



## REVIEW ARTICLE

# Prediction of excipient-excipient incompatibility: A latent threat to pharmaceutical product development

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### ABSTRACT

The importance of pharmaceutical excipients in the creation of any dosage form is critical. These excipients are occasionally to blame for product underperformance and dosage form deterioration. Product deterioration and underperformance could be attributed to incompatibilities between drug and excipient or sometimes excipient and excipient either due to the presence of reactive impurities in the excipients or a reaction between the functional groups present on the excipients. Although the drug and excipient incompatibilities are monitored and reported, excipient-excipient incompatibilities are overlooked due to a paucity of the literature. Pharmaceutical companies used to work in a controlled environment (compatibility tests between excipients to determine the best excipients for dosage form creation) and utilize mitigation measures to suppress any incompatibilities between excipients when necessary. These tactics take time and money to implement, and they increase the cost of developing a dosage form. However, the primary goal of this review is to highlight some of the most prevalent excipient-excipient incompatibilities that can occur during dosage form development, possible incompatibility reactions, as well as a potential method for predicting excipient-excipient incompatibilities based on structural information. The structure incompatibility relationship strategy to forecast incompatibilities between diverse excipients is an idea based on the reactivity of pharmaceutical excipients, and it might be a useful tool in reducing the time, cost, and product failures during the product development due to excipient-excipient incompatibilities.

**KEY WORDS:** Excipient-excipient incompatibility, Reactive impurities, Functional groups, Degradation reactions, Quantitative structure-property relationship

### INTRODUCTION

According to International Pharmaceutical Excipients Council, Excipients are compounds other than the active pharmaceutical ingredient (API) that have been tested for safety and are included in drug delivery systems on purpose. They are frequently used to preserve, support, or improve stability, bioavailability, or patient acceptance, as well as to aid in product identification and improve other qualities that boost overall medication safety, efficacy, or delivery during storage or usage.<sup>[1]</sup> These excipients are occasionally the cause of product underperformance and failure. This flaw may be traced back to the interactions between API and excipient, excipient and excipient,

API and package, and excipient and package. Reactive impurities in the excipients such as (peroxides, aldehydes, reducing sugars, organic acids, nitrates, and nitrites),<sup>[2]</sup> API,<sup>[3]</sup> and packaging material<sup>[4]</sup> are usually the cause of these interactions. Even at low quantities, these reactive contaminants can cause product deterioration and stability concerns, compromising product quality and patient safety. The chemical functional groups on the API, excipients, and packaging materials carry out the

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degradation reactions.<sup>[5]</sup> A number of API and excipient interactions have been documented, but less attention has been paid to the excipient-excipient interaction, which can also contribute to stability issues and eventually product failure. The interaction of Crosscarmellose sodium with basic excipients can delay tablet dissolution property of an acid labile drug<sup>[6]</sup> and magnesium stearate can alter rate controlling function of Eudragit RS and RL (thickening or coagulation),<sup>[7]</sup> or the efficacy of disintegrants such as Crosscarmellose sodium may be slightly decreased in tablet formulations made by either the wet-granulation or direct-compression method that contain hygroscopic excipients such as sorbitol.<sup>[8]</sup> Excipient incompatibilities are assumed to be caused by the reactive impurities in the excipients, which may be accompanied by one of the degradation processes such as hydrolysis, oxidation, photodegradation, micellization, complexation, decarboxylation, and so on.

To avoid such incompatibilities in finished product, compatibility studies of excipients with other excipients are carried out to find out best combination of excipients which are compatible with each other<sup>[9]</sup> or the QbD approach may help before dosage form development. Although these approaches have been documented in the literature, in this article, we focus on quantitative structure property relationship (QSPR) approach that can be utilized in predicting excipient-excipient interactions. It is a quantitative aspect to Structural Property Relationship in which we build a mathematical relationship between a molecule's property and the function of its descriptors.<sup>[10]</sup>

### EXCIPIENT-EXCIPIENT INCOMPATIBILITY

Excipients are added to an API to help with the development process, whether it is to increase bulk, provide stability, improve bioavailability, or deliver the medication to the right place. There are permissible limits to be used in the formulation, beyond these limits, they will produce effects which may be harmful to the human body or may start interacting with each other leading to incompatibilities. These incompatibilities are of major concern in terms of product shelf life, therapeutic response, and patient safety. Excipient-Excipient incompatibilities can be physical, such as changing the rate of dissolving or the uniformity of dose of a solid formulation, or chemical, such as degradant production caused by impurities in excipients or functional groups on excipients. Degradation processes can be identified as oxidation, hydrolysis, auto oxidation, racemization, and photolysis. Although drug-excipient incompatibility receives more attention, caution should be exercised when selecting excipients for formulation development rather than relying on mitigation strategies such as use of antioxidants, nitrogen blanketing, and scavengers. Whether it is an API-excipient interaction or an excipient-excipient interaction, the ultimate consequence

is product underperformance. Table 1 depicts some of the excipient-excipient incompatibilities.<sup>[8]</sup>

### CAUSE OF INCOMPATIBILITIES

The excipients are manufactured in accordance with cGMP and still it is a complicated process that incorporates raw materials, solvents, reaction initiators, and other processing aids. These excipients may be manufactured via grinding, acid hydrolysis, and chain reactions. As a consequence, they may contain impurities such as raw material impurities, residual solvents, reaction initiators (for example, peroxides in polymer production), and even metallic catalysts. Although the manufacturer keeps these contaminants under tight control and below acceptable levels, during storage and transit, the amount of contaminants might rise to the point where they interact with functional groups of an API or other excipients, causing different degradation reactions. Alternatively, certain excipients may include bound water that, when released, might initiate a hydrolysis process and presence of aldehydes and peroxides, may causing a substance to oxidize. Most common chemical functional groups such as esters, amides, hydroxyl groups, and amines have been found to induce incompatibility in excipients. Table 2 depicts common impurities, their method of detection, and their mitigation strategies.

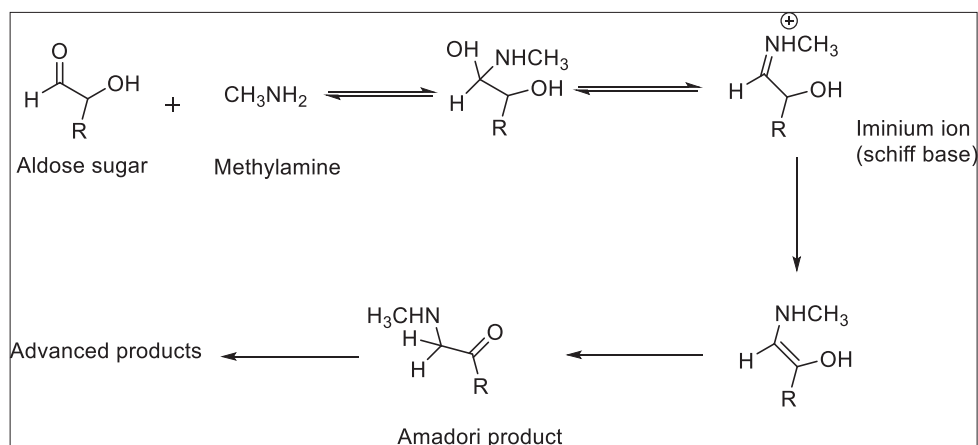
### INCOMPATIBILITIES CAUSED BY REACTIVE IMPURITIES

#### Millard's reaction

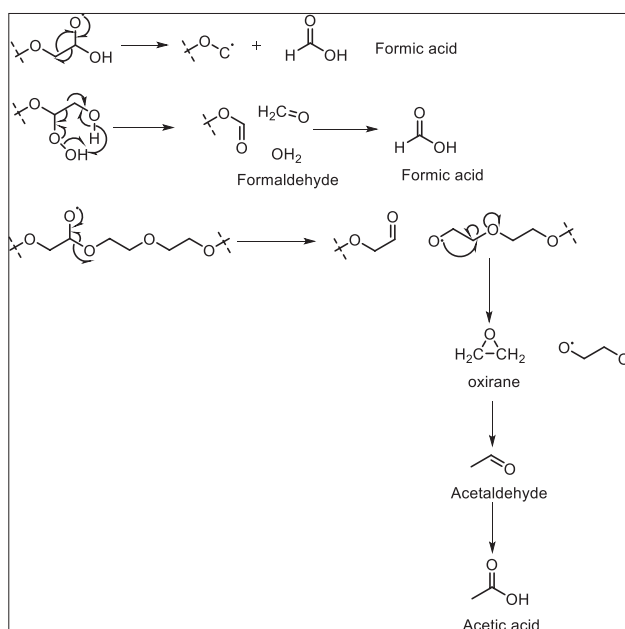
This is a unique reaction that occurs when carbonyl compounds, particularly reducing sugars like lactose, interact with substances that contain free amino groups, such as proteins, amines, and amino acids resulting in brown discoloration of the compound. When pharmaceutical scientists noticed the dark staining of an API product containing a reducing sugar as a diluents (lactose) in the presence of the lubricant (magnesium stearate), the reaction became a hot issue in pharmaceutical sciences. The brown staining was a physical sign of the drug's degradation. Such reaction is proposed to proceed by the addition of amine compound to the exposed site of the reducing sugar to generate an iminium ion intermediate, which can either be modified by ring formation to form a glycosamine compound or deprotonated to form the enol form of the Amadori rearrangement product. Antidepressant drug fluoxetine is prone to Millard's reaction in the presence of lactose.<sup>[23]</sup> Reaction of an aldose sugar with amine is depicted in Figure 1.

#### Oxidation

One of the main process responsible for the pharmaceutical dosage forms instability is oxidation. The presence of contaminants in excipients (peroxides, Aldehydes, and metals),



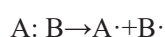
**Figure 1:** Reaction of aldose sugar with primary amine results in the formation of amadori product.



**Figure 2:** Auto-oxidation of Polyethylene glycol.

integration of ambient oxygen into the formulation, or the existence of hydrogen and hydroxyl ion species in an API can cause this reaction. When an API or an excipient loses electrons and acquires electronegative atoms or radicals, (when oxygen is added and hydrogen is removed), it is said to be oxidized.

Pharmaceuticals are more sensitive to auto oxidation, a free radical chain reaction triggered by molecular oxygen can result in free radical formation by homolytic fission of a covalent bond in such a way that each atom or group retains one of the parent bond's electrons

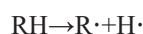


The radicals formed in autoxidation are unstable so they take electrons from other substances in the formulation

and thereby lead to oxidation of the formulation. The autoxidation consists of three steps, namely, initiation, propagation, and termination and Figure 2 depicts the auto-oxidation mechanism of PEG.<sup>[24]</sup>

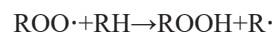
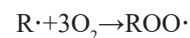
### Initiation

It is the first step in chain reaction of oxidation and is catalyzed by molecular oxygen, heat, light, metals, and other secondary substrates. This involves the generation of free radicals which further carry out different type of reactions with other substances. Initiation can be caused by electron transfer processes, light-induced events, or metal catalysis cleaving a weak link in a polymeric excipient such as polysorbates and polyethylene glycols.



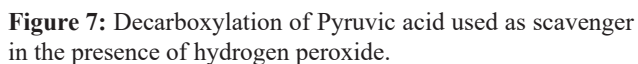
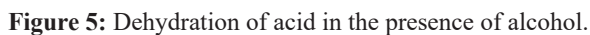
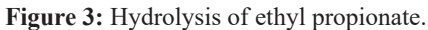
### Propagation

With the help of diffusion limited molecular oxygen species, the substrate-radical produced during the initiation process will change to a peroxy radical, and these peroxy radicals can either add or extract hydrogen atoms to alkenes to perpetuate an oxidation chain reaction. A hydro peroxide of the drug or an excipient, which might function as an oxidant for the drug, is one of the by-products of this chain reaction.



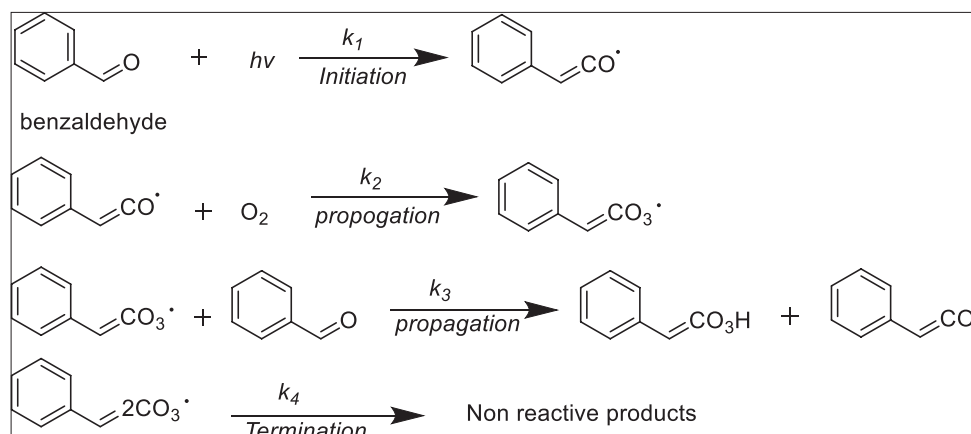
### Termination

Termination is used to render radicals non-reactive or to stop the chain reaction from continuing. In this reaction, two radicals react with one other, with one becoming oxidized and the other becoming reduced. It entails the

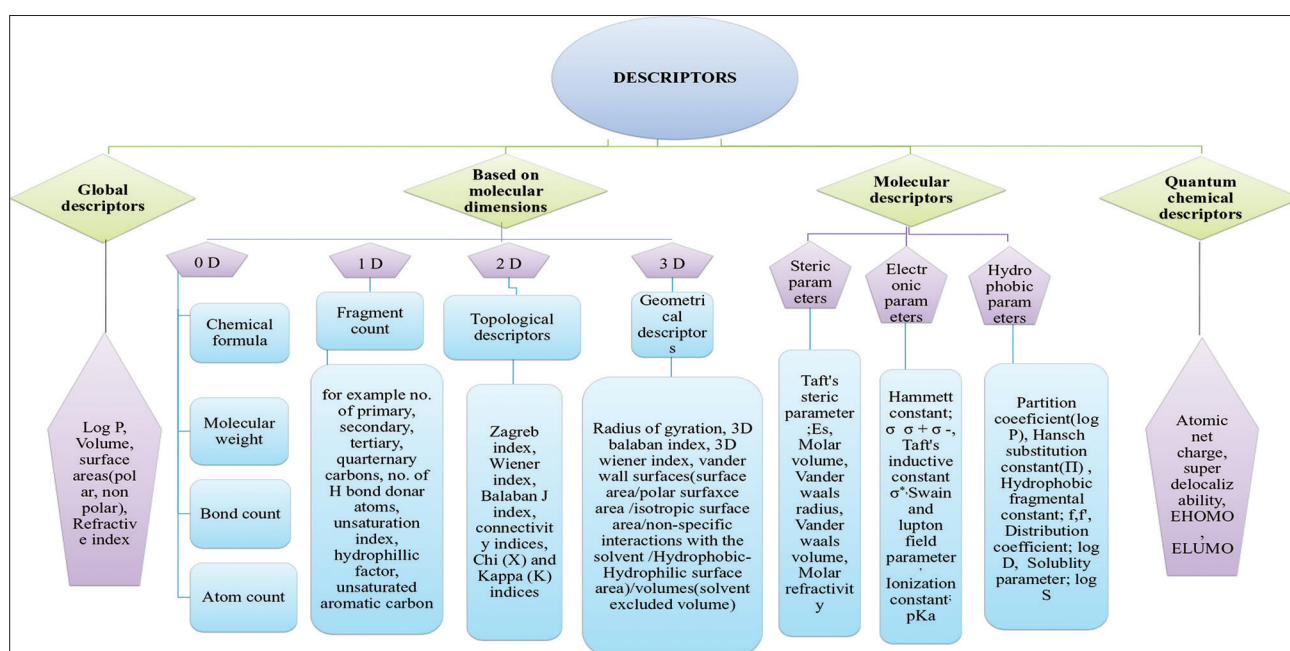


## Hydrolysis

Raw materials are required for any product development in the pharmaceutical sector. These basic materials are created



**Figure 8:** Photolytic degradation of benzaldehyde in presence of light and oxygen.



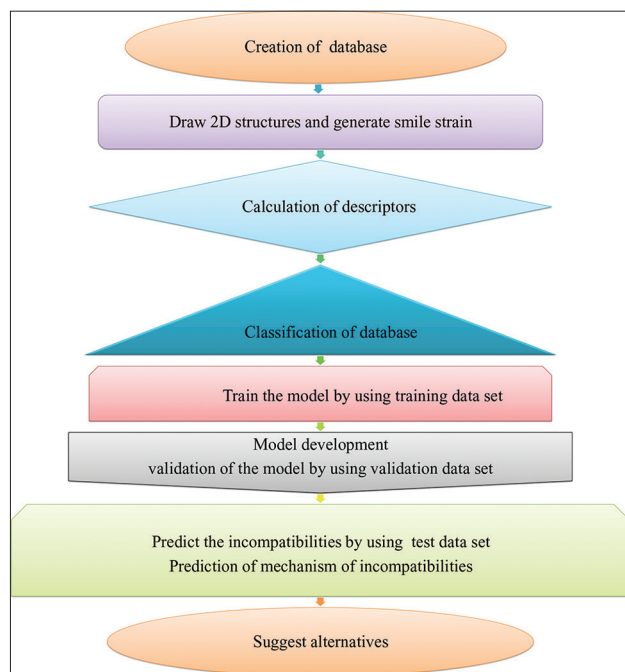
**Figure 9:** Different descriptors that can be used for establishing structure incompatibility relationship.

by a variety of synthetic or semi-synthetic methods that need the use of a solvent to complete the process. Solvents can be either aqueous or non-aqueous but aqueous solvent (water) is the preferred solvent for every manufacturer due to its availability, flexibility, compatibility, and cost. Although water is removed from the raw material once it has been fully synthesized, some part of it remains in the form of unbound and bound moisture despite the stringent control strategy by the vendor, which can carry out the hydrolysis reaction when released in tiny amounts in the final formulation. Or even during the pharmaceutical product, development water is employed as a solvent (in binder solutions, in granulations, coating solutions, or parenteral formulations) which can react with the functional groups such as amide and ester groups of the API or excipients leading to degradation of the drug product.<sup>[25,26]</sup> The chemistry involved in hydrolysis of any molecule is determined by

the reactivity of an electrophilic carbon atom (usually a carbonyl carbon) combined with a freely moveable leaving group. Depending on whether acidic or basic catalysts are present, the electrophilicity of the carbonyl group (or other centre) to which the leaving group is connected plays a role in modifying the reaction.<sup>[27]</sup> An ester/amide bond is found in many APIs and the excipients. These ester/amide compounds are primarily hydrolyzed through nucleophilic attack of hydroxide ion or water at the ester group/amide group. The kind of group present on the drug substance or excipient is linked to the nucleophilic attack, with electron-withdrawing groups enhancing hydrolysis and electron-donating groups inhibiting hydrolysis. However, because the carbonyl carbon of the amide bond is less electrophilic and the leaving group, an amine, is a poorer leaving group, amide bonds are less susceptible to hydrolysis than ester bonds. Decomposition rate is influenced also by the steric variables;

the larger the group, the slower the decomposition rate, and vice versa. Aspirin, atropine, scopolamine, hydrocortisone sodium succinate, methylprednisolone sodium, cocaine, and pilocarpine are some of the ester-containing medications sensitive to hydrolysis. Non-polymeric excipients such as

ethyl propionate [Figure 3], aspartame [Figure 4], benzyl benzoate, glyceryl monostearate, parabens, palmitates, lecithin, and polymeric excipients such as cellulose phthalate, cellulose acetate, hydroxypropyl cellulose, PLGA, and methylcellulose are prone to hydrolysis.



**Figure 10:** Key steps involved in the development of structure incompatibility relationship model.

## Dehydration

The reaction in which an API or excipient loses its water molecule. An example of dehydration of carboxylic acid and ethanol with formation of ester is shown in Figure 5. In the case of glucose<sup>[29]</sup> and lactose interaction,<sup>[30]</sup> dehydration leads to the formation of 5-(Hydroxy methyl) furfural shown in Figure 6.

## Decarboxylation

Excipients and APIs containing carboxylic acid group in their structures are prone to decarboxylation reaction.<sup>[31]</sup> Reaction of pyruvic acid in presence of hydrogen peroxide yields acetic acid and carbon dioxide as end product as shown in Figure 7. Pyruvic acid is used as a hydrogen peroxide scavenger in formulations.<sup>[32]</sup>

## Photolysis

Absorption of photons of infrared,<sup>[33]</sup> visible, and ultraviolet light,<sup>[34]</sup> as well as other kinds of electromagnetic radiation,

**Table 1:** Some examples of excipient- excipient incompatibilities compiled from literature

| Name of the excipient                                                                 | Incompatible excipient                           | Remarks/outcome                                                                                                                                                 |
|---------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Aspartame                                                                             | Magnesium stearate and dibasic calcium phosphate | Magnesium stearate may elevate pH                                                                                                                               |
| Benzoic acid                                                                          | Kaolin                                           | The interaction of benzoic acid with kaolin may reduce benzoic acid's preservative activity.                                                                    |
| Benzyl alcohol                                                                        | Methyl cellulose and polysorbate 80              | Polysorbate 80 reduces the antimicrobial activity of benzyl alcohol                                                                                             |
| Carboxymethyl cellulose sodium                                                        | Gelatin and pectin                               | Complex or coacervate formation                                                                                                                                 |
| Citric acid monohydrate                                                               | Sucrose                                          | Citric acid can cause precipitation of sucrose from the syrups                                                                                                  |
| Crosscarmellose sodium                                                                | Basic excipients and Sorbitol                    | Dissolution slow- down of a tablet due to interaction of CCS with basic excipients.<br>Sorbitol reduces disintegrant efficiency of CCS in tablet formulations . |
| Glycerin                                                                              | Zinc oxide and basic bismuth nitrate             | Black discoloration of glycerin                                                                                                                                 |
| HPC                                                                                   | Parabens and anionic polymers                    | Increase in viscosity of HPC due to anionic polymers                                                                                                            |
| Low substituted HPC                                                                   | Alkaline substances                              | Increase in disintegration time of a tablet                                                                                                                     |
| Hypromellose phthalate                                                                | MCC and CMC calcium                              | Splitting of film coatings                                                                                                                                      |
| Magnesium oxide                                                                       | Eudragit RS                                      | Retard drug release                                                                                                                                             |
| Mannitol                                                                              | Xylitol, potassium chloride and sodium chloride  | Salted out by KCl and NaCl                                                                                                                                      |
| Eudragit L 30 D, RL 30 D, L 100-55, and RS 30 D<br>Eastacryl 30D, Kollicoat MAE 30 D, | Incompatible with magnesium stearate             | Magnesium oxide generated by the magnesium stearate may affect the Ph                                                                                           |

**Table 2:** Incompatibilities due to impurities present in excipients, the methods of detection and their mitigation strategies.

| Name of the impurity  | Type of reaction caused              | Example of excipient                                                                              | Mitigation                                                  | Analytical methods of detection                                                                                                       |
|-----------------------|--------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Reducing sugars       | Maillard reaction (Amadori product)  | Lactose, dextrose, MCC, starch                                                                    | Control pH, particle size                                   | RP-HPLC (11), flow injection gravimetry.                                                                                              |
| Peroxides             | Oxidation                            | Polysorbates, polyethylene glycol (PEG), povidone/crospovidone, and Hydroxypropyl cellulose (HPC) | Use of antioxidants, pH modifiers, radical chain scavengers | HPLC-based HPO assay (12,13), ferrous oxidation–xylenol orange method (FOX2) (14), titanium sulfate method, iodide titration methods. |
| Aldehydes             | Oxidation (formyl adducts)           | PEG, polysorbate, HPC, povidone, hypromellose and starch                                          | Use of antioxidants                                         | Headspace GC (15–18), colorimetric assay, GC-MS (19).                                                                                 |
| Organic acids         | Oxidation                            | PEG, PVA, fatty acids                                                                             | Use of antioxidants, pH modifiers                           | GC-MS, Ion exchange HPLC method (20).                                                                                                 |
| Nitrates and nitrites | Adduct formation (nitroso compounds) | MCC, starch, croscarmellose sodium, sodium starch glycolate, povidone, crospovidone, and lactose  | Stabilizers, Scavengers                                     | Ion exchange HPLC method (21).                                                                                                        |
| Elemental impurities  | Oxidation                            | Buffering agents                                                                                  | Metal chelators, Antioxidants                               | Inductively coupled plasma–atomic emission spectroscopy, atomic absorption spectroscopy (22).                                         |

by an API or excipient initiates photo degradation. It has been demonstrated that effect of solvent and temperature also contributes to the photolysis of the APIs and excipients.<sup>[35,36]</sup> The molecule is stimulated when it absorbs light, and this excited molecule produces a degradation product as a result of the oxidation process. The key ingredient that feeds the photo degradation process is oxygen, such as singlet oxygen species.<sup>[37]</sup> Figure 8 shows the effect of light and oxygen in the degradation of benzaldehyde.<sup>[38]</sup>

These reactions are taken into account before the formulation of dosage forms to avoid interactions in the finished product over the shelf life term. Instead of using excipients that are susceptible to be involved in the chemical interactions results in product degradation, it is preferable to employ less reactive alternatives. This information is obtained from compatibility investigations between the excipients and APIs or other excipients. These experiments are primarily accelerated stability studies using the differential scanning calorimetry. If no alternative excipients are available, mitigation methods such as antioxidants, pH modifiers, radical chain scavengers, stabilizers, and metal chelators can be used. These processes are time consuming and expensive. To overcome these drawbacks, theoretical modeling such as QSPR modeling may be useful in formulation development.

### QSPR IN PREDICTING EXCIPIENT-EXCIPIENT INCOMPATIBILITIES

QSPR refers to the establishment of a relationship between the property and structural descriptors. SAR has long been used by chemists in the production of novel molecules

and can be elaborated as an art of playing with chemical functional groups and finding out the best groups providing activity to the molecule and discarding the groups diminishing the activity of the molecule. For example, they used to work with groups like electron donating groups provide more activity in a chemical compound than electron withdrawing groups, or alpha beta unsaturated groups produce greater activity, and so on. After advancement in scientific knowledge and technologies, scientists linked quantitative component to the SAR in computational work, which is why it is termed as quantitative structure activity relationship. Its primary application was in ligand-based drug design, particularly when the target remained unclear. During the development of novel APIs, several of the molecules may possess activity but maximum show no activity. As a result, scientists try to determine the structural features that offer activity to a compound and aim to establish a mathematical relationship. QSAR may be used to estimate the activity of unknown compounds and to narrow down a large pool of compounds into a shortlist before going to wet laboratory for synthesis and development.

Activity = function (property 1, property 2.....)

Property could be size of molecule, shape of molecule, number of hydrogen bond forming groups, electrostatic charges, and so on.

QSPRs and quantitative structure toxicity relationships allow the chemists to predict properties such as log P, ionization potential, and other physicochemical properties as well as APIs toxicity profile.

Property = function ( $x_i$ ) QSPR

Toxicity = function ( $x_i$ ) QSTR

Activity = function ( $x_i$ ) QSAR

Whereas  $x$  denotes the descriptors/features/properties of the compound.

The chemoinformatics evaluate molecular similarity, search for compounds in a structure database, and identify potential molecules with desirable therapeutic and physicochemical properties. QSPR is a discipline that connects APIs physicochemical properties to its chemical structure. This method employs a set of descriptors, which are a set of numerical values or properties. The structural characteristics of the molecule are resembled by these descriptors. A model is created (using statistical approaches and linking descriptors with the property under investigation) to predict the compound's physicochemical and biological features.<sup>[39]</sup> Similarly, excipient-excipient incompatibilities can also be predicted by establishing structure property relationship.

Descriptors are mathematical representations of molecular qualities created by various methods or commercially accessible software and are referred to as molecular descriptors/molecular properties/molecular features. These descriptors give the best approaches for quantifying the physical and chemical information of molecules. Molecular descriptors can discover compounds with similar physical or chemical features based on their descriptor values and can help with similarity searches in molecular libraries.<sup>[40]</sup> These descriptors can be used for structure incompatibility relationship and are classified in Figure 9 as

- Descriptors based on molecular dimensions<sup>[41,42]</sup>
- Molecular descriptors<sup>[43]</sup>
- Quantum chemical descriptors<sup>[44,45]</sup>
- Global descriptors<sup>[46,47]</sup>

## Smiles

Simplified molecular input line entry systems are representations of the compound's 2D chemical structure, from which descriptors for the experimental property under investigation are to be derived. For example, smile format of D-Glucose is as follows c1c(c(c(c(o1)o)o)o)o.

## QSPR model

It is a mathematical model that uses chemical structural information to predict physicochemical and pharmaceutical properties of substances. It is created by combining input data (usually in the form of descriptors) with any statistical method.<sup>[48]</sup> We are aware that the QSPR model may predict the physicochemical characteristics of a molecule based on structural information. Physicochemical properties include organoleptic properties, dissociation constant, diffusion coefficient, boiling point, solubility, stability, viscosity, partition coefficient, reactivity, and release characteristics. In the past, QSPR has been used in a variety of pharmaceutical

research. One such research presented the application of QSPR modeling to anticipate the influence of excipient physicochemical features on the release characteristics of the acidic medication Ibuprofen. The model was found to be promising in terms of predicting formulation properties (release kinetics) in this investigation, as evidenced by squared correlation coefficients ( $>0.9$ ).<sup>[49]</sup>

Researchers anticipated the influence of degree of polymerization on the biopharmaceutical characteristics of hydroxypropyl methylcellulose. To create QSPR models, the physicochemical attributes of several grades of cellulose ethers (HPMC) were compared to those of nateglinide (NTG)-containing tablets (*in vitro* and *in vivo* properties). The formulation features were well predicted by the QSPR model.<sup>[50]</sup>

Another study established computer models by linking polymer properties to formulation features of basic heterocyclic drug (glipizide). The created models exhibited high predictability for the property under consideration.<sup>[51]</sup>

The aqueous reaction rate constants of organic compounds with hydroxyl radicals were predicted using QSAR approach in another investigation. The developed model showed satisfactory performance for the property under examination.<sup>[52]</sup>

For retrosynthetic investigation of deep highway networks, researchers used a data-driven technique (DHN). They completed the retrosynthetic reaction prediction job in two steps: First, they created a DHN model to predict which reaction group (composed of chemically comparable reaction rules) was used to make a molecule. A DHN trained on the subset of reactions inside the discovered reaction group was used to predict the transformation rule utilized to build a molecule once a reaction group was identified. They used their multi scale model to predict the first retrosynthetic reaction step for 40 authorized medications and compared its prediction ability to a conventional model trained on all machine-extracted reaction rules as a control. Their multi-scale technique generated valid reactants from retrosynthetic reaction predictions with a success rate of 82.9%. On the validation set of 40 pharmaceutical compounds, the control model trained on all machine-extracted reaction rules had a success rate of 58.5%, indicating a considerable statistical improvement with our approach to match known first synthetic reactions of the tested medications in this study. While their multi scale approach did not outperform state-of-the-art rule-based systems curated by expert chemists, it does represent a significant improvement in retrosynthetic analysis and can be easily adapted for application in a variety of artificial intelligence strategies.<sup>[53]</sup>

According to the above-mentioned literature, QSPR models are the greatest potential tools for reducing the

pharmaceutical industry's cost, time, and personnel by delivering superior predictions based only on the compound's structural information. On the similar lines, QSPR can be used to predict excipient-excipient incompatibilities due to chemical reactivity.<sup>[54,55]</sup> Excipients are inert substances in terms of therapeutic response, but they include chemical functional groups in their structures that make them reactive with other excipients, resulting in excipient-excipient incompatibilities. To predict excipient-excipient incompatibilities using QSPR, we need to build a predictive model which can predict reactivity of the excipients by considering their structural information. The first step is to choose the relevant descriptors to represent the molecule. Descriptor selection is a difficult and time-consuming procedure that determines the model's fate. Poor forecasts and model failure will result from using random or incorrect descriptors. It is normally accomplished by associating descriptors with the attribute under examination, in this instance reactivity, and then picking the most applicable descriptors. Some of the descriptors which look promising in predicting reactivity are quantum chemical descriptors (atomic net charge, super delocalizability, EHOMO, and ELUMO),<sup>[44,45]</sup> local reactivity descriptors (Fukui function namely  $f_k^+$  for nucleophilic attack;  $f_k^-$  for electrophilic attack and  $f_k^0$  for the radical attack),<sup>[56,57]</sup> electronic descriptors (ionization potential, Hammett constant  $\sigma + \sigma^-$ , Taft's inductive constant  $\sigma^*$ , Swain, and Lupton field parameter)<sup>[58,59]</sup> and many others.

## DEVELOPMENT OF MODEL

A model may be built using a variety of statistical approaches, including linear regression, multiple regression, PLS regression, and non-linear methods such as artificial neural networks, associative neural networks, K closest neighbors, and so on.<sup>[60,61]</sup> Before proceeding to the predictions, the QSPR model is assessed by choosing a high  $R^2$  for the experimental data and a low RMSE for the anticipated data. A good prediction model has a high  $R^2$  and a low RSME.<sup>[62]</sup> After the model has been developed and validated, it will be able to discover similarities in the chemical database and distinguish between the different functional groups that are prone to degradative processes. The overall process of predicting excipient-excipient incompatibility from the chemical structures is summarized in Figure 10.

## CONCLUSION

Excipient-excipient incompatibility is a hidden hazard to the pharmaceutical business that might occur during development or after a dosage form has been launched in the market. This hazard can result in the reduction of the product's shelf life and cause it to perform poorly. Drug products are made at a great cost and with the intention that a patient will benefit from them, but if any incompatibility

occur in the drug product due to impurities in the excipients or the functional groups of the excipients begin to react with each other, the degradation product's level in the product may rise, posing a risk to the patient's safety, dosage form stability, shelf life and eventually a loss to the inventor of the drug product. These circumstances can be minimized by utilizing experimental strategies such as conducting stability studies of excipients or applying DOE approach to the dosage form development. However, the knowledge of excipient reactivity is of utmost importance for the successful development of dosage form. This assessment could be obtained from the outcome of predictive structure incompatibility model at a rapid pace, minimum cost, and with less efforts of manpower. It has been believed that different vendors use different routes of synthesis for the manufacture of same excipient which can pose direct impact on the level of impurities and it is advisable to use the excipients from the vendors which use similar method of synthesis and impose strict control on the level of reactive impurities.

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