



# Drug-drug cocrystals: Opportunities and challenges

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## Abstract

Recently, drug-drug cocrystal attracts more and more attention. It offers a low risk, low-cost but high reward route to new and better medicines and could improve the physiochemical & biopharmaceutical properties of a medicine by addition of a suitable therapeutically effective component without any chemical modification. Having so many advantages, to date, the reported drug-drug cocrystals are rare. Here we review the drug-drug cocrystals that reported in last decade and shed light on the opportunities and challenges for the development of drug-drug cocrystals.

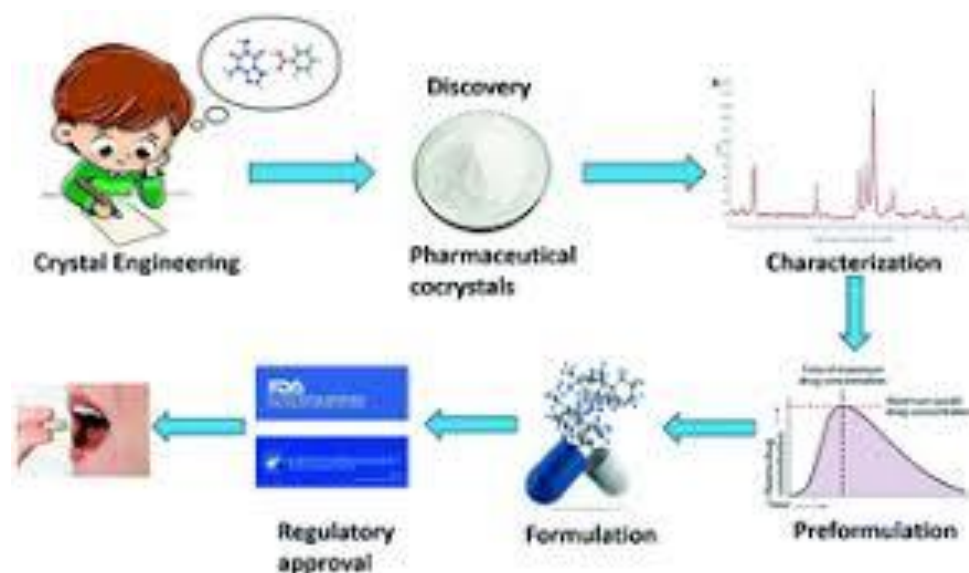
## Keywords:

Drug-drug cocrystal Drug combination Cocrystal Physicochemical property

## Introduction

At the cellular and organ levels, complex diseases such as cancer, diabetes, infectious diseases, and cardiovascular diseases are associated with multiple alterations in molecular pathways and complex interactions. The combination of multiple therapeutic agents into unit doses has become a popular drug development strategy, because mono-therapy (i.e. targeting a specific receptor) is no longer considered effective in the management of many complex disorders, such as infectious diseases, HIV/AIDS, cancer, diabetes, and cardiovascular disease. The use of cost-effective and multiple-targeting fixed-dose drug combinations (FDC) can help reduce pill load without the additional risk of adverse events or drug resistance, thereby improving patient compliance by simplified disease management. Drug combinations would also facilitate the reduction of managerial and manufacturing costs by reducing the outflow related to packaging and drug prescriptions. Fixed-dose combination products can comprise simple drug-drug combinations or drug device combinations, such as drug-eluting stents or drug-biological products for use in cancer therapy. The advantages of FDC are often overshadowed because of various disadvantages, including issues with stability, and solubility differences and incompatibility between the parent drugs. Therefore, it is necessary to develop alternative technologies and methodologies that facilitate the development of therapeutic hybrids to counter such problems. An alternative to combining two or more drugs into a dosage form is the use of multicomponent solids, such as salts, mesoporous complexes, co-amorphous systems, and co-crystals,

compris-ing two or more active pharmaceutical ingredients (APIs). Of all these types of system, co-crystals with expanded patent portfolios have garnered the interest of the pharmaceutical industry. The development of the first co-crystal can be traced back to 1844, when Wohler synthesized quinhedrone complex, which was later found to be a 1:1 co-crystal of quinone and hydroquinone. According to the FDA, co-crystals are defined as 'dissociable multicomponent solid crystalline supramolecular complexes composed of two or more components within the same crystal lattice where in the components are in neutral state and interact via nonionic interactions.



## MATERIALS AND METHODS

### Materials

Duloxetine hydrochloride was a kind gift sample from Medreich Ltd, (Bangalore, India). Hydroxypropyl methylcellulose E 15 and Eudragit RL 100 were gift samples from Dr. Reddy's Laboratories (Hyderabad, India). Dichloromethane AR, methanol HPLC and AR were procured from Merck Ltd., (Mumbai, India). Propylene glycol was purchased from Fine chemicals, (Chandigarh, India). Phenol red was purchased from Hi-Media Laboratories Pvt. Ltd., (Mumbai, India)

### Methods

#### Preformulation studies

#### Solubility studie

The solubility of DLX HCL in pH 6.6 phosphate buffer, distilled water and 7.4 pH phosphate buffer was determined by phase equilibrium method. An excess amount of drug was taken into 50-ml conical flasks containing 20 ml of pH 6.6 phosphate buffer, distilled water and 7.4 pH phosphate buffer. These flasks were closed with aluminium foil and placed on a rotary shaker at room temperature for agitation for about 48 hours. After 24 h, the solution was filtered through a 0.2- $\mu$ m Whatman filter paper; the filtrate was collected, and the amount of drug solubilized was then estimated by measuring the absorbance at 290 nm using a UV spectrophotometer (Elico Pvt Ltd, Hyderabad). The studies were repeated in triplicate (n=3), and the mean was calculated.

## Drug excipients compatibility studies

### Fourier transform infrared (FTIR) spectroscopy

The Fourier transform infrared (FTIR) spectra for the samples were obtained using KBr disk method by FTIR spectrophotometer (BX I, Perkin Elmer, USA). Pure drug DLX, a Physical mixture of DLX and HPMC E15, a Physical mixture of DLX and Eudragit RL 100 and a Physical mixture of DLX, HPMC E15 and Eudragit RL100 were prepared and subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000  $\text{cm}^{-1}$  spectral region with a resolution of 4  $\text{cm}^{-1}$  Ex

### vivo drug permeation studies through porcine buccal mucos

The aim of this study was to investigate the permeability of buccal mucosa to duloxetine hydrochloride. It is based on the generally accepted hypothesis that the epithelium is the rate-limiting barrier in buccal absorption. The oral mucosa of pigs resembles that of humans more closely than any other animal in terms of structure and composition and therefore porcine buccal mucosa was selected for drug permeation studies.

### Tissue preparation (Isolation)

Porcine buccal tissue was taken from a local slaughterhouse. It was collected within 10 min after the slaughter of the pig and tissue was stored in Krebs buffer solution. It was transported immediately to the laboratory and was used within 2 h of isolation of buccal tissue. The tissue was rinsed thoroughly using phosphate buffer saline to remove any adherent material. The buccal epithelium was carefully separated from the underlying connective tissue with surgical technique, and then the remaining buccal mucosa was carefully trimmed with the help of surgical scissors to a uniform thickness. Sufficient care was taken to prevent any damage to the buccal epithelium. Finally, the membrane was allowed to equilibrate for approximately one hour in receptor buffer to regain the lost elasticity.

### Evaluation of the d Weight variation test

#### veloped buccal patches

Six patches each equivalent to 2.89  $\text{cm}^2$  Thickness variation test area was cut from each plate and their weight was measured individually using Shimadzu digital balance and the average weight was calculated. The mean $\pm$ SD values were calculated for all the formulated patches.

### The thickness of the patches

The thickness of the patches was measured at six different points of the patch by digital gauge (Mitutoyo, Japan). The mean $\pm$ SD values were calculated for all the formulations.

### Folding endurance

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 200 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance of patch

### Surface pH of films

The method adopted by Bottenberg et al. the used to determine the surface pH of the patches. A combined glass electrode was used for this purpose. The bioadhesive buccal patch was made in contact with 1 ml of distilled water and allowed to swell for 1-2 h at room temperature. The surface pH of the patches was measured by bringing the pH meter electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute.

## Assay of the patches

The formulated patches were assayed for drug content in each case. Three patches from each formulation equivalent to 2.89 cm<sup>2</sup> Procedure area were assayed for content of drug. Each formulation was casted in triplicate and one patch from each was taken and assayed for content of drug.

## CONCLUSION

Buccal delivery is an attractive alternative route for administration of drugs that has low bioavailability due to extensive first-pass metabolism. The following conclusion could be drawn from the results of various experiments. Duloxetine hydrochloride could permeate through the porcine buccal membrane as evidenced from the results of ex vivo drug permeation studies. FTIR studies concluded that there was no interaction between drug and excipients. The buccal patches of Duloxetine hydrochloride could be prepared by the solvent casting method with mucoadhesive polymers like HPMC E15 and Eudragit RL100. The prepared patches were smooth, elegant in appearance, uniform in weight, thickness, content uniformity and showed no visible cracks and showing good folding endurance. The Physicochemical properties of all the formulations were shown to be within limits. The surface pH of all the formulations was in an acceptable salivary pH (5.8 to 7.4). Hence, they do not cause any irritation to the buccal cavity. The optimised buccal patch F4 showed satisfactory drug release rates with the Higuchi model release profile. Buccal patches had shown good mechanical properties measured in terms of tensile strength and elongation at break values. Optimised buccal patches developed for DLX possess reasonable bio-adhesion measured in terms of peak detachment force and work of adhesion. From the stability studies, it has concluded that the buccal patches have maintained their integrity in the natural human saliva and exhibiting sufficient strength of the system throughout the experiment. Ex vivo permeation studies for optimised patches was conducted and shown satisfactory drug permeation. This could demonstrate that the optimised formulations could meet the target flux. Good in vitro ex vivo correlation for optimised buccal patch of Duloxetine hydrochloride demonstrates the validity of the release tests conducted. Hence, present study concludes that the Duloxetine hydrochloride could be delivered through the buccal route. Further work was recommended to support its efficacy claims by pharmacokinetic and pharmacodynamics studies in a human being

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