

Activity of inactive ingredients: Foundations for innovation in drug excipients

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Agenda

1. Inactive ingredients: A brief overview
1. Making inactive ingredients an active area of research
1. Identifying unknown activities of inactive ingredients
2. Ensuring dynamic research into inactive ingredients



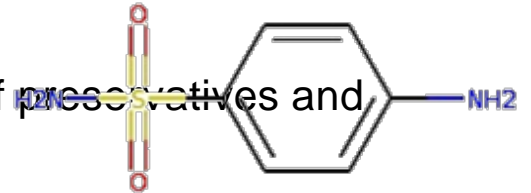
The Word “Excipients”

- The legal/medical definition is:
 - “A **usually** inert substance (as gum arabic, syrup, lanolin, or starch) that forms a vehicle (as for a drug or antigen); especially: one that in the presence of sufficient liquid gives a medicated mixture the adhesive quality needed for the preparation of pills or tablets.”



Excipients, Toxicology, and Regulation

- 1902-1937 Elixir Sulfanilamide incident
 - The original study on the effect of preservatives and coloring agents on digestion/health
 - Treats streptococcus
- 1907 – 7 colors listed as suitable for foods
- 1937 – Killed more than 100 people across 15 states (October, 1937) after request for liquid delivery rather than tablet/powder formulation (June, 1937)
- 1958 – List of 200 substances published as “generally regarded as safe” (GRAS)
- 1958/1960 – The liquid was diethylene glycol
 - Amendments requiring manufacturers to demonstrate safety of food/color additives
 - Commonly found in anti-freeze and incredibly toxic
- 1966 – FDA/NAS/NRC collaborate to evaluate safety of 4,000 drugs used between 1938 and 1962
- 1968 – Dr. E. B. Massengill, claimed no responsibility; the chemist, Harold Watkins, killed himself
- 1969 – President Nixon orders review of GRAS list due to cyclamate toxicity study
 - Charged for mislabeling as “elixir” rather than “solution”
 - Banned in the US today
- 1982 – Red book published (toxicological principles)
 - Led to the 1998 Food, Drug, and Cosmetic Act law
 - No safety checks prior – poison was only bad for business



Little Return for Excipient Development

- New excipient applications treated like new drug applications
- New excipient → higher costs, more development time → less market time → lower profits → NO DEVELOPMENT INTEREST
- FDA only known source of published inactive ingredient database

| New excipients | | | | | | | record_ updated |
|--------------------|-------------------------|------------------------------------|----------------------------------|----------------------------------|-----------------------|--|-----------------|
| .ALP | Initial development | Safety evaluation | Marketing application and launch | Consumer acceptance | Marketing exclusivity | | |
| .ALP | | | | | | | Y |
| .ALP | | | | | | | Y |
| .ALP | | | | | | | Y |
| .ALPHA.-TOCOPHEROL | ORAL | SOLUTION | | H4N855PNZ1 | 1.05 MG/1ML | | Y |
| .ALPHA.-TOCOPHEROL | ORAL | TABLET | | H4N855PNZ1 | 0.7 MG | | Y |
| NDA products | | | | | | | Y |
| .ALP | Preclinical development | Phase I, II an III clinical trials | | Marketing application and launch | Marketing exclusivity | | |
| ACI | | | | | | | |
| SOI | | | | | | | |

Inactive ingredient database, January 2016



FDA CERSI Project

- Project title: Chemoinformatic Tools to Predict the Effects of Excipients in Generic Drugs
- **Goal 1: A community database of FDA excipients**



Simplifying Available Information

- Displays products containing the excipient
- Where available, posts usage over time data
- Classification

The screenshot shows the 'Excipients Browser' website. The top navigation bar includes 'CERSI', 'Excipients', 'Home', 'Molecular', 'Oral', 'Unresolved', and 'Rarely Used'. The main content area is titled 'Excipients Browser' and features a search bar with 'ascorbyl palmitate' entered. Below the search bar is a JSME Molecular Editor. The left sidebar shows a list of excipients with their molecular weights and chemical structures, including '1-AMINOCYCLOHEXANEA...' and 'ACRYLIC ACID-ISOOCTYL A...'. The right sidebar shows a line graph of 'Usages' over time, with data points for 2012-07 and 2012-12. The graph shows a significant peak in usage in 2012-07 and another peak in 2012-12.

Excipients Browser

The Excipients Browser was created with support from a CERSI grant from the FDA. Any errors of omission or commission in the database are the responsibility of the Irwin and Shoichet labs. Please report any error or provide feedback about the database. You must use the database at your own risk. The goal of the project is to curate and disseminate information about excipients, the assumed-inactive substances found in food and drugs. This includes: colors, flavors, stabilizers, bulking and delivery agents, fillers, packaging, and other purposes.

Molecular
Explore small molecule excipients.

Oral
Explore excipients that are administered orally.

Unresolved
Explore non-molecular or ambiguous excipients.

Rarely Used
Explore excipients that are rarely used.

The aim of this project is to encourage innovation in drug delivery and formulation by providing easily accessible and searchable information about these important yet often overlooked substances.

perhaps an error you would like to report. Many pages have a comment section at the bottom, where you can tell us what you think! We also welcome feedback by email to chemistry4biology@gmail.com or on twitter

2012-07 2012-12

■ Usages


<http://excipients.ucsf.bkslab.org>



Further Utilities Added to Excipients Browser

- Cleanup of the molecular page, more data included
- Reorganization by active substance rather than brand
- **Active substance** and **brand** pages for formulation differences

CERSI Excipients Home Molecular Oral

Products Using Citric Acid Monohydrate 

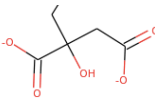
| Substances | Brands (including those substances) |
|---|---|
| 1. Acetaminophen , Caffeine , Aspirin | Citramon |
| 2. Eucalyptus Globulus Leaf , Aconitum Napellus , Pelargonium Sidoides Root , Ipecac , Bryonia Alba Root , Gelsemium Sempervirens Root , Phosphorus | Umcka Fastactives Berry |
| 3. Citric Acid Monohydrate , Potassium Citrate | Cytra-K Crystals , Potassium Citrate Citric Acid Crystals |
| 4. Triclosan | Forest Fresh |
| 5. Carboxymethylcellulose Sodium , Hypromelloses | Genteal Moderate To Severe |

Data provided by [OpenFDA](#)

Excipients (61 Total)

Excipients_name

1. Benzoic Acid



Searchable)

Substances

Status

GRAS-Generally recognized as safe.

13-12014-02015-02016-07

Comments brands on a budget

Creating Opportunities for Innovation

- Linking to available resources (purchasing, analoging,...)

CERSI E ZINC Substances Catalogs Tranches Biological More About

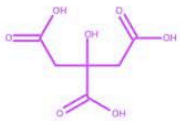
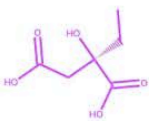
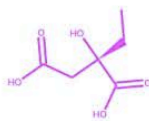
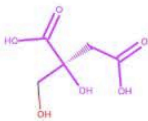
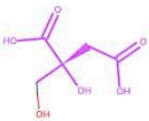
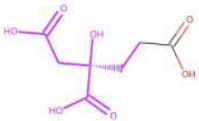
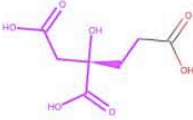
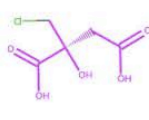
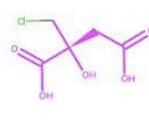
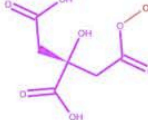
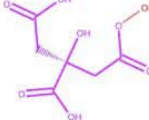
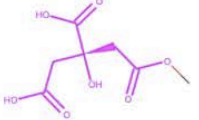
CITR « 1 » Get Total /substances/subsets/for-sale Filters Lookup

Molecu

SMILE

Mwt. 189.0

172 Items Total

| | | | | | |
|--|---|---|--|--|---|
| <p>ZINC895081 Citrate</p>  <p>1.00</p> | <p>ZINC901372 2-Hydroxy-2-Ethylsuccinic Acid</p>  <p>0.74</p> | <p>ZINC901373 2-Hydroxy-2-Ethylsuccinic Acid</p>  <p>0.74</p> | <p>ZINC14455108</p>  <p>0.74</p> | <p>ZINC14455109</p>  <p>0.74</p> | <p>ZINC1532902 Homocitrate</p>  <p>0.70</p> |
| <p>ZINC2018106</p>  <p>0.70</p> | <p>ZINC200539836</p>  <p>0.70</p> | <p>ZINC200539862</p>  <p>0.70</p> | <p>ZINC59819811</p>  <p>0.68</p> | <p>ZINC59819816</p>  <p>0.68</p> | <p>ZINC3593496</p>  <p>0.65</p> |
| <p>ZINC3593497</p> | <p>ZINC14686444</p> | <p>ZINC5855796</p> | <p>ZINC5855952</p> | <p>ZINC221251800</p> | <p>ZINC221251858</p> |

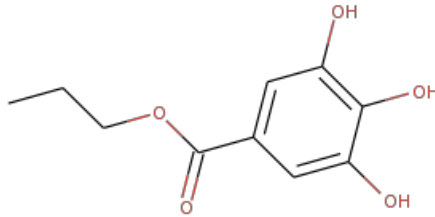
FDA CERSI Project

- Project title: Chemoinformatic Tools to Predict the Effects of Excipients in Generic Drugs
- Goal 1: A community database of FDA excipients
- **Goal 2: To investigate the pharmacology of molecular excipients**

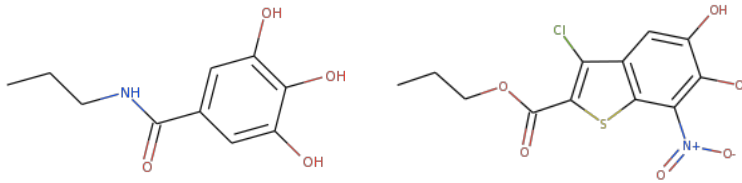


Similarity Ensemble Approach (SEA)

Propyl Gallate (antioxidant)

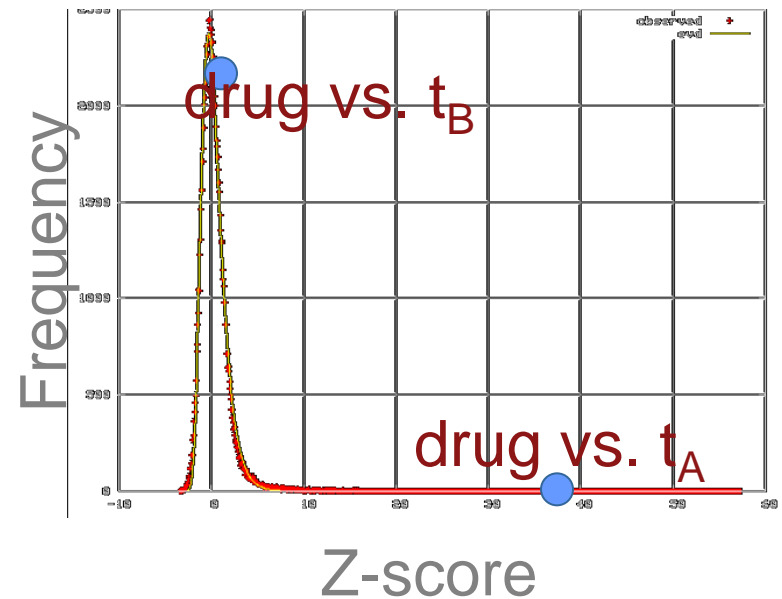


Prediction: COMT
Catechol O-Methyltransferase
Known binders ($IC_{50} < 10\mu M$):



SEA scores: 10^{-10} to 10^{-23}

Statistical model



Confirmed Activity of Excipients

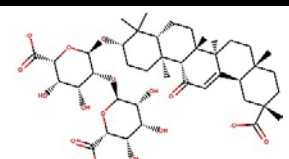
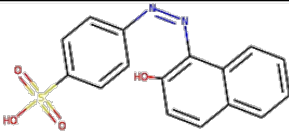
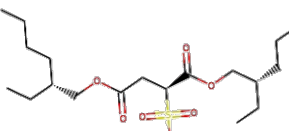
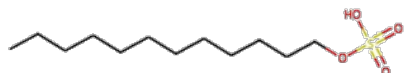
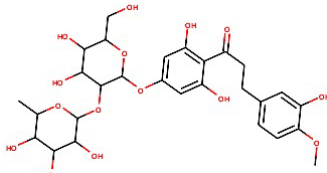
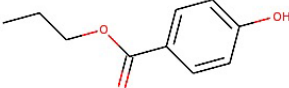
| Excipients | Predictions | Tested | Confirmed | False Positive - Aggregators | Solubility issues |
|------------|-------------|--------|-----------|------------------------------|-------------------|
| 445 | 21565 | 108 | 48 | 2 | 8 |

| Excipient | Structure | Target | SEA Score | IC50 | D/R Curve |
|--|-----------|--|----------------------|---------------------------------|-----------|
| D&C Red No. 3 Acid Orange 20 | | PRMT1 (Protein COMT (Catechol O- methyltransferase 1) containing protein 4) | 7.59E-27 1.41E-25 | 5402 nM 25 uM | |
| D&C Red No. 28 Propylparaben (Phloxine B) | | PRM5 (Protein arginine N-methyltransferase 1) | 2.69E-19 | 66% @ 699 nM 10uM | |
| D&C Brown No. 1 D&C Red No. 28 Propylparaben | | BRD4 (Bromodomain- containing protein 4) SLC22A6 (Solute carrier family 22 member receptor beta) 6/OAT1) | 1.11E-27 2.53E-10 | 46 uM 58% @ 64 nM 10uM | |



Specific Targets: Transporters (OATP2B1)

| | |
|--|---------------|
| Excipients | 445 |
| Predictions | 47 |
| Tested | 18 |
| Confirmed | 9 |
| Total OATP2B1 Inhibitors | 24 identified |
| <u>New OATP2B1 predictions after recycling data</u> | 1/4 hits |
| OATP1B1 predictions/testing | 7/13 hits |

| Excipient | Structure | Ki (uM) |
|-------------------------------|---|---------|
| Glycyrrhizin |  | 165.3 |
| D&C Orange No. 4 |  | 1.9 |
| Docusate Sodium |  | 2.3 |
| Lauryl Sulfate |  | 2.8 |
| Neohesperidin Dihydrochalcone |  | 17.9 |
| Propylparaben |  | 198.2 |



Revitalizing Excipients

- Resurgence in interest regarding excipients and development
 - Enhanced excipients database
 - Potential for “analoging”
- Identified several biological targets for several excipients
 - Enzymes found in the gut
 - Transporters found in the gut





Questions?

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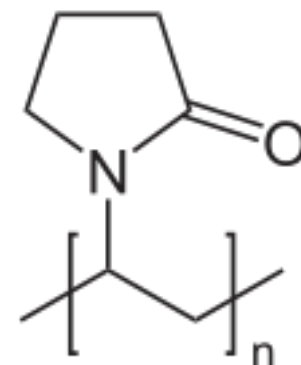
Extra slides



Polymers – described by monomer(s)?

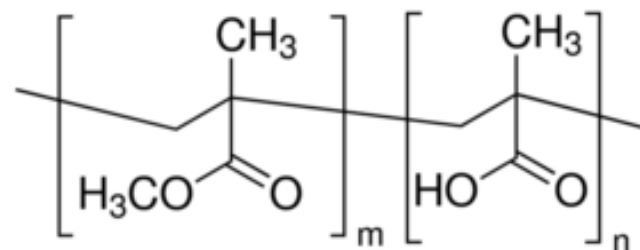
- Povidones

- <http://excipients.ucsf.bkslab.org/excipients/povidones/>
- <https://en.wikipedia.org/wiki/Polyvinylpyrrolidone>



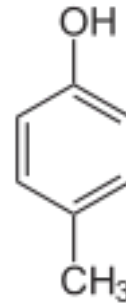
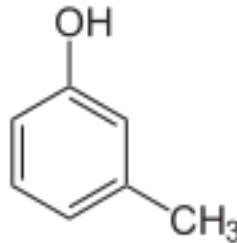
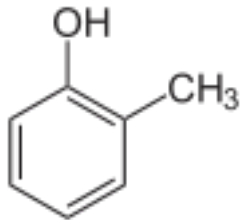
- Methacrylic acid – methyl methacrylate

- http://excipients.ucsf.bkslab.org/excipients/methacrylic_acid_-_methyl_methacrylate_copolymer_11/
- <http://www.sigmaaldrich.com/catalog/product/usp/1396604?lang=en®ion=US>



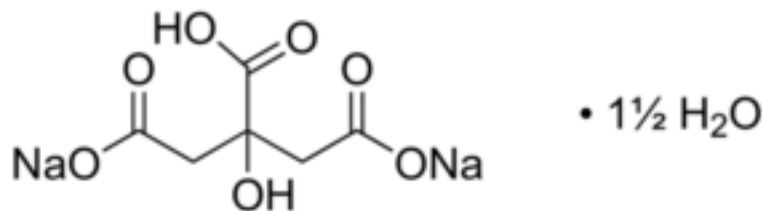
Mixtures – described by each component?

- Cresol
 - <http://excipients.ucsf.bkslab.org/excipients/cresol/>
 - <https://en.wikipedia.org/wiki/Cresol>



Salts – described by neutral form?

- Citrate (Disodium citrate sesquihydrate)
 - http://excipients.ucsf.bkslab.org/excipients/disodium_citrate_sesquihydrate/
 - <http://www.sigmaaldrich.com/catalog/product/aldrich/359084?lang=en®ion=US>



Some will remain non-molecular

- Air
- Flavor banana 8763
- Ink thinner
- Oatmeal
- Soap

