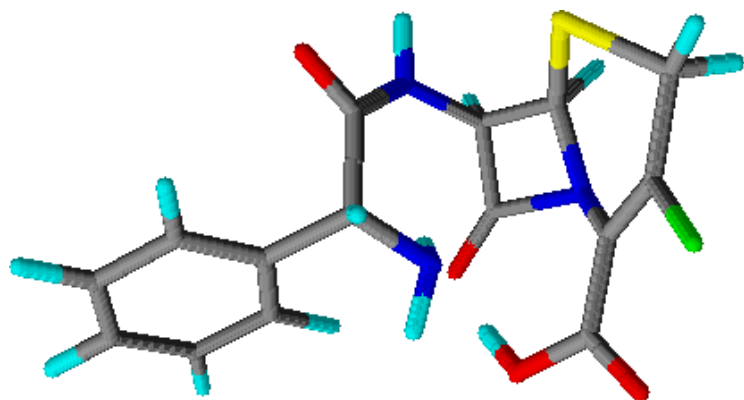


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What really happens to the API: Case studies in drug product chemistry.



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Regulatory Questions

Major concerns in approving a drug:

- 1- Drug Substance identification: what is the active pharmaceutical ingredient (API)?
- 2- Drug Product characterization: what is being delivered ``on the shelf'' of Canadians?



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Overview

- Intended transformations of active ingredients
- Unintended reactions with excipients
- Characterization methods

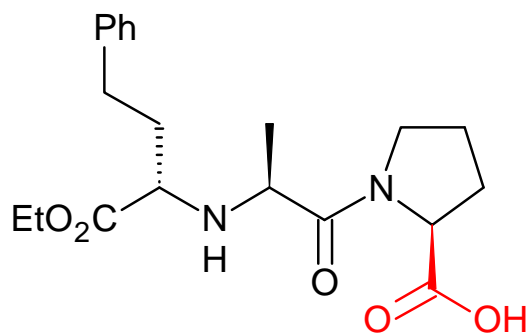


Intended transformations in drug products

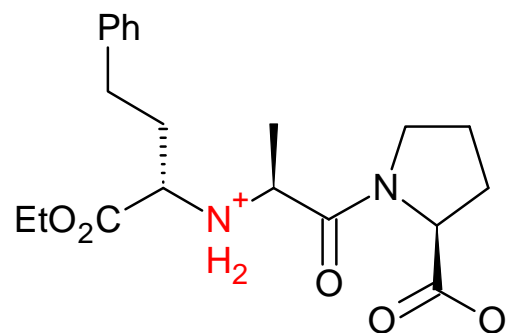
- Many APIs and excipients are acidic or basic.
- Acid-base reactions are among the fastest chemical reactions, especially when water is present.
- These properties are sometimes exploited to transform the active medicinal ingredient to increase solubility or stability, etc...

Intended transformations in drug products

Case 1: the acid-base chemistry of enalapril...



$pK_{a1} = 3.0$



$pK_{a2} = 5.4$

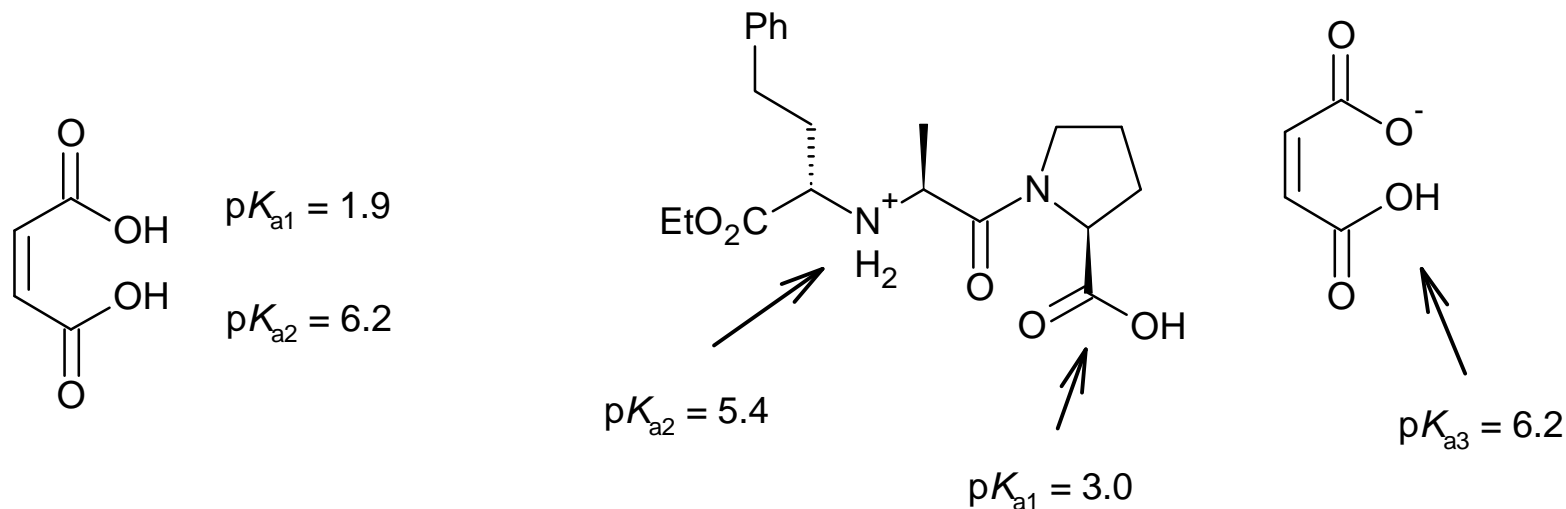


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Intended transformations in drug products

Case 1: ...and its maleate salt



Maleic acid protonates the proline $-\text{COO}^-$.

Knowledge of the pK_as tells us how many equivalents of a base can react and which groups react first.



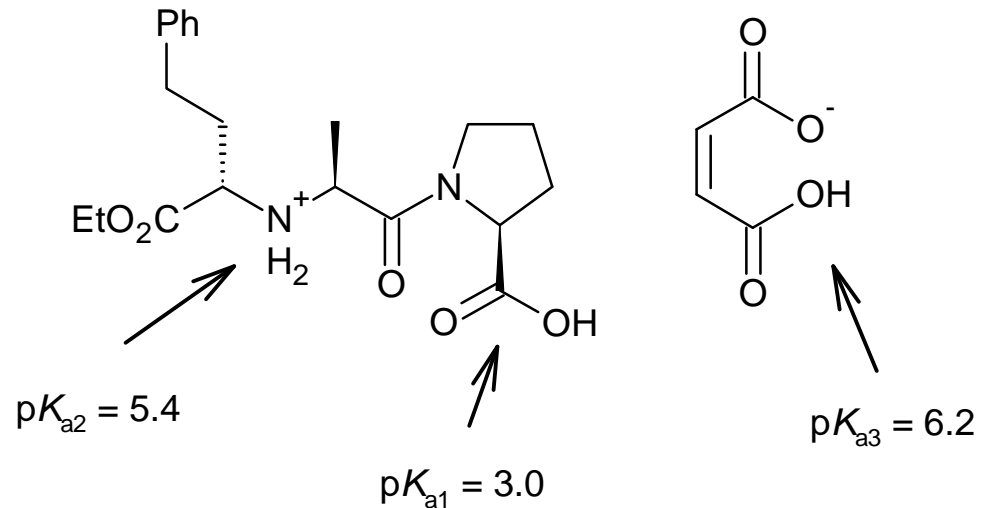
Intended transformations in drug products

Case 1 (cont'd):

What happens when 1 equivalent of a basic excipient is added?

2 equivalents?

3 equivalents?




Intended transformations in drug products

Case 1 (cont'd): US Patent 5690962

The patent describes the wet granulation of enalapril maleate with sodium bicarbonate and with sodium carbonate.

CO₂ is lost, driving the reaction to completion.

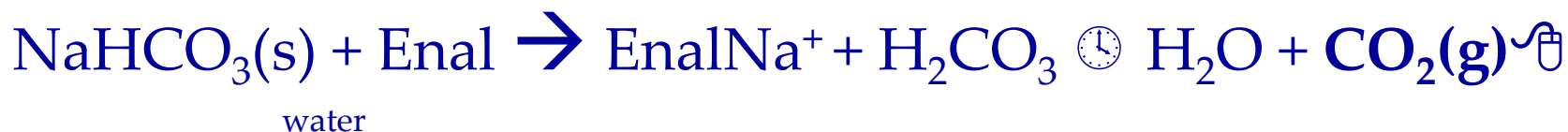
The loss of H₂O and CO₂ is measurable, signalling the end point of the reaction.

	
US005690962A	
United States Patent [19]	[11] Patent Number: 5,690,962
Sherman	[45] Date of Patent: *Nov. 25, 1997
[54] STABLE SOLID FORMULATION OF ENALAPRIL SALT AND PROCESS FOR PREPARATION THEREOF	[56] References Cited
[75] Inventor: Bernard Charles Sherman, Willowdale, Canada	U.S. PATENT DOCUMENTS
[73] Assignee: Apotex Corporation, Buffalo Grove, Ill.	4,374,829 2/1983 Harris et al. 424/177
[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,573,780.	4,743,450 5/1988 Harris et al. 424/440
[21] Appl. No.: 711,826	5,350,582 9/1994 Merdavic et al. 424/464
[22] Filed: Sep. 10, 1996	5,573,780 11/1996 Sherman 424/464
Related U.S. Application Data	
[63] Continuation of Ser. No. 511,297, Aug. 4, 1995, Pat. No. 5,573,780.	<i>Primary Examiner</i> —James M. Spear
[51] Int. Cl.⁶ A61K 9/14; A61K 9/16	<i>Attorney, Agent, or Firm</i> —Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.
[52] U.S. Cl. 424/489; 424/464; 514/777; 514/970	[57] ABSTRACT
[58] Field of Search 424/464, 465, 424/489	There is disclosed a stable pharmaceutical solid composition comprising enalapril as the sodium salt, which is made by the steps of:
	i) mixing enalapril maleate with a carrier, an alkaline sodium compound, and water
	ii) drying the wet mass, and;
	iii) further processing the resultant dried mass into tablets.
	When the water is added in the aforesaid process, an acid-base reaction occurs which converts the enalapril maleate into the more stable enalapril sodium salt.
	8 Claims, No Drawings



Intended transformations in drug products

Case 1 (cont'd):



Q: Why is the reaction complete?

Hint: An equilibrium is no longer an equilibrium when something is continuously removed.

A: Even though carbonate and bicarbonate are weak bases, the loss of CO_2 from the system can drive an acid-base reaction to completion regardless that the pK_a s may be close.



Intended transformations in drug products

Case 2: Formulation with a strong base

An API has three pK_a s:

$pK_{a1} = 3.5$ (-COOH)

$pK_{a2} = 4.1$ (amino)

$pK_{a3} = 6.0$ (amino)

The basic excipient is NaOH (the second pK_a of water is ~ 15)

Manufacturing process:

Step 1: mix API, NaOH (excess),
H₂O, other excipients

Step 2: granulate

Step 3: dry

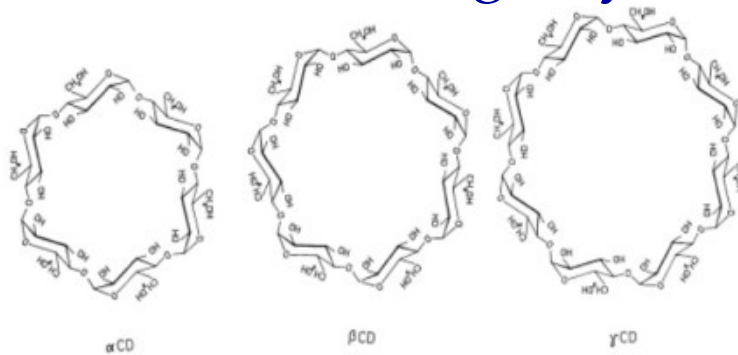
Step 4: compress

Problem: What is the API in the final dosage form?



Intended transformations in drug products

Case 3: Formulation containing a cyclodextrin



- Formation of inclusion complexes with APIs in some cases (e.g. metformin)
- Extent of complex formation highly dependent on process
- Used to modulate the release or stability of the active

Ref: G. Corti, G. Capasso, F. Maestrelli, M. Cirri and P. Mura, *J. of Pharm. & Biom. Anal.*, 3 (2007) pp. 480-486

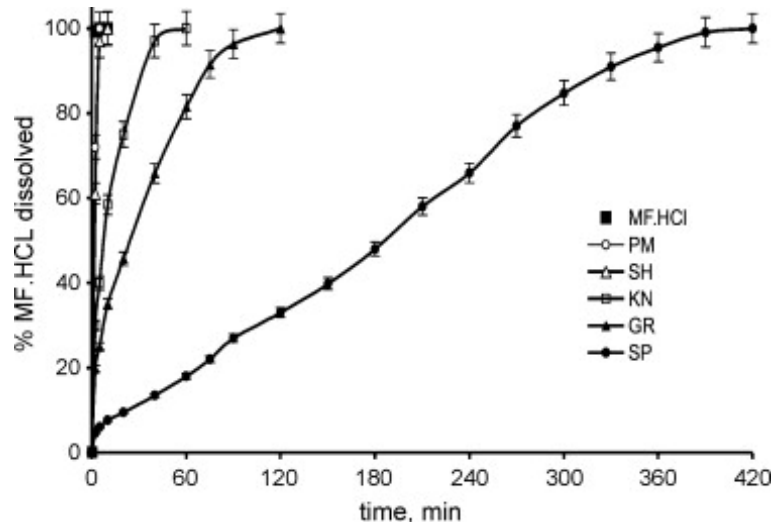


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Intended transformations in drug products

Case 3 (cont'd):



- Spray-drying created the highest level of complexation in the case of a metformin – triacetyl-beta-cyclodextrin mixture.

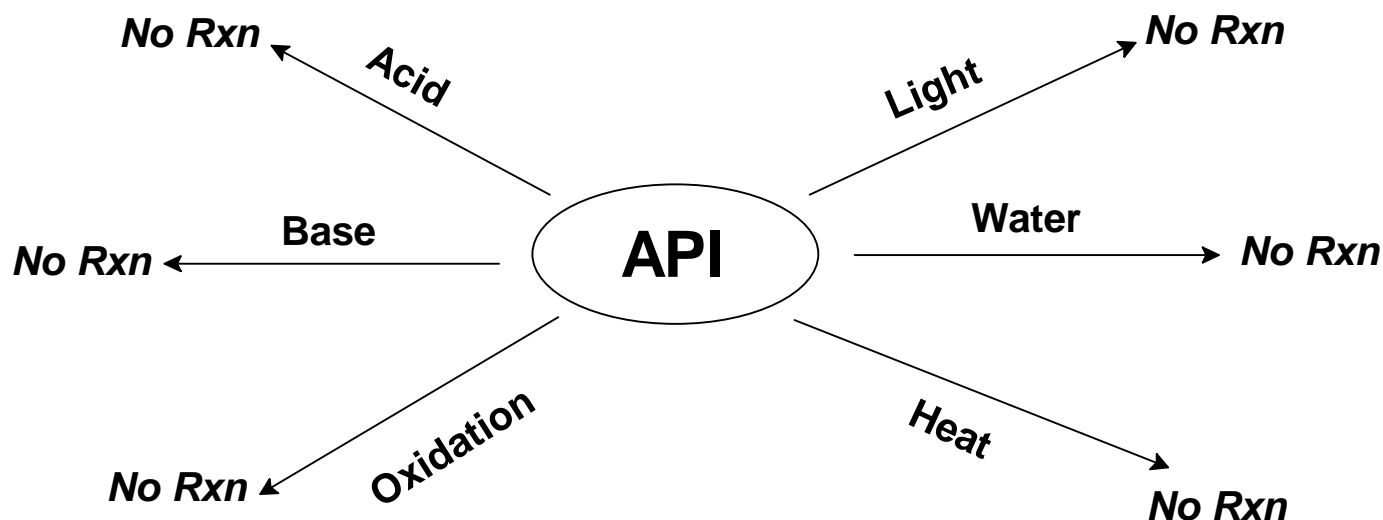
Ref: G. Corti, G. Capasso, F. Maestrelli, M. Cirri and P. Mura, *J. of Pharm. & Biom. Anal.*, 3 (2007) pp. 480-486



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APIs are robust...



Notable exceptions...

Prodrugs are supposed to fall apart. But not until *in vivo*.

Reactive drugs (e.g. many antibiotics) require special care in manufacture and storage.



...if it weren't for excipients.

- APIs and excipients can interact in numerous ways and give rise to numerous problems.

e.g. Binding, complexation phenomena

- Insoluble excipients with acidic or basic functional groups may exhibit ion exchange properties leading to:

differences in dissolution profiles

low recovery

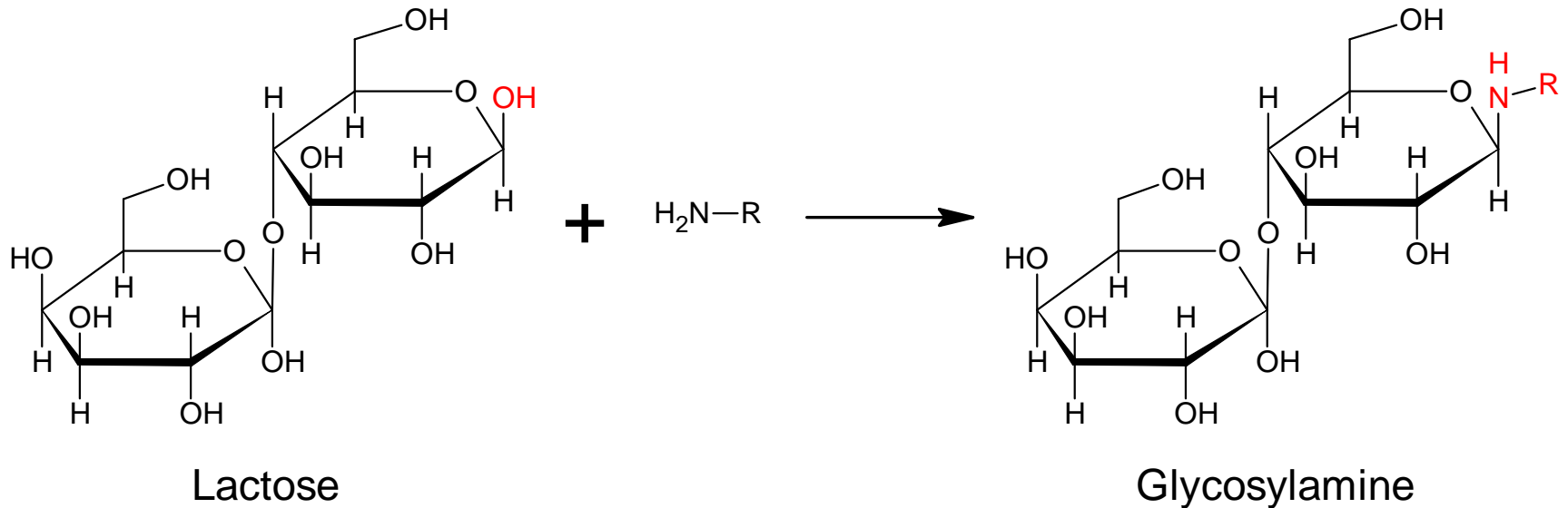
altered bioavailability



Unintended reactions with excipients

Case 1:

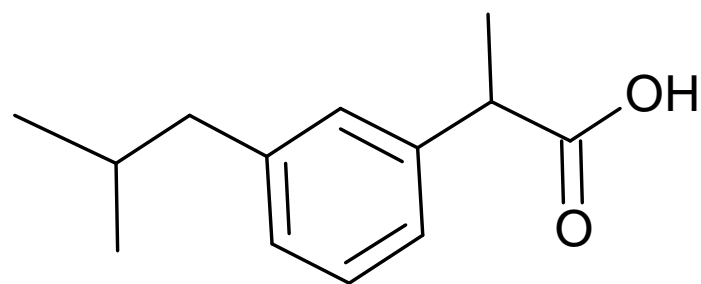
Maillard reaction (reaction generating degradants)



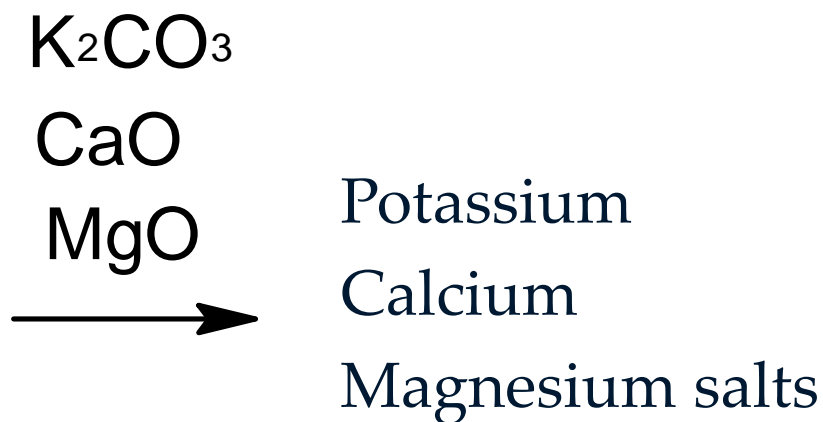
Unintended reactions with excipients

Case 2:

Acid-base reaction of ibuprofen



Ibuprofen



Unintended reactions with excipients

Case 3:

Company claims:

“Our API is a HCl salt with $pK_a \sim 6$. On stability, we see that it converts to the free base. About 70% conversion. We don't think it's a problem.”

The responsible excipient: croscarmellose sodium.

What's happening?

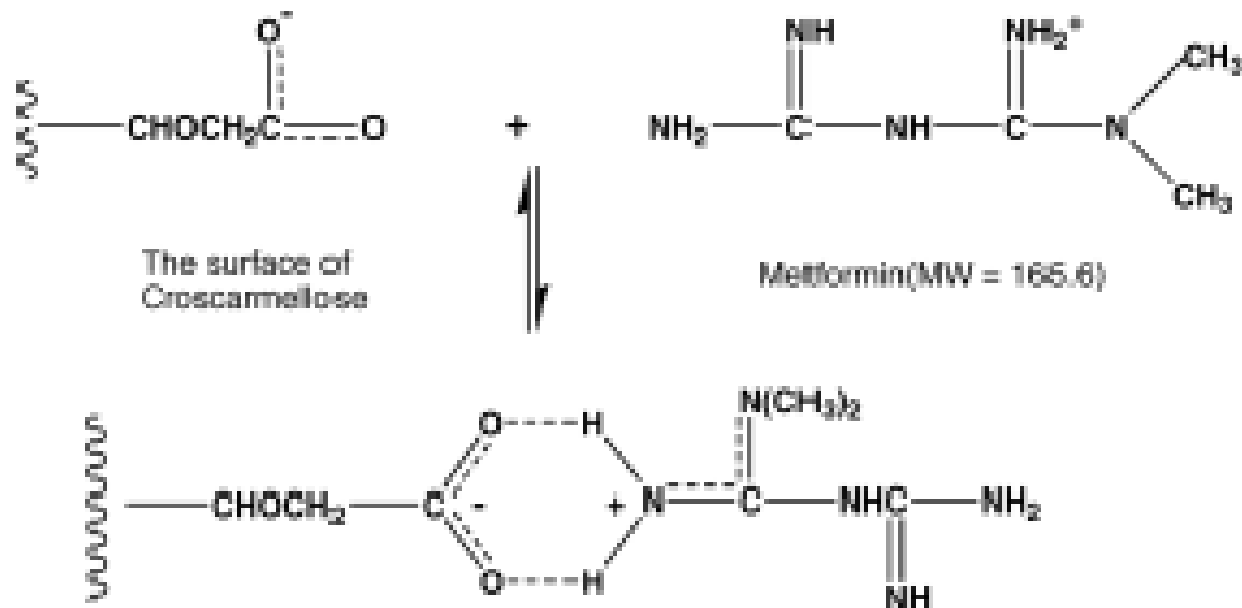
(Think ion exchange resin)

The excipient doesn't have a single pK_a ... it has thousands upon thousands of pK_a s. Some of those carboxylate pK_a s are sufficiently basic carboxylates and thousands-fold more numerous than the API.



Unintended reactions with excipients

(a). Metformin-Croscarmellose interaction :



Creation of a meta-stable six-member complex
based on ion-dipole interactions and two hydrogen bonds



Characterization methods

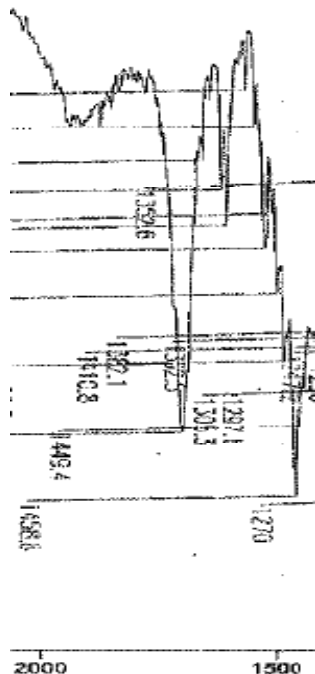
- Methods included in most drug product monographs are incapable of detecting changes in salt form, or changes from the free base to the salt (and vice-versa).
 - HPLC assay methods can detect formation of new covalent bonds or adducts only when the recovery of the active is reduced or if secondary peaks are appearing, but unable to detect changes in salt.
- Use of solid-state methods would be necessary.

Characterization methods

- Solid-state NMR spectroscopy
- DSC
- XRPD
- Raman spectroscopy
- NIR and IR spectroscopy



Example 1: Use of IR to detect changes in the API



Before



After



Take-home thoughts

- It is essential to have a good understanding the reactions that could take place e.g. Given knowledge of API pK_a s, excipient properties and the manufacturing process
- Drug-Excipient interaction studies play an important role.
- Use of appropriate characterization methods
→ you should be able to conclude whether the salt form of the API has changed.
- Labelling should correctly identify the medicinal ingredients and their quantities.

Questions or Comments?

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