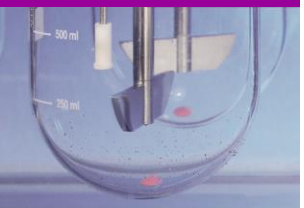
Interpolymer complexes as carriers for gastrointestinal drug delivery: challengers and problems

Assoc.Prof. Rouslan Moustafine

Director of the Institute of Pharmacy,

Co-founder and R&D Director of «InterLEK» LLC



COLOTAN

1st Symposium “Colon targeting of drugs: current state of the art” - virtually 18th June 2021

Interpolymer complexes – a new class carriers for drugs delivery

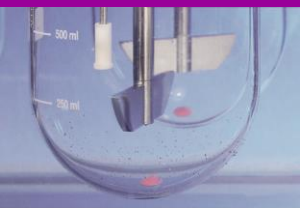
Recent progress in the polymer chemistry combined with modern pharmaceutical science revealed a new class of carriers, interpolymer complexes (IPCs), the unique physicochemical properties of which present broad possibilities for using them to create innovative drugs forms

Prof. V.A. Kabanov

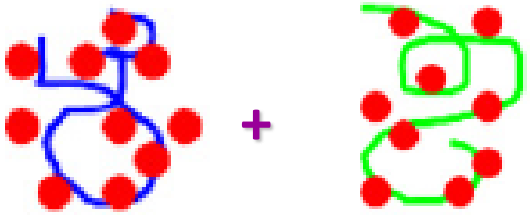
Prof. A.B. Zezin

Prof. V.A. Kemenova

Kemenova V.A., Mustafin (Moustafine) R.I., Alekseev K.V., Scorodinskaya A.M., **Zezin A.B.,** Tenchova A.I., **Kabanov V.A.**,Application of interpolymer complexes in pharmacy. ***Pharmaciya***, 60 (1), 67-72 (1991) [in Russian].



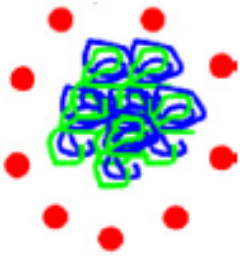
Schematic representation of IPC formation



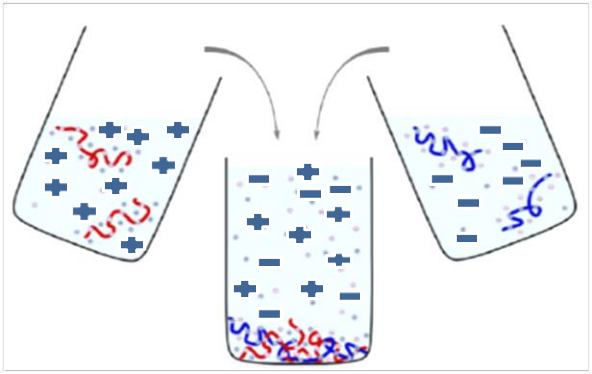
Interaction between two macromolecules

"Ladder" structure

IPC particle



Agglomeration of IPC particles



* V.V. Khutoryanskiy ***Int. J. Pharm***. (2007).

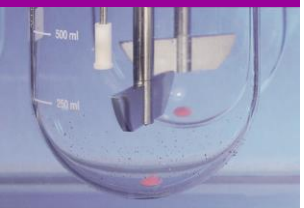
The first results of using interpolymer complexes for oral matrix drug delivery purposes

Prof. T. Nagai (Japan)

T. Takahashi, K. Takayama, Y. Machida, T. Nagai, Characteristics of polyion complexes of chitosan with sodium alginate and sodium polyacrylate, Int. J. Pharm. 61 (1990) 35–41.

K. Takayama, M. Hirata, Y. Machida, T. Masada, T. Sannan, T. Nagai, Effect of interpolymer complex formation on bioadhesive property and drug release phenomenon of compressed tablet consisting of chitosan and sodium hyaluronate, Chem. Pharm. Bull. 38 (1990) 1993–1997.

K. Saton, K. Takayama, Y. Machida, Y. Suzuki, T. Nagai, Disintegration and dissolution characteristics of compressed tablets consisting of hydroxypropyl cellulose and carboxyvinyl polymer, Chem. Pharm. Bull. 37 (6) (1989) 1642–1644.



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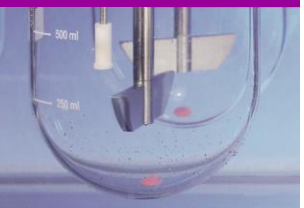
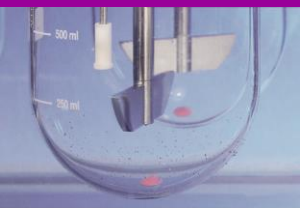


Why pharmaceutically acceptable polymers?

1

EUDRAGITs – pharmaceutically acceptable copolymers (pharma polymers)

The unpredictable toxicity of novel synthetic homo-(block)-(co)polymers limits their practical application as independent carriers of biologically active compounds. The problem can be solved by finding polymer carriers that regulate the duration and location of drug action and comply with medical and pharmaceutical requirements.



Pharmaceutical Poly(meth)acrylates

Global Acceptance by international registration authorities

EVONIK INDUSTRIES

X = monograph (X) = draft submitted ( ) = planed

	Ph. Eur.	NF	JPE	US DMF
EUDRAGIT® E 100	X	X	X	#1242
EUDRAGIT® E PO	X	(X)	X	#1242
EUDRAGIT® L 30 D-55	X	X	X	#2584
EUDRAGIT® L 100-55	X	X	X	#2584
EUDRAGIT® NE 30 D	X	X	X	#2822
EUDRAGIT® NE 40 D				#2822
EUDRAGIT® NM 30 D	X	( )	( )	#2822
EUDRAGIT® L 100	X	X	X	#1242
EUDRAGIT® S 100	X	X	X	#1242
EUDRAGIT® RL 100	X	X	X	#1242
EUDRAGIT® RL PO	X	X	X	#1242
EUDRAGIT® RS 100	X	X	X	#1242
EUDRAGIT® RS PO	X	X	X	#1242
EUDRAGIT® RL 30 D		X	(X)	#1242
EUDRAGIT® RS 30 D		X	(X)	#1242
EUDRAGIT® FS 30 D	( )	( )	( )	#13941

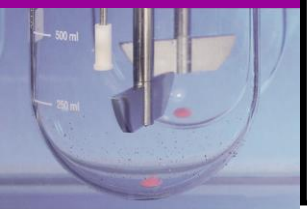
EDQM

USP U.S. Pharmacopeia The Standard of Quality℠

JP Japanese Pharmacopoeia

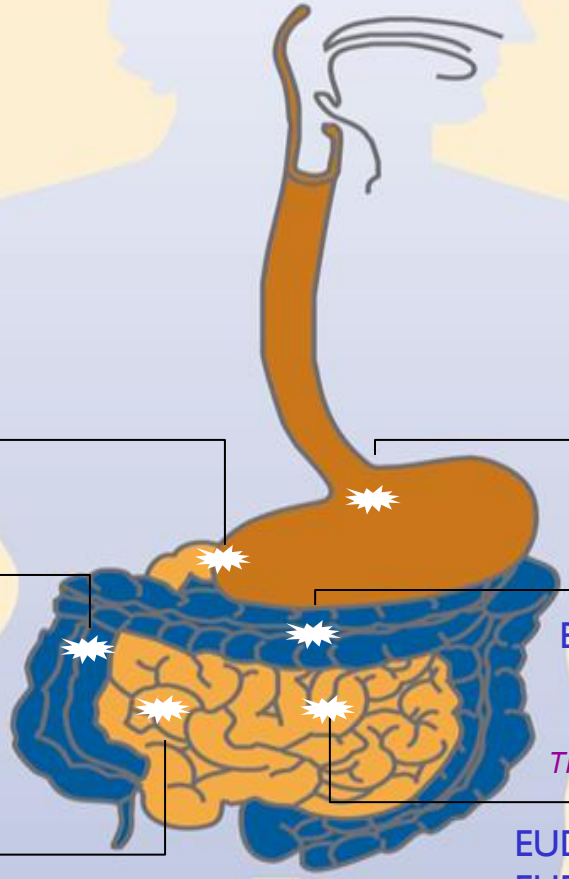
FDA

EUDRAGIT® ProductsPharma Polymers PH-GM / Dr. B. Skalsky 2009-06-06 Evonik Röhm GmbH / Slide 16



EUDRAGIT®
types and their functions

EVONIK INDUSTRIES



Duodenum pH > 5.5

EUDRAGIT® L 30 D-55
EUDRAGIT® L 100-55

Jejunum, pH 6-7

EUDRAGIT® S 100
EUDRAGIT® FS 30 D

Ileum, Colon delivery > 7.0

EUDRAGIT® S 100
EUDRAGIT® FS 30 D

Stomach pH 1-4

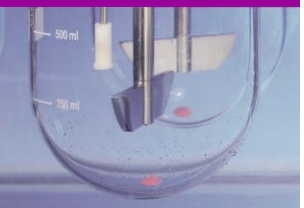
EUDRAGIT® E 100
EUDRAGIT® E PO

Jejunum, pH 6-7

EUDRAGIT® L 100

pH independent
Time controlled release

EUDRAGIT® NE 30 D
EUDRAGIT® RS 30 D
EUDRAGIT® RL 30 D



Classification of the tailoring release profiles (Colorcon®)

www.colorcon.com/formulation/app/tailoring-release-profiles

Delayed

Ascending

Enteric

Intestinal

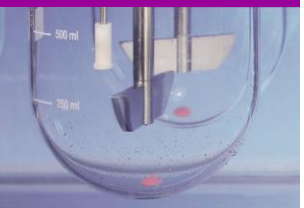
First Order

Modified Enteric

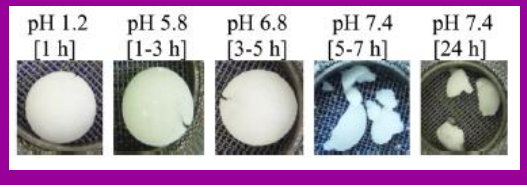
Pulsatile

Biphasic

Zero Order

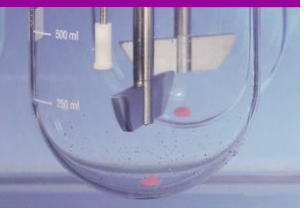


The problems of using EUDRAGIT® copolymers in matrix drug delivery



Due to copolymer structure and pH-dependent solubility Eudragit® grades has some difficulties in their using in matrix drug delivery systems (DDS):

- gastro-resistant polyanions (L100-55, L100, S100, FS) are leads to disintegrating of the matrix tablets within stomach region;
- gastro-soluble polycations (E100, EPO) are dissolving in stomach region;
- physical mixtures of polyanion and polycation grades due copolymer structure are also have ability to disintegrate in mimicking gastro-intestinal tract (GIT) conditions.



The first attempt to study a combination of two oppositely charged EUDRAGIT® RS/L100 types

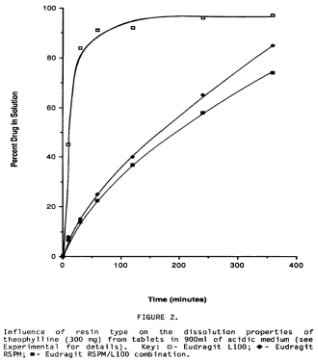


FIGURE 2.

Influence of resin type on the dissolution properties of theophylline (300 mg) from tablets in 900ml of acidic medium (see Experimental for details). Key: □- Eudragit L100; ◆- Eudragit RSPM; ■- Eudragit RSPM/L100 combination.

COLLEGE of PHARMACY
THE UNIVERSITY OF TEXAS AT AUSTIN

Prof., **James W. McGindy** is the member of Editorial Advisory Boards of numerous international peer-review journals: "*Journal of Pharmaceutical Sciences*", "*European Journal of Pharmaceutical Sciences*", "*Drug Development and Industrial Pharmacy*", "*Journal of Microencapsulation*", "*Pharmaceutical Development and Technology*", "*Journal of Drug Delivery Science and Technology*".

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(8), 1409-1427 (1987)

CONTROLLED-RELEASE THEOPHYLLINE TABLET FORMULATIONS CONTAINING ACRYLIC RESINS, II. COMBINATION RESIN FORMULATIONS

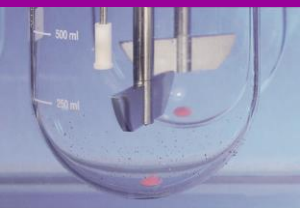
Claud G. Cameron* and James W. McGinity

Drug Dynamics Institute, College of Pharmacy
The University of Texas at Austin, Austin, Texas 78712-1074

*Present Address: Marion Laboratories, Inc.
Kansas City, Misssouri 64134

ABSTRACT

Theophylline tablet formulations containing a combination of cationic and anionic acrylic resins were prepared and evaluated. Equal amounts of Eudragit RSPM (cationic resin) and Eudragit L100 (anionic resin) were included at the 15% level (total polymer content) into the tablet formulations. Pressure-hardness profiles with theophylline-resin compacts (4:1) demonstrated that compacts containing the RSPM resin were the most compressible. The dissolution profiles for theophylline in acidic media showed slower release rates from tablets containing the combined resins than from those containing each of the single resins. It was proposed that this decrease in drug release rate was a result of a solid state interaction between the oppositely charged polymers.



J.W. McGinity, C.G. Cameron, G.W. Cuff, ***Drug Dev. Ind. Pharm.***, 9(1&2), 57 (1983).
C.G. Cameron, **J.W. McGinity**, ***Drug Dev. Ind. Pharm.***, 13(8), 1409-1427 (1987).

IPECs prepared from the pharmaceutically acceptable polymers

The polymer—polymer complexes are prepared from copolymers that have been widely used in pharmacy for decades.

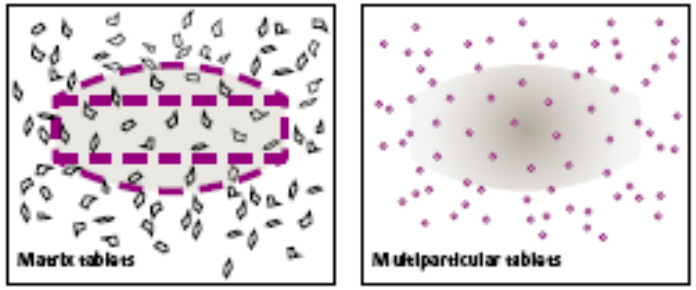
- The behavior of the copolymers *in vivo* has been thoroughly studied. Their safety has been proven clinically. This enables delivery systems to be created without the risk of increasing the toxicity, which can be reduced even more by combining synthetic (co)polymers. It should be noted that such compositional synergism changes in principle the regulation of their individual properties.

Moustafine R.I. Role of intermacromolecular interactions between pharmaceutically acceptable polymers in application of the oral drug delivery systems (mini-review) **Russ. J. Gen. Chem.** , (2014).

INTERPOLYMER COMBINATIONS OF CHEMICALLY COMPLEMENTARY POLYMERS – AS AN INSTRUMENT OF ORAL DRUG DELIVERY SYSTEMS DEVELOPING

Originally existing matrix systems:

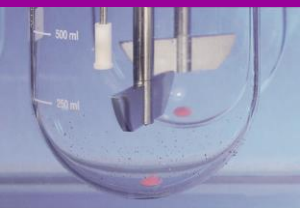
1. **EUDRACOL® - EUDRAGIT® RL /EUDRAGIT® FS (pellets);**
2. **CODES™ - EUDRAGIT® E100 /EUDRAGIT® L100 (tablet)**



Developing matrix systems:

1. **EUDRAGIT® E100(EPO) RL/ EUDRAGIT® L100-55, L100, S100, FS;**
2. **EUDRAGIT® E100(EPO), RL /Sodium Alginate/ pectin;**
3. **EUDRAGIT® E100(EPO) /CARBOPOL®'s;**
4. **EUDRAGIT® L100-55, L100 / chitosan**

Mustafin (Moustafine) R.I., INTERPOLYMER COMBINATIONS OF CHEMICALLY COMPLEMENTARY GRADES OF EUDRAGIT COPOLYMERS: A NEW DIRECTION IN THE DESIGN OF PERORAL SOLID DOSAGE FORMS OF DRUG DELIVERY SYSTEMS WITH CONTROLLED RELEASE (REVIEW) **Pharm. Chem. J.**, **45**(5) 285 – 295 (2011).



2 IPCs based on oppositely charged EUDRAGIT copolymers for developing colon-targeting DDS

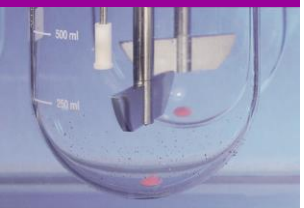
Professor Abdul Basit

BPharm, PhD, MRPharmS

UCL

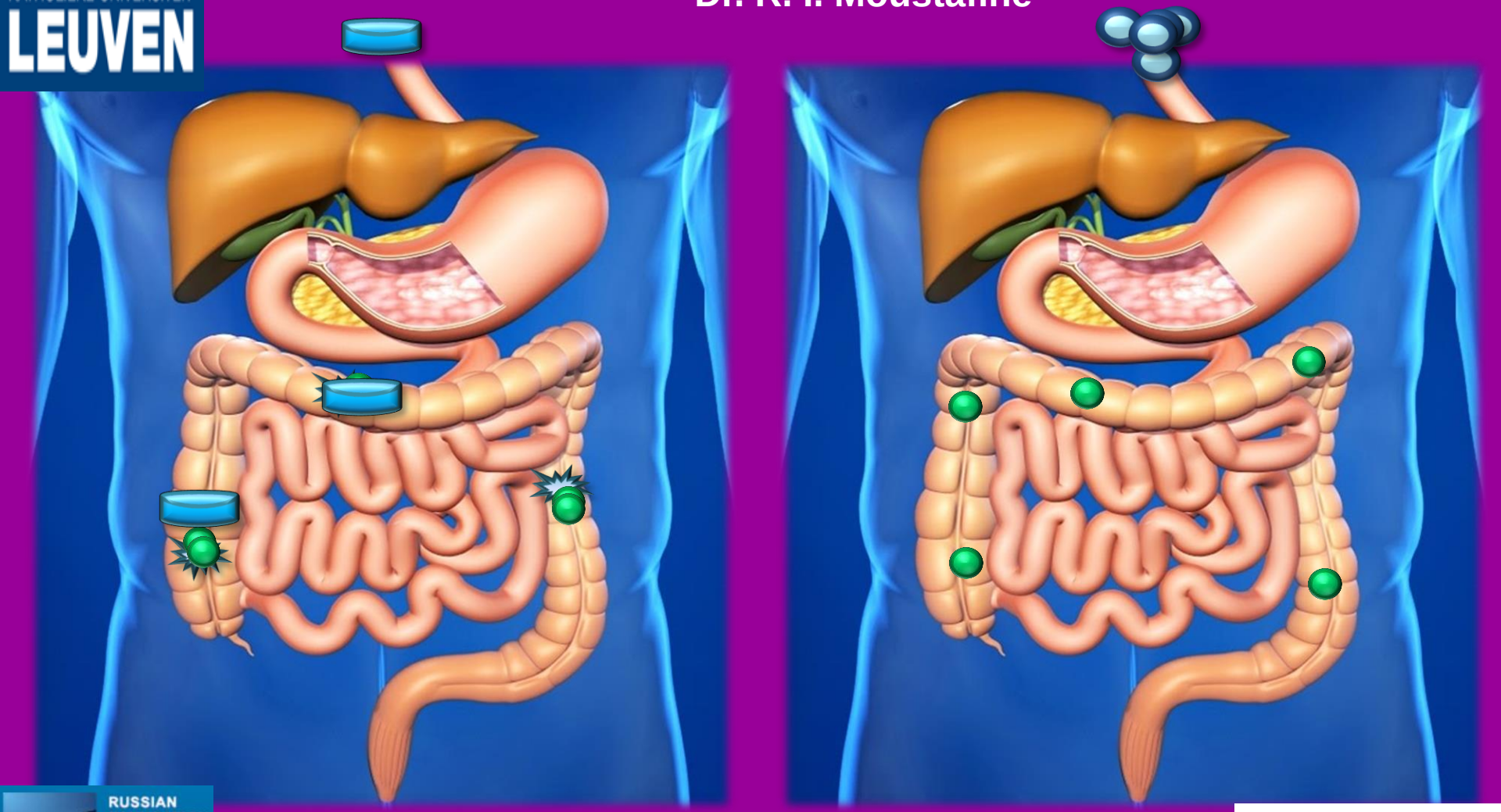
UCL SCHOOL OF PHARMACY

"It's a Dirty Job, but Somebody Has to Do It"



THE MATRIX TABLETS (LEFT) & MICROCAPSULE (RIGHT), WITH THE AIM OF TARGETED DRUG DELIVERY TO THE COLON

Head of the project – Director of the Institute of Pharmacy, Dr. R. I. Moustafine

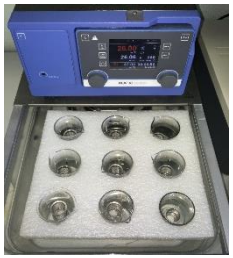


RUSSIAN FOUNDATION FOR BASIC RESEARCH

RSF Russian Science Foundation

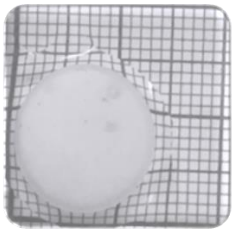
FUNCTIONING:

Microparticulate or matrix oral DDS

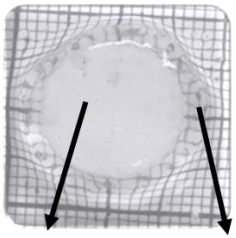


Start

2h in pH=1.2



6h (4h in pH=6.8)



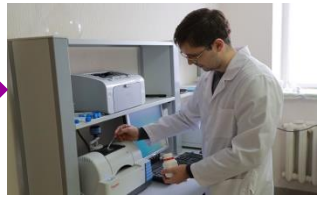
Non-hydrated core Gel layer

freeze-drying

- Thermal analysis
- ATR-FTIR
- Elemental analysis

Freeze-dryer

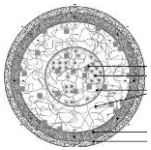
Elemental analysis

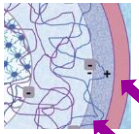


ATR-FTIR

DSC/TGA-IR characterization

Matrix DDS functioning

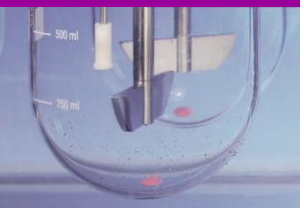




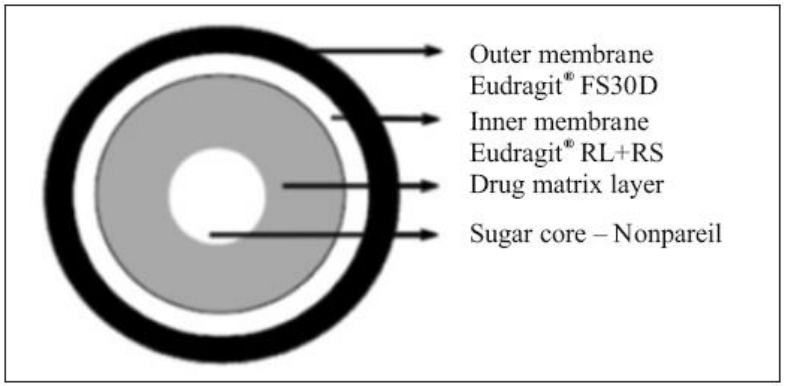
Outer layer

Inner layer

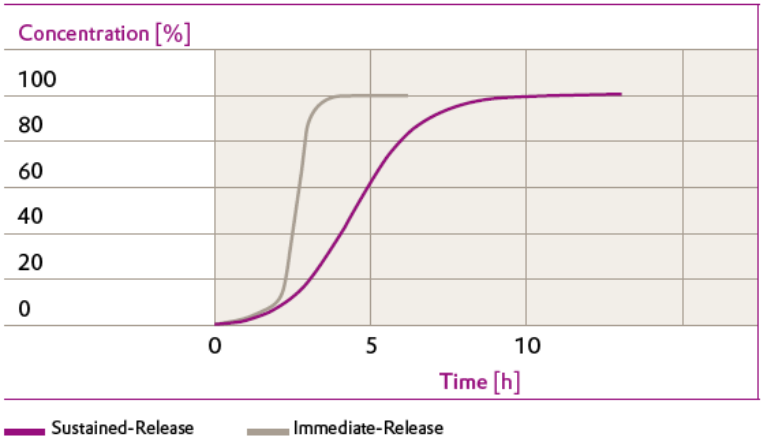
Microparticulate DDS functioning

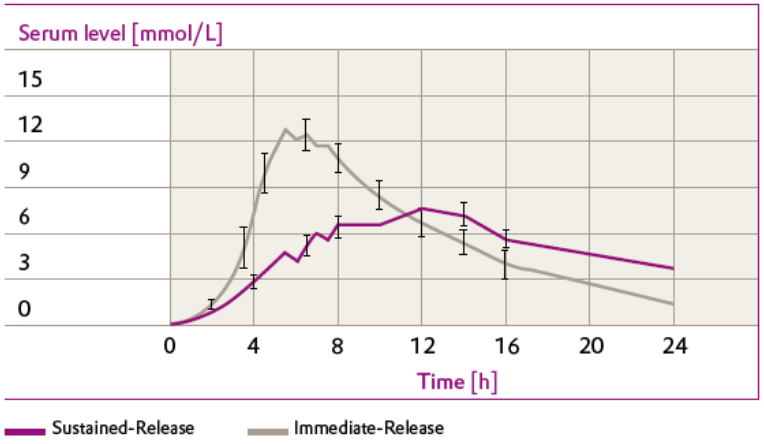


FUNCTIONING: Principle of action of colon-targeting oral drug delivery system - **EUDRACOL®**

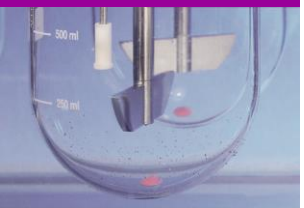


The developed construction fabricated and registered by **Evonik Pharma GmbH** under the name **EUDRACOL®** is today one of the first commercial product on the market in which the principle of interpolymer interaction of countercharged **Eudragit®** copolymers for targeted drug delivery is used.





V.K. Gupta, T.E. Beckert, and J.C. Price, ***Int. J. Pharm.***, 213, 83 – 91 (2001).



FUNCTIONING: Comparison of the release profiles of 5-ASA from the pellets, coated by different films within **EUDRACOL®** system

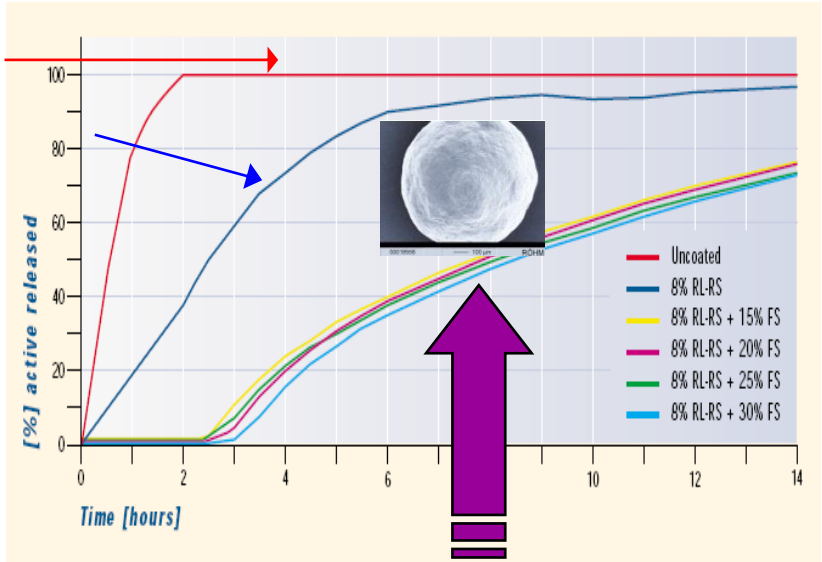
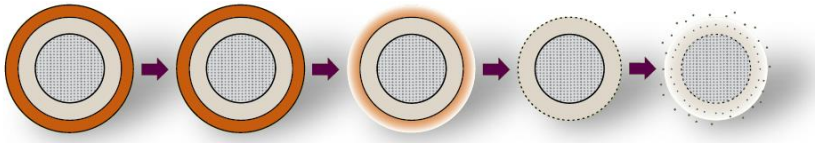


Figure 3. Release profiles of 5-ASA from pellets with a dual-layer coating and from pellets carrying only a single (the inner) coating, in comparison with uncoated 5-ASA cores. Dissolution conditions: pH 1.2 during the first two hours; then pH 7.0 (phosphate buffer to USP).

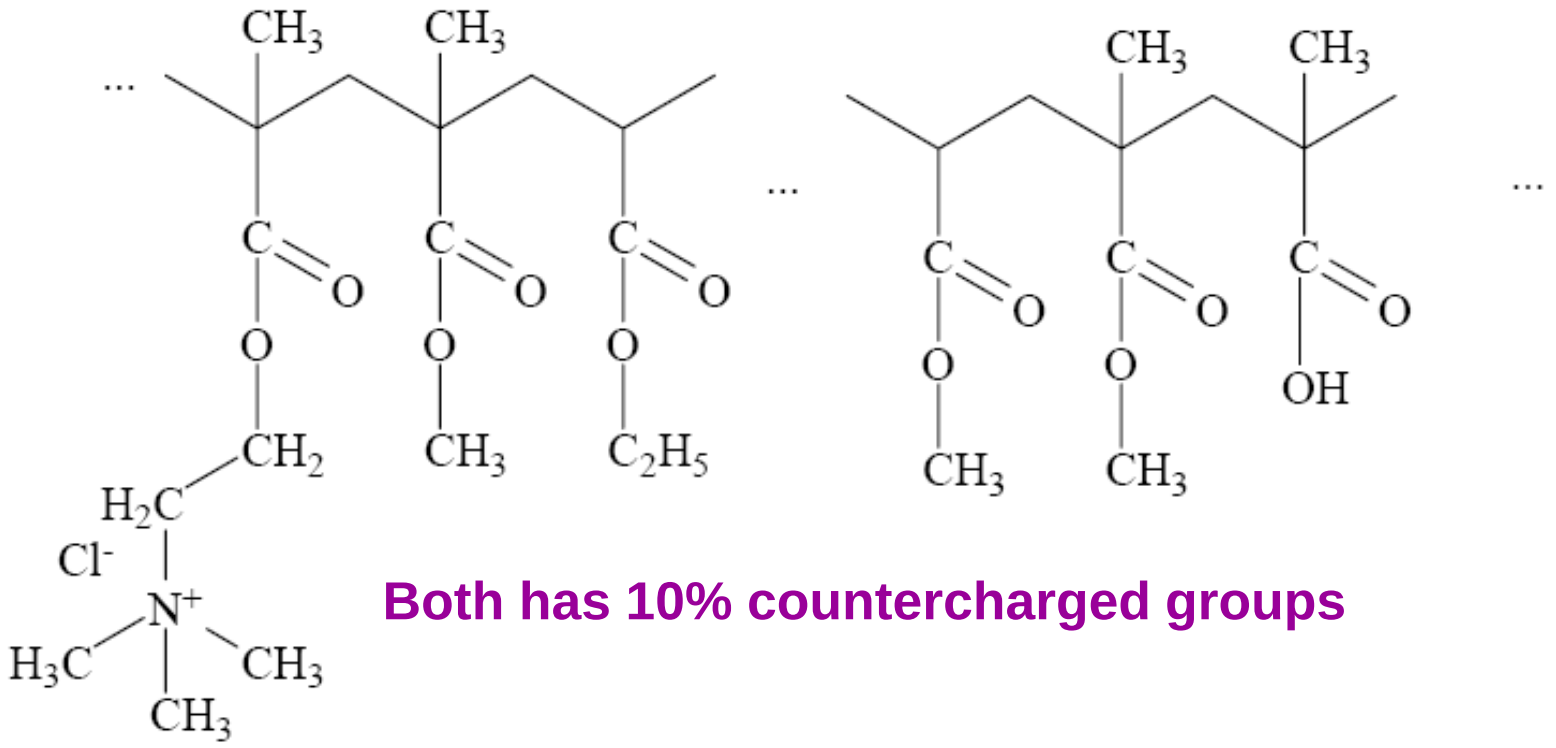


Testing of the system using the release of 5-aminosalicylic acid (5-ASA) showed that the release profiles were characterized by an unexpected slowing of the drug release rate. The researchers took into account the opposite charges of the used copolymers and hypothesized that there may have been macromolecular interactions of reactive groups on portions of the polymer chains located at the boundary of each layer.

V.K. Gupta, T.E. Beckert, N.J. Deusch, et al., Investigation of potential ionic interactions between anionic and cationic polymethacrylates of multiple coatings of novel colonic delivery system. ***Drug Dev. Ind. Pharm.***, 28(2), 207 – 215 (2002).

FUNCTIONING:

Structural monomer units fragments of Eudragit® copolymers used in **EUDRACOL®** system



Both has 10% countercharged groups

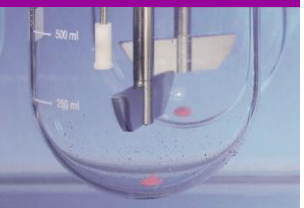
EUDRAGIT® RL (inner layer)

Poly(ethylacrylate-co-methylmethacrylate-co-trimethylammonium ethylmethacrylate chloride) 1:2:0.2; MW 150 kDa; **with high permeability**

EUDRAGIT® FS (outer layer)

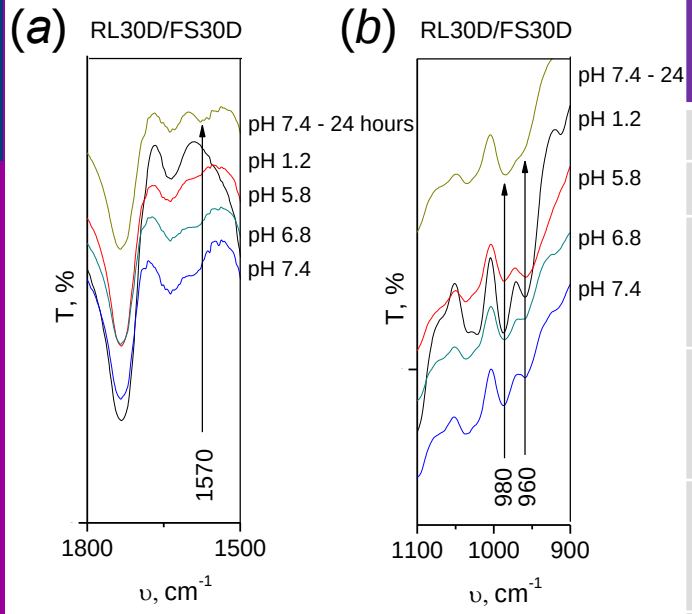
Poly(methacrylate-co-methylmethacrylate-co-methacrylic acid) 7:3:1

MW 220 kDa; **Soluble at pH > 7.2**



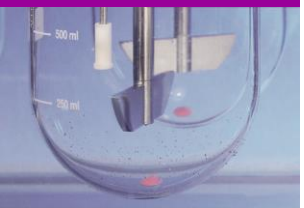
FUNCTIONING: Investigation of the interaction between countercharged EUDRAGIT® copolymers in double-layer films

(presented in 8th PBP (APV/APGI) World Meeting, Istanbul, 2012)



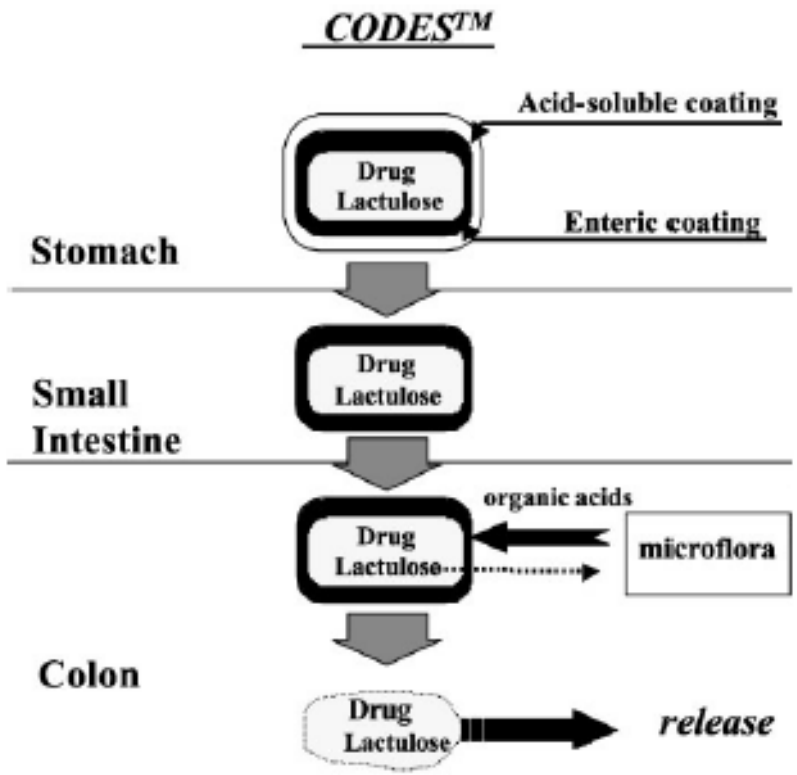
FTIR spectra of tested matrices made up from RL30D/FS30D bilayer systems during GI transit conditions in the range of: 1800 – 1500 см$^{-1}$ (*a*), 1100 – 900 см$^{-1}$ (*b*).

Sample name	Tested conditions	Tg (°C)
RL30D	Milled dried film made up from the dispersion	71.5
FS30D	Milled dried film made up from the dispersion	35.3
FS30D/RL 30D 1:1 w/w	Milled double-layer dried film (until swelling)	48.8
FS30D/RL 30D 1:1 w/w	Milled dried compressed matrices made up from milled double-layer dried film (after 1h swelling at pH 1.2)	44.1
FS30D/RL 30D 1:1 w/w	Milled dried compressed matrices made up from milled double-layer dried film (after 2h swelling at pH 5.8)	43.0
FS30D/RL 30D 1:1 w/w	Milled dried compressed matrices made up from milled double-layer dried film (after 2h swelling at pH 6.8)	42.5
FS30D/RL 30D 1:1 w/w	Milled dried compressed matrices made up from milled double-layer dried film (after 2h swelling at pH 7.4)	39.6
FS30D/RL 30D 1:1 w/w	Milled dried compressed matrices made up from milled double-layer dried film (after 24h swelling at pH 7.4)	52.1



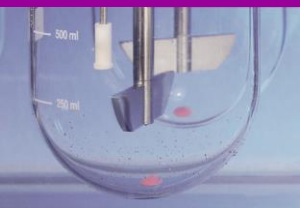
Moustafine R.I., Bodrov A.V., Kemenova V.A., et al., ***Int. J. Pharm.***, **439** 17–21 (2012).

FUNCTIONING:
Principle of the action of colon-targeting oral drug delivery system - **CODES™**



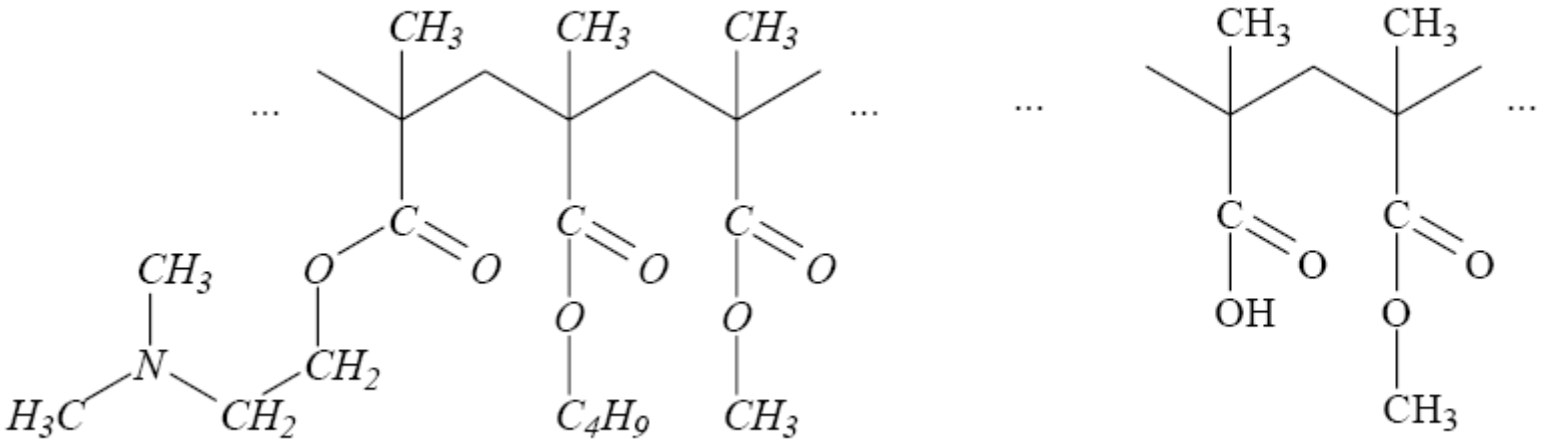
A very successful oral DDS - **CODES™** that provided targeted delivery to the colon was prepared by coating bilayer films based on **Eudragit E100** and **L100** types copolymers on the tablet core containing the drug (mesalazine etc.) and the synthetic disaccharide lactulose.

M. Katsuma, S. Watanabe, S. Takemura, et al., ***J. Pharm. Sci***., 93(5), 1287 – 1299 (2004).



FUNCTIONING:

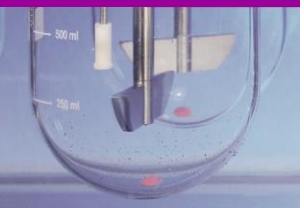
Structural monomer units fragments of Eudragit® copolymers used in **CODES™** system



25% and 50% countercharged groups respectively

EUDRAGIT® E100 (inner layer)
Poly(butyl acrylate-co-(2-dimethylaminoethyl)-methacrylate -co- methylmethacrylate)
1:2:1; MW 150 kDa; **Soluble at pH < 5.0**

EUDRAGIT® L100 (outer layer)
Poly(methylmethacrylate-co-methacrylic acid)
1:1; MW 135 kDa; **Soluble at pH > 6.0**



DEVELOPMENT:

Nanosized, microparticulate or matrix oral DDS

Nanosized DDS development

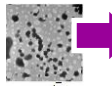
DLS characterization

Freeze-dryer

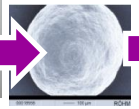
USP 4 release using nano-adaptors

Microparticulate DDS development

Freeze-dryer



TEM



SEM

DSC/TGA-IR characterization

USP 1, 2, 3, 4 release

Matrix DDS development

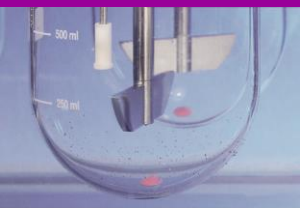
Vacuum-dryer

Composition & structural characterization

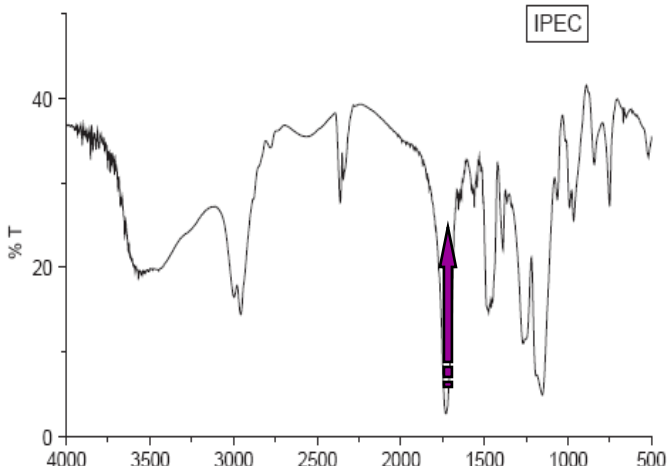
Technological characterization

Tableting

USP 1, 2, 3, 4 release



DEVELOPMENT:
Investigation of the **Eudragit®E100/L100** system as a potential carrier for oral DDS



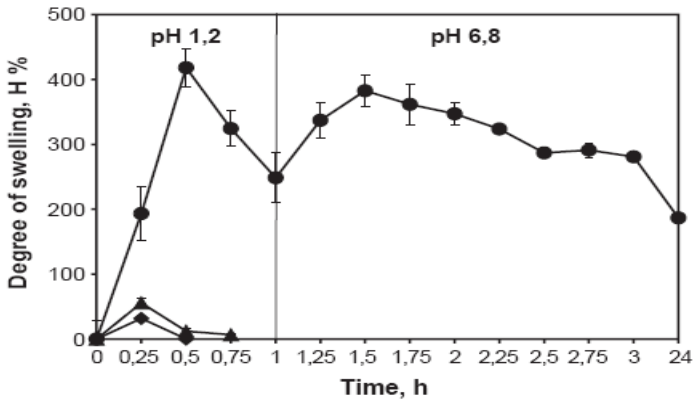


Fig. 6. Degree of swelling of IPEC (●), physical mixture of EE and EL (1:1) (▲) and pure EE (◆).

R.I. Moustafine et al. / Journal of Controlled Release 103 (2005) 191–198

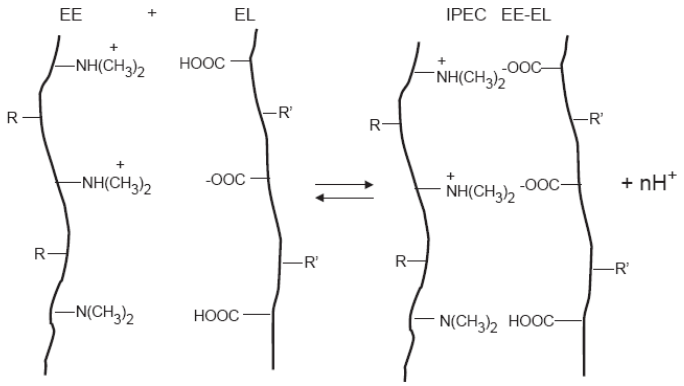


Fig. 5. Scheme of the interpolymer reaction between EE and EL at pH 6.0. R and R′ are non-ionized monomer units.

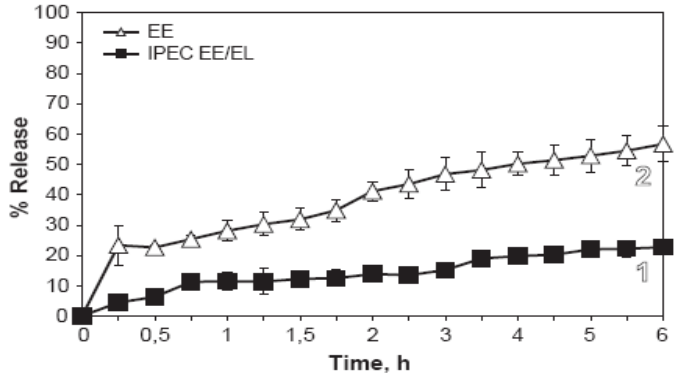
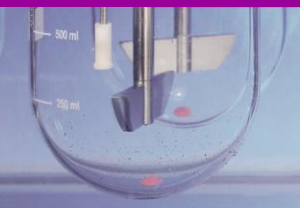


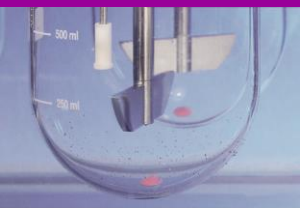
Fig. 7. Release of ibuprofen from matrix tablets prepared from pure EE or IPEC. Error bars indicate standard deviations (n=3).



R.I. Moustafine, T.V. Kabanova, V.A. Kemenova, and G. Van den Mooter, ***J. Control. Release***, **103**, 191 – 198 (2005).

DEVELOPMENT: Investigation of the **EUDRAGIT® E100/L100-55** system as a potential carriers for drugs delivery to the different intestinal regions

(partly presented in 5th PBP (APV/APGI) World Meeting, Geneva, 2006)



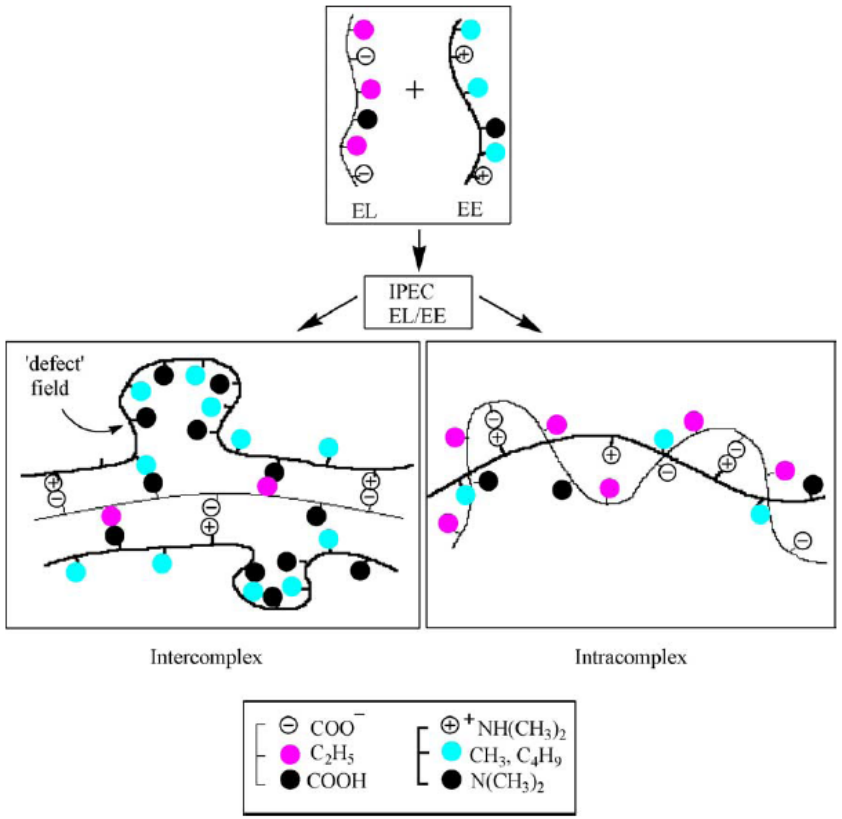


Fig. 6. Schematic representation of the ionic interactions between EL and EE.

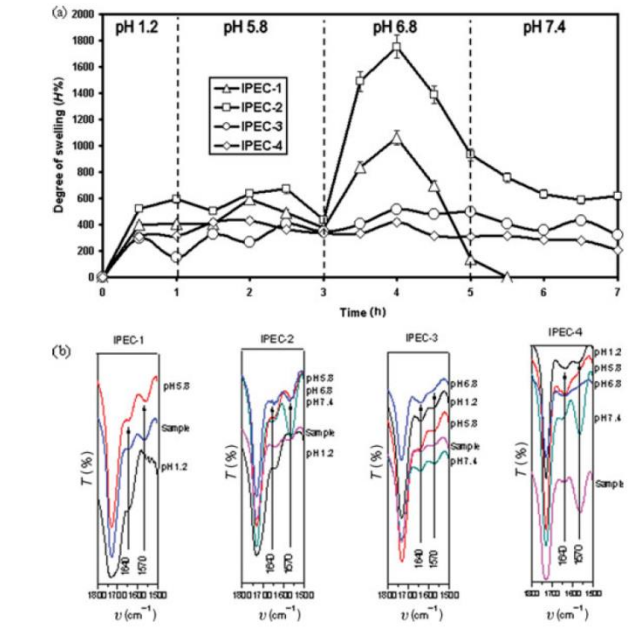
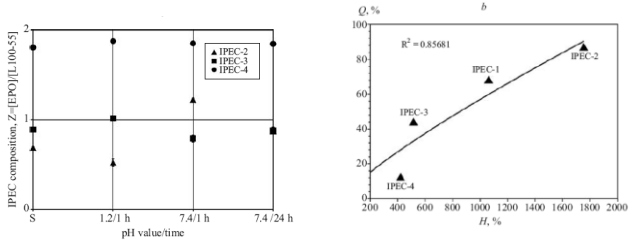


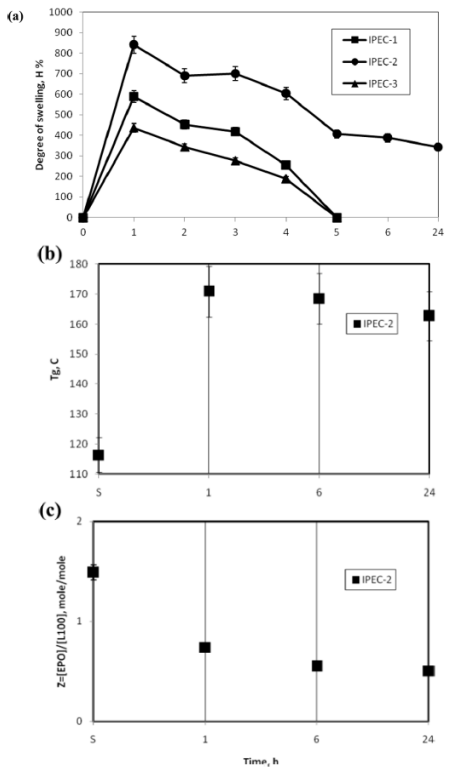
Figure 4. (a) Degree of swelling of interpolyelectrolyte complexes (IPECs) EPO/L100-55 with different composition in gastrointestinal conditions ($n = 3$; ±SD); (b) FTIR spectra of polycomplex matrices during swelling test.

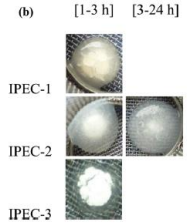


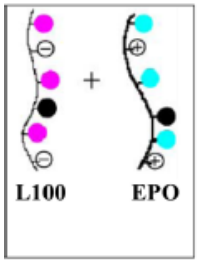
R.I. Moustafine, I.M. Zaharov, V.A. Kemenova, ***Eur.J.Pharm.Biopharm.***,63(1), 26 – 36 (2006).
R.I. Moustafine, V.L. Bobyleva, A.V. Bukhovets, et al., ***J. Pharm. Sci.***, 100(3), 874 – 885 (2011).

DEVELOPMENT:
colon-specific DDS based on EUDRAGIT® EPO/L100 copolymers

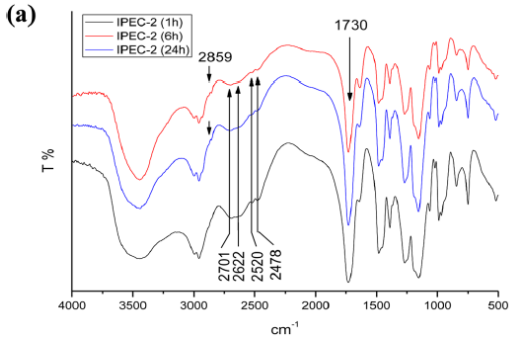
Dr. Sitenkova (Bukhovets) A.V.

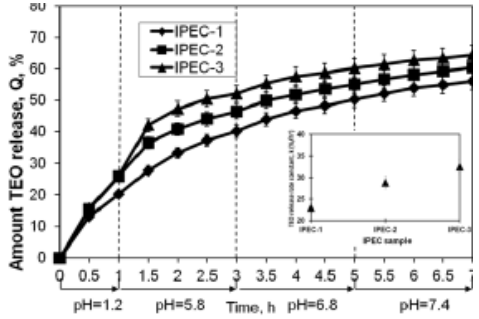


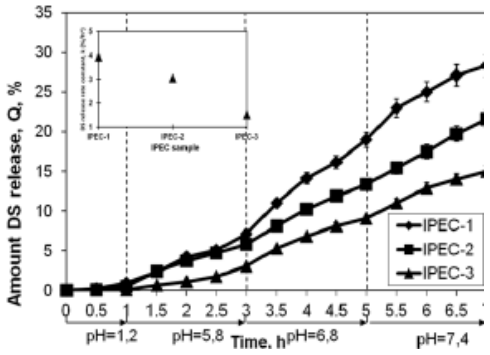




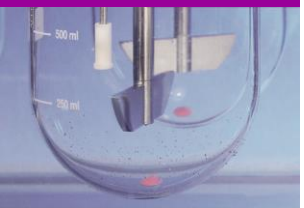
IPECs L100/EPO







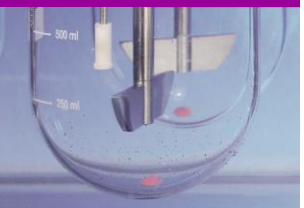
Moustafine R.I., Bukhovets A.V., Sitenkov A.Y. et al. Eudragit E PO as a Complementary Material for Designing Oral Drug Delivery Systems with Controlled Release Properties: Comparative Evaluation of New Interpolyelectrolyte Complexes with Countercharged Eudragit L100 Copolymers // ***Mol. Pharm.***, **10** 2630−2641(2013).



DEVELOPMENT: Comparative *in vitro/in vivo* assessment of polycomplex colon-targeting DDS based on EUDRAGIT® EPO/S100

(presented in 38th CRS Annual Meeting, Maryland, U.S.A., 2011)

Dr. Sitenkov A.Y.



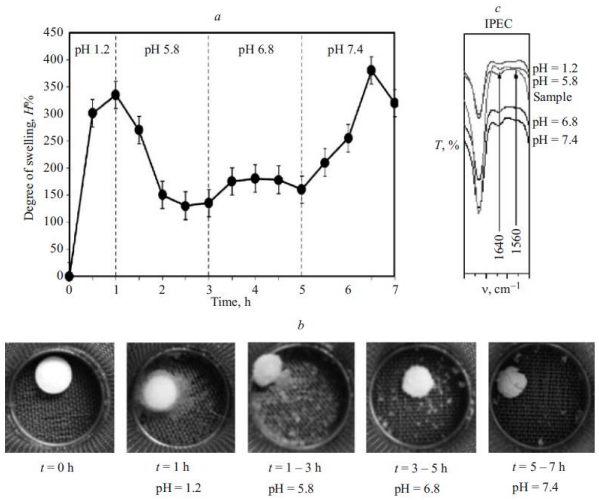


Fig. 7. Swelling profile (a), monitoring of changes of external appearance (b), and structural transformations (c) during swelling of polycomplex matrices obtained from IPEC EPO/S100, $Z = 1.26$, under conditions imitating passage through the GI tract.

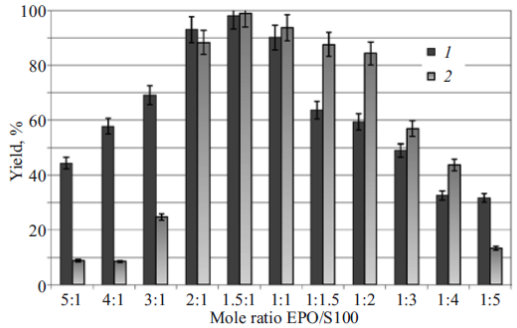


Fig. 2. Gravimetric analysis of precipitates of IPEC EPO/S100 at various mole ratios and orders of mixing copolymer solutions: EPO/S100 (*1*) and S100/EPO (*2*).

In our case DS release from the polycomplex matrices has "intestinal" type of release profiles.

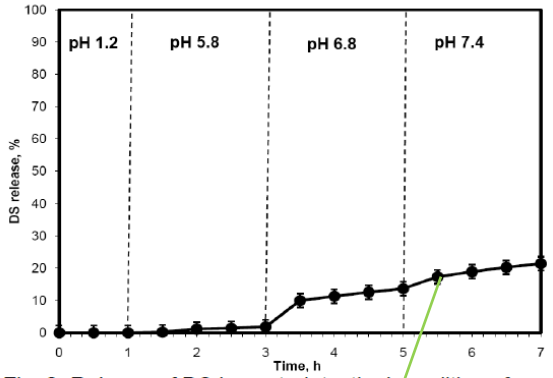
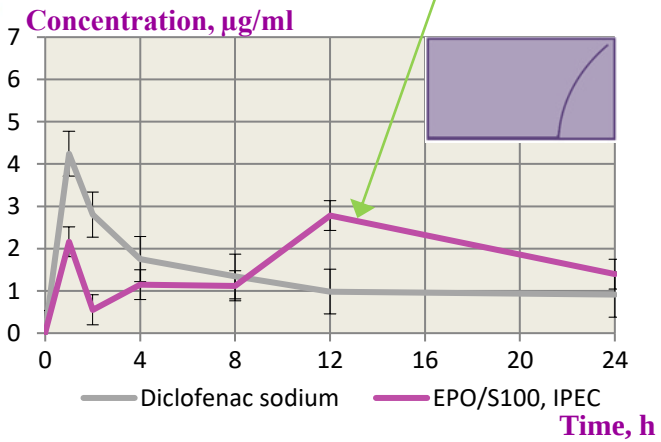


Fig. 2. Release of DS in gastrointestinal conditions from matrices made up of IPEC EPO/S100 (n=3±SD).



Moustafine R.I., Bukhovets A.V., Sitenkov A.Y. et al., ***Pharm.Chem. J.***, **45**(9) 568 – 574 (2011).

Characterization of (meth)acrylate copolymer complexes, prepared in organic solutions

EVONIK INDUSTRIES

No. 14/03 | Issue 2007 | Page 2

Pharma Polymers
News

Pharma Polymers Belongs to Evonik, the Creative Industrial Group for Chemicals, Energy and Real Estate

A new industrial group joined Germany's corporate landscape on September 12. Evonik Industries. The creative company based in Essen is one of the global leaders for specialty chemicals, an expert for power generation from coal and renewable energies, and also one of the largest private housing construction enterprises in Germany. Evonik Industries has now replaced the former RAG Beteiligungs-AG after a four-year restructuring period. The previous corporate brand Degussa no longer exists, but the Chemicals Business Area remains intact. More information on Evonik can be found at www.evonik.de and www.evonik.com.

The christening of Evonik Industries was the highlight of the company's strategic realignment and also the last step prior to entering the capital market in the first half of 2008. Apart from the new name and logo, the new brand features the corporate color deep purple. Evonik's strengths - creativity, specialization, self-renewal and reliability - are also the values represented by Pharma Polymers on the global market.

What has changed, what will remain the same?

Both our agreements and your contacts remain the same under our new name Evonik Röhm GmbH in Germany and Evonik Degussa outside Germany. Our appearance has changed, and this concerns both our business stationery and publications like the Pharma Polymers News.
We at Pharma Polymers are proud to continue developing and marketing EUDRAGIT® products and drug delivery technologies worldwide as part of Evonik Industries. Under the Evonik umbrella brand, our team remains at your disposal also in the future to support you with all your challenges.

Jonas Ide
Product Manager EUDRAGIT®

Dear Readers:

This is the first issue of Pharma Polymers News in the new corporate design of the Evonik group brand. Since we joined the Chemicals Business Area of Evonik Industries on September 12, we are devoting our cover story to the creative industrial group for chemicals, energy and real estate.

This new issue of Pharma Polymers News is appearing just in time for the Annual Meeting of the American Association of Pharmaceutical Scientists from November 11-15 in San Diego, USA. At the AAPS, we will be present at booth no. 1309. Our researchers from the USA, Germany and India are presenting technical posters concerning EUDRAGIT® and drug delivery technologies. You can read the abstracts on Page 2 of this newsletter, and there you will also find the links to the complete posters.

On September 17 we inaugurated the new extension to our research center in India. We took this occasion to present the focal points of the work performed by the 30-odd staff members there, and to report on the opening ceremony. Turn to page 3 of this PPN for further details.

Our potpourri of news on page 4 mainly tells you about staff changes and events in the first half of 2008. The events calendar has also been given a facelift and rounds off the news letter in the corporate design of Evonik.

Sincerely yours,

Jonas Ide
Product Manager EUDRAGIT®

Page 1 | Page 2 | Page 3 | Page 4

News on EUDRAGIT® and Drug Delivery Technologies at the AAPS

November 11 - 15
For the Complete Posters Click here.

Analytical Characterization of (Meth)acrylate Copolymer Complexes

The purpose was to characterize the interactions between cationic (EUDRAGIT® E PO) and anionic (EUDRAGIT® L 100-55, EUDRAGIT® L 100, EUDRAGIT® S 100, Preparation 4155 F) (meth)acrylate copolymers in organic systems. Analytical methods like GC/MS, IR, NMR, DSC and TGA analyses proved, as compared with the physical mixture, the formation of a complex that is stable up to approx. 150°C, with T_g values between those of the pure polymers.

Formation of Precipitates Prepared by Combining Differently Charged (Meth)acrylate Copolymers

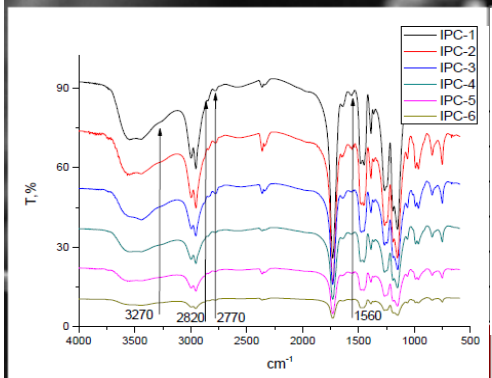
The interaction of cationic (EUDRAGIT® E PO) and anionic (EUDRAGIT® L 100-55, EUDRAGIT® L 100, EUDRAGIT® S 100, Preparation 4155 F) (meth)acrylate copolymers in organic solutions leads to the formation of precipitates. Their amount depends on the polymer ratios, order of addition, concentration and percentage of active groups.

Gallardo D., Skalsky B., **Kleinebudde P.**, ***Pharm. Ind.*, 73**(11) 1875 – 1884 (2011).

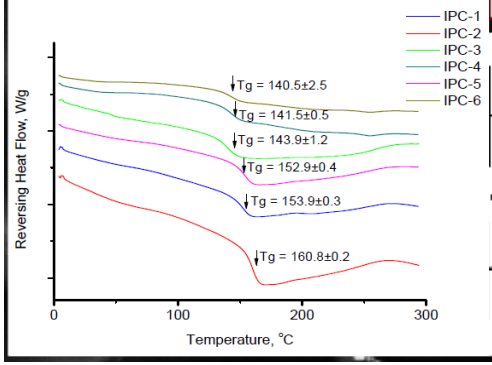
DEVELOPMENT: Characterization of (meth)acrylate copolymer complexes, prepared in organic solutions

(presented in AAPS World Meeting, Chicago, U.S.A., 2012)

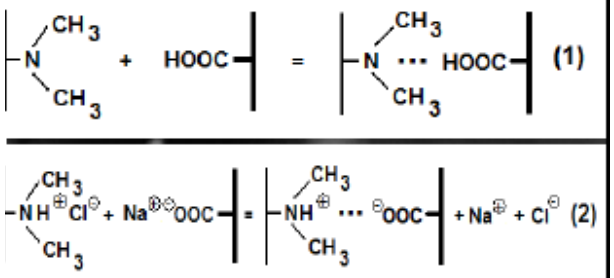
Figure 2: FTIR spectra and MTDSC data of physical mixture and IPCs obtained in different solvents

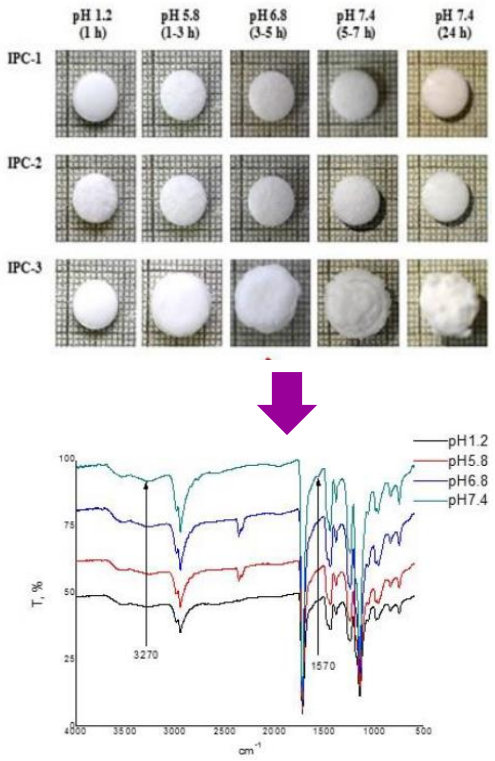


Sample	pH	N%	Composition of IPC [EPO]:[S100], (mol/mol)
IPC-1	1.2	1.60 ± 0.01	1:3.15
	5.8	1.64 ± 0.01	1:3.09
	6.8	1.65 ± 0.02	1:3.08
	7.4	1.68 ± 0.02	1:2.99
IPC-2	1.2	1.44 ± 0.00	1:3.73
	5.8	1.49 ± 0.02	1:3.57
	6.8	1.59 ± 0.01	1:3.24
	7.4	1.52 ± 0.02	1:3.44
IPC-3	1.2	1.92 ± 0.17	1:2.44
	5.8	1.90 ± 0.01	1:2.46
	6.8	1.93 ± 0.05	1:2.41
	7.4	1.99 ± 0.01	1:2.30



Schemes of interpolymer reaction formed by hydrogen (1) and ionic (2) bonding in non-aqueous and aqueous media.





A.V. Bukhovets, N. Fotaki, V. V. Khutoryansky R.I. Moustafine, Interpolymer Complexes of Eudragit® Copolymers as Novel Carriers for Colon-Specific Drug Delivery. ***Polymers***, 12(7), 1459 (2020).

DEVELOPMENT: Dissolution testing for **IPC** matrices based on **Eudragit®EPO** and **Eudragit® S100** copolymers prepared in organic solutions

(presented in AAPS World Meetings, Orlando, U.S.A., 2015)

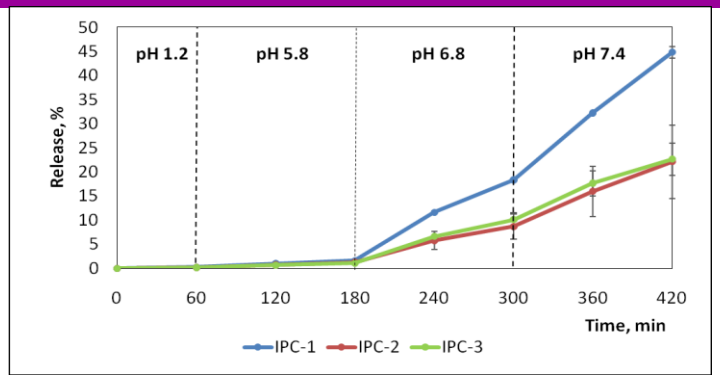


Fig. 1. Release profiles of IND from IPCs in buffer solutions (Flow through cell apparatus)

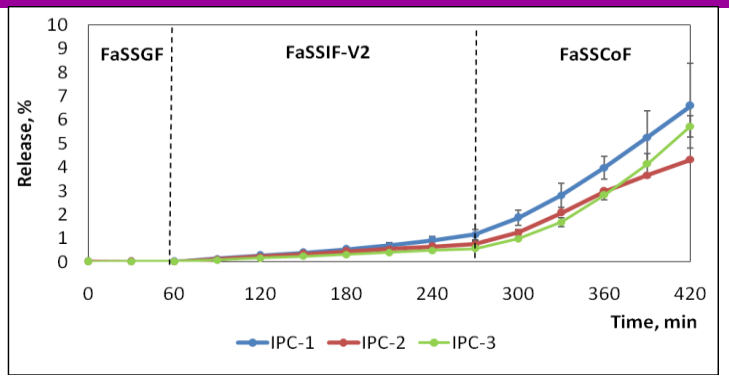


Fig. 2 Release profiles of IND from IPCs in biorelevant media (Flow trough cell apparatus)

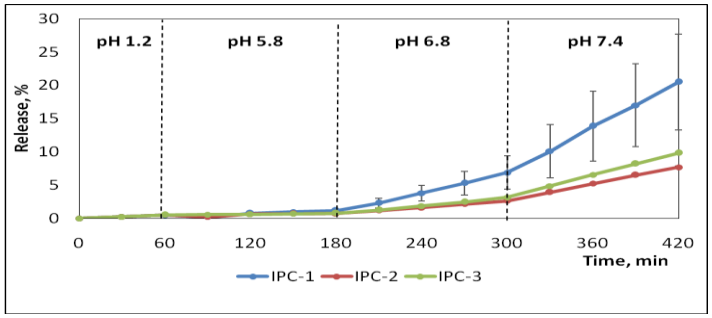


Fig.3. Release profiles of IND from IPCs in buffer solutions (BIO-DIS Reciprocating Cylinder Apparatus)

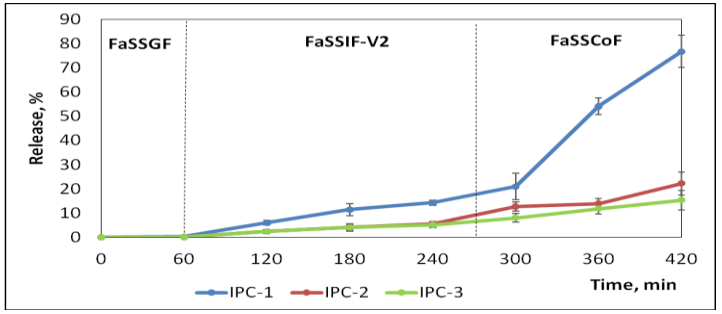
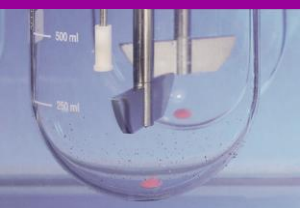


Fig.4. Release profiles of IND from IPCs in biorelevant media (BIO-DIS Reciprocating Cylinder Apparatus)

Dr. Sitenkova (Bukhovets) A.V.

RUSSIAN FOUNDATION FOR BASIC RESEARCH
RFBR



Sitenkova (Bukhovets) A.V., Fotaki N., Khutoryanskiy V.V., Moustafine R.I. ***Polymers***, 12(7), 1459 (2020).

Sitenkova (Bukhovets) A.V., Sitenkov A.Y., Moustafine R.I. ***Polym. Adv. Tech.*** 32,2761–2769 (2021).

DEVELOPMENT: Characterization of (meth)acrylate copolymer complexes, prepared in organic solutions

Dr. Sitenkova (Bukhovets) A.V.

The use of organic solvents for preparing interpolymer complexes based on Eudragits® not only leads to the new pharmaceutical materials with unique physicochemical properties, but also made their application more technologically relevant.

Dissolution of Eudragits® in organic solvents was a straightforward process that did not require any further adjustments and resulted in solutions with greater concentrations.

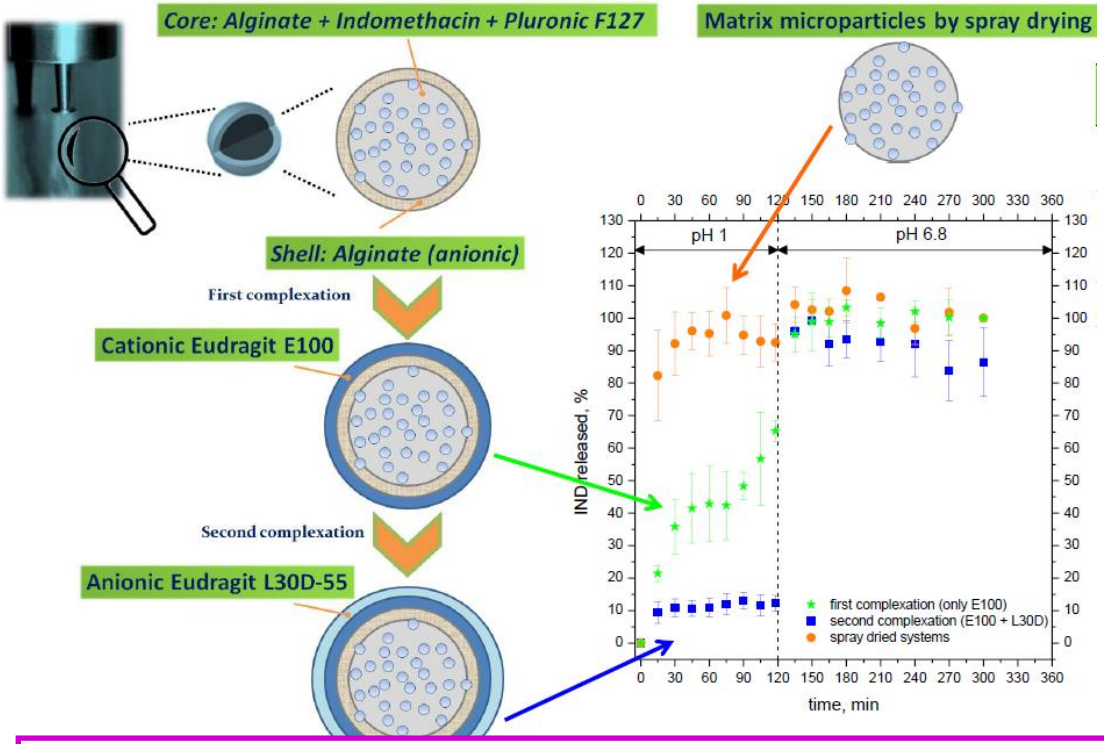
The preparation of aqueous solutions of Eudragits® was more complicated as it required adjustment of pH.

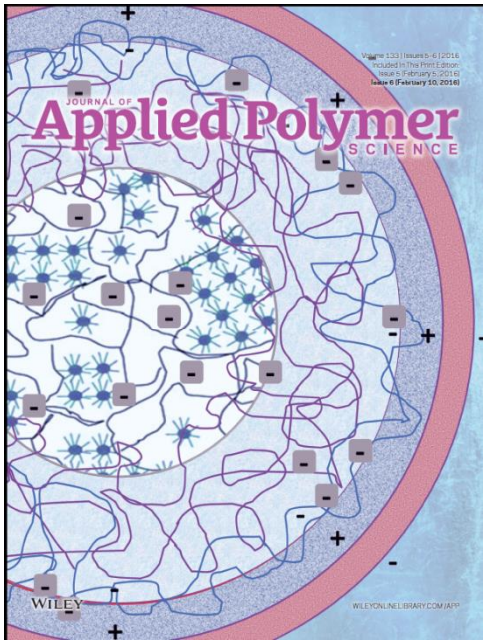
R.I. Moustafine, A.V. Bukhovets (Sitenkova), A.Y. Sitenkov, I.I. Semina, “Interpolymer carrier for oral systems of controlled delivery of APIs”, ***Patent (RU)*** №2725879 (26.07.2018; 7.07.2020).

DEVELOPMENT: Enteric shell-core **microparticles** production by coupling ultrasonic atomization and polyelectrolyte complexation

(presented in 42ed CRS Annual Meeting, Edinburg, Scotland, 2015)

Dr. Sitenkov A.Y.



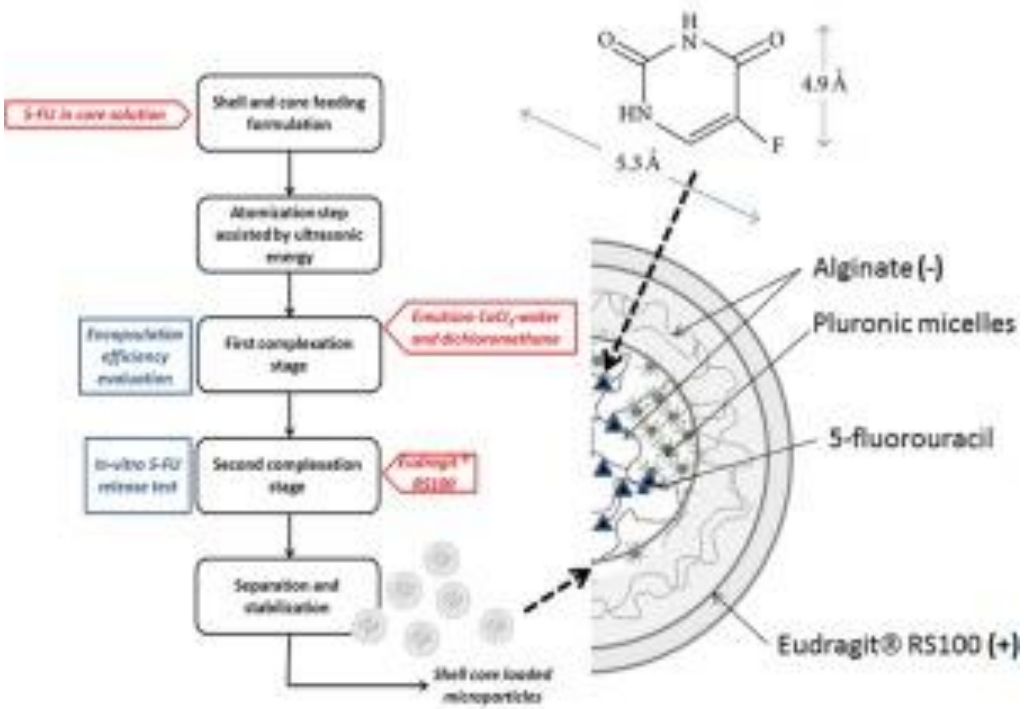


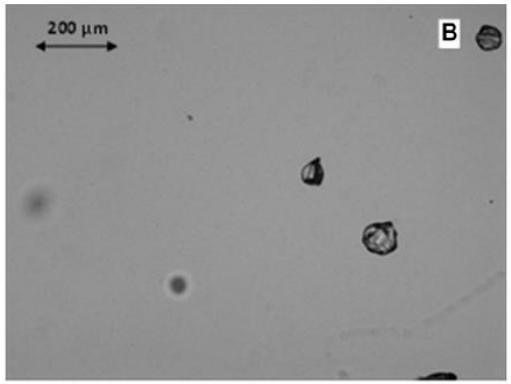
WILEY: This publication is featured as a cover image of the journal issue!

Dalomoro A., A.Y. Sitenkov, Lamberti G., Barba A.A., Moustafine R.I. ***J. Appl.Polym.Sci.***, 133 (6), 1–9 (2016).

DEVELOPMENT: Hydrophilic drug (5-fluorouracil) encapsulation in shell-core **microcarriers** by two stage polyelectrolyte complexation method

Dr. Sitenkov A.Y.





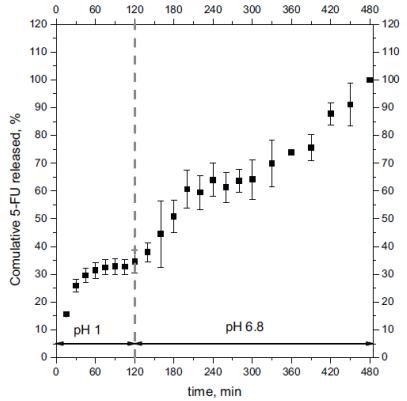


Fig. 7. Percentage of 5-fluorouracil (5-FU) released from tablets made of 5-FU loaded shell–core microparticles.

Dalomoro A., A.Y. Sitenkov, Cascone S., Lamberti G., Barba A.A., Moustafine R.I. ***Int. J. Pharm.***, 518, 50–58 (2017).

Development of microcarriers by hot-melt extrusion (HME) method based on Eudragit® E PO/L100-55(L100) binary systems for IND colon-specific oral drug delivery

(presented in RTAC-2016, Saint-Petersburg, Russia, 2016)

HME carried out on a single screw extruder Randcastle (USA) using the identified preliminary studies mDSC.

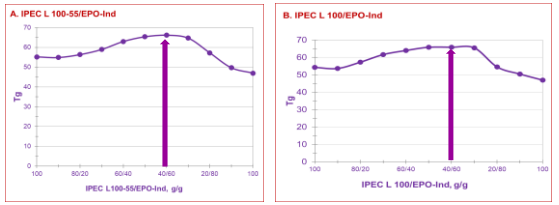


Figure 1a. Tg temperature versus Ind/IPEC ratio based on L100 **(A)** and L100-55 **(B).**

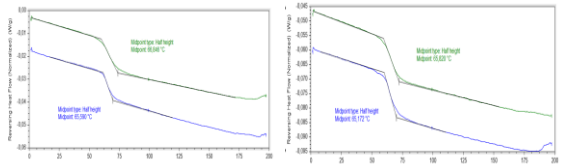


Figure 1b. Thermograms of IPEC extrudates: (EPO/L100)-Ind **(A)**, (EPO/L100-55)-Ind **(B)** and samples obtained by simulating HME conditions on mDSC.

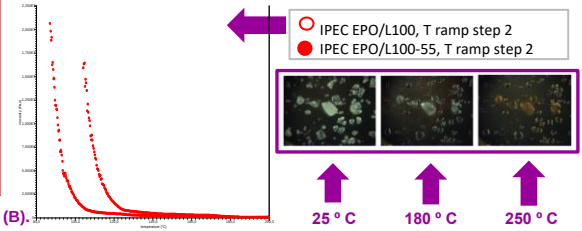
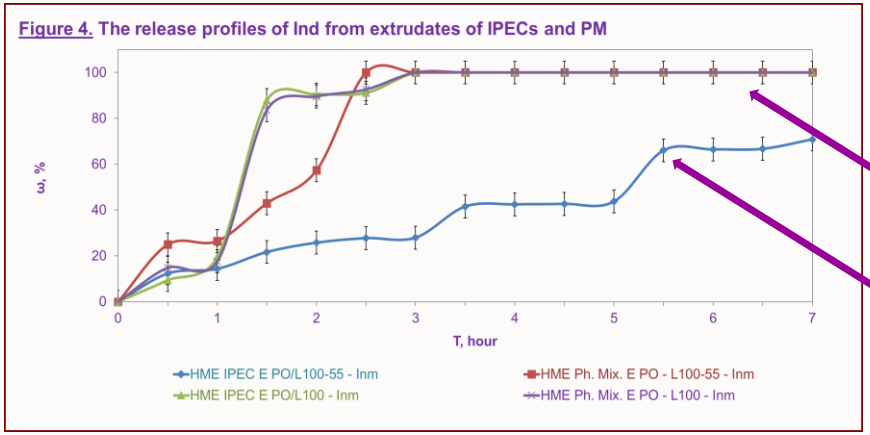
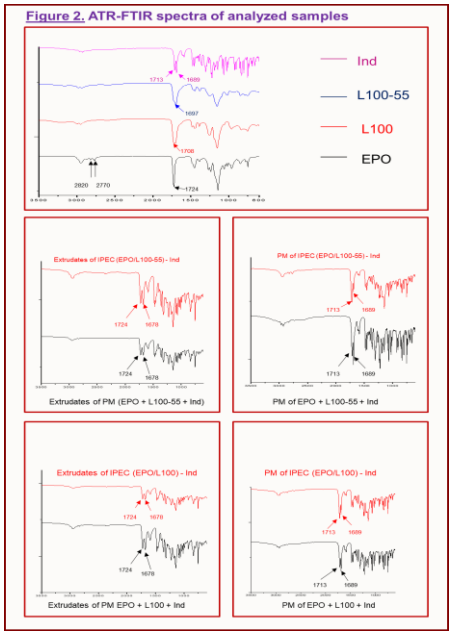


Figure 3. Melt viscosities and photomicrographic images of IPECs at different temperatures based on L100 **(A)** and L100-55 (B).



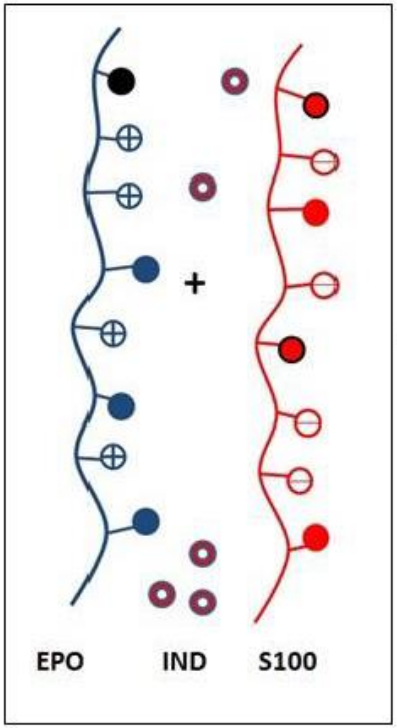


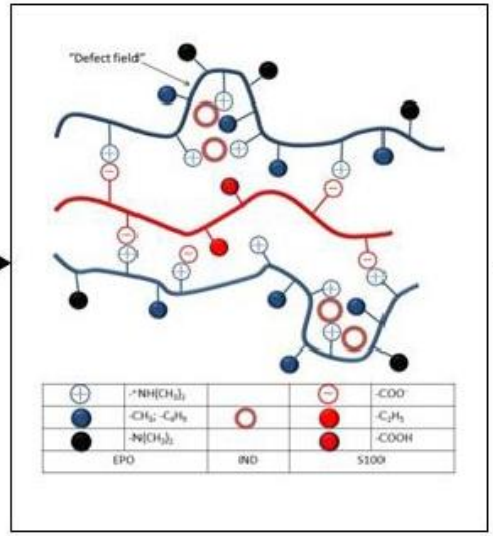
PhD student Nasibullin S.F.

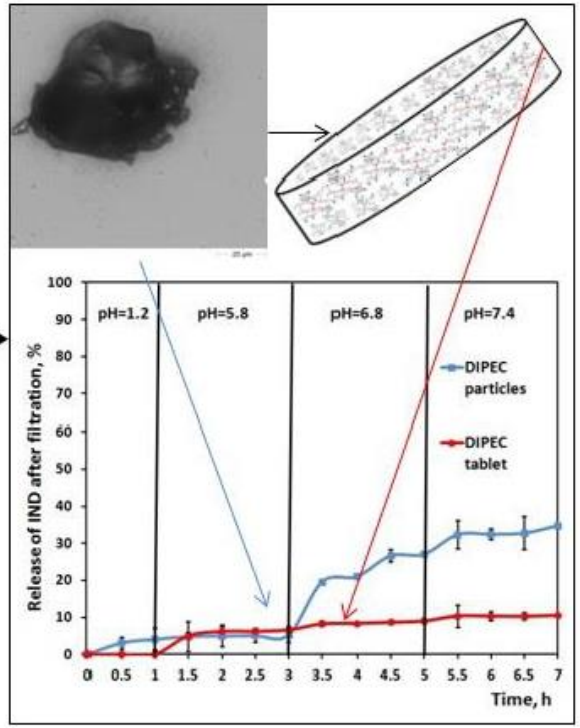
Moustafine R.I., Nasibullin S.F., Nurgatina G.R., Duong T., Nikolakakis I., Kachrimanis K., Van den Mooter G. et al. in preparation for publication.

DEVELOPMENT: Indomethacin-containing interpolyelectrolyte complexes based on **Eudragit®EPO** and **Eudragit® S100** copolymers as a novel microparticulate or matrix oral DDS

(presented in AAPS World Meeting, Orlando, USA, 2015)







Dr. Sitenkov A.Y.

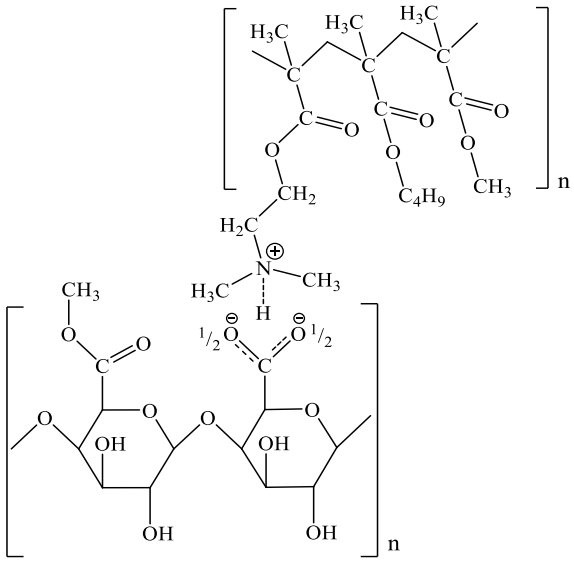
R.I. Moustafine, A.Y. Sitenkov, A.V. Bukhovets, S.F. Nasibullin, B. Appeltans, T.Kabanova, V. Khutoryanskiy, G. Van den Mooter, ***Int. J. Pharm***., 524, 123–131 (2017).

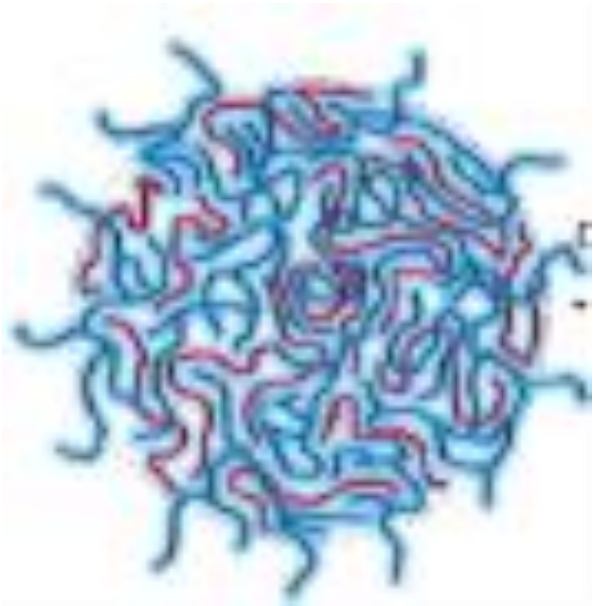
CONTENTS

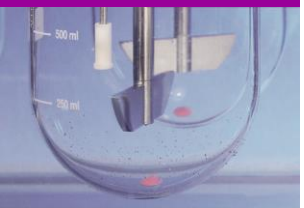
Presented on:
Annual Meeting of the AAPS, Orlando, FL, (U.S.A), 2015

3

IPCs based on EUDRAGIT copolymers and oppositely charged polymers for developing colon-targeting DDS







Investigation of interaction between **EUDRAGIT® L100(S100)** and **Chitosan** as basis for design colon-specific DDS

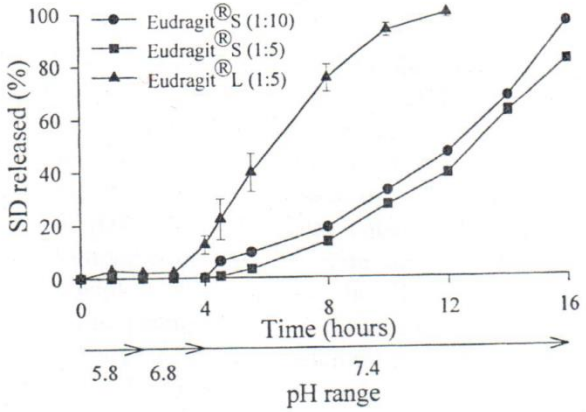


Fig. 4. Effect of the coating polymer and the core-to-coat ratio on the in vitro release of SD (data shown are the mean±standard deviations, $n=3$).

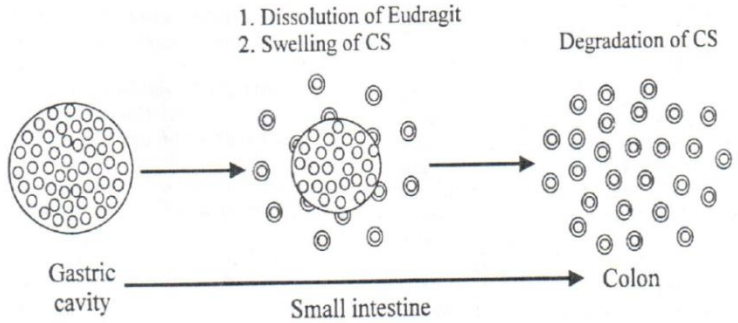
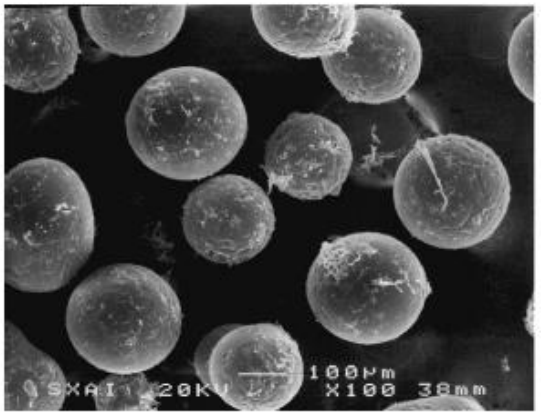
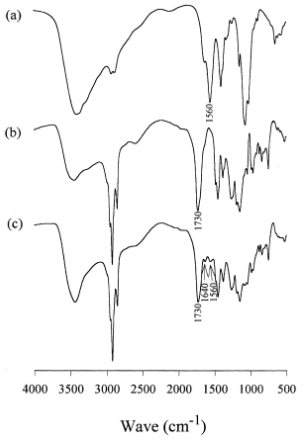


Fig. 6. Scheme of the possible mechanism of drug release





M.L. Lorenzo-Lamoza, C. Remuñán-Lopez, J.L. Vila-Jato and M.J. Alonso, ***J. Control. Release***, 52 109 – 118 (1998).

Comparative evaluation of carriers based on **Eudragit®L100(L100-55)** and **chitosan** as polycomplex matrix DDS

(presented in 9th *Eur. Sym. Control. Drug Del.*, Noordwijk aan Zee, 2006)

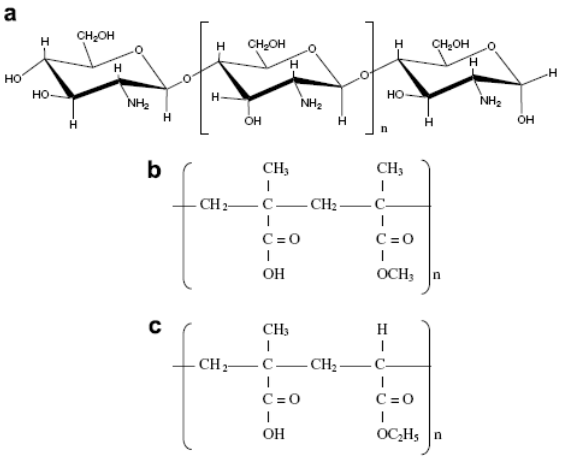


Fig. 1. Molecular structures of chitosan (a) Eudragit L100 (b) and Eudragit L100-55 (c).

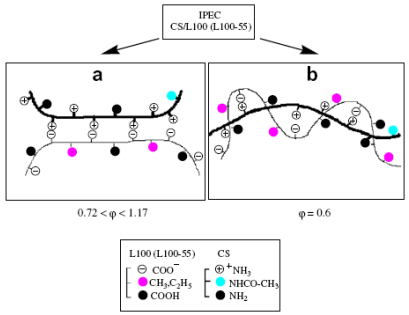
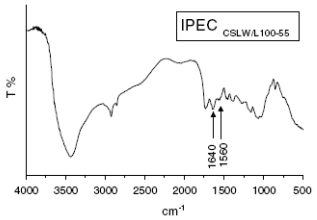
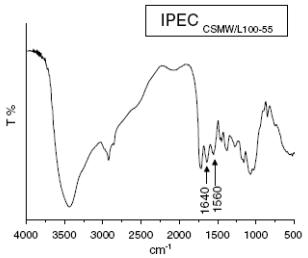


Fig. 2. Schematic representation of the ionic interactions between CS and L100 or L100-55.





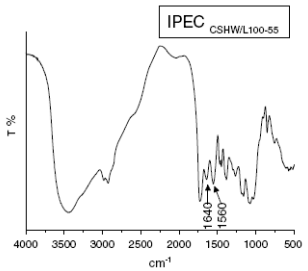


Table 1
Characteristic composition of IPEC CS/L100, detecting by elementary analysis

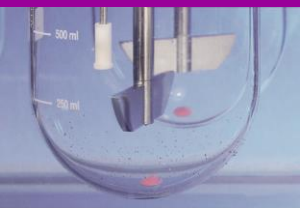
Type of CS	Experimental value (mean, $n = 2$) (%)		Calculated value (%)		IPEC composition	
	C	N	C	N	φ	Molar ratio [CS]/[L100]
CS_{LW}	49.21	4.37	49.25	4.36	1.17	1/0.85
CS_{MW}	43.64	3.68	43.64	3.64	0.89	1/1.13
CS_{HW}	44.26	3.60	44.25	3.59	0.82	1/1.22

Table 2
Characteristic composition of IPEC CS/L100-55, detecting by elementary analysis

Type of CS	Experimental value (mean, $n = 2$) (%)		Calculated value (%)		IPEC composition	
	C	N	C	N	φ	Molar ratio [CS]/[L100-55]
CS_{LW}	47.14	2.95	47.12	2.96	0.60	1/1.69
CS_{MW}	45.12	3.35	45.11	3.34	0.72	1/1.38
CS_{HW}	45.34	3.54	45.36	3.53	0.79	1/1.26

Reviewer comments:

Reviewer #3: This is an interesting combination of natural and synthetic polymers to create interpolyelectrolyte excipients for controlled release. Publication is recommended.



R.I. Moustafine, E.B. Margulis, L.F. Sibgatullina, et al., ***Eur. J. Pharm. Biopharm***., 70(1), 215 – 225 (2008).

Comparative evaluation of carriers based on **Eudragit®EPO** and **Sodium Alginate** for colon-specific DDS

(presented in 34th CRS Annual Meeting, Long Beach, U.S.A., 2007)

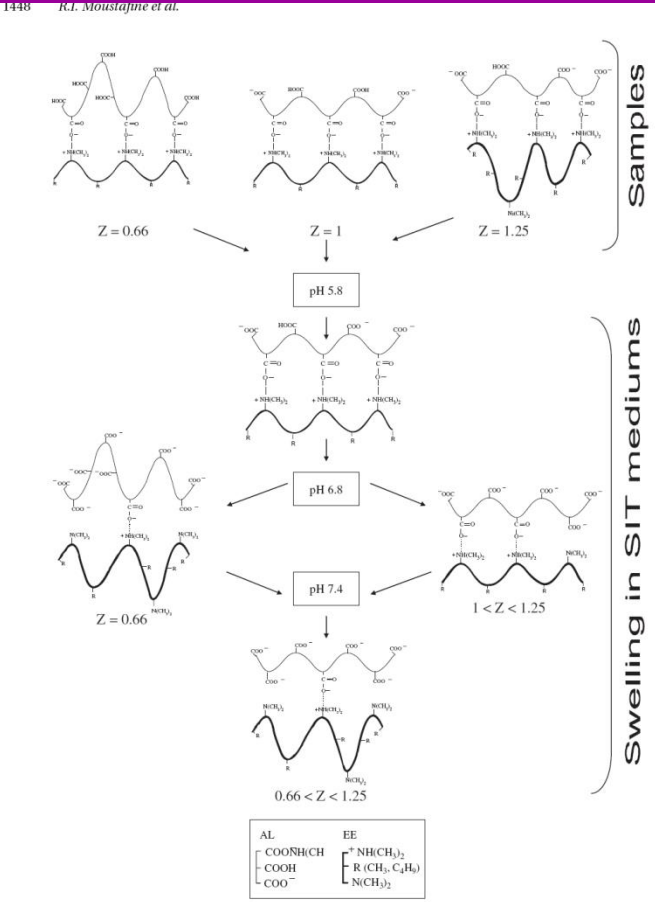
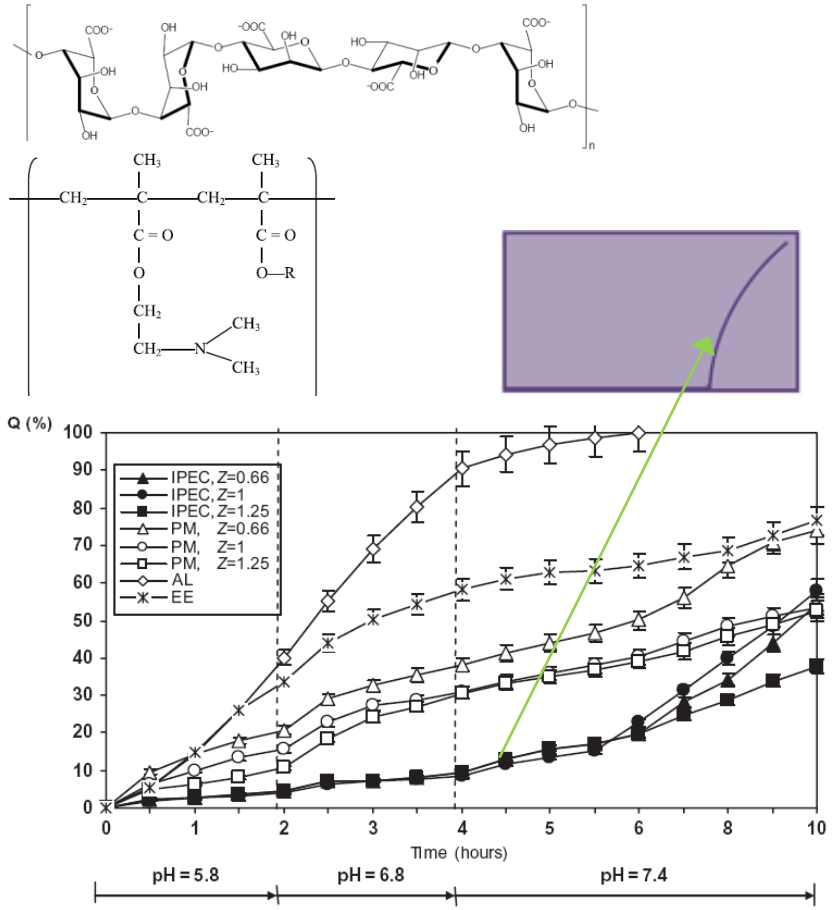


Figure 6. Schematic representation of the IPEC structures that were formed by ionic interactions between EE and AL at different pH v tested mediums.



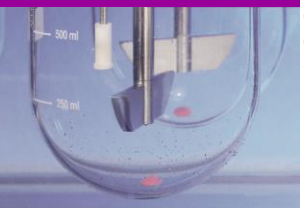
R.I. Moustafine, A.R. Salachova, E.S. Frolova, et al., ***Drug Dev. Ind. Pharm.***, 35(12) 1439 – 1451 (2009).

R.I. Moustafine, V.A. Kemenova, G. Van den Mooter, ***Int. J. Pharm.***, 294, 113–120 (2005).

A novel matrix polycomplex carrier based on **EUDRAGIT® EPO/ Pectin** system for oral drugs delivery

(presented in AAPS World Meetings, Chicago, Orlando, U.S.A., 2012, 2015)

PhD student Nasibullin S.F.



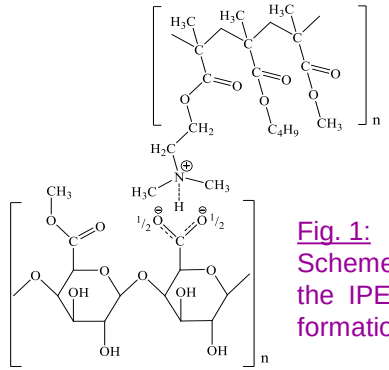
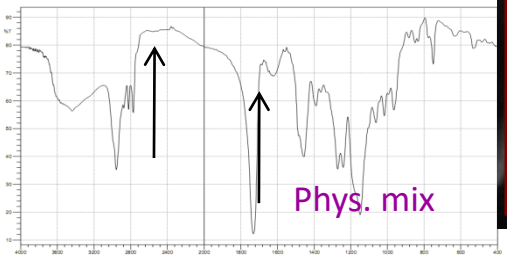
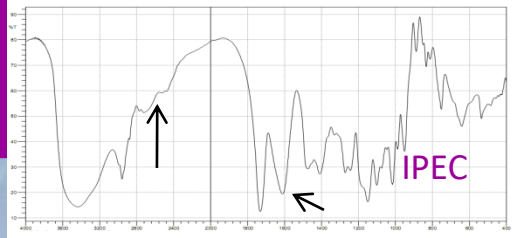
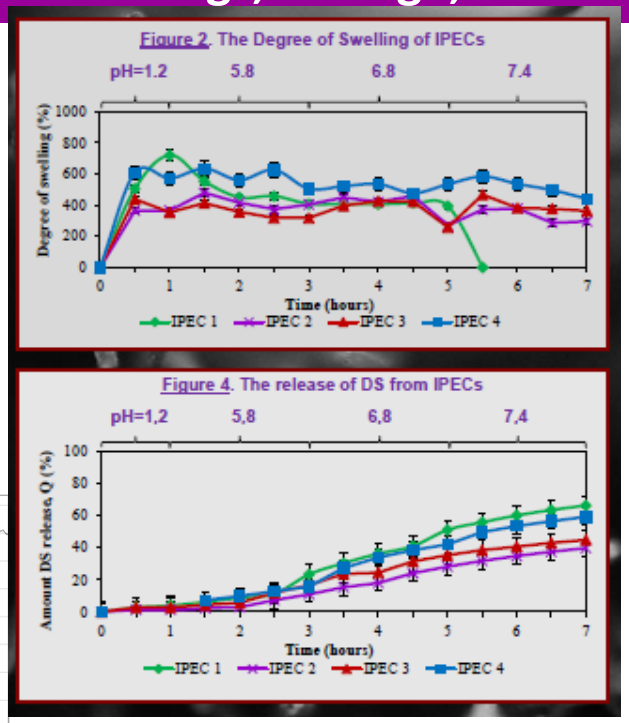


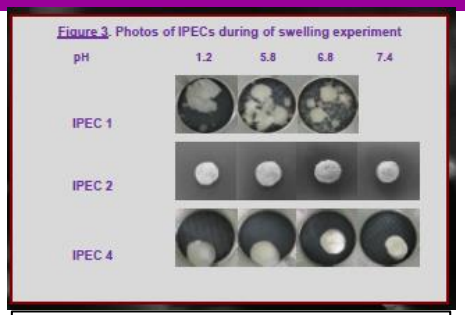
Fig. 1: Scheme of the IPEC formation

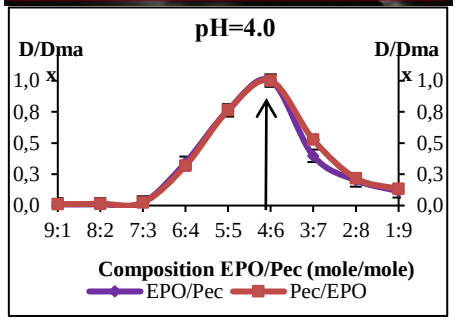
Fig. 3: . FT-IR spectra of phys. mix and synthesized I PECs











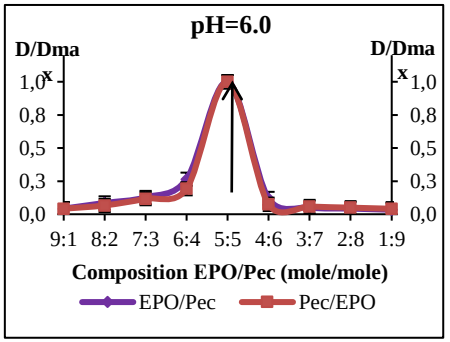


Table 1. Characteristics of IPEC E PO / Pectin Systems

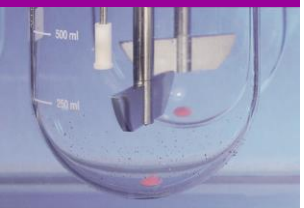
	IPEC composition	
polycomplex type	Z = [E PO] / [Pectin]	E PO : Pectin (mol/mol)
IPEC 1	0.575	1 : 1.74
IPEC 2	0.709	1 : 1.41
IPEC 3	0.738	1 : 1.35
IPEC 4	1.399	1 : 0.71

Moustafine R.I., Nasibullin Sh.F., et al., In preparation for publication.

Design of **polycomplex matrix system (PMS)** based on **Eudragit®EPO/Carbopols for colon targeting**

(presented in 38th CRS Annual Meeting, Maryland, U.S.A., 2011)

Dr. Timergalieva (Garipova) V.R.



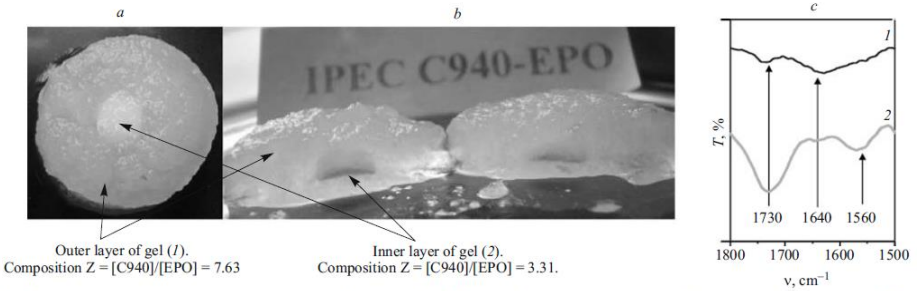


Fig. 2. Elemental analysis (*a*, *b*) and IR spectra (*c*) of the outer (*1*) and inner (*2*) layers of the polycomplex matrix after treatment with media simulating passage through the GIT.

TABLE 1. Main Pharmacokinetic Parameters of the Polycomplex Matrix System Compared with Voltaren® Retard

Pharmacokinetic parameter	PMS	Voltaren® retard
C_{max}, μg/mL	3.378	2.327
t_{max}, h	8	1
$AUC_{0-\tau}$, μg·h/mL	47.47	19.392
$AUC_{0-\infty}$, μg·h/mL	57.402	39.207
$AUMC_{0-\tau}$, μg·h/mL	462, 432	212.566
$AUMC_{0-\infty}$, μg·h/mL	820.391	1128.55
MRT, h	14.292	34.21
$C_{max}/AUC_{0-\infty}$ absorption coefficient	0.059	0.059

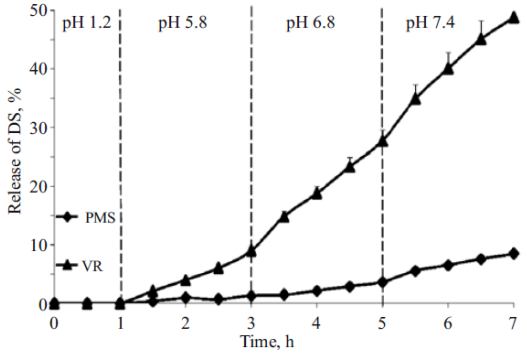


Fig. 1. Release profiles of diclofenac sodium (DS) from the polycomplex matrix system (PMS) and Voltaren® retard (VR) tablets under conditions imitating movement through the GI tract.

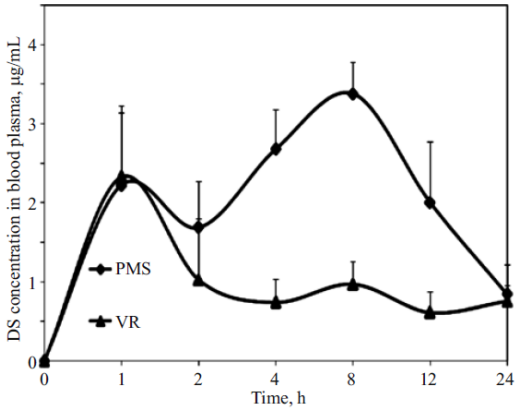


Fig. 2. Pharmacokinetic profiles of diclofenac sodium (DS) in rabbit blood plasma after administration of the polycomplex matrix system (PMS) and Voltaren® retard (VR) tablets.

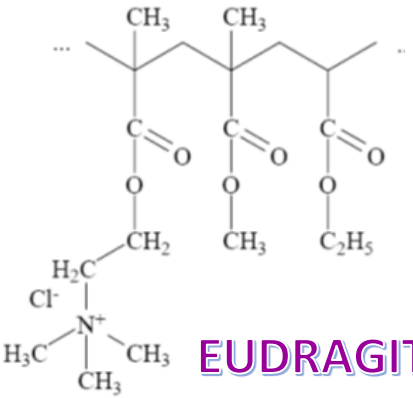
Moustafine R.I., et al., **Patent (RU)** 2445118 (2009); Moustafine R.I., et al., **Patent (RU)** 2467766 (2012).

Timergalieva (Garipova) V.R., Gennari C.G.M., Cilurzo F., Moustafine R.I. Interpolyelectrolyte complexes based on Carbopol® and oppositely charged polymer as new carriers for oral controlled diclofenac delivery. ***Polym. Adv. Tech.*** 32,2744–2752 (2021).

CONTENTS

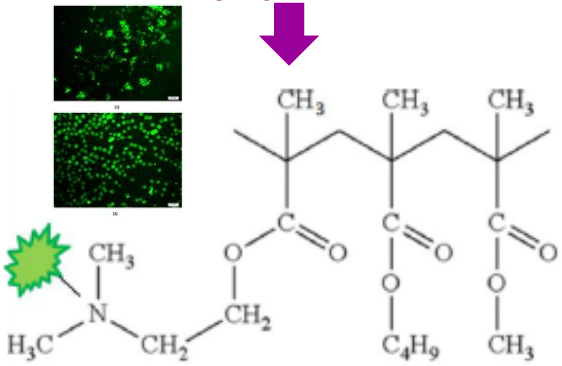
4 Future perspectives of IPECs carriers based on EUDRAGITs copolymers for developing a new DDS

Interpolymer complexation with a zwitter polycation



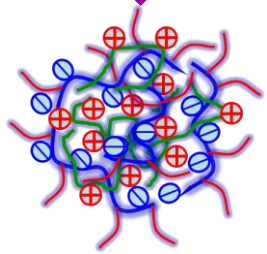
EUDRAGIT®RL

Interpolymer complexation with a fluorescein-labeled polycation



EUDRAGIT®EPO

Interpolymer complexation with a PEGylated polyanion



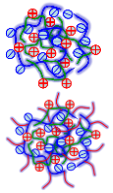
PEGylated

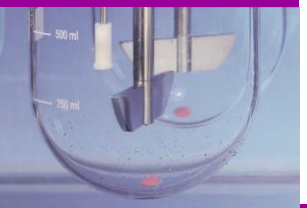
EUDRAGIT®L 100-55

Polycomplex matrices for colon-specific DDS

University of Reading

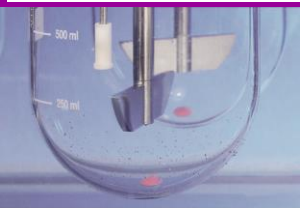
Nanosized transmucosal nasal DDS for brain delivery



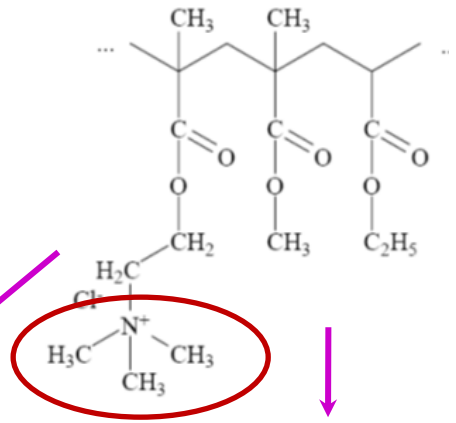


Characterization of a new interpolyelectrolyte complexes between Eudragit® RL and countercharged Eudragit® polyanions

(presented in CESPT-2016, Belgrade, Serbia, 2016)

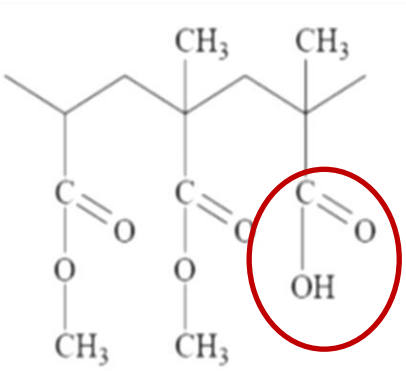


EUDRAGIT®RL

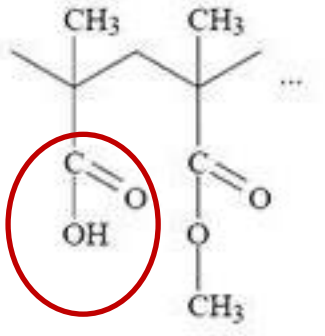


Polycation has 10% countercharged groups

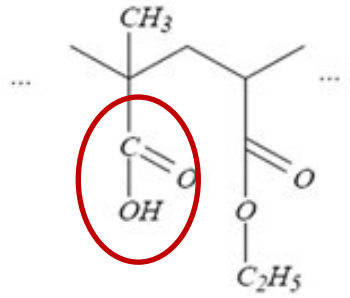
EUDRAGIT® FS



EUDRAGIT®L100 (S100)



EUDRAGIT®L 100-55



Polyanions with 10% (FS), 30% (S100) and 50% (L100, L100-55) countercharged groups

EUDRAGIT® Application Guidelines 12th Edition, Evonik Industries AG (2012)

IND release studies of the matrices prepared from the blends by two USP methods (III, IV) in GIT mimicking conditions

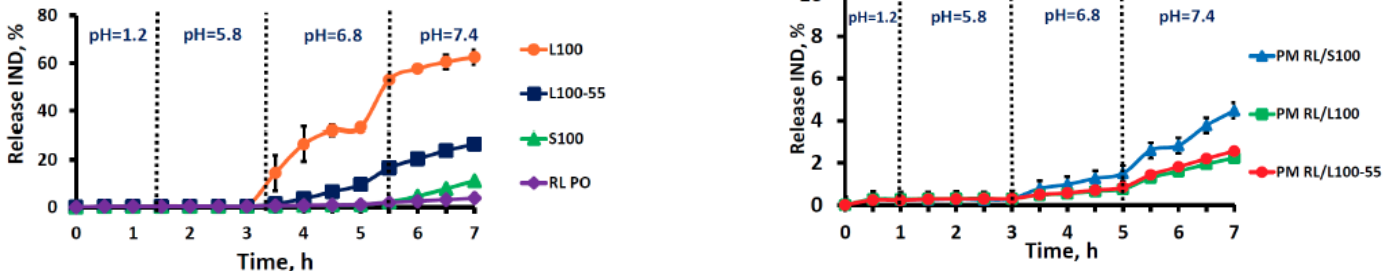


Figure 10. IND release profiles in GIT mimicking conditions from tablets based on: (a) individual copolymers and (b) physical mixtures – PM by using USP IV method (n = 3; ±SD).

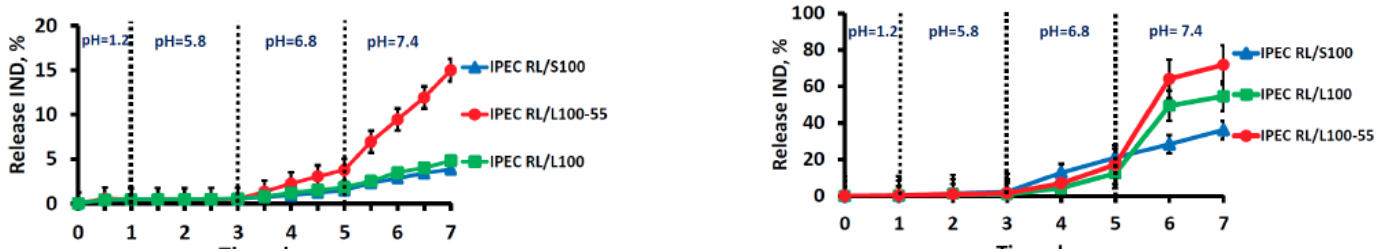


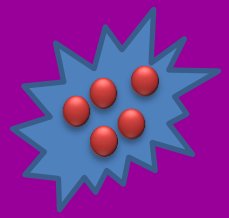
Figure 11. IND release profiles in GIT mimicking conditions from tablets based on IPECs by using (a) USP IV and (b) USP III methods (n = 3; ±SD).

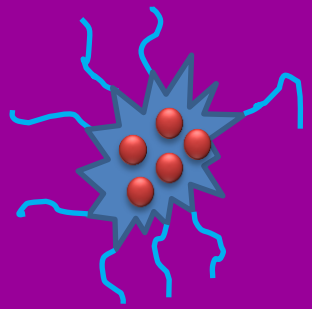
Moustafine R.I., Porfirieva N.N., Nasibullin Sh.F., et al., In preparation for publication.

DEVELOPMENT OF TRANSMUCOSAL DOSAGE FORMS

Prof. of the University of Reading (UK) V. V. Khutoryansky, Director of the Institute of Pharmacy, Dr. R. I. Moustafine,
Chair of Central Research Laboratory, Prof. I.I. Semina

PhD student
Porfiryeva N.N.





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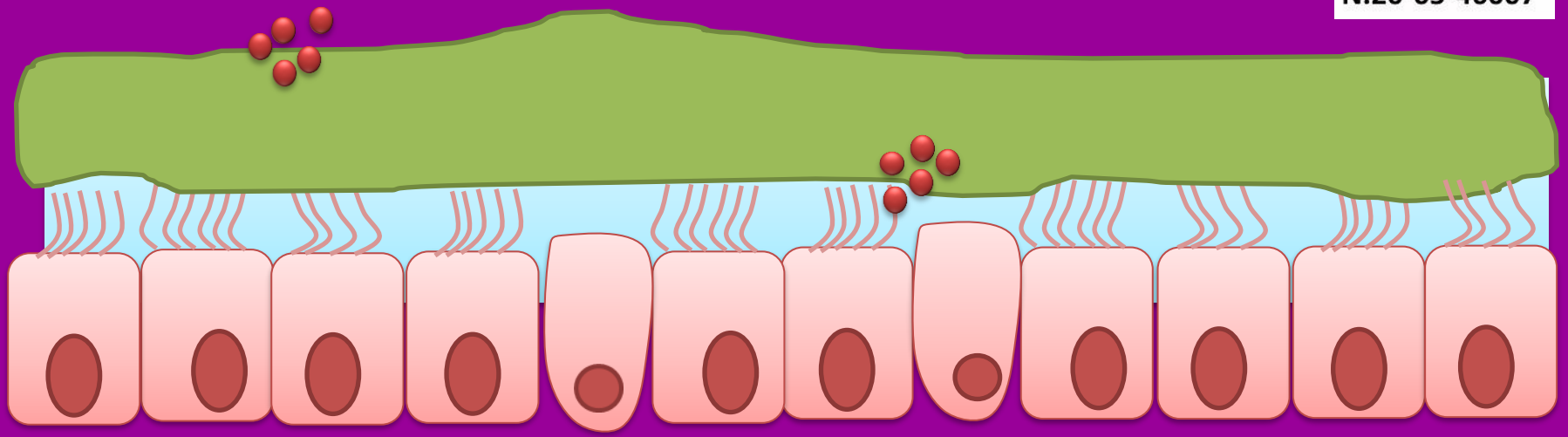
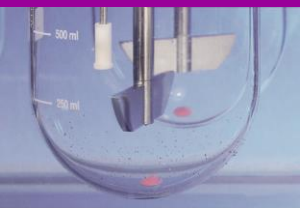


Porfiryeva N.N., Nasibullin S.F., Abdullina S.G., Tukhbatullina I.K., Moustafine R.I.*, Khutoryanskiy V.V.* (2019). Acrylated Eudragit® E PO as a novel polymeric excipient with enhanced mucoadhesive properties, ***Int. J. Pharm.***, 562, 241-248.
Porfiryeva N.N., Semina I.I., Salakhov I.A., Moustafine R.I.*, Khutoryanskiy V.V.* Mucoadhesive and mucus-penetrating interpolyelectrolyte complexes for nose-to-brain drug delivery. ***Nanomedicine: Nanotechnology, Biology and Medicine.*** Accepted for publication15.06.2021.

CONCLUSIONS

- **Combining grades of oppositely charged Eudragit® copolymers give a lot of possibilities for simply regulation of the dissolution profiles of different drugs (APIs) in desirable direction.**
- **This study demonstrates the potential of IPECs based on Eudragit® copolymers for the successful formulation into oral drug delivery to site-specific gastrointestinal tract regions, including colon.**
- **Chemically modified Eudragit® copolymers and IPECs with its participation, demonstrates the potential to be used in nasal transmucosal APIs delivery to the brain.**



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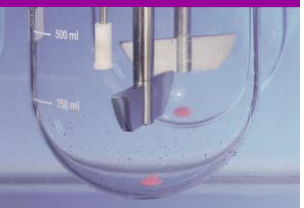

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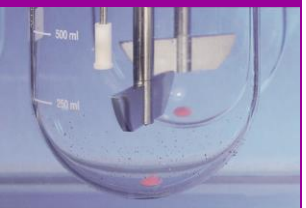

Thank you for your attention!

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