MUNI
PHARM

Abuse-resistant dosage forms

Assoc. Prof. Dr. Jan Gajdziok, Ph.D.
gajdziokj@pharm.muni.cz

Department of Pharmaceutical Technology, Faculty of Pharmacy, MU

Introduction

- non-therapeutic use of medicines is a global societal problem
- health + economic + human „dimension“

- formulation of physically + chemically resistant DF
- interaction with alcohol

- **drug abuse**
- **addiction**
- **opioid analgesics**
- **resistance to manipulation**
- **modification of the DF**

MUNI PHARM

Content

- an overview of the principles used against drug abuse
- DF manufacturing technologies to stop drug abuse
- examples of preparations for individual technologies - ADF formulations
- new approaches in the research and development phase
- alcohol and dose-dumping

- **drug abuse**
- **addiction**
- **opioid analgesics**
- **resistance to manipulation**
- **modification of the DF**

MUNI PHARM

Definition of terms

Misuse/abuse of medicines - administering to cause a non-therapeutic effect or taking unusually high doses for an unusually long time

Addiction syndrome = disease - a set of emotional, cognitive, behavioural and somatic changes as a result of repeated use of addictive and psychotropic substances
- a strong need to get a substance - craving
- lack of self-control in relation to substance use
- growth tolerance
- withdrawal syndrome
- neglecting other activities in favour of the substance
- use of the substance despite the adverse effects

- alcohol, opioids, cannabinoids, sedatives and hypnotics, cocaine, stimulants (including caffeine), hallucinogens, tobacco, volatile solvents...

MUNI PHARM

"The administration of drugs for the purpose of producing a non-therapeutic effect or the use of unusually high doses for an unusually long period of time."

Abuse of drugs

- **global** health and economic problem (Opioid crisis in the US - increasing prescription and availability of opioids over the last 20 years)
  - 600k deaths from overdose in the last 25 years!!!
- Czech Republic - National Conference "Psychoactive Drugs 2020"
  - women and the elderly population (sleep disorders, benzodiazepine dementia, depression, etc.)
  - In 2020 an estimated 900 thousand people in the Czech Republic!!!

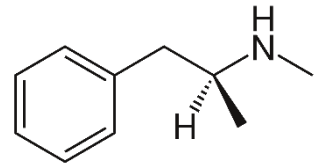
- in controlled release DF, external influences result in the release of the entire active substance in a short period of time - **dose dumping**

- external influences - **mechanical** (cutting, crushing, grinding) + **chemical** (dissolving of DF, combination with alcohol) manipulation

MUNI PHARM

Raw data

- 2011-2016 OECD (25 countries): opioid-related deaths >20% (USA, Canada, Sweden, Norway, Ireland, England and Wales)
- 2016 USA: 1.7 million people > 12 years on stimulants of which 667k MAF



- 2012-2018 EMCDDA: overdose deaths of people over 50 higher by 75%
- 2018 EU: 8 300 overdose deaths
- 2020 Czech Republic: 900 k (8-10% of adults)

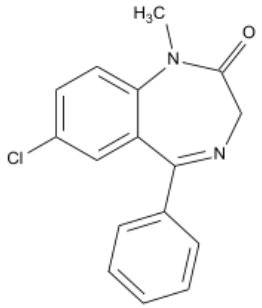
- a more sophisticated drug policy
- **DF formulation technology to make abuse more difficult**

MUNI PHARM

Most commonly abused drugs and DF

- Opioid analgesics, hypnotics, sedatives, psychostimulants
- Non-addictive: antidepressants, laxatives, non-opioid analgesics, vitamins, etc.

- Tablets, capsules, transdermal LF, sublingual and buccal films, parenteral DF



Route of administration in drug abuse influence the manipulation
- crushing for p.o., nasal, inhalation
- dissolving and extraction for i.v.

MUNI PHARM

Strategies to limit abuse

1. **Physical barriers -** preventing chewing, crushing, cutting, grating solid DF
2. **Chemical barriers -** limitation of extractability (water, alcohol, org. sol.)
3. **Combination of agonists and antagonists -** disrupt, reduce or abolish the euphoria associated with opioid receptor action
4. **Aversion -** inducing an unpleasant effect if the preparation is manipulated before use or a higher dose is used
5. Application systems with **specific** API **release** or drug delivery methods that offer resistance to abuse (depot injections, implants)
6. **Prodrugs -** inactive until biotransformed in the body (intravenous injection or intranasal abuse unattractive)
7. **Combined approaches**

MUNI PHARM

Classification of resistant formulation approaches

- formulation technologies/approaches target known or expected application ways of abuse
- extractability of the active substance
- bioavailability after DF manipulation
- preventing the distribution of the drug in the body after use by an alternative route of administration
- decrease in the effect of the substance after manipulation with DF

Primary approach - limiting mechanical and chemical manipulation – dissolving, crushing
Secondary approach - influence on the drug effect – prodrugs, antagonists, enz. inhibitors
Tertiary approach - bad feeling after use – bitter substances, colours, aversive substances

Primary approach to prevent drug abuse

- Focuses on the **unauthorized manipulation with** DF (physical and chemical)
- Increased time and energy required to create a form suitable for exploitation
- Combinations are often used
- **Physical and chemical barrier**
- **Viscosity enhancers – thickeners**
- **Absorption modifiers**
- **Dissolving modifiers**

MUNI PHARM

Physical and chemical barrier

- layer **preventing rapid release of the drug**, mechanically and chemically resistant

  - polyethylene oxide (plastic deformable, gelling); **sucrose acetate isobutyrate** - SAIB (*in situ* rigid gel, viscous lipophilic liquid), **polycarbophiles, carbomers, HPMC, xanthan gum (**strength + gelation - unsuitable for injection, nasal, inhalation abuse)

  - waxes, titanium dioxide, fatty acids - increased mechanical resistance to handling

- **matrix** drug systems with high **mechanical resistance**

  - PEO, SAIB, carbomers, xanthan, hypromellose + appropriate manufacturing processes (HME, heat treatment)

MUNI PHARM

Physical and chemical barrier - the most important excipients

Polyethylene oxide (PEO, PEG)
- quickly hydrates in aqueous environment, forms gel
- plastic deformability - problematic crushing
- thermoplastic properties - HME

Sucrose acetate isobutyrate (SAIB)
- esterification of two acetic acids and a sucrose molecule
- colourless, tasteless, viscous liquid, highly lipophilic
- drug carrier for injection - *in situ* viscous depot
- increase of mechanical resistance of solid DF

Carbomers
- acrylic derivatives
- enormous water absorption - gelation (not suitable for i.v., nasal or inhalation)

Xanthan gum
- an anionic polysaccharide of bacterial origin
- hydration - gelation

Hypromellose

Physical and chemical barrier

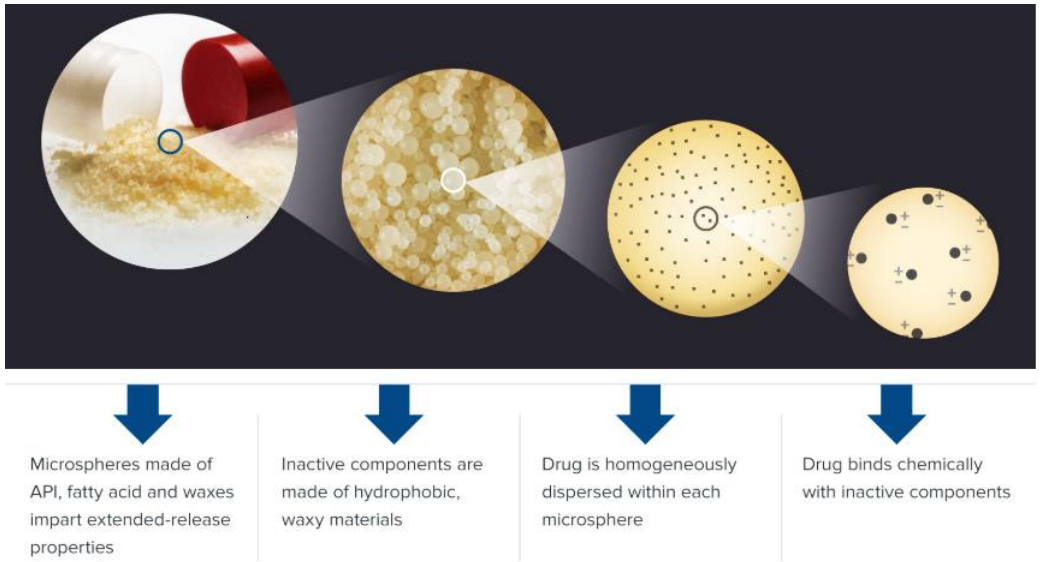
Technology	Owner of the technology	Preparation	Manufacturer	API	DF	Excipient
DETERx®	Collegium Pharmaceutical, Inc. (USA)	Xtampza®	Collegium Pharmaceutical, Inc (USA)	**oxycodone**	ER capsule	**Waxes and fatty acids**
Intac®	Grünenthal GmbH (D)	Nucynta®	Janssen Pharmaceuticals, Inc. (USA)	**tapentadol**	ER tablet	**PEO**
		Opana®	Endo Pharmaceuticals, Inc. (IRL)	**oxymorphone**	ER tablet	**PEO**
Oradur™	Pain Therapeutics Inc. (USA) Durect Corporation (USA)	Remoxy™	Pain Therapeutics, Inc. (USA)	**oxycodone**	ER capsule	**SAIB**
		ORADUR® - Methylphenidate	Orient Pharma Co., Ltd. (TWN)	**Methylphenidate**	ER capsule	**SAIB**
OraGuard™	CIMA labs Inc. (USA)	Vantrela®	Teva Pharmaceutical Industries Ltd (ISR)	**hydrocodone**	ER tablet	**HPMC**
Securel™	Relmada Therapeutics, Inc. (USA)	LevoCap®	Relmada Therapeutics, Inc. (USA)	**levorphanol**	ER capsule	**HPMC**
RESISTEC™	Purdue Pharma L.P. (USA)	OxyContin®	Purdue Pharma L.P. (USA)	**oxycodone**	ER tablet	**PEO**
		Hysingla™	Purdue Pharma L.P. (USA)	**hydrocodone**	ER tablet	**PEO**

Technology	Owner of the technology	Preparation	Manufacturer	API	DF	Excipient
SentryBond™	Inspirion Delivery Technologies LLC (USA)	MorphaBond™	Inspirion Delivery Technologies LLC (USA)	**morphine**	ER tablet	**Xanthan gum, HPMC**
		Roxybond™	Inspirion Delivery Technologies LLC (USA)	**oxycodone**	IR tablet	**Xanthan gum, HPMC**
Guardian™	Egalet Corporation (USA)	Arymo®	Egalet Corporation (USA)	**morphine**	ER tablet	**PEO**
OROS® Push-Pull™	ALZA Corporation (USA)	Exalgo™	Mallinckrodt Pharmaceuticals (IRL)	**hydromorphone**	ER tablet	**PEO**
Acuform®	Depomed, Inc. (USA)	Xartemis®	Mallinckrodt Pharmaceuticals (IRL)	**oxycodone paracetamol**	ER tablet	**PEO**

Physical and chemical barrier

DETERx - patent Collegium Pharmaceutical, Inc. (USA)

- physical resistance to crushing, chewing and chemical extraction
- spray cooling
- CR



Xtampza ER - oxycodone myristate (undissolved)

- extractability 12 % (vs. 83-98 % for HCl)
- 2016 FDA - ADF
- lipophilic matrix microparticles with myristic acid, beeswax, polyoxylglycerides, sterane Mg and colloidal silica in HPMC capsule
- after melting solidifies quickly - limitation i.v.

MUNI PHARM

Physical and chemical barrier

Intac - patent Grünenthal GmbH (Germany)

- HME of high molecular weight PEO
- matrix tbl. x pellets
- resistance to crushing - high strength ~ 500 N (nasal)
- gelling (i.v.)

Nucynta ER

- tapentadol HCl, FDA 2011

Opana ER

- oxymorphone HCl
- reformulation of the abused preparation

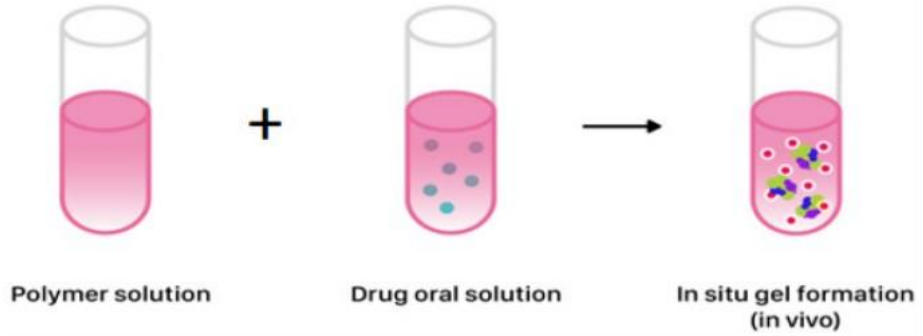
Physical and chemical barrier

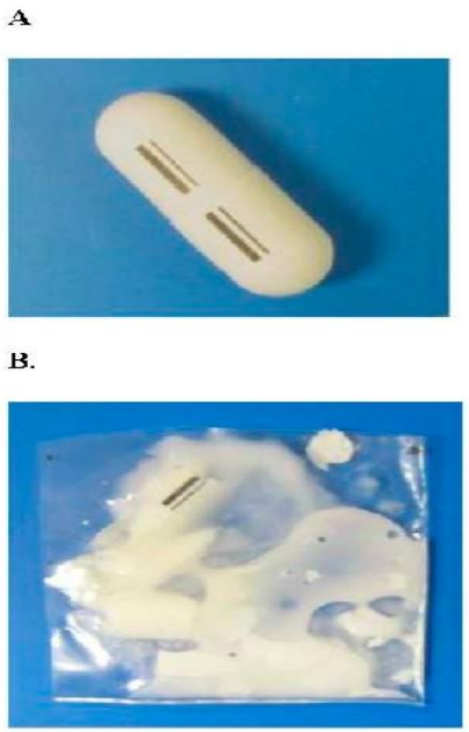
ORADUR - patent Pain Therapeutics and Durect Corporation (USA)

- viscous liquid mixture of SAIB (insoluble), cellulose acetobutyrate (CAB) and lactic acid ester (solvent)
- hard capsule
- suitable for hydro- and lipophilic drugs
- rigid *in situ* gel
- SAIB viscous in the temperature range -80 to +100 °C - formulation resistant to freezing and heating
- the contents of the capsule are insoluble in water
- resistant to i.v. and nasal abuse

Remoxy - oxycodone HCl
- resistance to EtOH
- not yet approved

ORADUR® -Methylphenidate ER - Taiwan (2019)





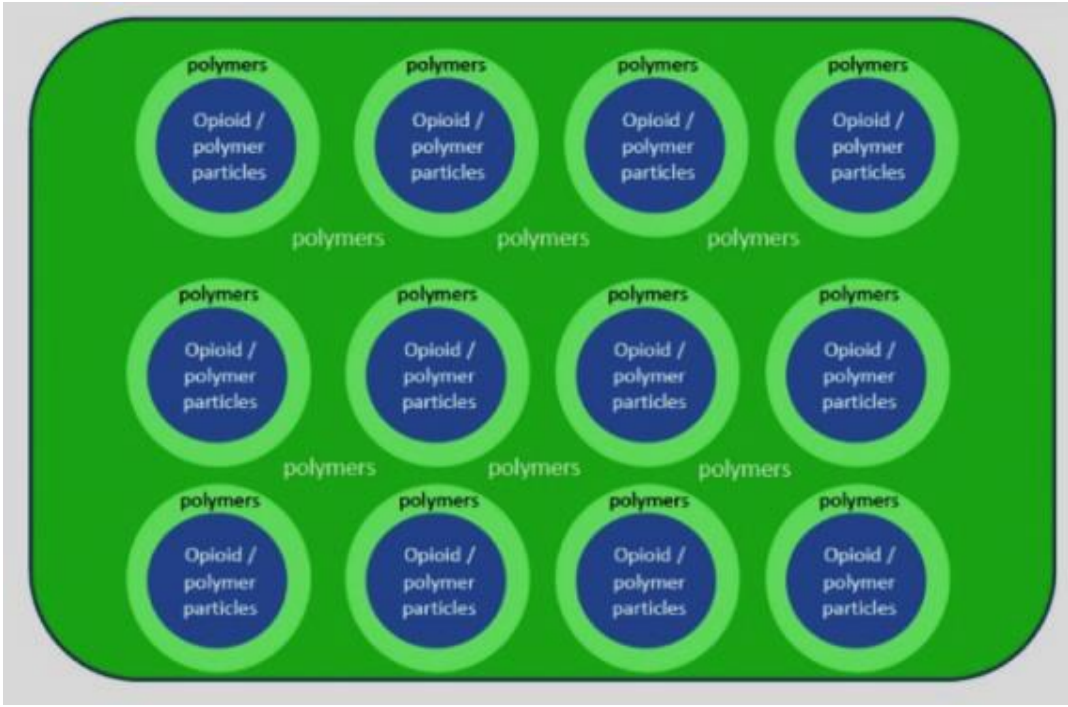
MUNI PHARM

Physical and chemical barrier

OraGuard - CIMA labs Inc. (USA)

- high polymer content granulate (EC, HPMC)
- coating (EC, Gly-behenate)
- extragranular HPMC
- compression into CR tbl.
- mechanical resistance, EtOH resistance, gelation

Vantrela ER - hydrocodone bitartrate
- FDA 2017



Physical and chemical barrier

RESISTEC - patent Purdue Pharma L.P. (USA)

- thermoplastic moulding PEO tbl.
- gelling

Oxycontin - oxycodone, reformulation 2010

SentryBond - Inspirion Delivery Technologies LLC (USA)

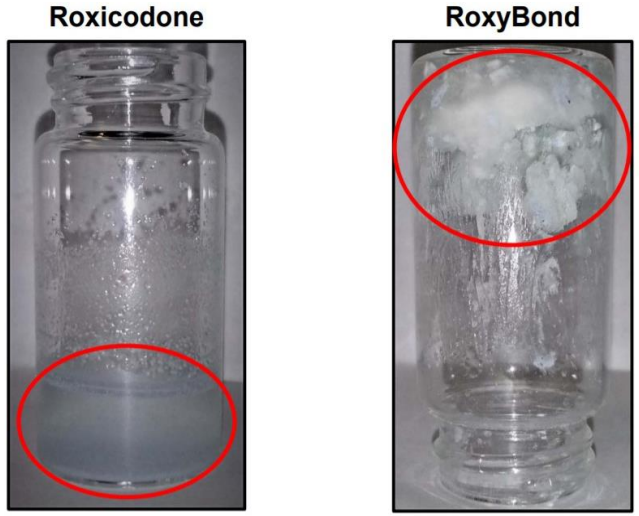
- DC tbl. HPMC + xanthan, CR coating Eudragit NE
- resistance, gelation, EtOH resistance

RoxyBond IR - morphine sulphate

- FDA 2015

MorphaBond - oxycodone, without Eudragit NE

- FDA 2017



MUNI PHARM

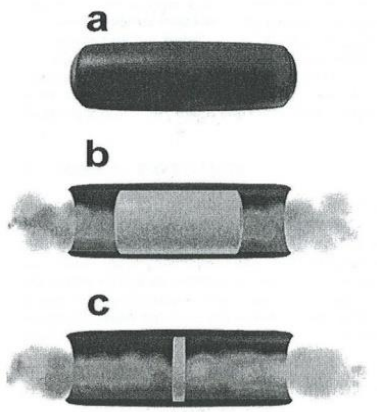
Physical and chemical barrier

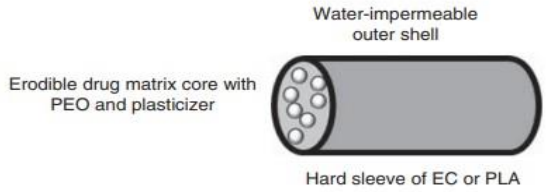
GUARDIAN - Egalet Corporation (USA)

- IR and CR
- injection moulding of molten PEO with PEG-monostearate into a solid mould
- insoluble coating EC + CSA
- erosion release - cylindrical tbl.

Arymo ER - morphine sulfate, FDA 2017

- mechanical resistance, gelation



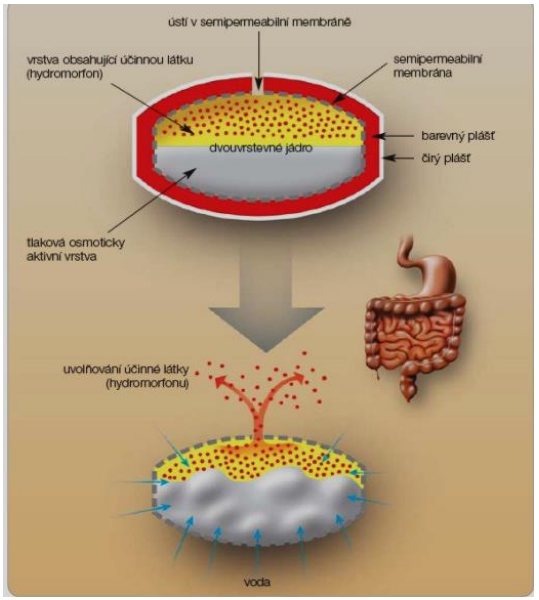


OROS Push-Pull - patent ALZA Corporation (USA)

- osmotic pump
- double-layer core tbl. and a semi-permeable, mech. resistant membrane
- Layer I - API + PEG + PVP
- Layer II - PEO + NaCl + HPC
- water permeation through semipermeable membrane, saturated solution + polymer swelling
- release of the drug through a laser-created hole

Exalgo - hydromorphone HCl

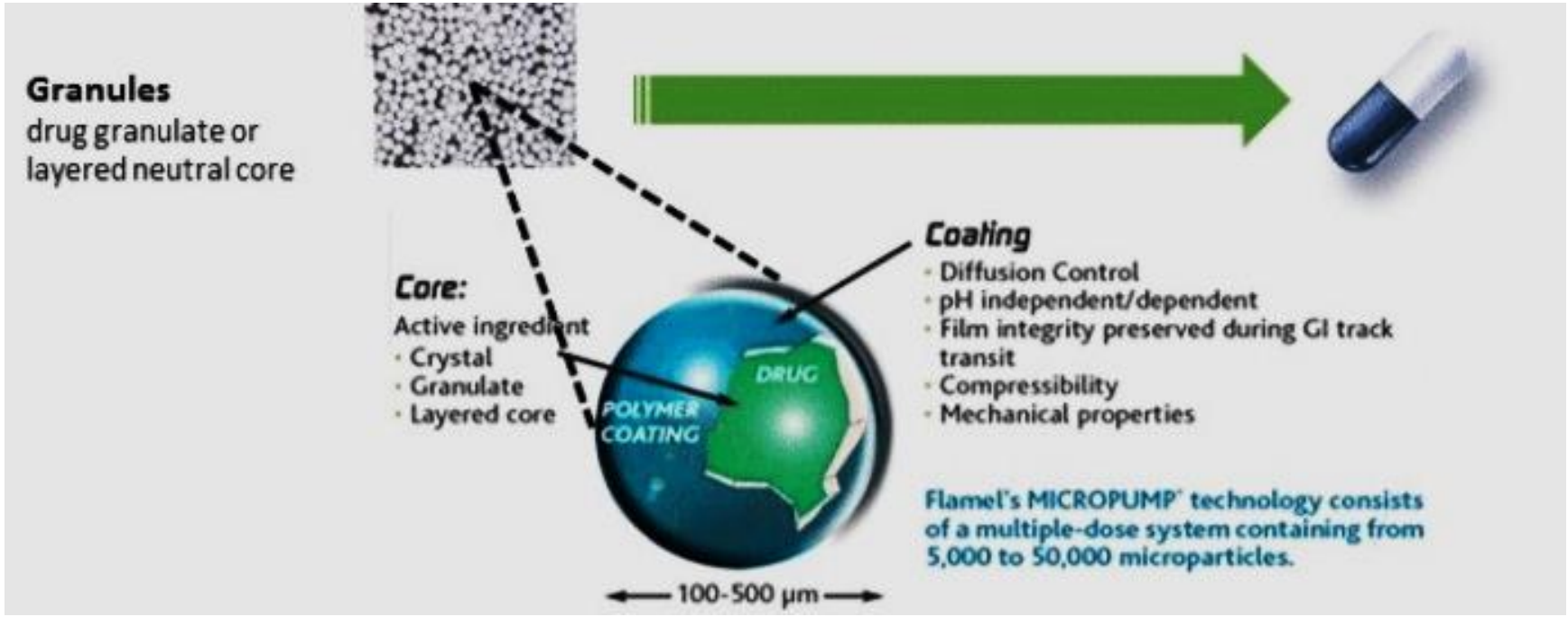
- FDA 2010
- mechanical resistance



Physical and chemical barrier

Trigger lock + Micropump - Avadel Pharmaceutical (Ireland)

- API coated inert microparticle cores
- layer of lipids and polymers
- possibility of multiple layers of different APIs
- up to 88% API, high mech. resistance
- possibility of combination with viscosity-enhancing excipients (HPMC, PEO)



Addition of viscosity modifiers

- suitable for solid DF - addition of a water-gelling agent
- i.v. limitation + reduction of release rate

- *Natural polymers* - alginates, starches, arabic gum, xanthan gum
- *Semisynthetic polymers* - hypromellose, carmellose sodium salt
- *Synthetic polymers* - PEO, polylactic acid, polyglycolic acid, carbomers

Addition of viscosity modifiers

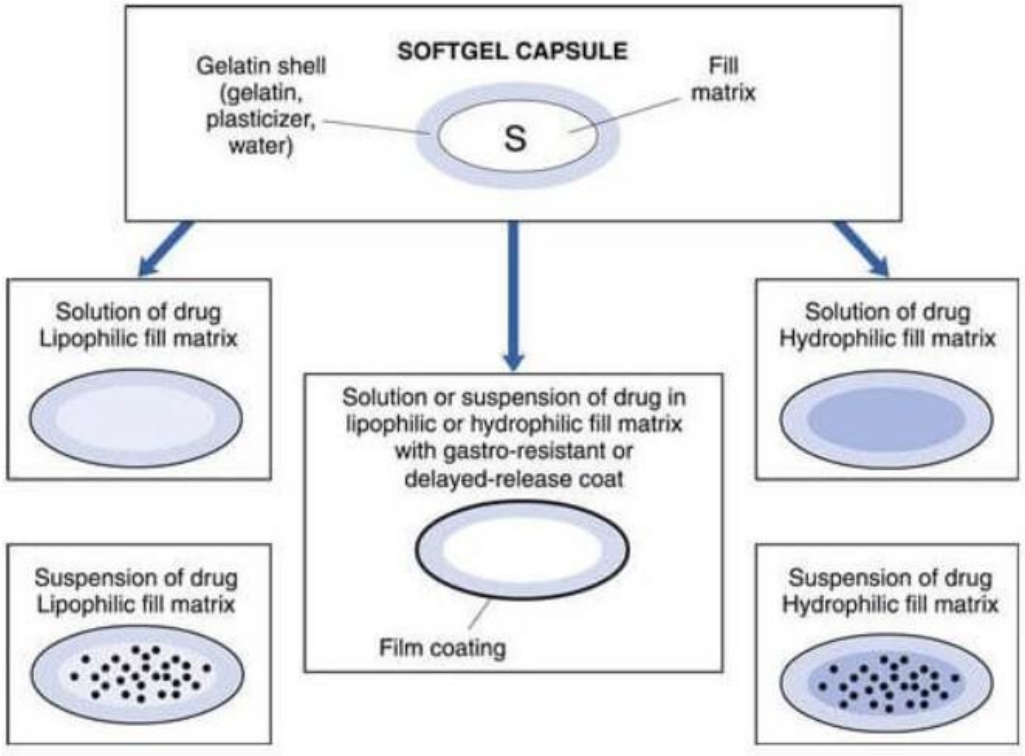
BeadTek - Alkermes Pharma (Ireland)

- two types of indistinguishable pellets - I. API + II. PEO
- agglomeration by movement in a fluidized bed
- tangential spraying of PVP binder in IPA

Zohydro ER - hydrocodone bitartrate, FDA 2013

Optigel Lock - Catalent Inc. (USA)

- soft capsule
- API liquid or semi-solid dispersion
- gel-forming polymers - HPMC, PEO

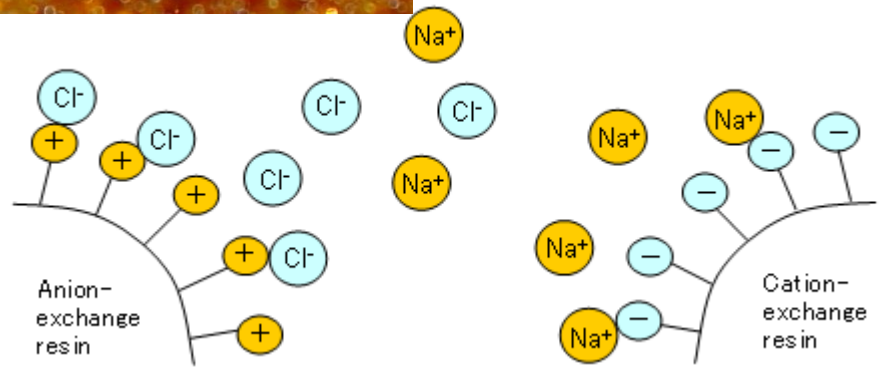


Modification of absorption rate

- use of ion-exchange resins
- resins bind charged drugs and provide CR (polyresinates)
- ion-exchange usually for Na+ or Cl- ions from GIT fluid
- the ion-exchange equilibrium depends on the type of resin, particle size and amount of drug
- increasing the dose does not increase the rate of drug release

Nobuse - Tri Pharma (USA)

- resin
- PVAc coating (release modification, mechanical resistance)



MUNI PHARM

Modification of drug solubility

- to ensure that the drug is absorbed by the body, but at the same time to reduce the risk of potential abuse
- API solubility dependent on t, pH, particle size, solvent, etc.

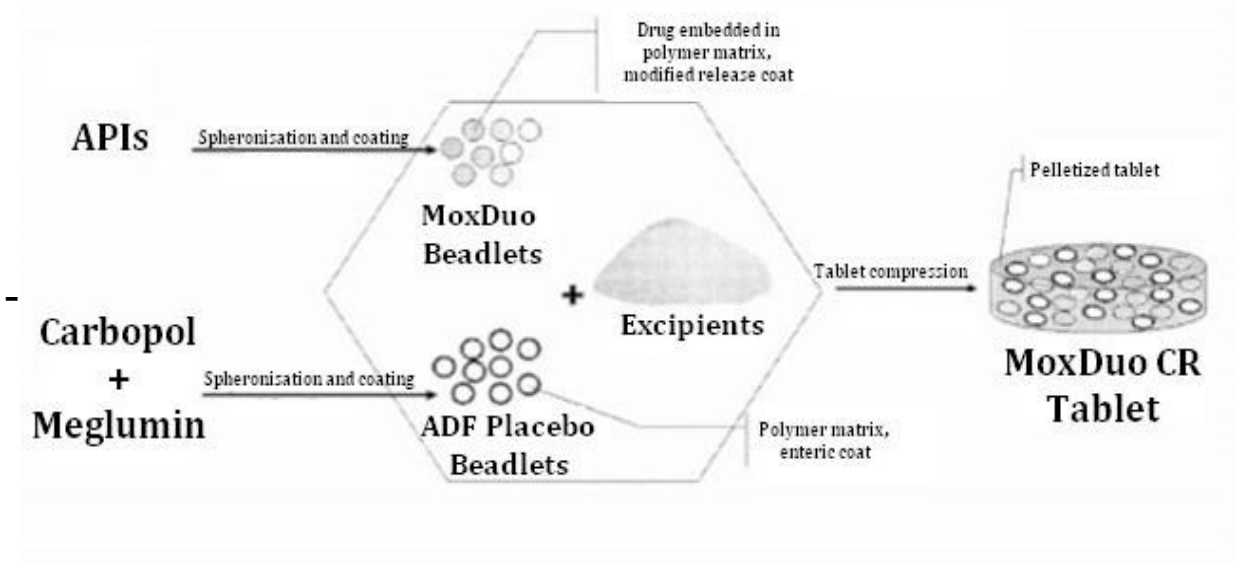
- change in **pH** after handling, precipitation of the drug occurs and makes injection impossible
- **meglumine** - alkalization leading to methadone precipitation (difficult to filter and extract)
- **carbonates** - for drugs soluble at low pH - limit solubility in overdose

Stealth Beadlets - patent QRxPharma Limited (Australia)

- hydrophilic and hydrophobic excipients + meglumine
- combined approach - mechanical resistance, gelation, solubility limitation

MoxDuo CR - oxycodone + morphine

- 3 types of pellets, spheronization, tablet pressing
- pellets with meglumine coated with Eudr L - solubility in distal parts of the intestine



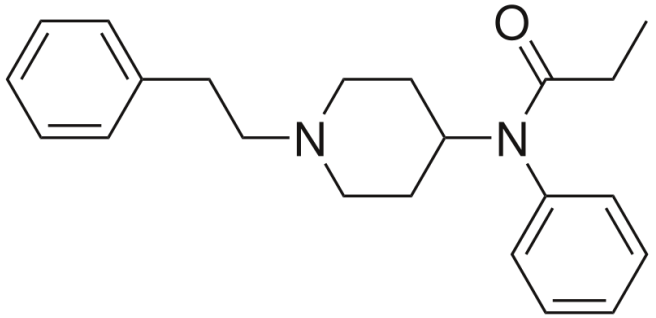
Secondary approach to prevent abuse

- modifying the contents of a DF to interfere with the effect of the drug under circumstances causing abuse

- there is no modification of the physical properties of the DF, as by the primary approach

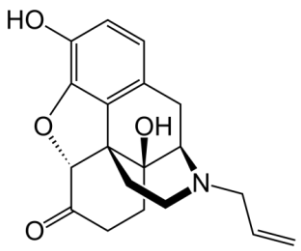
MUNI PHARM

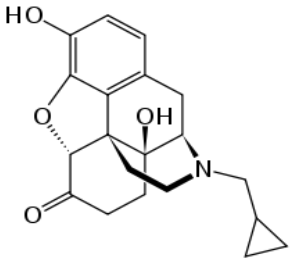
Antagonists of the drug



- are used in opioids
- antagonists block the euphoric effect (higher receptor affinity) only when DF is manipulated
- without manipulation the antagonist has no effect

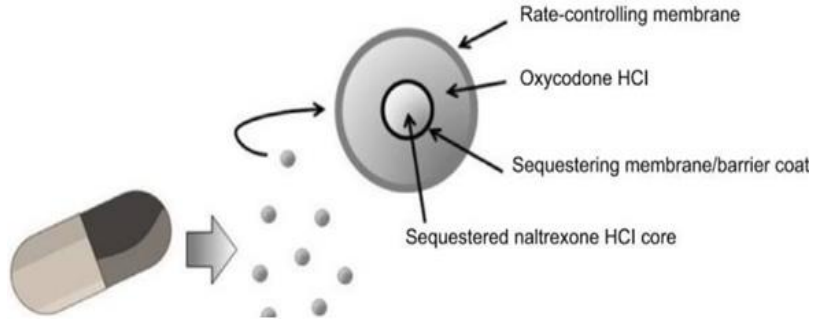
  - **Naloxone** - not isolated in DF, bioavailability after p.o. use is very low (2%) - strong first-pass
  - **Naltrexone** - in DF is isolated by forming a separate core (bottom layer) from the drug by a membrane (coating) and its antagonistic action appears only after physical manipulation





MUNI PHARM

Antagonists of the drug

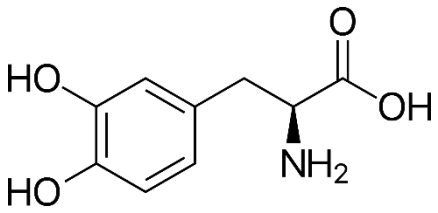


Troxyca® ER

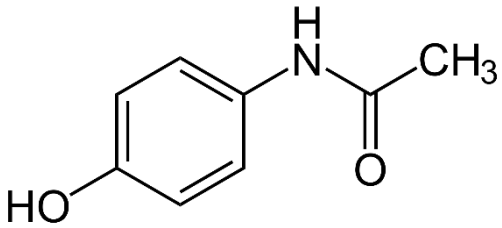
Preparation	Manufacturer	DF	API/antagonist	Remark.
Targiniq™	Purdue Pharma L.P. (USA)	ER tablet	Oxycodone/Naloxone 2:1	PEO - mechanical resistance, gelation Thermoplastic moulding
Troxyca®	Pfizer Inc. (USA)	ER capsule	Oxycodone/Naltrexone 100:12	Pellets - API shell, core antagonist After crushing nasal and i.v. abuse restrictions
Embed®	King Pharmaceuticals, Inc. (USA)	ER capsule	Morphine/Naltrexone 100:4	Pellets - layering on inactive sucrose cores, 2 separate layers
Valoron® N	Pfizer Deutschland GmbH (D)	ER tablet	Tilidine/Naloxone 100:8	1978, limitations i.v.
Suboxone®	Reckitt Benckiser Group (GBR)	ER sublingual tablet	Buprenorphine/Naloxone 4:1	Newly also in film form Restrictions i.v.
Talwin® NX	Sanofi Aventis (FRA)	Tablet	Pentazocine/Naloxone 100:1	

MUNI PHARM

Prodrugs



Levodopa - dopamine



Proparacetamol (i.v) - Paracetamol (low solubility and stability in physiological fluids)

- API often - low bioavailability, solubility, absorption, strong F-P, instability, poor site of action specificity, adverse organoleptic properties, toxicity
- Prodrugs can improve physicochemical properties (solubility, chemical stability, taste, odour), receptor selectivity, FK and FD properties and therapeutic index
- They enter the body as inactive - biotransformation (enzymatically x non-enzymatically)
- Usually targeted chemical modification
- They also occur naturally - phytoestrogens, levodopa
- **Restriction of drug bioavailability after use by other route (p.o.) - activation in GIT required**

MUNI PHARM

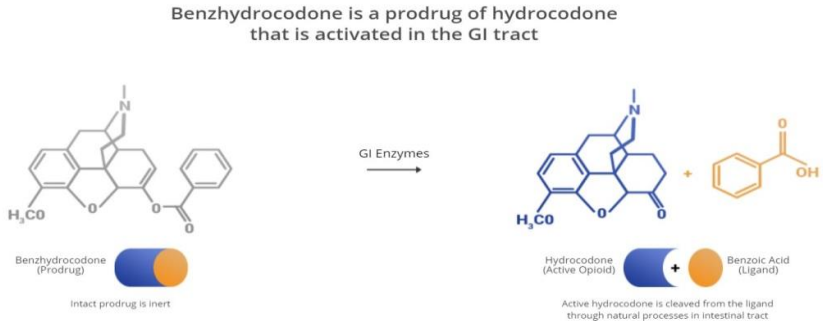
Prodrugs

Vyvanse - Takeda Pharmaceutical Company (Japan)

- prodrug formed by a covalent bond between dextroamphetamine and lysine (lisdexamfetamine)
- ADHD
- hydrolysed to active substance, i.v. administration triple Tmax

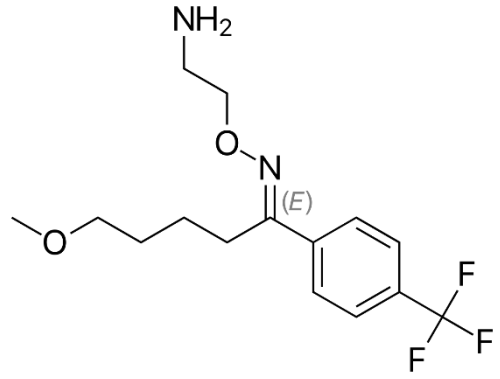
Apadaz - KemPharm (USA)

- hydrocodone + benzoic acid = benzhydrocodone - bioactivation in GIT (ester bond cleavage)



Enzyme inhibitors

- no clinical use yet
- **blocking the enzymatic conversion of the formation of more active metabolites**
- inhibitor separated similar to naltrexone
- CYP2D6 transforms codeine and hydrocodone into the more active metabolites morphine and hydromorphone
  - an inhibitor of this enzyme is **fluvoxamine** (SSRI antidepressant)



MUNI PHARM

Tertiary approach to prevent drug abuse

- does not limit the ability to manipulate DF, but it does make the sensations of abuse (after manipulation, overdose, change of administration route) unpleasant

- use of **irritants** for nasal and inhalation; **dyes** or **nauseating** substances for p.o.

- often a combination with other approaches

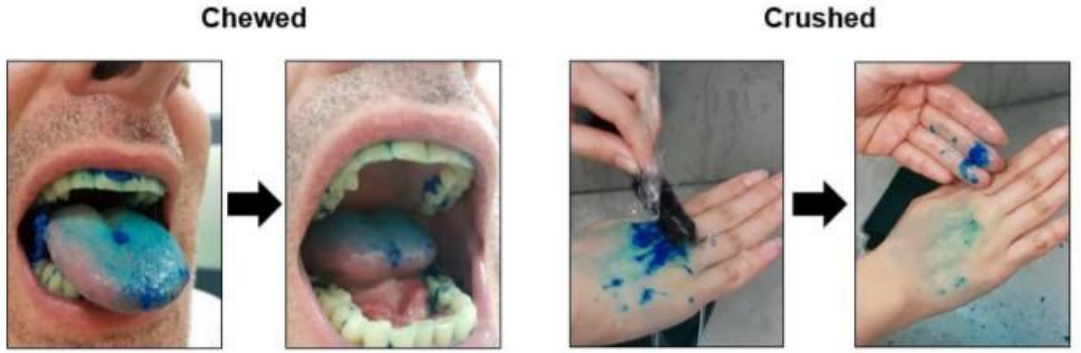
Aversive substances

- elicitation of unpleasant sensory sensations
- problem is individual susceptibility
- majority of aversive agents are isolated - action after DF manipulation, overdose
  - Mg stearate: p.o. no effect - nasally irritating
- Irritation of mucous membranes after oral or inhalation administration
  - Capsaicin
  - Sodium lauryl sulphate
  - Bitter tasting substances (sucrose octacetate)
  - Essential oils (menthol, citrus oils)
- Nausea and vomiting after p.o. overdose
  - Kefalin
  - Zinc sulphate

MUNI PHARM

A tertiary approach to prevent drug abuse

Preparation	Manufacturer	API	DF	Aversive substances	Effect of aversive substance
Lomotil®	Pfizer Inc. (USA)	diphenoxylate	IR tablet	Atropine (0.025 mg)	Nausea, vomiting, mild tachycardia
Motofem®	Sebela Pharmaceuticals, Inc. (IRL)	diphenoxine	IR tablet	Atropine	Nausea, vomiting, mild tachycardia
Oxaydo®	Egalet Corporation (USA)	oxycodone	IR tablet	Sodium Lauryl Sulphate (+PEO)	Irritation of the nasal mucosa (+ gelation at i.v.)
Aximris® XR	IntelliPharmaceutics (CAN)	oxycodone	ER tablet	Sodium Lauryl Sulfate, Magnesium Stearate (+PEO)	Tissue irritation (nasal), gelation (i.v.)
Acurox®	Acura Pharmaceuticals (USA)	oxycodone	IR tablet	Niacin (30 mg)	Nausea, tingling, headache, hot flashes - withdrawn
Rohypnol®	Hoffmann-La Roche, Inc. (CHE)	flunitrazepam	IR tablet	Blue dye	Tissue and fluid staining
IPC Oxy	IntelliPharmaceutics (CAN)	oxycodone	ER tablet	Blue dye, sodium lauryl sulfate (+PEO)	Tissue staining and irritation, gelation
Rexista™	IntelliPharmaceutics (CAN)	oxycodone	ER tablet	Blue dye	Tissue staining



IPC Oxy

MUNI PHARM

ADF-labelled opioids

- since 2013, FDA support for abuse-deterrent formulations (ADFs)
- 2021 FDA approved: *OxyContin ER*
  Hysingla ER
  Xtampza ER
  RoxyBondTM IR
- original preparations with high price

MUNI PHARM

ADF-labelled opioids

– support for the development of generics

testing: 1) laboratory studies of manipulation and extraction of the active substance *in vitro*

- Particle size after disintegration by melting, crushing, grinding
- Solubility of API in solvents
- Amount of API extracted using specific methods
- Amount of drug released over time
- Remaining amount of API in DF after manipulation

2) pharmacokinetic studies - rate of increase of c API in plasma, values are compared manipulated vs. intact DP; evaluation of the influence of food and alcohol; agonist/antagonist method - FK of both; adverse effects of aversive substances

3) study of potential abuse

4) post-marketing abuse monitoring

2014 EMA: recommendations for the evaluation of modified release dosage forms - dose dumping with alcohol only

MUNI PHARM

Alcohol-resistant dosage forms

- alcohol can alter the mechanism and rate of drug release - **dose dumping**
- drug release from DF is monitored for 2 hours in 5%, 20% and 40% ethanol - ingestion simulation
- ethanol less polar than water (better solubility of lipophilic substances)
- formulation of matrix systems - release based on matrix penetration, hydration, swelling, drug diffusion, matrix erosion, etc.

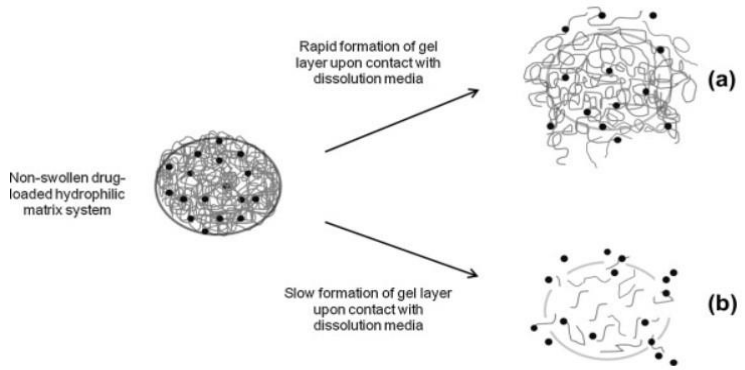
EDACS - Akela Pharmaceuticals (USA)

- polyacrylate matrix formulated by HME
- mechanically and ethanol resistant

Alcohol-resistant dosage forms

Physicochemical factors of DF influenced by EtOH

- API solubility - matrix systems (EDACS - HME, acrylates)
- wettability - limitation by EVA, EC
- swelling - HPMC
- mechanical properties of the product - HME technology

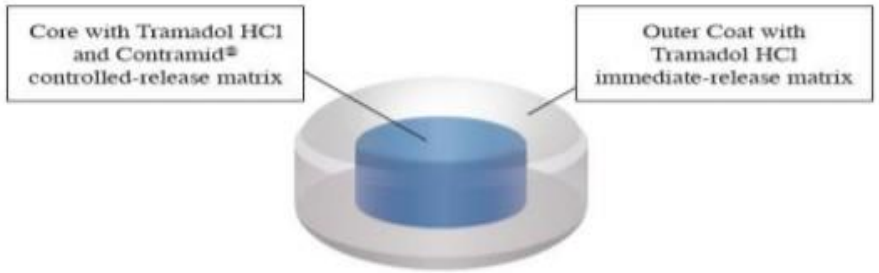


Alcohol-resistant dosage forms

Tridural ®

- tramadol hydrochloride extended-release DF

- two layers contributing to alcohol resistance
  - Contramid® is a modified corn starch with a high content of amylose (70%) and amylopektin (30%)
  - coating of xanthan gum



Locktab® , Oraguard™ , Trigger Lock™ , OROS ® , Intac®

MUNI PHARM

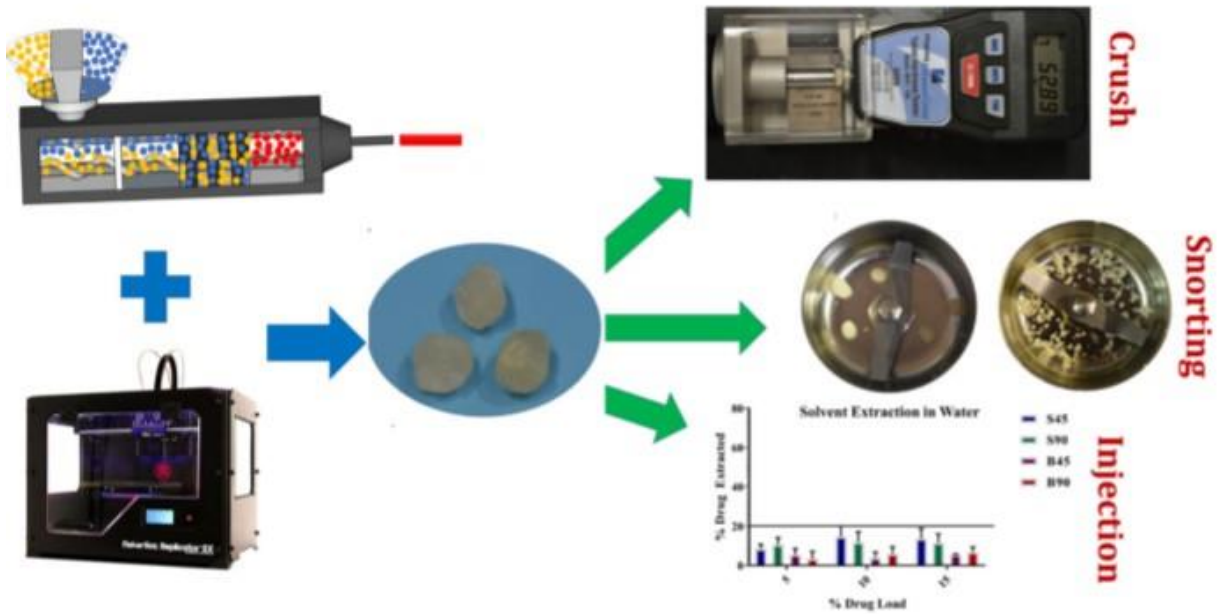
Modern trends in anti-abuse technologies

Crosslinked forms of carboxymethylcellulose (XCMC), carboxymethyl starch (X-SSG)

swelling - viscous gel, superdisintegrants, binding with cationic drugs (CR)

Hot melt extrusion and 3D printing (FDM)

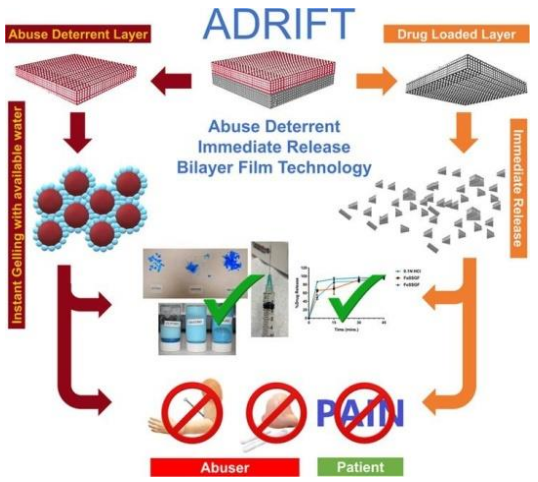
- DFs mechanically resistant, limited nasal, i.v. abuse
- applications HPC, PEO, PLA, PVA



Modern trends in anti-abuse technologies

ADRIFT technology

- immediate-release, abuse-resistant, double-layer film
- solvent casting
- oral film contains a layer of active ingredient (with PVA) and a second layer of AquaSolve™ - hypromellose acetate succinate + triethyl citrate
- use of sodium salt of polyacrylamide starch (forms a viscous gel in water) → prevents intravenous abuse
- crushing to particles > 2 mm



Summary

1) The most studied approach to DF manufacturing to prevent abuse - **physical and chemical barriers** that either impart mechanical resistance to DF or prevent the preparation of solutions suitable for extraction or straight injection.
2) The use of **opioid antagonists** where the effect occurs after manipulation.
3) The use of **aversive substances limits the individual's susceptibility**.
4) The abuse of drugs is often associated with the use of **alcohol**, which potentiates their effects. Preventing the so-called **dose dumping** effect, in CR DF, to avoid rapid release of the full dose.

Conclusion

- Appropriate DFs - one step in the fight against drug abuse - the need for a comprehensive solution
- Development in the last 10 years
- The problem is the high price
- 3D printing

Thank you for your attention

MUNI PHARM