Drug - Excipient interactions

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Stability

- Extensive chemical degradation: a substantial loss of potency
- Degradation products may result in adverse events or be unsafe
- Instability may cause
- Undesired change in performance, i.e. dissolution/bioavailability
- Substantial changes in physical appearance of the dosage form
- causing product failures
- Requirement for approval by regulatory agencies

Factors Affecting Formulation Stability

- **Drug & Excipient**
  - Chemical structure
  - Impurity profile
  - Physical form
  - Moisture content
  - Particle size
  - Surface area
  - Morphology
- **Formulation**
  - Drug : excipient ratio
  - Processing method
  - Mixing/milling
  - Powder packing
- **Environment**
  - Temperature
  - Relative humidity
  - Packaging
  - Light
  - Oxygen

Chemical Degradation

- Hydrolysis
  - **Esters**
  - **Carboxylic acid esters**
  - **Amides**
  - **Imides**
- Dehydration
- Isomerization and Racemization
- Decarboxylation and elimination
- Oxidation
- Photodegradation

Drug-Excipient Interaction

- Excipients are usually biologically inactive, the same cannot be said from a chemical perspective. Excipients, and any impurities present, can stabilise and/or destabilise drug products.

- Considerations for the formulation scientist:

  Chemical structure of the API

  Type of delivery system required

  Proposed manufacturing process

- Initial selection of excipients should be based on:

  Expert systems; predictive tools

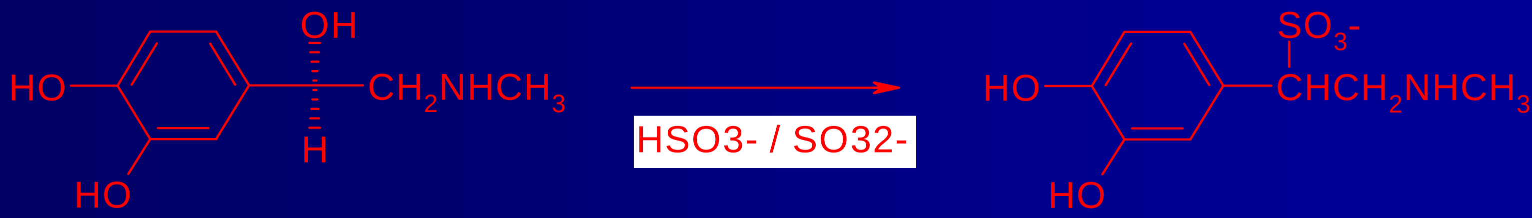
  Desired delivery characteristics of dosage form

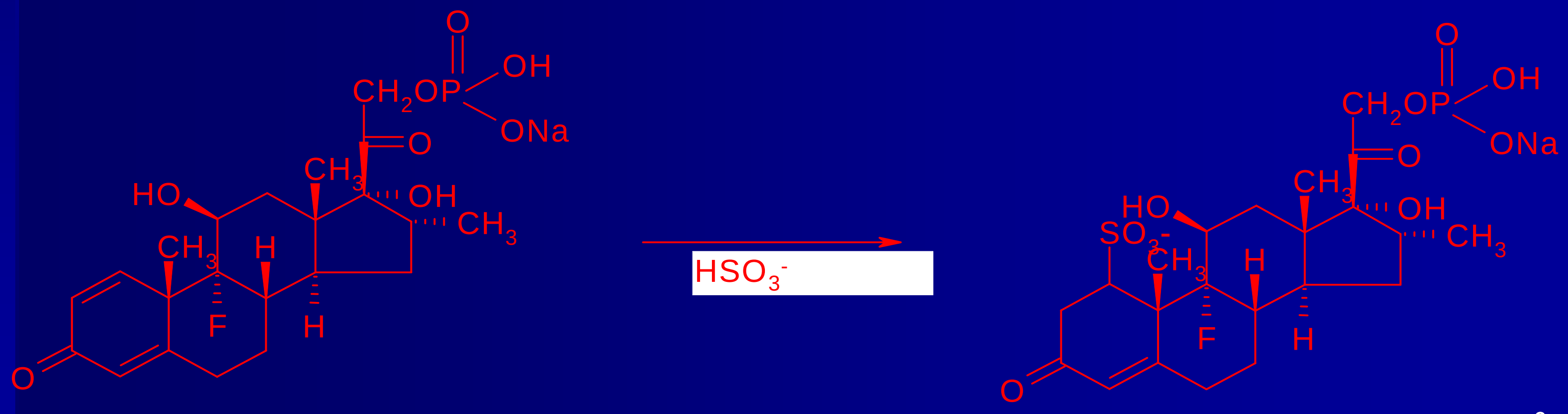
  knowledge of potential mechanisms of degradation, e.g. Maillard reaction

- The objective of drug/excipient compatibility considerations and practical studies is to delineate, as quickly as possible, real and possible interactions between potential formulation excipients and the API. This is an important risk reduction exercise early in formulation development.

Excipient Interactions

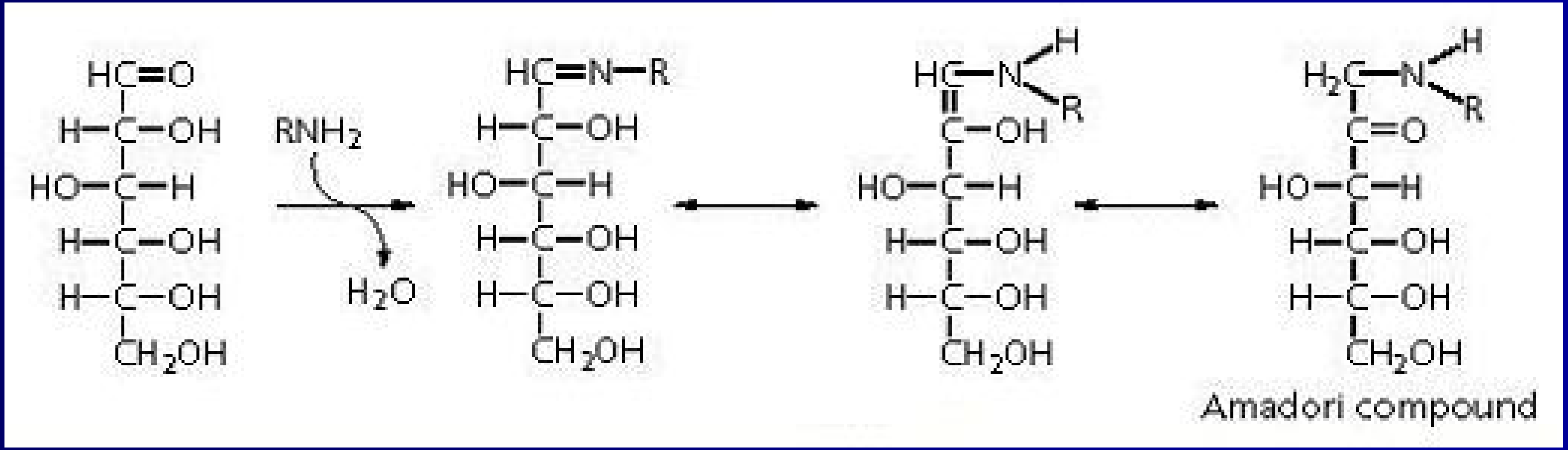
- Reactions of Bisulfate





Excipient Interactions

- Reactions of amines with reducing sugars



Excipient Interactions

- Transesterification Reactions

Known Incompatibilities

functional Group	Incompatibilities	Type of Reaction
primary amine	mono and disaccarides	amine-aldehyde and amine-acetal
ester, cyclic, lactose	basic components	ring opening, ester-base, hydrolysis
carbonyl, hydroxyl,	silanol	hydrogen bonding
aldehyde	amine, carbohydrates	aldehyde-amine, Schiff base or glycosylamine formation
carboxyl	bases	salt formation
alcohol	oxygen	oxidation to aldehydes and ketones
sulfhydryl	oxygen	dimerization
phenol	metals	complexation
gelatin capsule shell	cationic surfactants	denaturation

Excipient Interactions

- **Excipient Moisture**

Amount of water: High moisture content of poly vinyl pyrrolidone and urea enhances Aspirin hydrolysis.

Decreased drug stability for ascorbic acid, dry syrups of cephalexin, powders of cysteine derivatives and urea-linolic acid inclusion complex.

Ascorbic acid and silica gel

Thiamine hydrochloride tablets : Magnesium stearate and MCC

Propantheline bromide : Sodium alluminum gel

Excipient Moisture

- **Physical state of water:**

  Weakly absorbed water: Loose water or surface water

  Strongly absorbed water: Excipient having higher adsorption energy decrease water reactivity, decrease in relative hydrolysis rates.

  Moisture adsorption Equilibrium: Excipient that adsorbs more moisture adsorbs more strongly, resulting less free water for strongly adsorbing excipient before it is reaching equilibrium. Relative reactivity is decreased.

  Hydrated Drugs and excipient: Excipients can form hydrates may enhance drug degradation by giving up their water of crystallization during grinding.

  Lactose hydrate enhances degradation of 4-Methoxyphenylamino acetate hydrochloride upon grinding.

Excipient Moisture

- **Mobility of water molecules :**

Effect of water mobility on drug stability, spin – lattice relaxation time and spin-spin relaxation time by NMR and dielectric relaxation time by dielectric relaxation spectroscopy.

Water mobility in polymer solutions/gels will effect the drug degradation. Mainly used for polymeric excipients like Poly vinyl pyrrolidone, Gelatin , PEG.

Excipient Interactions

- **pH : Surface acidity of excipients contribute to drug degradation**

Eg: Isomerization of vitamin D2

Oxazolam degrades in the presence of MCC may be attributed to carboxylic acid groups on the cellulose surface in addition to effect of water.

- **Melting :** Effect of sterate in Aspirin is due to change in melting behavior.
- **Oxidation:** Dye excipients enhance oxidation and photodegradation
- **Catalysis :** Metal ions used as Pharmaceutical excipients or present as impurities catalyze drug degradation. Triggers oxidation and photodegradation

Excipient Interactions

- **Physical stability**

Crystallization of amorphous drugs:

Nifedipine co precipitated with PVP undergoes partial crystallization during storage.

Oxyphenbutazone converts to anhydrous form with lower solubility during storage under conditions of high humidity

Haloperidone converts to crystalline in presence of HPC,MC, HPMC and PVA.

Crystallization of amorphous excipients also occur during storage effects the drug release.

Drug-Excipient Compatibility Testing

- In the typical drug/excipient compatibility testing program, binary (1:1 or customised) powder mixes are prepared by triturating API with the individual excipients.

- These powder samples, usually with or without added water and occasionally compacted or prepared as slurries, are stored under accelerated conditions (80°/75%RH, 60°C/ambient RH, 40°/75%RH) and analysed by stability-indicating methodology, e.g. HPLC.

- Alternatively, binary samples can be screened using thermal methods, such as DSC/ITC. No need for stability set-downs; hence cycle times and sample consumption are reduced. However, the data obtained are difficult to interpret and may be misleading; false positives and negatives are routinely encountered.

Drug-Excipient Compatibility Testing

- Prototype formulations: The amount of API in the blend can be modified according to the anticipated drug-excipient ratio in the final compression blend.
- However, the binary mix approach takes time and resources and….it is well known that the chemical compatibility of an API in a binary mixture may differ completely from a multi-component prototype formulation.
- This is a more complex system to interpret.

Drug-Excipient Compatibility Testing

- Drug-excipient interactions can be studied using both approaches in a complementary fashion. The first tier approach is to conduct short-term (1-3m) stability studies using generic prototype formulations under stressed conditions, with binary systems as diagnostic back-up:
  - Chemical stability measured by chromatographic methods
  - Physical stability measured by microscopic, particle analysis, *in vitro* dissolution methods, etc.
  - The idea is to diagnose any observed incompatibility from the prototype formulation work then hopefully identify the “culprit” excipients from the binary mix data.
  - Hopefully, a prototype formulation can then be taken forward as a foundation for product development.
- Can apply statistical models (e.g. 2n factorial design) to determine the chemical interactions in more complex systems such as prototype formulations, with a view towards establishing which excipients cause incompatibility within a given mixture.

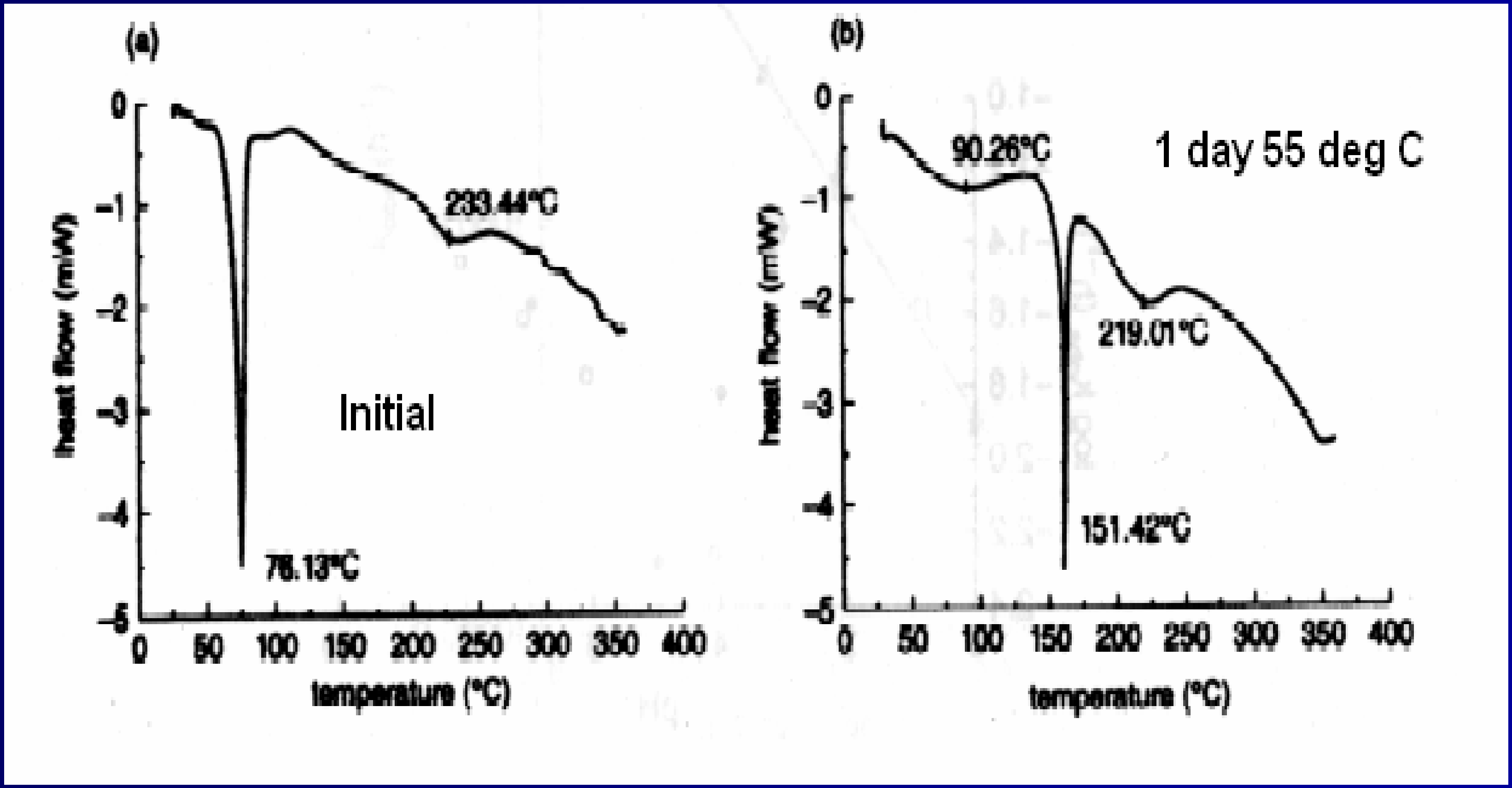
Drug-Excipient Compatibility Testing – More predictive Model

- Storage of 200 mg drug excipient blends in a closed vials at 50°C with 20 % added water.
- Study reveals: role of chemical nature of excipient, ratio of drug-excipient blend, pH, role of moisture , temperature, humidity, light.
- This approach avoids late stage development surprises.

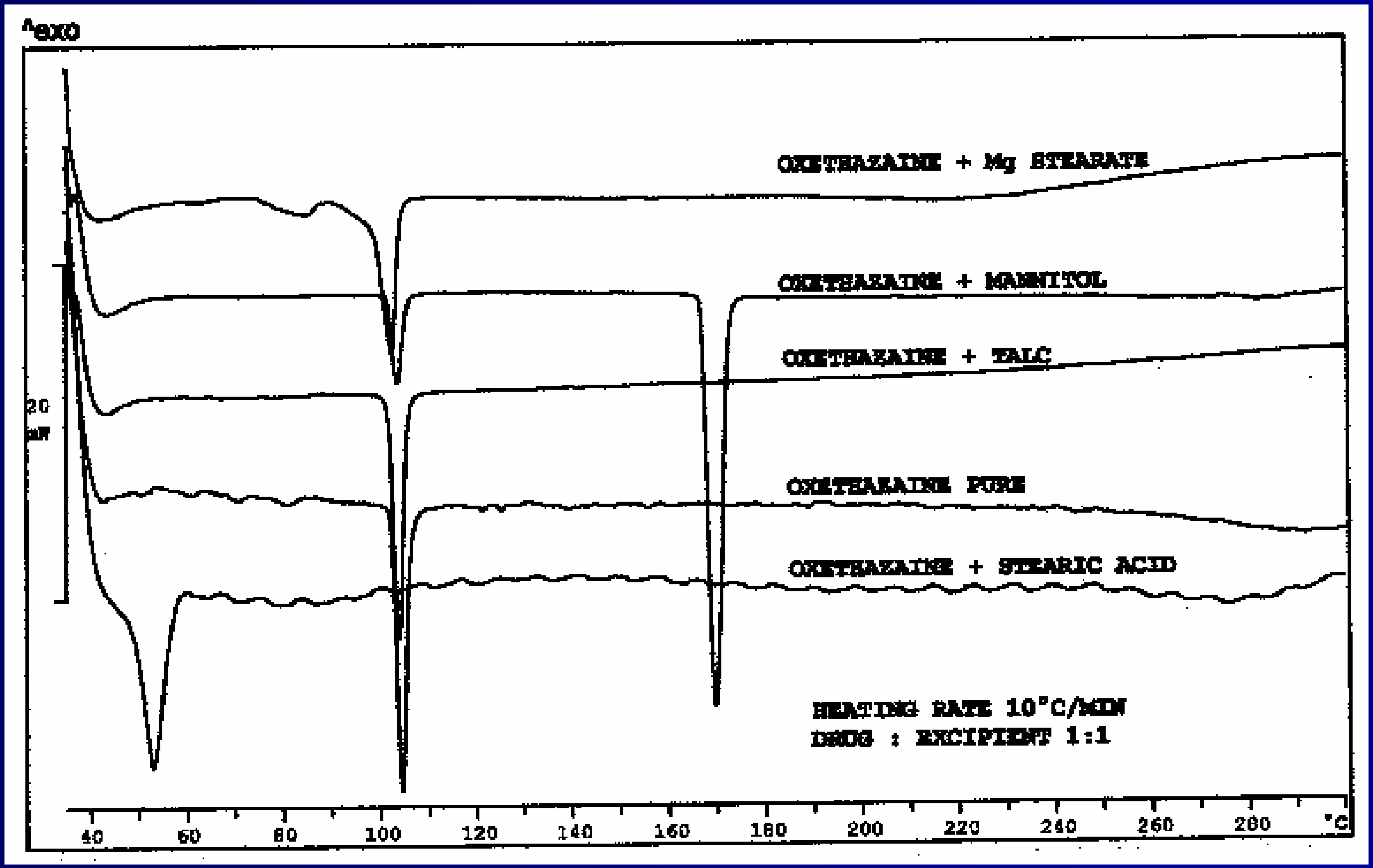
Detection & Characterization

- Thermal Analysis
  DSC, DTA, DTG & Isothermal calorimetry
- Chromatography
  HPLC, GC
- Diffuse reflectance spectroscopy
- IR, XRD
- LC-MS/MS,NMR

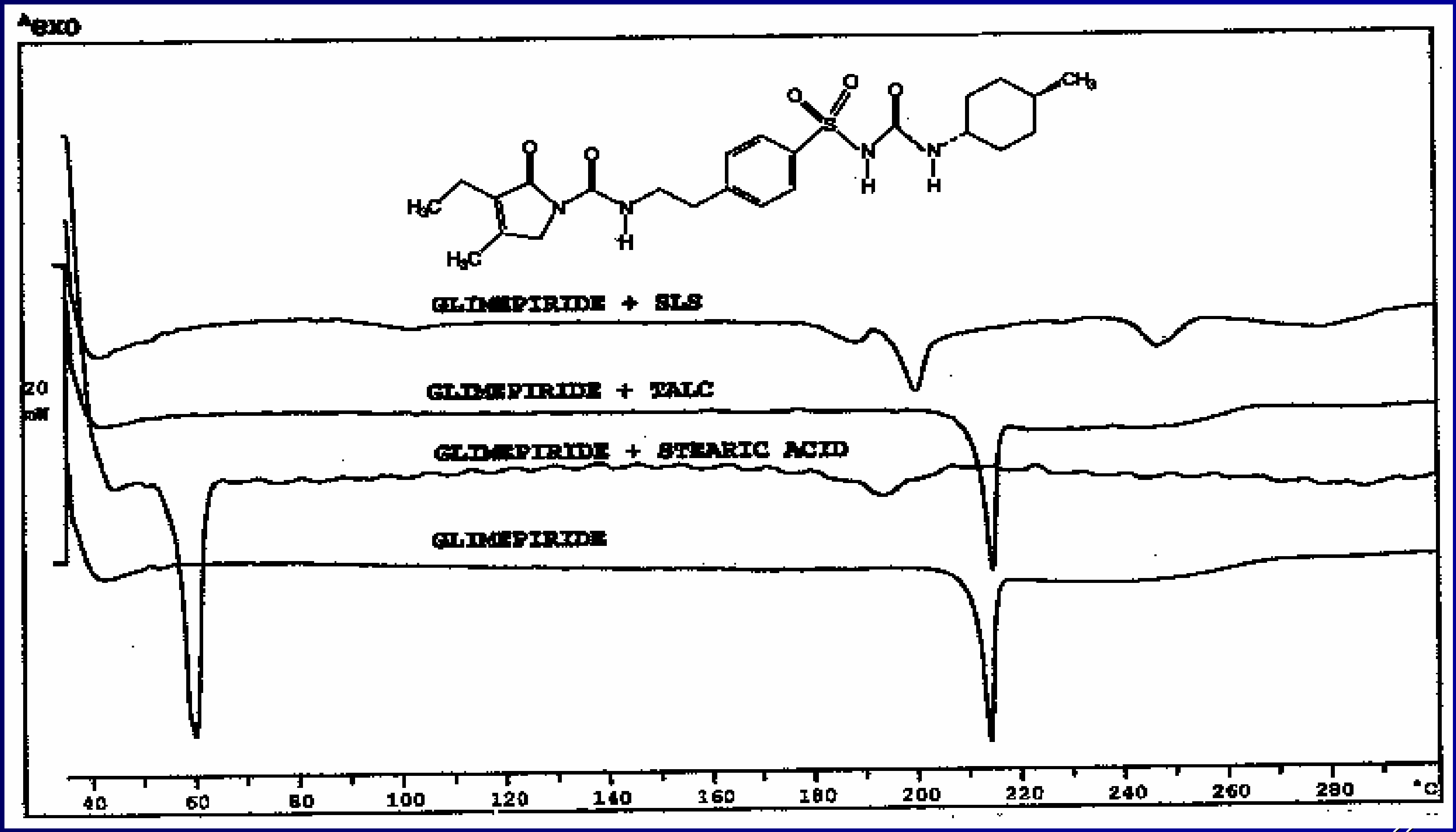
Ibuprofen-Mg Oxide interaction by DSC



Excipient Interaction Study (Oxethazaine)



Excipient Interaction Study (Glimiperide)



Isothermal Calorimetry

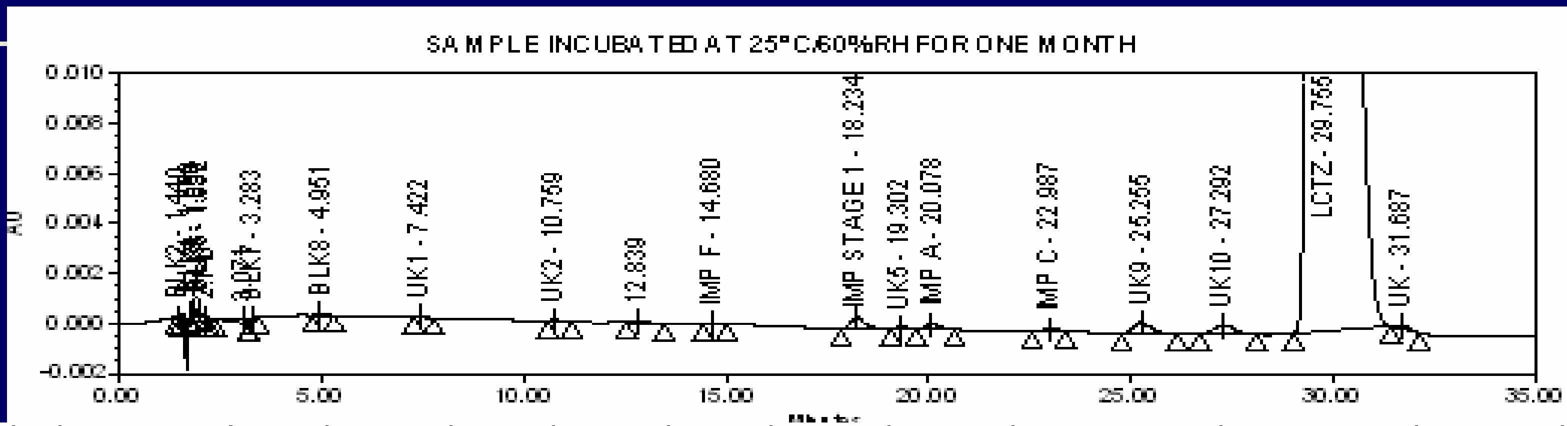
Time-averaged integration power (*P*) values for 16 excipients tested for compatibility

Functional class	Excipient	Interaction power
Diluents	Dibasic calcium phosphate	5.23
	Microcrystalline cellulose	2.92
	Lactose monohydrate	−0.345
	Pregelatinised starch	−1.31
Lubricants	Calcium stearate	12.15
	Sodium stearyl fumarate	10.66
	Magnesium stearate	6.51
	Zinc stearate	2.08
	Hydrogenated cottonseed oil	0.516
	Stearic acid	0.512
	Colloidal silicon dioxide	0.32
Binders and disintegrants	Sodium starch glycolate	7.12
	Povidone K30	2.59
	Crospovidone	2.37
	Hydroxypropyl methylcellulose	1.78
	Hydroxypropyl cellulose	1.66

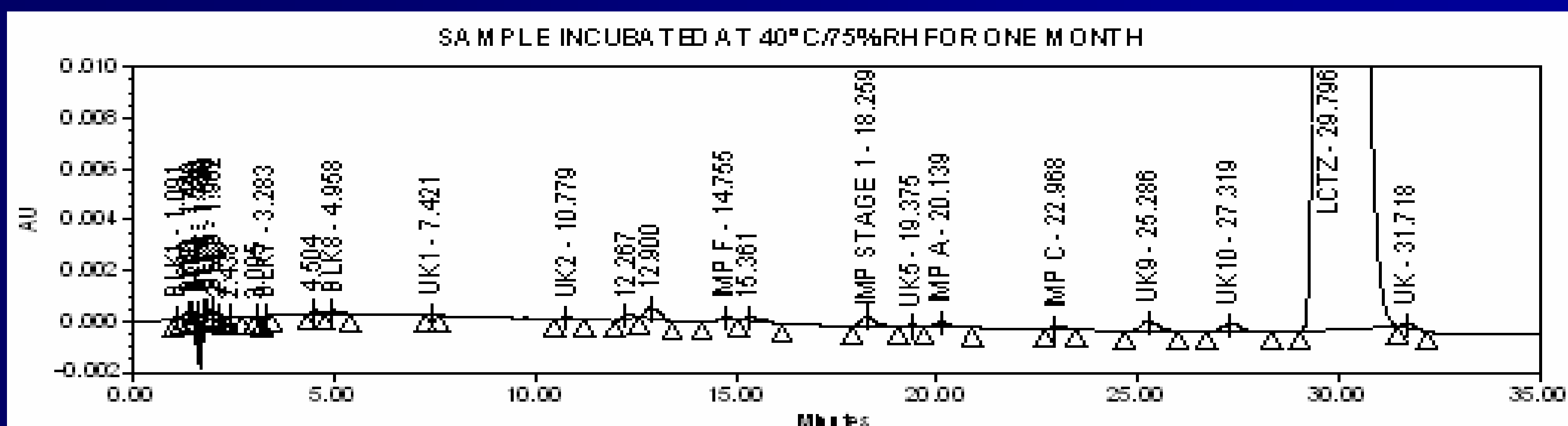
Results from an HPLC-based compatibility (parallel) study for ABT-627 [51]

	Area percent impurities		
Excipient	Initial	After 3 weeks	After 5.2 weeks
Dibasic calcium phosphate	0	0.006	0.22
Microcrystalline cellulose	0	0.056	0.108
Pregelatinised starch	0.05	0.048	0.102
Lactose monohydrate	0	0.051	0.076
Magnesium stearate	0.546	1.23	2.04
Stearic acid	0	0.05	0.03
Povidone K30	0.059	0.10	0.54
Sodium starch glycolate	0	0.21	0.51
Crospovidone	0.052	0.25	0.39
Drug only (control)	0	0.07	0.05

Levocetirizine- Lactose anhydrous interaction study by HPLC

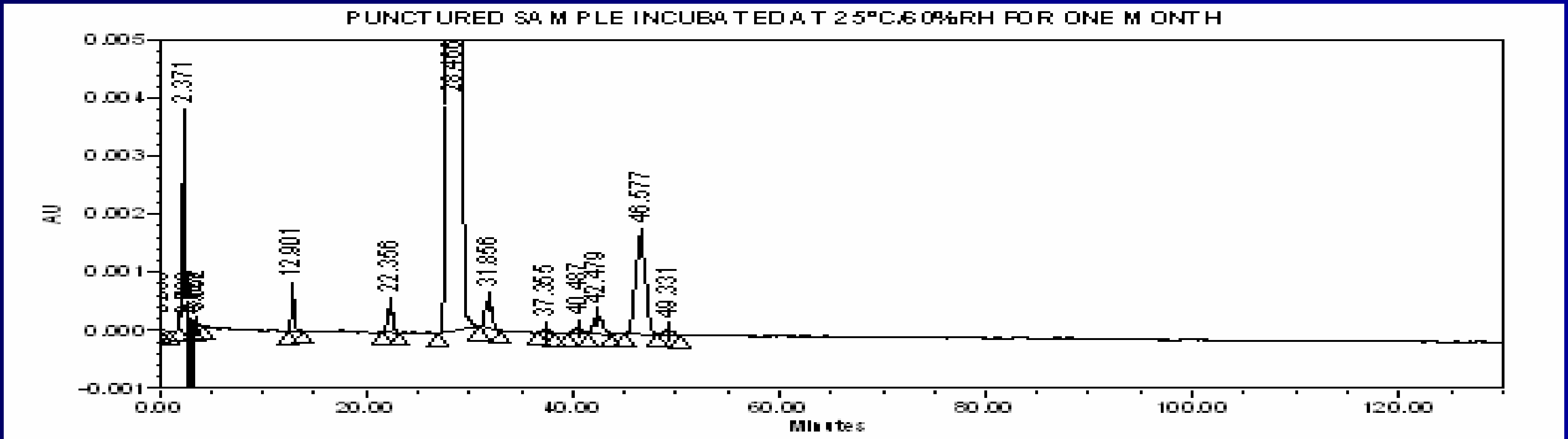


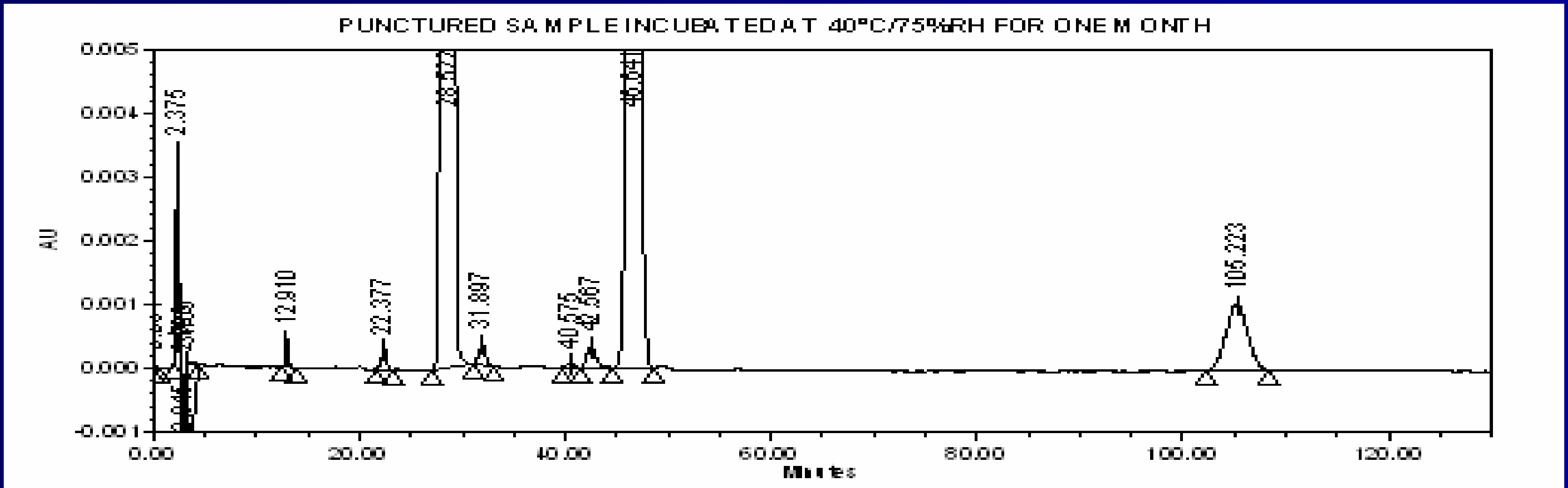
13		12.839	2487	0.02		100			5548	3.89	1.64



17		12.900	10289	0.07		416			5922	1.08	1.31

Rosuvastatin with Ac-Di-sol (Cross carmasol)





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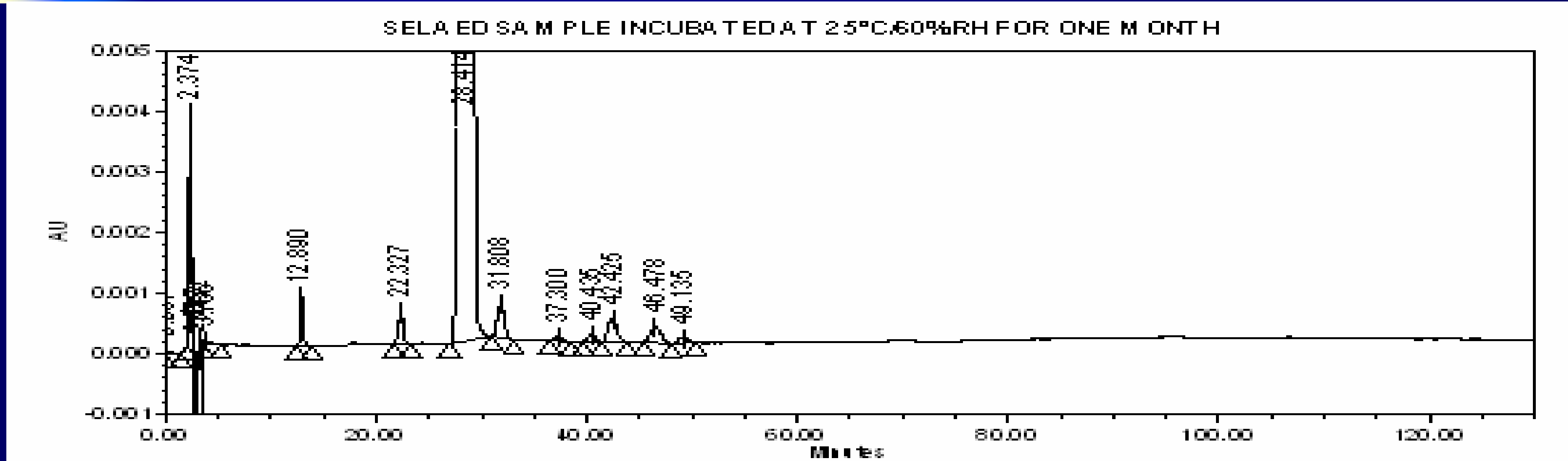
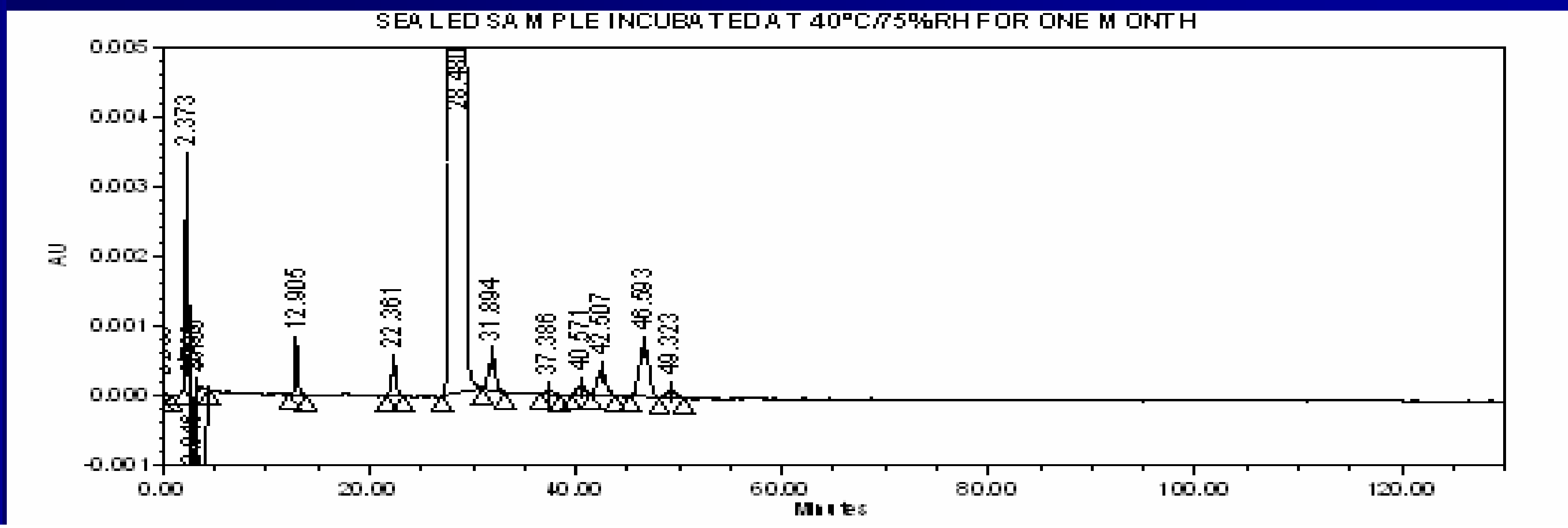
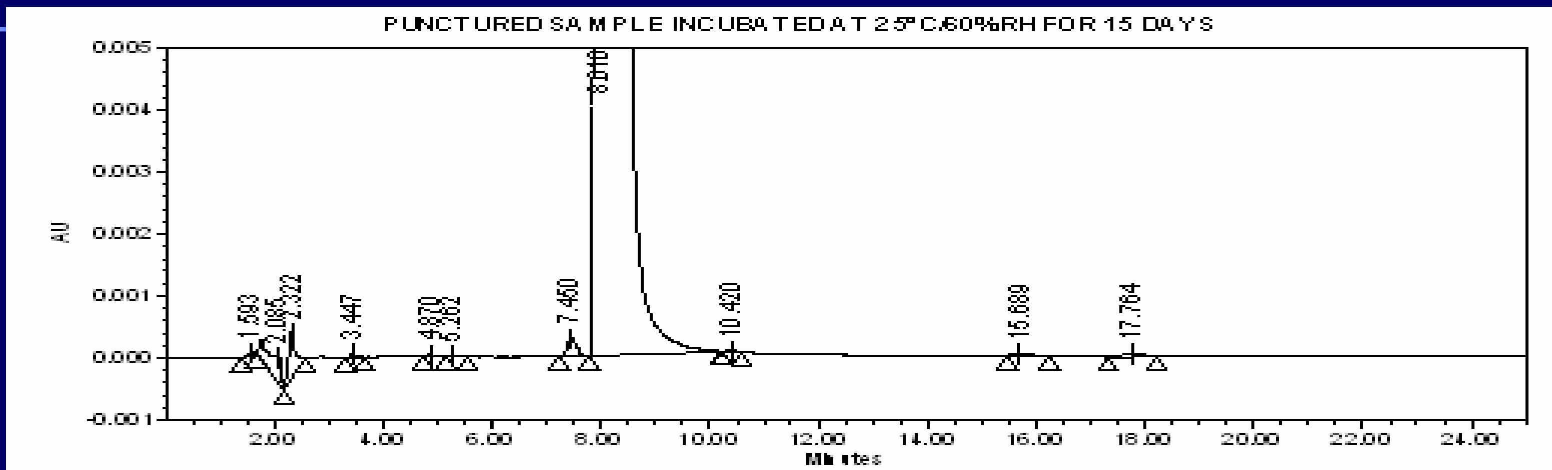
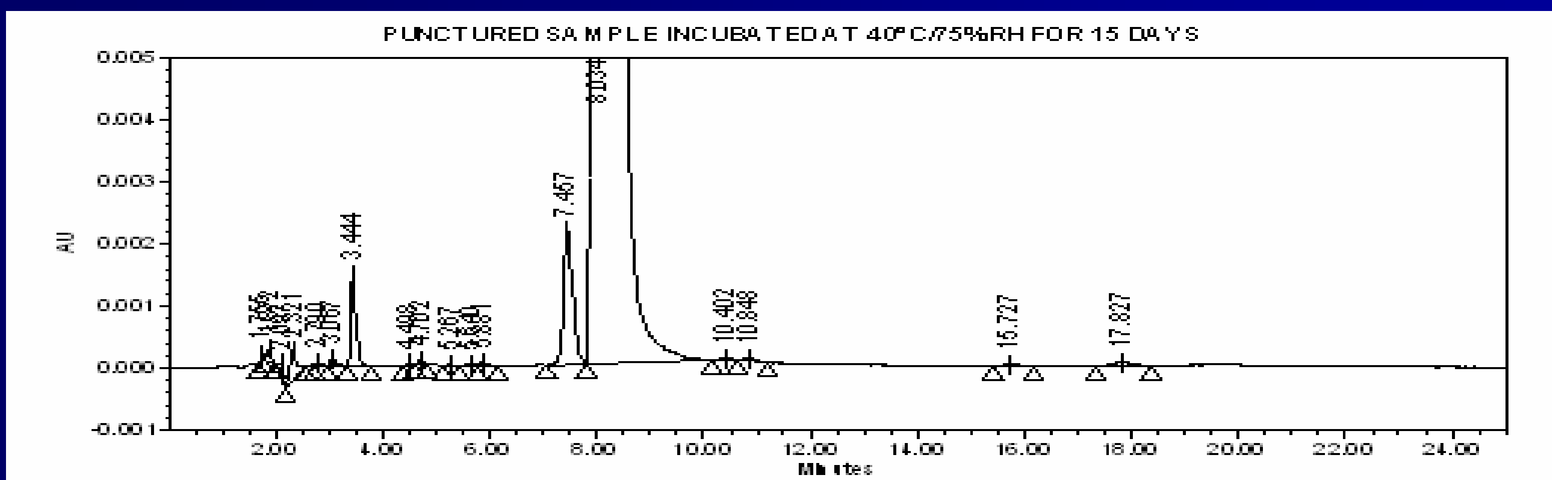


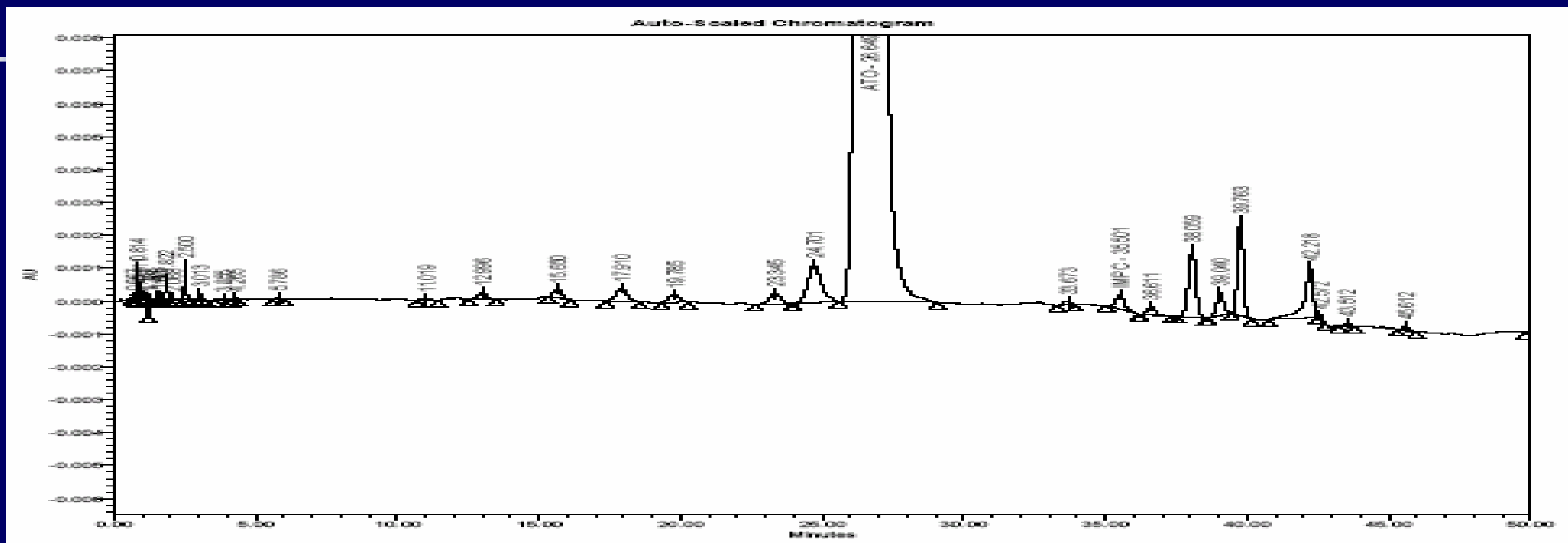


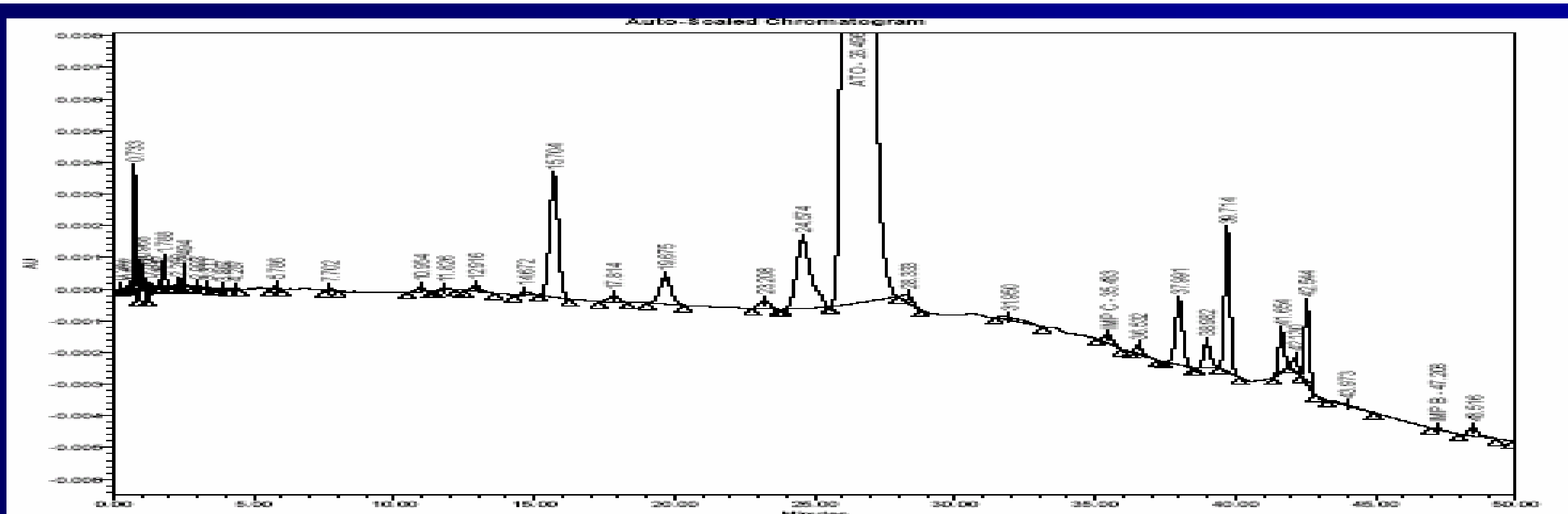
Ropinirole interaction with with colloidal silicondioxide





Atorvastatin with Meglumine

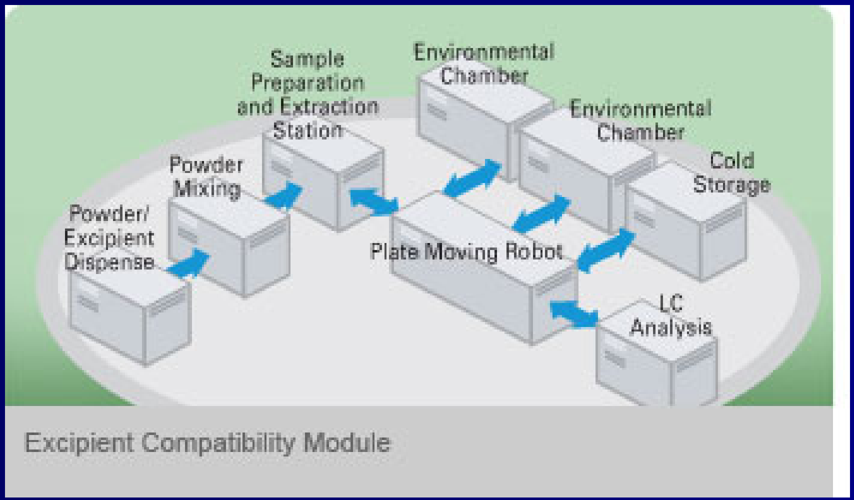




Drug Combinations

- Objective is to minimise incompatibilities: Degradation pathways of the two APIs could be different, so a stabilisation strategy for API #1 could destabilise API *#2*.
- In this situation, first intent strategy could be to prepare, separate compression blends of each individual API and compress as a bi-layer tablet
  - Disadvantages: adds complexity and bi-layer rotary presses are expensive
- Alternatively, could compress one of the APIs and over-encapsulate this into a capsule product, along with the powder blend from the second API
  - Disadvantage are that capsule size could be large, it requires specialised encapsulation equipment to fill tablets and blend... process is more complex and expensive

Symyx work station



Prepare: Increase the Scope of Your Study

• **Test a variety of excipients and excipient compositions** for compatibility with a range of drug/API concentrations/loadings.

• **Create, schedule, and replicate sample stressing conditions including** temperature, time/duration, humidity/moisture level, pH, and light exposure.

www.symyx.com

Concluding Remarks

Drug-excipient studies are an important foundation tool early in the development of drug products. They influence stability by ....

- Drug dissolution
- Melting time of suppositories
- Drug release rate
- Drug leakage
- Aggregation, precipitation & conformation
- Moisture adsorption
- Discoloration
- mechanical strength

Know more about your drug and excipients to minimize Late stage development surprises

Thanks…….

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