanism of CMCS microcapsules followed Fickian diffusion, while for the BGCS microcapsules anomalous diffusion and polymer relaxation was dominant ($0.432 \leq n \leq 0.582$). The significant variation of k values (from 0.923 to 12.52) of CMCS microcapsules at different pHs was consistent with pH-sensitive drug release behavior. Zhao et al. (20) integrated a biopolymer multilayered wall, obtained using LBL self-assembly, with a chondroitin sulfate (CS) core. GA was introduced to cross-link the multilayered wall structure and a model drug BSA labeled with fluorescein isothiocyanate (FITC-BSA) was microencapsulated by pH-controlled loading. The electrostatic interaction between polycations and polyanions in a multilayered microcapsule wall and the integration of a CS matrix permitted the control of loading and release of charged drug molecules. The release of FITC-BSA was studied in phosphate-buffered saline (PBS pH 7.4) or 1 ml HCl solution (pH 5.0 or 1.0). A burst release was observed during the first 65 min, and it was followed by a sustained and pH controlled release. The diffusion based drug release was significantly different among the investigated pH values, and it was faster at a higher pH, due to decreased electrostatic attraction between the negatively charged BSA above its isoelectric point (pI) (pH 5.0) and CS.

Intracellular pH-triggered drug release has attracted a lot of attention as an advanced strategy in cancer therapy, based on an extracellular/intracellular environment difference in pH, particularly in subcellular compartments such as endo-/lysosomes. Traceable pH-sensitive microcapsules based on polyurethane (PU) were loaded with doxorubicin and sodium bicarbonate and assessed for the pH-triggered intracellular drug release by Niu et al. (19). The PU microcapsules were highly sensitive to endo/lysosomal pH (pH∼5.0), and when they were incubated in such acidic media for 24 h, sodium bicarbonate quickly produced CO_2 bubbles to microperforate or disintegrate the PU wall, resulting in rapid release of 85% of doxorubicin from the aqueous core of the microcapsules. In contrast, when drug-loaded microcapsules without sodium bicarbonate were incubated at pH 5.0 for 24 h, only 7.14% of the drug was released. Moreover, all PU microcapsules containing sodium bicarbonate exhibited a dense morphology and smooth surface in PBS pH 7.4. Confocal laser scanning microscopic analysis showed that such microcapsules were easily internalized by BGC 823 and Hela cells, and doxorubicin was quickly released in the endo-/lysosome environment.

Drug release from enzyme-responsive microcapsules

The polymer wall of microcapsules can be designed as a membrane that is subject to gradual disintegration under the influence of specific enzymes, which triggers the release of the microencapsulated drug. In a study of Guo et al. (8), a soluble small molecular fraction from corn starch (amylose content was 27.5%±0.3%, protein content < 0.10%) (CS) and commercial soluble starch (SigmaAldrich, USA) (SS) were used independently to microencapsulate corn oil at wall material/core material mass ratio 2:1. SS based microcapsules (MSS) had a higher oil holding capacity than the CS based one (MCS). The encapsulated oil of both microcapsules could be slowly released under the

gradual hydrolytic action of α-amylase and amyloglucosidase during *in vitro* simulated human digestion. The encapsulated oil was released more slowly in MCS, i.e., the oil release ratio of MCS was significantly lower than that of MSS at 180 min of enzymatic hydrolysis ($p < 0.05$), likely due to significantly lower water solubility and higher molecular weight and resistance to enzymatic hydrolysis. A polyelectrolyte polyallylamine hydrochloride (PAH)/poly-L-glutamic acid (PLGA) nanofilm assembled by the LbL technique was used by Craig et al. (7) as a microcapsule wall which degrades in the presence of glutamyl endopeptidase (V8) from *Staphylococcus aureus* and releases the model drug FITC-dextran from the aqueous core. PLGA was applied as a component in the nanofilm due to the substrate specificity of the V8 protease. Such a concept allowed drug release only in the presence of a Staphylococcal infection, while the nanofilm stayed intact and no drug was released in a noninfected wound when there were only human wound enzymes (e.g., human neutrophil elastase (HNE)) present. The study revealed the need for a higher V8 concentration and/or longer contact time in order to maximize the V8 enzyme triggered degradation of the microcapsule wall and subsequent drug release.

Drug release from multi-stimuli responsive microcapsules

In recent literature, examples of the design of more complex microcapsule-type carriers have been demonstrated, which provide highly specific drug delivery and multiple sensitivity with adjustable controlled-release characteristics, e.g., drug release in particular tumor cells. A common method is to form polymer networks that consist of cleavable chemical bonds in the presence of the reducing agent glutathione (GSH), whose concentration is many times higher in tumor cells compared to healthy ones. Moreover, disulfide bonds can also be cleaved in an oxidizing environment (i.e. increased levels of reactive oxygen species), which is also typical of cancer cells. Therefore, in targeted areas, such as tumor cells, where endogenous reducing tripeptide GSH is present at higher concentrations, rapid drug release can be triggered (16, 17). Shi et al. (17) designed a folic acid (FA) decorated reductive-responsive ε-poly-L-Lysine (ε-PL)-based microcapsules (FA-ε-PLMCs) with soybean oil core loaded with Coumarin 6 (C6) as a model hydrophobicdrugs. Moreover, C6 could be delivered selectively into Hela cells *via* folate-receptor (FR)-mediated endocytosis. The walls of FA-ε-PLMCs were formed by cross-linking of sulfhydryl groups (-SH) under ultrasonication. C6 released easily, due to the cleavage of disulfide bonds under reductive environment (mixture of DMF and PBS (v/v = 1:2)), with various levels of GSH (0 μM, 10 μM, 10 mM)). In a related study, Cui et al. (16) applied the sonochemical method for preparation of multi-stimuli responsive (smart) CHI-based microcapsules (MSRS-CS-MCs) from FA functionalized thiolated CHI. The shells of MSRS-CS-MCs were decorated with FA (the targeting molecule) and red fluorescent dye RITC. OA-Fe3O4 MNPs and green fluorescent dye Coumarin 6 (C6) (a model hydrophobic drug) were encapsulated into the MSRS-CS-MCs. MSRS-CS-MCs show potential for: selective folate-receptor-mediated targeting functionality to the HeLa cells, magnetic response, and reduction-responsive controlled release of hydrophobic drugs in PBS with GSH (10 μM, 10 mM). The results indicated redox-responsive ability

of microcapsules for rapid triggered release of C6 caused by the GSH mediated cleavage of disulfide cross-linking bonds. Less than 6% of C6 was released without GSH in 48 h, less than 10% with the addition of 10 μM GSH, while more than 82% of C6 was released within 24 h in the presence of 10 mM GSH. Mackiewicz et al. (15) reported the synthesis and characterization of a gel microcapsule based on thermo-responsive poly(N-isopropylacrylamide) and degradable cystine crosslinker, that is temperature-, pH-, ROS- and GSH-sensitive and enables controlled fast or slow degradation of the microcapsules and burst or sustained/prolonged release of doxorubicin, depending on pH and concentration of the reducing agent (GSH) and oxidizing agent (H_2O_2), respectively. The microcapsules undergo degradation by the GSH and H_2O_2 through three steps: i) swelling of the microcapsules and loosening of the polymer network; ii) degradation into single polymer particles; iii) complete degradation. The degradation stages corresponded with initial diffusion, slow drug release and increase in the cumulative release after 340 h. The polymer degradation rate in phosphate buffer (pH = 7.4; 0.15 M) or acetic buffer (pH = 5.0; 0.15 M), mediated by the oxidizing agent, was concentration dependent within the range of 0.1 – 1% and led to a prolonged drug release. In the presence of 10 mM glutathione microcapsules swelled and did not degrade completely; thus, only the initial burst release was observed due to the competition of GSH and doxorubicin in the interactions with the carboxylic groups. The study of Li et al. (14) described magnetic microcapsules (MMC) with magnetic nanoparticles shell (MS) or with magnetic Fe_3O_4 nanoparticles core (MC) prepared by sonicating the hydrophobic drug-loaded oil phase in an albumin aqueous solution. The reductant dependent release kinetics and mechanism of the MMC exposed to an external stimulus were investigated. MMC-MS and MMC-MC were different in size, structure and morphology; however, they both showed prominent magnetism-mediated targeted drug delivery of C6, while the sulfhydryl-crosslinked shell structure provided a redox-responsive controlled drug release behavior for the hydrophobic model drug from both MMC. The obtained results indicated that the crosslinked shell structures of the MMC could restrain the drug diffusion from the inner core, while the sulfhydryl-crosslinked structures allowed a redox-responsive behaviour. Moreover, the release rate or the released drug amount can be adjusted by changing the content of the reducing agent. For clarification of the drug release mechanism, two semi-empirical equations were established by Ritger and Peppas (Table II). The release process was divided into two stages. During the first release stage, the n values ($0.43 < n < 0.85$) indicated an anomalous transport release mechanism of C6. During the second release stage, $n < 0.43$ corresponded to combined erosion and diffusion mechanisms.

Conclusion

Microencapsulation of drug substances is among the most favored pharmaceutical technologies to provide immediate or controlled release for several hours, days, weeks or months. Moreover, microparticle carriers can be designed to release a drug substance under the influence of the appropriate stimuli (magnet, heat, light, ultrasound, pH or enzymes) to achieve a targeted drug delivery at the site of action. The drug release profile

is a key characteristic of polymer microparticles that needs to be aligned with a specific application by altering microparticle properties (e.g., particle size and size distribution, wall thickness, structure and porosity) by the proper selection of excipients, microencapsulation method and process parameters. In the majority of cases, the drug release process is complex and insufficiently clarified. Both microspheres and microcapsules have the ability to control drug release *via* diffusion, but the release mechanism may also include surface desorption, surface erosion, swelling, shrinkage, osmosis, or wall disintegration. Mathematical modeling plays an important role in the drug release data quantification and understanding of the drug release process. It should also be mentioned that the mathematical drug release models commented on in this article are (semi)empirical, but there are also mechanistic models described in the literature as well. Although drug release modeling of microparticles, especially multistimuli-responsive microcapsules, is still in the early stage, it is clear that the development of reliable and accurate mathematical models for the evaluation of drug release kinetics is of essential importance for the design of novel drug delivery systems based on microparticle carriers and optimization of microencapsulation methods.

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Matematičko modelovanje *in vitro* oslobađanja lekovitih supstanci iz nosača tipa polimernih mikročestica

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Kratak sadržaj

Inkorporiranje aktivnih supstanci u nosače tipa polimernih mikročestica (mikroinkapsulacija) je značajna tehnološka strategija u farmaceutskoj industriji kojom se može postići poboljšanje kvaliteta, funkcionalnosti, bezbednosti i/ili terapijske efikasnosti farmaceutskih preparata za različite puteve primene. U fokusu aktuelnih istraživanja u ovoj oblasti je inkapsulacija malih molekula i makromolekula u mikročestice na bazi biokompatibilnih sintetskih polimera i biopolimera, kao što su polipeptidi i polisaharidi, u cilju postizanja željene kinetike oslobađanja aktivne supstance. Raznovrsnost u pogledu strukture i veličine mikročestica, izbora polimera i postupaka izrade, omogućava kreiranje mnoštva nosača na mikroskali (npr. monolitne matriksne mikrosfere, šuplje mikrokapsule, mikrokapsule sa vodenim ili uljanim jezgrom, stimulus-senzitivne mikrokapsule), pri čemu se može manipulisati njihovim uticajem na biofarmaceutski profil lekovitih supstanci. Dosadašnji rezultati ukazuju da je *in vitro* proučavanje kinetike oslobađanja aktivne supstance jedan od ključnih aspekata karakterizacije nosača tipa mikročestica, pri čemu primena matematičke analize (modelovanja) profila oslobađanja predstavlja značajno oruđe za sagledavanje mehanizama procesa oslobađanja lekovite supstance iz nosača, kao i za procenu uticaja i optimizaciju formulacionih i procesnih parametara u postupku mikroinkapsulacije. U radu je dat pregled reprezentativnih studija u okviru kojih je vršeno matematičko modelovanje eksperimentalno dobijenih podataka tokom oslobađanja model supstanci različitih fizičko-hemijskih osobina iz mikročestica, ilustrovan je značaj navedenog pristupa u obradi podataka i ukazano je na potencijalna ograničenja.

Ključne reči: mikroinkapsulacija, polimerne mikročestice,
in vitro oslobađanje lekovite supstance,
matematičko modelovanje kinetike oslobađanja lekovite supstance