Degradation Plot

Prediction of degradation products and pathways

Incompatibility Report

Client:
Altox

Username:
alany@altox.com.br

Study Number:
Incompatibility_Altox_Metamizole_DegradationPlot_20230918171835

Date:
2023/09/18 - 17:18:38

Program Version:
1.3.3

Molecular Query

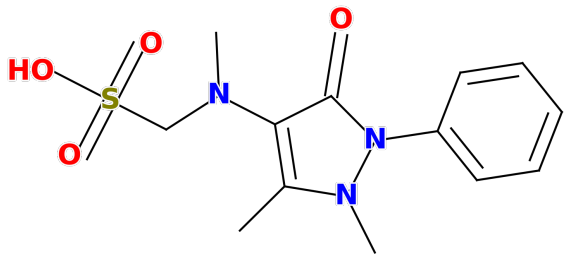
Name:
Metamizole

CAS:
50567-35-6

Exact Mass:
311.09397721

Common Name:
Metamizole

Iupac Name:
[(1,5-dimethyl-3-oxo-2-phenylpyrazol-4-yl)-methylamino]methanesulfonic acid



CID:
3111

SMILES:
CC1N(C)N(C2C=CC=CC=2)C(=O)C=1N(CS(O)(=O)=O)C

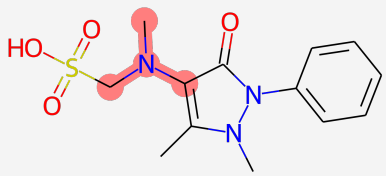
Model Summary

The interaction between API (Active Pharmaceutical Ingredient) and excipients is a crucial aspect of drug formulation. Excipients play an important role in determining the efficacy and safety of a drug by influencing various factors such as solubility, stability, and bioavailability. Understanding the reactivity of functional groups present in API and excipients is essential in predicting their potential interactions.

This report provides an analysis of the interaction between API and excipients through the Degradation Plot software that utilizes a comprehensive knowledge-base about functional groups and their reactivity. The Degradation Plot employs state-of-the-art algorithms to analyze the functional groups present in the API and excipients, and predict their potential interactions based on the known reactivity of these functional groups[1]. The results generated by the software provide valuable insights into the compatibility of the API and excipients and help in identifying potential issues that may arise during formulation. In addition, one of the key features of the software is its ability to predict some potential reaction between API and excipient impurities based on the functional groups present in each. The software considers the known reactivity of functional groups and applies it to the specific API and impurity combinations being analyzed.

Model 1 - Incompatibility study

In this section, we present a visual representation of the molecular structure of the API, with a specific functional group highlighted that has the potential to react with excipients. Accompanied by a detailed description of the reaction, this section provides insight into the chemical interactions that can occur between the API and excipients. Additionally, the risk functional groups present in excipients are also identified and discussed, highlighting their potential to impact the stability and efficacy of the drug. This information is crucial in understanding the potential interactions between API and excipients and in optimizing drug formulation to ensure the desired outcomes are achieved.



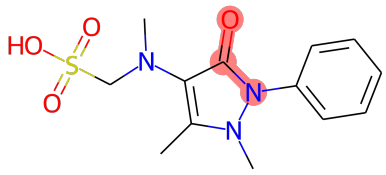
Tertiary amine

Risk groups formula in Excipients: -O-O-

Risk Excipient type: Excipients containing peroxide impurities

Risk Excipients: Hydroxypropyl Cellulose, Lanolin, PEG, Polymethacrylate , Polyoxyethylene Alkyl Ethers, Polyoxyethylene Sorbitan Fatty Acid Esters (Polysorbate 20; Polysorbate 40; Polysorbate 60; Polysorbate 80), Polyoxyethylene Stearates, Polyvinyl Acetate Phthalate, PVP, PVPP

Description: Drug substances that are prone to oxidation can be negatively affected by excipients that contain hydroperoxides, such as PVP, crospovidone, and HPC. When these peroxides come into contact with drugs, they can cause oxidative reactions. For example, they may undergo nucleophilic addition, such as Michael addition, resulting in the formation of an epoxide. They may also participate in electrophilic displacement, leading to the formation of an N-oxide (in the case of tertiary amines), a hydroxylamine (for primary and secondary amines), or a sulfoxide. To minimize the risk of oxidation, it is recommended to avoid using excipients that may contain peroxide impurities when working with drugs that are easily oxidized. However, if this is not possible, it is essential to choose the source of the excipient carefully and monitor the level of peroxide impurities in each batch. This will help ensure the stability and efficacy of the drug.



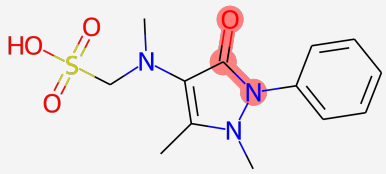
Amide

Risk groups formula in Excipients: -COOH; ArOH; -SO3H

Risk Excipient type: Acidic excipients

Risk Excipients: Ascorbic Acid, Boric acid, Carbomer, Citric Acid, Edetate Disodium, Gelatin, HPMCAS, Monobasic sodium phosphate, Palmitic Acid, Phenol, Polymethacrylate , Shellac, Stearic Acid, Succinic Acid, Tartaric Acid, Thymol, Vanillin

Description: Amides such as carbonamides, sulfamides, and phosphoramides are prone to slow hydrolysis when exposed to acidic or alkaline conditions and moisture, even at low temperatures. Hence, it is crucial to monitor the stability of these compounds and steer clear of acidic or alkaline substances, as well as strong hygroscopic materials.



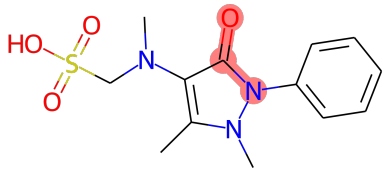
Amide

Risk groups formula in Excipients: -NH2; RNC=NNR'

Risk Excipient type: Alkaline excipients

Risk Excipients: Bentonite, Calcium Carbonate, Calcium Oxide, Calcium Phosphate, Calcium Phosphate, Dibasic, Calcium Phosphate, Dibasic Anhydrous, Calcium Phosphate, Dibasic Dihydrate, Magnesium Carbonate, Magnesium Hydroxide, Magnesium Oxide, Magnesium Silicate, Magnesium Stearate, Potassium Carbonate, Sodium Bicarbonate, Sodium Bisulfite, Sodium Carbonate, Sodium Starch Glycolate, Zinc Stearate

Description: Amides such as carbonamides, sulfamides, and phosphoramides are prone to slow hydrolysis when exposed to acidic or alkaline conditions and moisture, even at low temperatures. Hence, it is crucial to monitor the stability of these compounds and steer clear of acidic or alkaline substances, as well as strong hygroscopic materials.



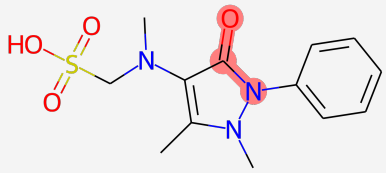
Amide

Risk groups formula in Excipients: R-OH

Risk Excipient type: Excipients with strong hygroscopicity

Risk Excipients: Acacia, Attapulgite, Bentonite, Calcium Oxide, Calcium Sulfate, Chitosan, Croscarmellose Sodium, Disodium Edetate, HPMC, HPMCAS, Hydroxyethyl Cellulose, Hydroxypropyl Cellulose, Hypromellose Phthalate, Lanolin, Magnesium Oxide, Microcrystalline Cellulose, PEG, Polyoxyethylene Sorbitan Fatty Acid Esters (Polysorbate 20; Polysorbate 40; Polysorbate 60; Polysorbate 80), Potassium Carbonate, PVP, PVPP, Silicon Dioxide, Sodium Carbonate, Sodium Carboxymethylcellulose, Sodium Chloride, Sodium Phosphate, Dibasic, Sorbitol, Starch

Description: Amides such as carbonamides, sulfamides, and phosphoramides are prone to slow hydrolysis when exposed to acidic or alkaline conditions and moisture, even at low temperatures. Hence, it is crucial to monitor the stability of these compounds and steer clear of acidic or alkaline substances, as well as strong hygroscopic materials.



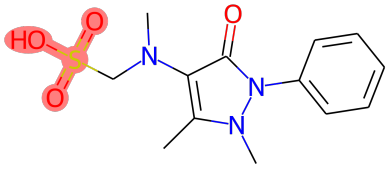
Amide

Risk groups formula in Excipients: HCOOH

Risk Excipient type: Excipients containing organic acid impurities

Risk Excipients: Croscarmellose Sodium, HPMC, Hydroxypropyl Cellulose, Lactose, Microcrystalline Cellulose, PEG, Polyoxyethylene Sorbitan Fatty Acid Esters (Polysorbate 20; Polysorbate 40; Polysorbate 60; Polysorbate 80), Propylene Glycol, PVP, PVPP, Sodium Starch Glycolate, Starch

Description: Excipients used in drug formulation may contain trace amounts of organic acid impurities such as formic acid, acetic acid, etc. Examples of such excipients include Hydroxypropyl methylcellulose, Polyvinyl alcohol cellulose acetate butyrate, Sodium starch glycolate and Polyvinyl alcohol. These impurities can interact with the amino or hydroxyl groups in drugs and form high levels of degradation products. Alcohol-containing drugs can also form esters with organic acids or undergo transesterification with esters. To minimize the risk of degradation, it is advisable to avoid using excipients that may contain organic acid impurities as much as possible. If this is not possible, the source of the excipient should be carefully chosen and the level of organic acid impurities in each batch should be monitored closely. This can help ensure the stability and efficacy of the drug.



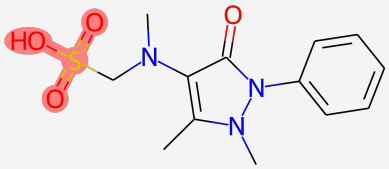
Sulfonyl hydroxide

Risk groups formula in Excipients: -NH2; RNC=NNR'

Risk Excipient type: Alkaline excipients

Risk Excipients: Bentonite, Calcium Carbonate, Calcium Oxide, Calcium Phosphate, Calcium Phosphate, Dibasic, Calcium Phosphate, Dibasic Anhydrous, Calcium Phosphate, Dibasic Dihydrate, Magnesium Carbonate, Magnesium Hydroxide, Magnesium Oxide, Magnesium Silicate, Magnesium Stearate, Potassium Carbonate, Sodium Bicarbonate, Sodium Bisulfite, Sodium Carbonate, Sodium Starch Glycolate, Zinc Stearate

Description: It's important to consider the pH of drugs that contain sulfonic acid groups, as they are highly acidic. Mixing these drugs with basic excipients can result in acid-base reactions that produce salts, potentially impacting the stability, form, efficacy and ADME properties of the drug.



Sulfonyl hydroxide

Risk groups formula in Excipients:

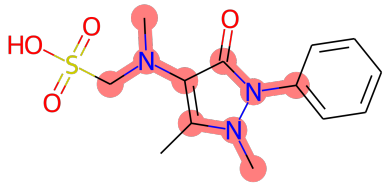
Risk Excipient type: Starch

Risk Excipients: Starch

Description: Starch should not be used as an excipient for drugs that have strong acidic groups, such as carboxyl or sulfonic acid groups. This is because the strong acidity of the drug can cause the gelatinization of the starch, disrupting the integrity of the starch molecules and altering their physical properties. To maintain the stability and desired properties of the formulation, it is advisable to choose alternative excipients for drugs with strong acidic groups.

Risk groups formula in Excipients: -NO2; RNO

Risk Excipient type: Excipients containing Nitrite or Nitrate impurities



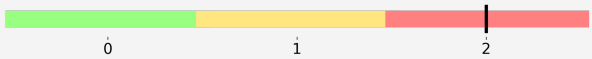
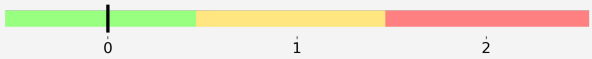
Nitrogen atom

Risk Excipients: Croscarmellose Sodium, Lactose, Microcrystalline Cellulose, PVP, PVPP, Sodium Starch Glycolate, Starch

Description: Nitrogen-based pharmaceutical compounds have the potential to generate N-nitroso compounds (NOCs) as degradation products due to interactions with nitrite or nitrate impurities present in excipients such as sodium starch glycolate, croscarmellose sodium, pre-gelatinized starch, PVP, PVPP, lactose, microcrystalline cellulose, and starch. To mitigate the risk of NOC formation, it is advisable to avoid excipients that may contain nitrite or nitrate impurities. If their use is unavoidable, it's crucial to carefully choose the source of excipients and closely monitor the nitrite or nitrate impurities present in each batch.

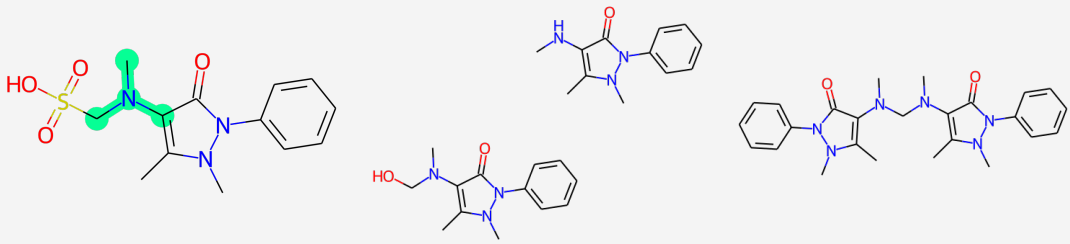
Conclusion - Risks

This section presents a prediction of the potential risk between a specific API and excipient. The prediction is made by evaluating the number of possible interactions between a specific functional group of the API and each excipient in our knowledge base. If no interactions are detected, the risk is categorized as low; if one interaction is detected, the risk is categorized as medium; and if two or more interactions are detected, the risk is categorized as high.

Excipients	Risk
PVPP, PVP, Sodium Starch Glycolate, Starch, Hydroxypropyl Cellulose, Croscarmellose Sodium, Polyoxyethylene Sorbitan Fatty Acid Esters (Polysorbate 20; Polysorbate 40; Polysorbate 60; Polysorbate 80), Sodium Carbonate, PEG, Microcrystalline Cellulose, Magnesium Oxide, Potassium Carbonate, Calcium Oxide, Bentonite, Calcium Carbonate, Calcium Phosphate, Magnesium Stearate, Magnesium Silicate, Magnesium Hydroxide, Magnesium Carbonate, Lanolin, Lactose, Calcium Phosphate, Dibasic, Polymethacrylate , Sodium Bicarbonate, HPMCAS, HPMC, Calcium Phosphate, Dibasic Anhydrous, Zinc Stearate, Calcium Phosphate, Dibasic Dihydrate, Sodium Bisulfite	 High risk
Silicon Dioxide, Shellac, Vanillin, Tartaric Acid, Ascorbic Acid, Succinic Acid, Sodium Chloride, Propylene Glycol, Sodium Phosphate, Dibasic, Sorbitol, Thymol, Stearic Acid, Acacia, Sodium Carboxymethylcellulose, Polyvinyl Acetate Phthalate, Edetate Disodium, Polyoxyethylene Stearates, Attapulgite, Boric acid, Calcium Sulfate, Carbomer, Citric Acid, Disodium Edetate, Chitosan, Gelatin, Hydroxyethyl Cellulose, Hypromellose Phthalate, Monobasic sodium phosphate, Palmitic Acid, Phenol, Polyoxyethylene Alkyl Ethers	 Medium risk
Sodium Ascorbate, Meglumine, Methylparaben, Phenylmercuric Acetate, Polacrilin Potassium, Potassium sorbate, Propylparaben, Propylparaben Sodium, Thimerosal, Sodium Benzoate, Sodium Citrate Dihydrate, Sodium Lauryl Lulfate, Sodium Metabisulfite, Sodium Stearate, Sodium Stearyl Fumarate, Sucrose, Maltose, Vitamin E Polyethylene Glycol Succinate, Mannitol, Dextrates, Lactitol, Chlorocresol, Aspartame, Calcium Alginate, Calcium Citrate, Calcium Disodiumedetate, Calcium Stearate, Cellulose, Cellulose Acetate, Cholesterol, Hard Fat, Cresol, Cyclodextrin, Dextrose, Docusate Sodium, Glucose, Glyceryl Monostearate, Glyceryl Palmitostearate, Xylitol	 Low risk

Model 2 - Reactions

This section provides an overview of the potential chemical reactions between the API and impurities present in excipients. The molecular structure of the API, impurity, and possible reaction product are displayed, along with a description of the interaction and identification of the excipients that may contain the reactive impurity.



Molecule	Impurity	Products
	Formaldehyde	

Description: The compounds MAA and HMA are in the reactant column.

Metamizol (or Dipyrone) can be hydrolyzed to form the compounds HMA, MAA and releasing formaldehyde and sulfite in the medium. HMA can react again with MAA in the presence of formaldehyde, leading to dimerization. All of these reactions are reversible; however, the reversible reaction from MAA and HMA to dimeric product is slower than that from MAA to HMA; at low concentrations the formation of dimeric product can be very low to negligible.

Excipients: Sodium starch glycolate, Polyvinyl pyrrolidone, Polyethylene glycols, Starch, Cellulose, Microcrystalline cellulose, HPMC, Fructose, Lactose, Sucrose, Glucose, Mannose

Incompatibility Graph

The incompatibility graph is created by clustering molecules from our experimental incompatibility database based on their similarity using a minimum spanning tree (MSP)[2]. This means that molecules that are closely connected in the graph have fragments or features considered similar to each other (nearest neighbors), while molecules that are farther apart are less similar.

Interpretation

In practice, by screening known molecules with similar structures and features to your target molecule, you will get knowledge about potential incompatibilities and/or compatibility with excipients. The inference assumes that similar molecules or neighbors (close to each other in chemical space) show similar properties (compatibility/incompatibility profile).

If three or more close neighbors have the same excipients considered incompatible or compatible, you have preliminary evidence of potentially useful or evitable excipients.

To interact with the graph, you can do the following:

- **Hover your mouse cursor over the nodes** to see the chemical structure of the molecules (your target molecule is highlighted in red) and the most similar neighbors are close to your target.
- **Click on the nodes** to view the neighbor's name and experimental incompatibility information.
- **Double-click on the nodes** to open a new page with the molecule image and descriptors. Make sure to keep the filter set to "MyMolecule" on the new page.
- Additionally, the graph allows for highlighting molecules based on specific descriptors. Click on the lower right corner "Mymolecule", choose a descriptor, and the nodes in the graph change color gradient based on the value of these descriptors.

Parameters

Similarity: locality-sensitive hashing (LSH forest) with ECFP fingerprint

Descriptors:

TPSA - The polar surface area (PSA) or topological polar surface area (TPSA) of a molecule is defined as the surface sum over all polar atoms or molecules, primarily oxygen and nitrogen, also including their attached hydrogen atoms.

LogP - LogP, or octanol-water partition coefficient, is a measure of how hydrophilic or hydrophobic a molecule is. It indicates how readily an analyte will partition between an aqueous and organic phase. A more polar, hydrophilic compound will have a lower logP (the value can even be negative), and prefer to “reside” in the aqueous phase. More non-polar, hydrophobic compounds will have a higher logP, and will partition into an organic phase. Typical values range from -3 (polar) to 7 (non-polar).

Gasteiger-Charge - The contribution to the atomic charge on the n-th step of iteration of charge. - electronegativity of n-th orbital on i-th atom.

Number of H acceptors - Acceptor count = the sum of the acceptor atoms. An acceptor atom always has a lone electron pair/lone electron pairs that is capable of establishing a H bond.

Number of H donors - Donor sites = the sum of the H atoms connected to the donor atoms.

Mass - Exact weight

The image below shows the QRCode with the link to the interactive graph of incompatibility.

Also available here

References

1. Wang, N., Sun, H., Dong, J., & Ouyang, D. (2021). PharmDE: A new expert system for drug-excipient compatibility evaluation. International Journal of Pharmaceutics, 607, 120962

2. Probst, D., Reymond, JL. Visualization of very large high-dimensional data sets as minimum spanning trees. J Cheminform 12, 12 (2020). https://doi.org/10.1186/s13321-020-0416-x