



# Ion Exchange Resins

## Utilization and Unique Solutions for Pharmaceutical Formulations

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# Commercial Examples

- Nicotine / Smoking cessation products (various companies)
- Vitamin B<sub>12</sub> stabilisation– various companies
- Paxil – paroxetine suspension (GSK)
- Diclofenac – extended release (Novartis)
- Sodium polystyrene sulfonate – active (various companies)
- Cholestyramine – active (BMS Questran and generics)
- Tussionex – chlorpheniramine and hydrocodone (UCB/Celltech)
- Delsym – dextromethorphan (UCB/Celltech)
- Betoptic – ophthalmic/betaxolol (Alcon)
- Novonorm – repaglinide (Novonordisk)





# Ion Exchange Resins

## Structure:

- Typically are either styrenic or acrylic polymers
- Typical functional groups
  - Cation exchange resins  $\Leftrightarrow$  Sulphonic or carboxylic acids
  - Anion exchange resins  $\Leftrightarrow$  amines or quaternary amines.





# Types of Resin Available

- Strongly acidic: Sulfonic acid/Styrenic polymer  
Amberlite® IRP69  
Amberlite® IRP70  
Amberlite® IR69F (Sodium Polystyrenesulfonate USP)
- Weakly acidic: Carboxylic acid/methacrylic polymer  
Amberlite® IRP64  
Amberlite® IRP88 (Polacrilin Potassium NF)
- Strongly basic: Quaternary amine/Styrenic polymer  
Duolite® AP143 (Cholestyramine USP)
- Other particle size versions are under development





# Resin Properties

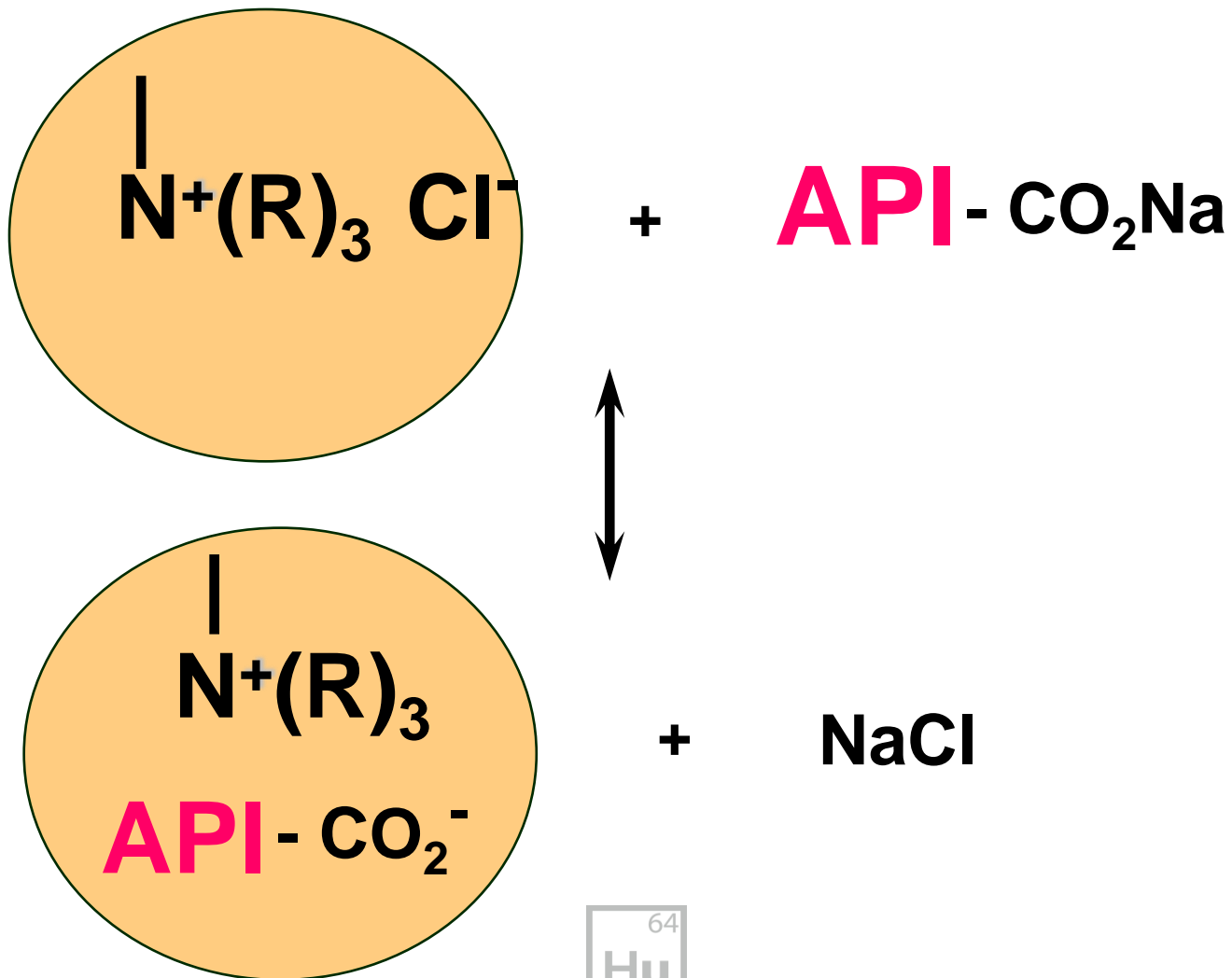
## Ion Exchange excipients :-

- are fine, free-flowing powders,
- have a particle size of 10 -150 microns,
- contain functional groups capable of exchanging ions and/or ionic groups,
- are insoluble in all solvents,
- are not adsorbed by the body,
- do not have a defined molecular weight
- are particularly suited to oral dosage forms (liquid or solid).





# Mode of Operation





# Resinate Properties

## Resin-drug complexes (Resinates):

- are fine, free-flowing powders
- have a particle size similar to the original resin
- can be ground to smaller size or agglomerated to larger size
- contain the API in salt form
- do not have a melting point
- API released *in vivo*





# Excipient Applications

- Stabilization
- Improved dissolution
- Physical form
- Reduced water uptake
- Polymorphism
- Taste-masking
- Extended release







# Stabilization

- Resinate can have greater stability than the pure drug





# Example - Vitamin B<sub>12</sub>

## Shelf-life

- B<sub>12</sub> ~3 months
- B<sub>12</sub> resinate >2 years

## *In vivo*

- B<sub>12</sub> – partially destroyed by stomach acid
- B<sub>12</sub> resinate – passes through stomach practically unchanged (ref: US 2,830,933)





# Improved Dissolution

Resinates can enhance the rate of dissolution of poorly soluble drugs:

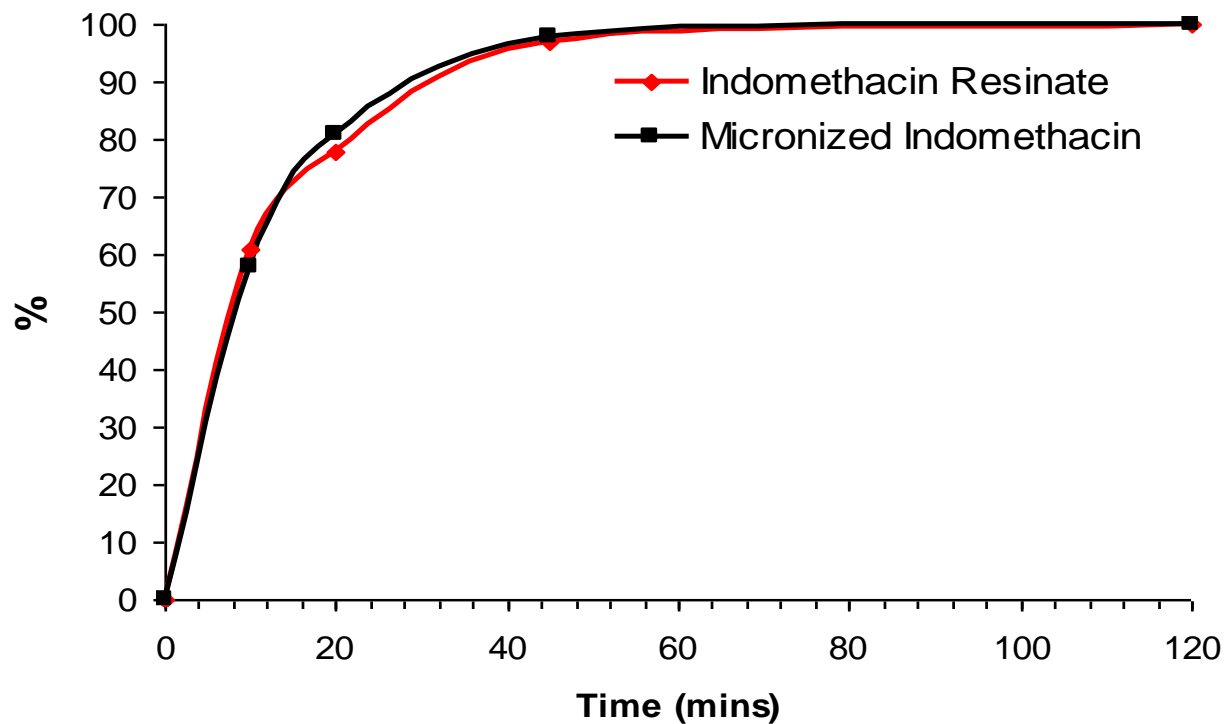
- Improved bioavailability
- No added solubility enhancers
- Micronization not required.





# Example - Indomethacin

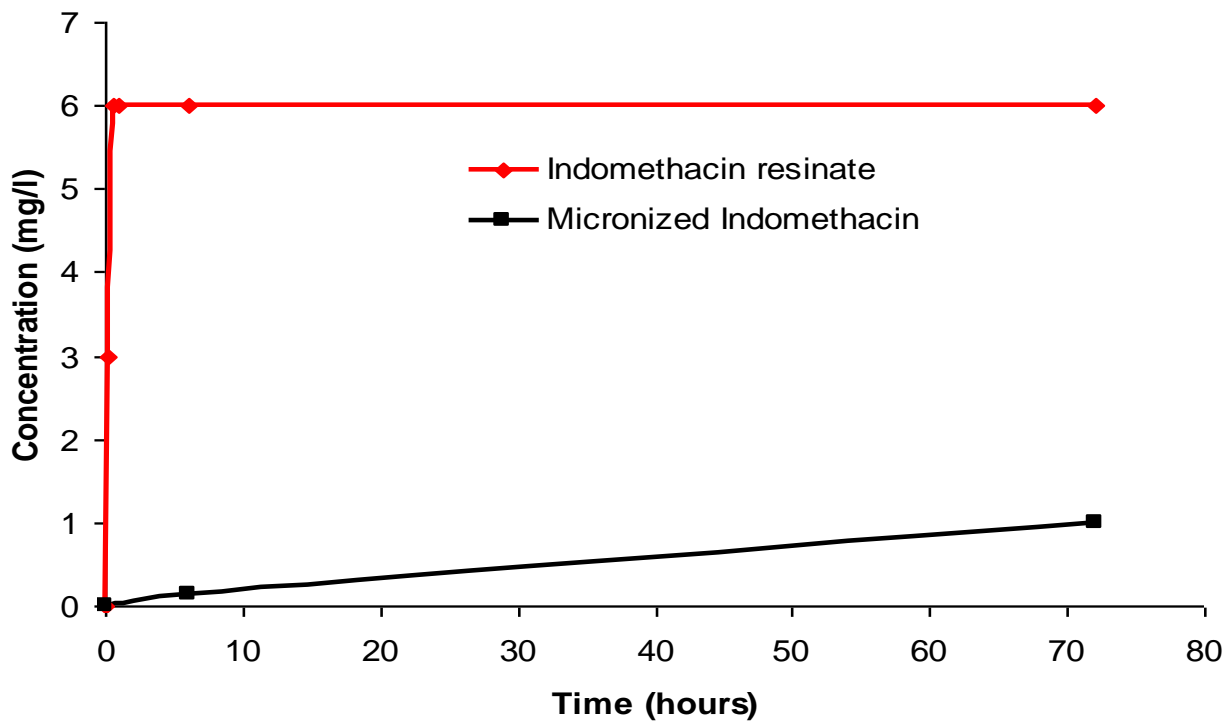
## Dissolution/Release of Indomethacin in Simulated Intestinal Fluid (pH 7.4)





# Example - Indomethacin

## Dissolution/Release of Indomethacin in Simulated Gastric Fluid





# Physical Form

- Resinates are non-melting solids
- Resinate is equivalent to a solid salt
- Low mp or liquid drugs can be made into solid oral dosage forms





# Example - Nicotine

## Physical form

- Nicotine is a high bp liquid (*ca* 247°C decomposes),
- Nicotine resinate is a stable solid,
- Formulated into chewing gum and lozenges,





# Reduced Water Uptake

Resinates can eliminate deliquescence and hygroscopicity problems during manufacturing and production.

- Needs no special formulation equipment or atmospheric controls,
- Drug is released by gastro-intestinal fluids.

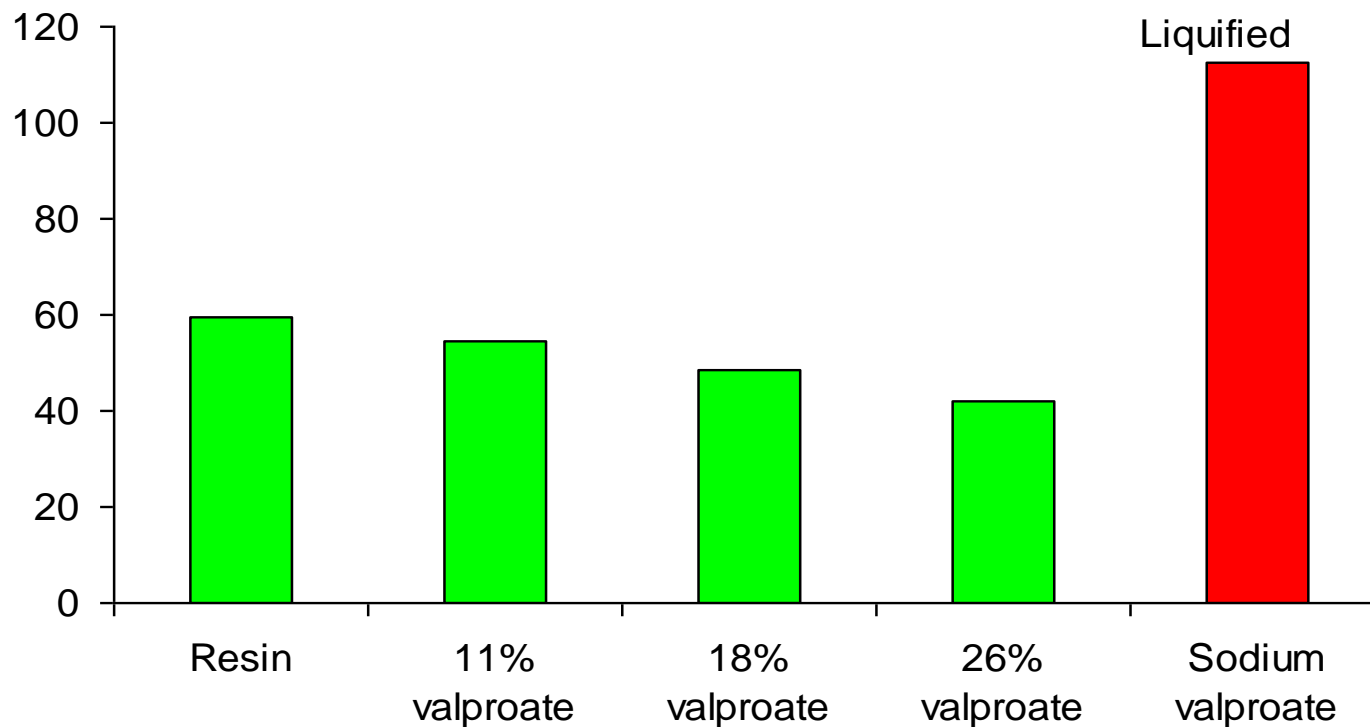






# Example - Valproate

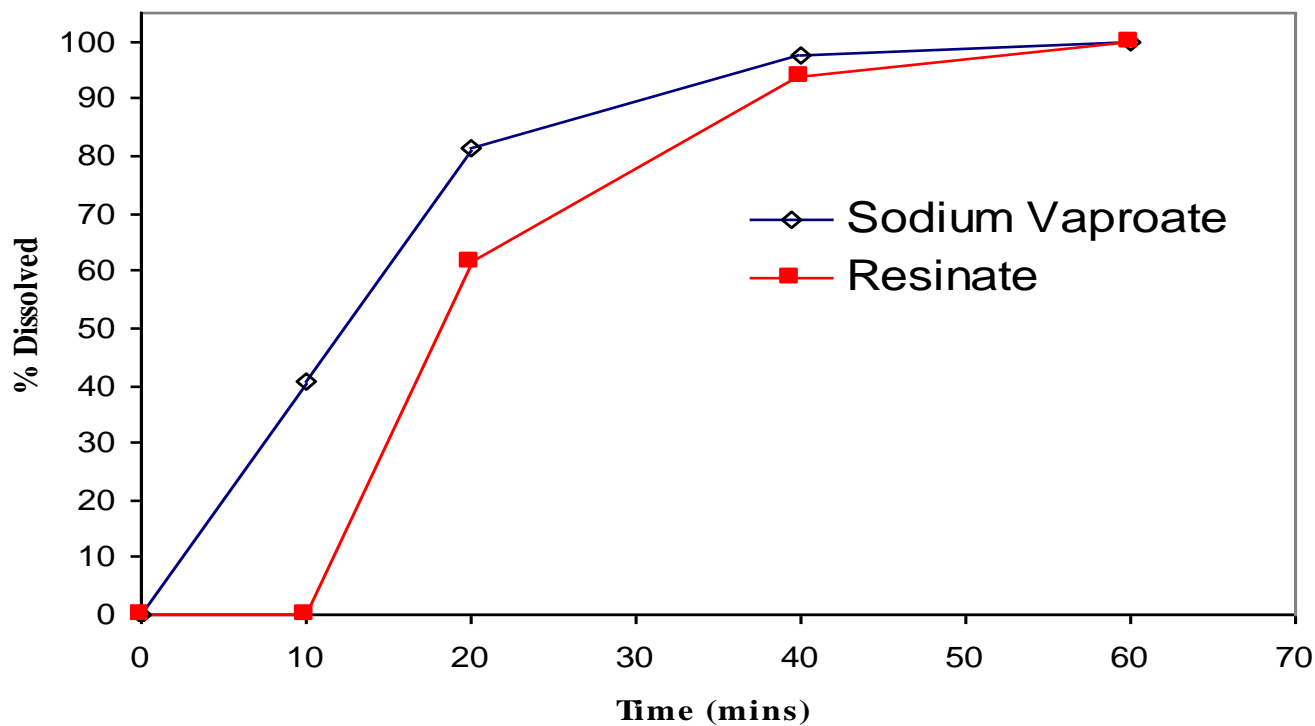
**% Wt gain, 24 hours @40C/75%RH**





# Valproate Release

## Release of Valproate from Resinates





# Polymorphism

Resinates can eliminate concerns over polymorphism

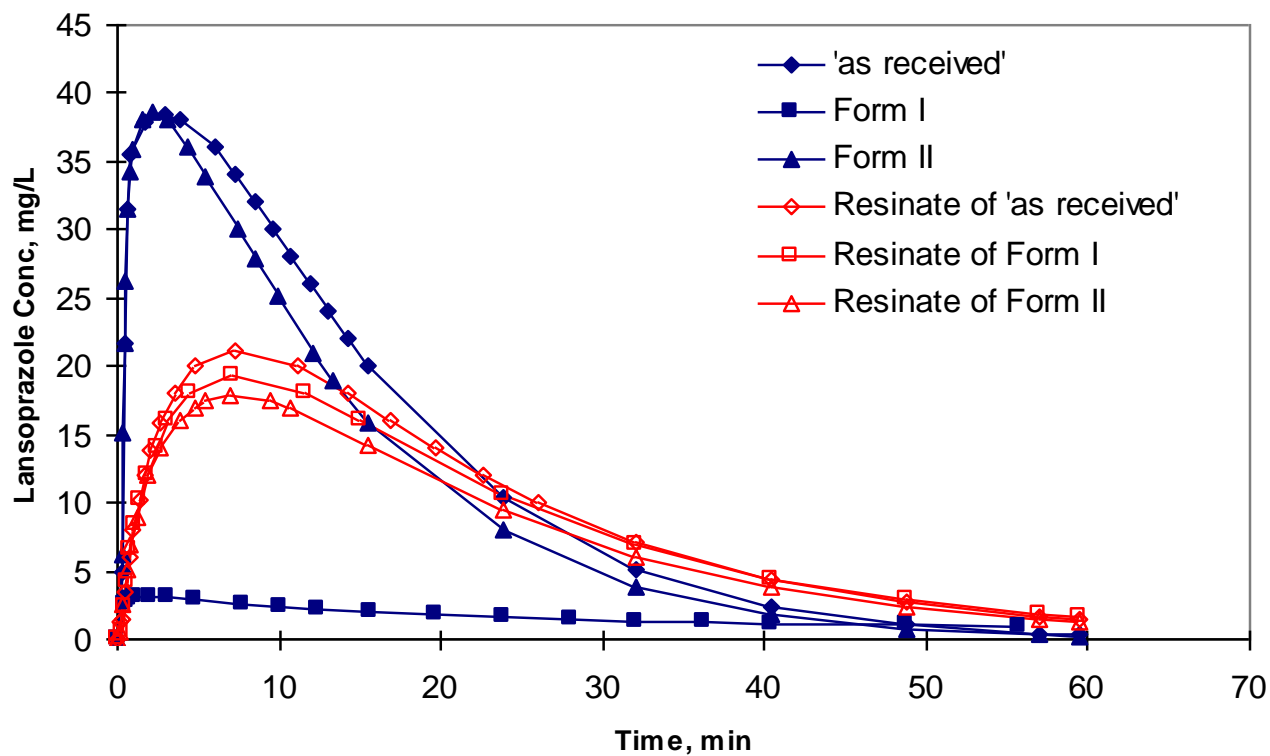
- Loading onto a resinate is independent of crystal form,
- Resinate is not crystalline,
- Resinate is amorphous, but cannot crystallize,
- Dissolution is independent of original crystal form.





# Example - Lansoprazole

## Dynamic *in vitro* Dissolution Profiles





# Taste Masking

- Resins can be used to mask the taste of bitter drugs in liquid and solid oral dosage forms,
- Alternative technology to encapsulation but with some significant advantages
  - Little chance of rupture of capsule
  - Rapid release in stomach environment





# Taste-masked Paroxetine

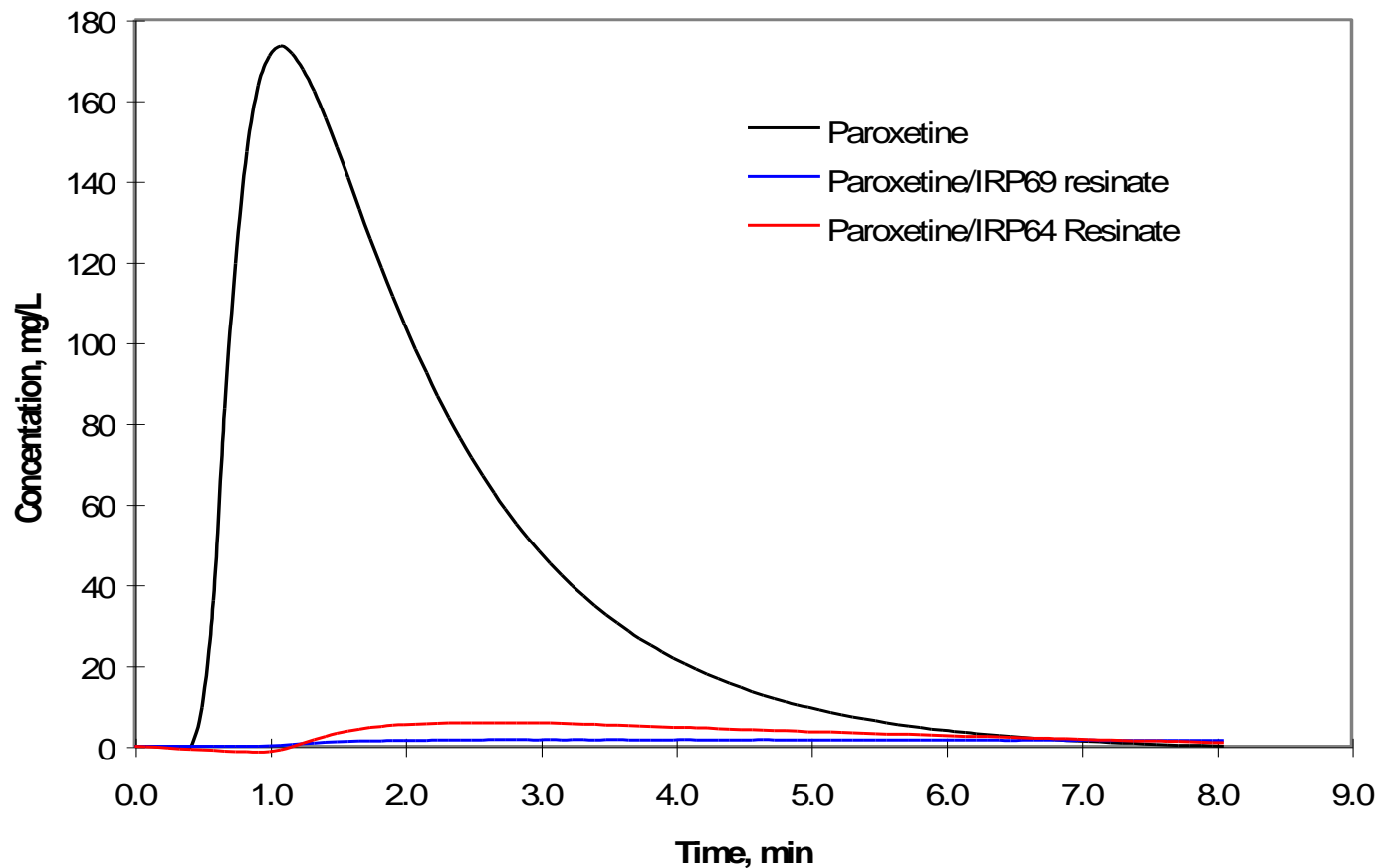
- Suspension formulation
- Taste masking using paroxetine loaded onto IRP88





# Taste-masked Paroxetine

## Taste Masking Ability of Pharmaceutical Grade IER's





# Controlled Release

Resins can be used to control the  
release rate of drugs

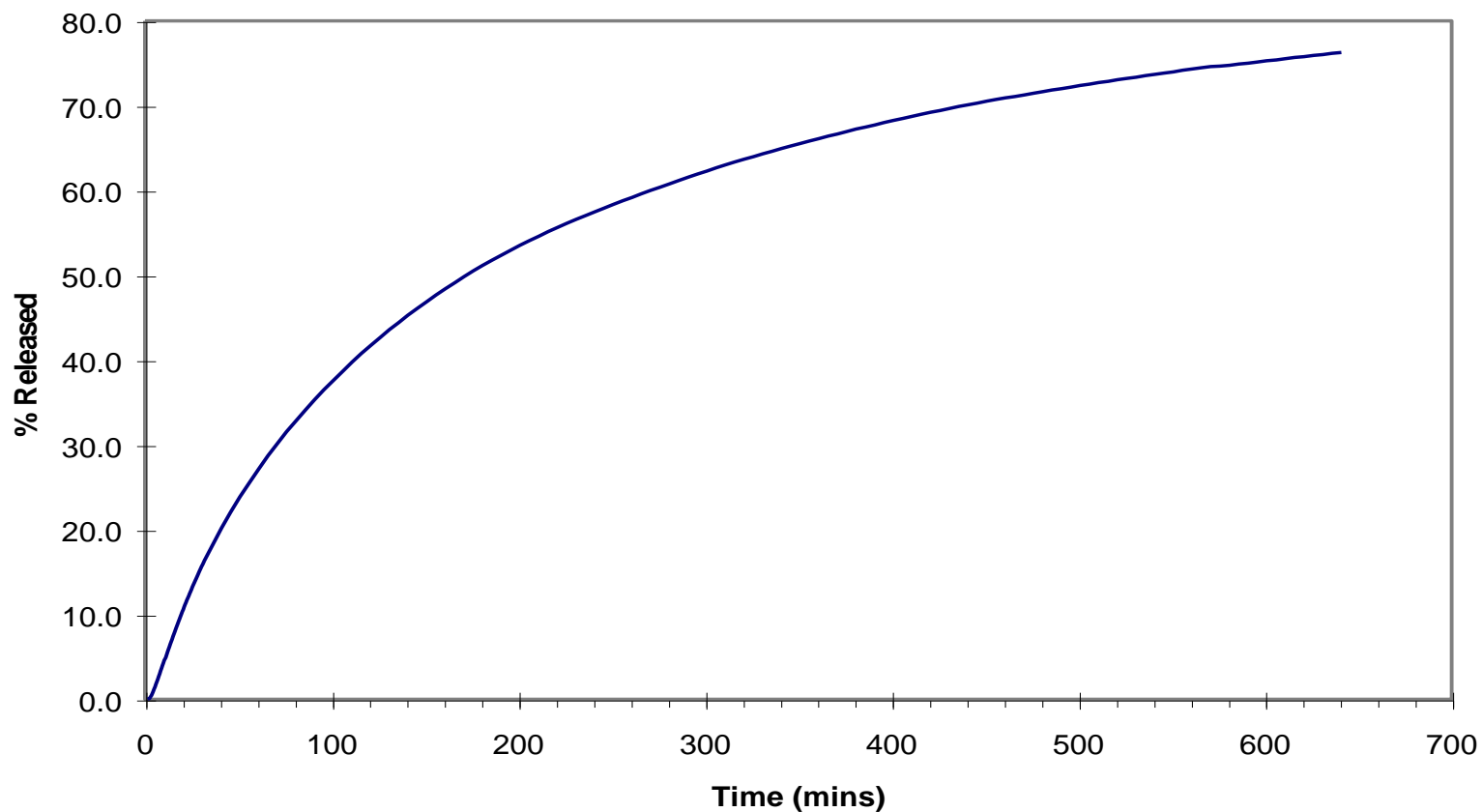






# Extended Release in SIF

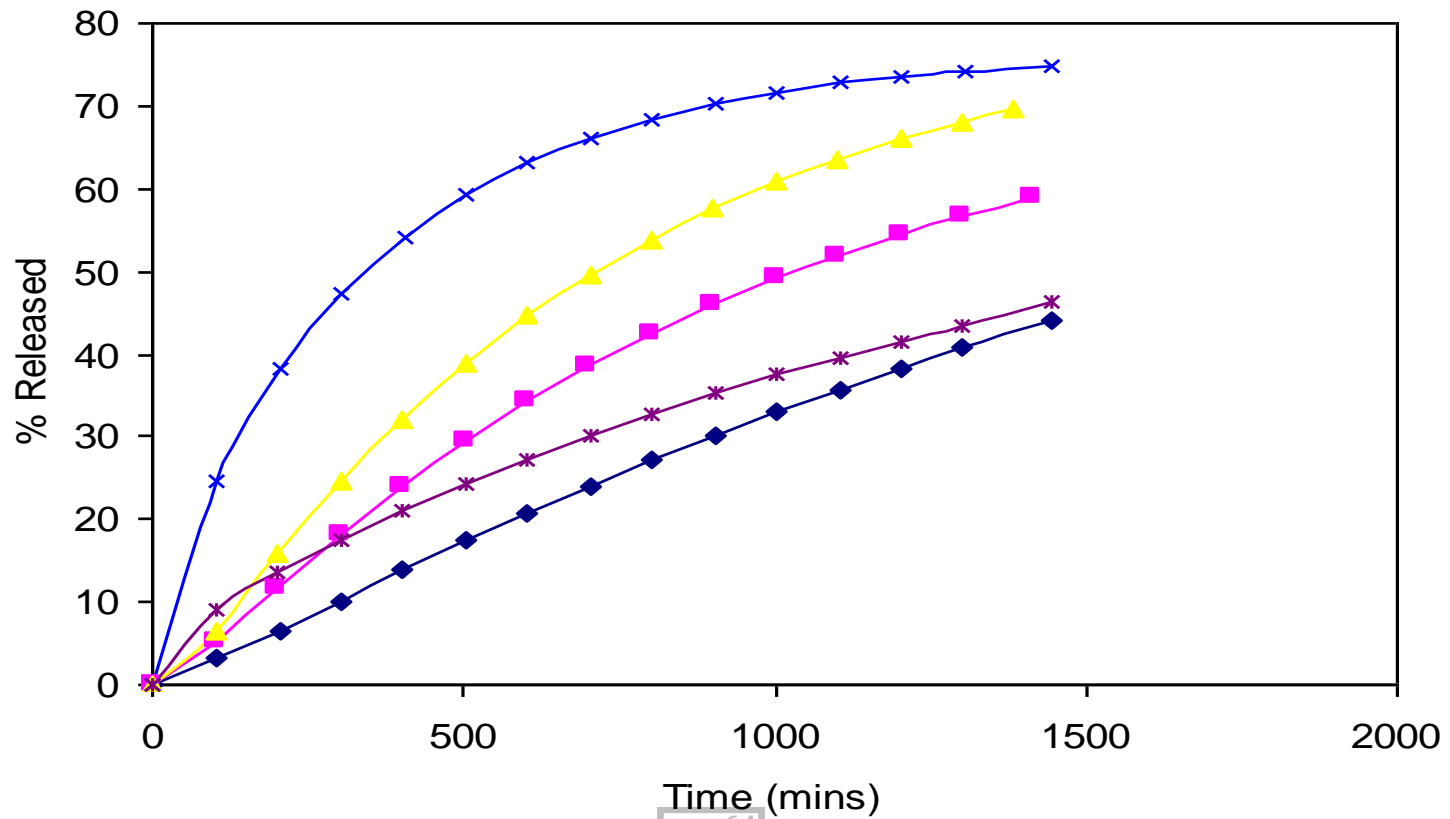
## Cumulative Release from Diclofenac Resinate





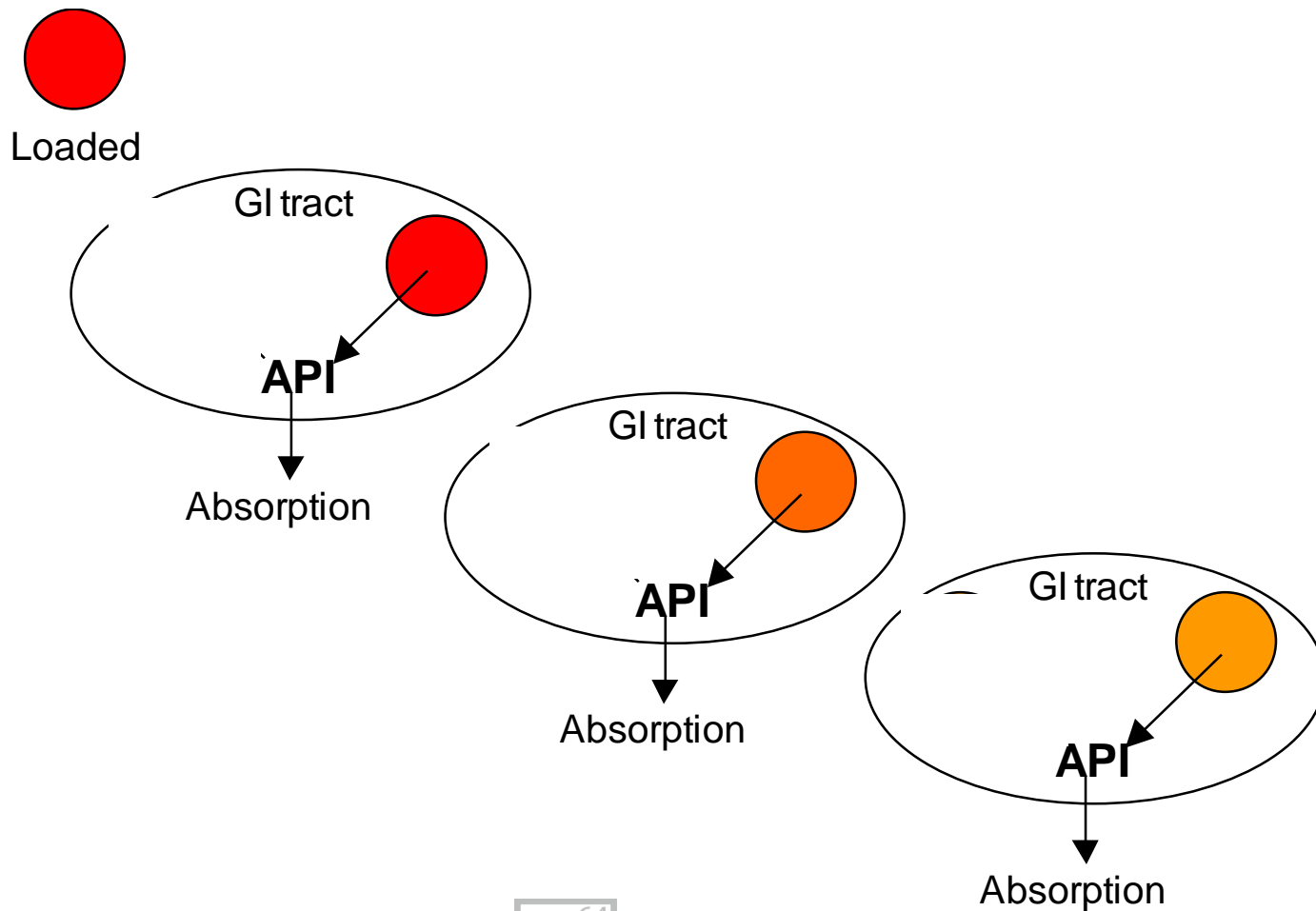
# Controlled Release

Controlled Release



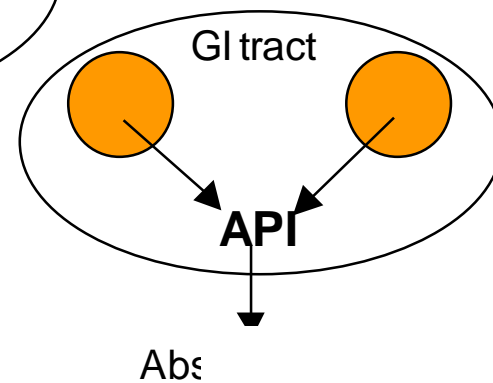
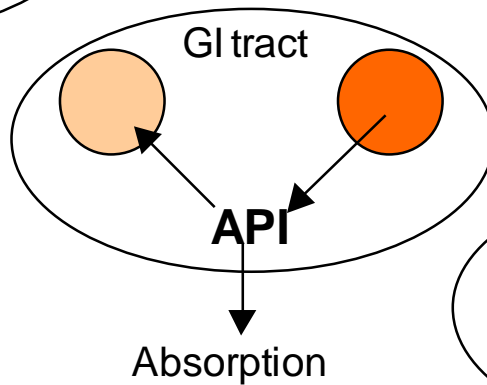
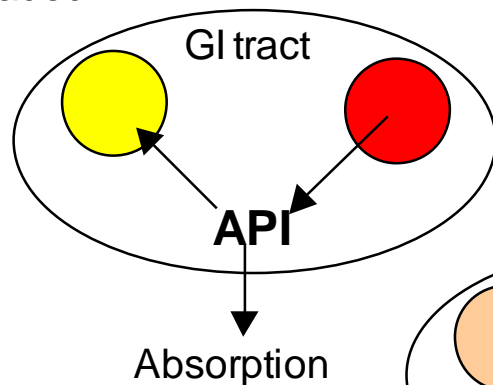
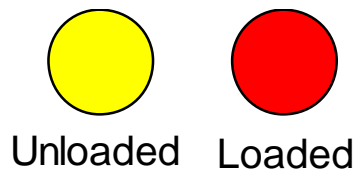


# ER Mechanism I





# ER Mechanism II





# Controlled Release

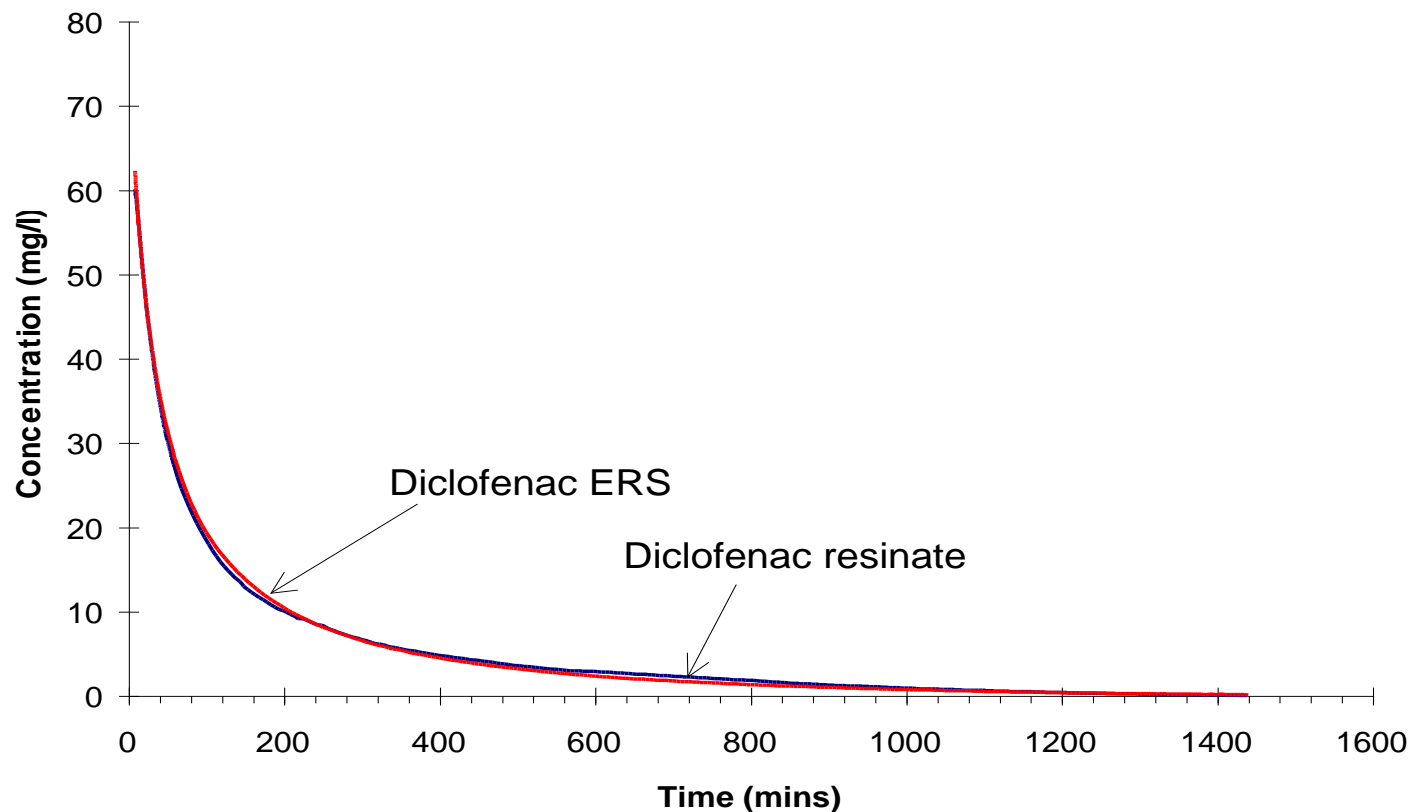
- Formulate resinate and unloaded resin
- Variables:
  - resin/resinate ratio,
  - particle size,
  - drug loading on the resinate
- Resinates can be coated for additional control





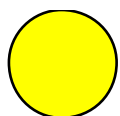
# Extended Release in SIF

## Release from Diclofenac ERS

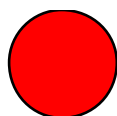




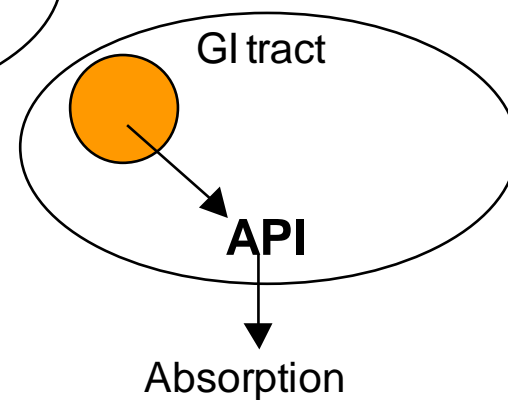
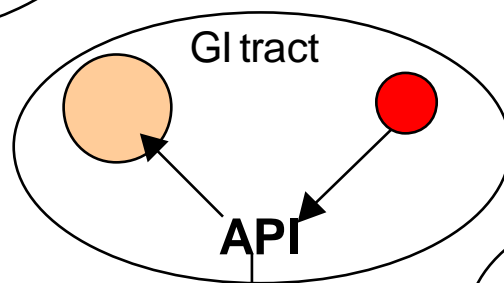
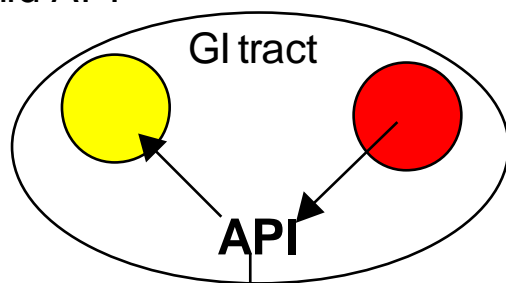
# ER Mechanism III



Resin



Solid API





# Summary of Applications

Ion exchange technology represent a possible solution for:

- Stability
- Poor solubility
- Low melting point
- Deliquescence/hygroscopicity
- Polymorphism
- Taste-masking
- Controlled release

