

ISSN: 2231-3354
Received: 29-07-2011
Revised on: 02-08-2011
Accepted: 04-08-2011

Drug-excipient interaction and its importance in dosage form development

Nishath Fathima, Tirunagari Mamatha, Husna Kanwal Qureshi, Nandagopal Anitha and Jangala Venkateswara Rao

Nishath Fathima, Tirunagari Mamatha, Husna Kanwal Qureshi, Nandagopal Anitha and Jangala Venkateswara Rao
Sultan-UI-Uloom College of Pharmacy, Banjara Hills, Hyderabad - 500034, A.P., India.

ABSTRACT

Excipients are included in dosage forms to aid manufacture, administration or absorption. Although considered pharmacologically inert, excipients can initiate, propagate or participate in chemical or physical interactions with drug compounds, which may compromise the effectiveness of a medication. Excipients are not exquisitely pure. Even for the most commonly used excipients, it is necessary to understand the context of their manufacture in order to identify potential active pharmaceutical ingredients interactions with trace components. Chemical interactions can lead to degradation of the active ingredient, thereby reducing the amount available for therapeutic effect. Physical interactions can affect rate of dissolution, uniformity of dose or ease of administration.

Key words: Excipient, Drug, Interaction, Physical, Chemical.

INTRODUCTION

Pharmaceutical dosage form is a combination of active pharmaceutical ingredients (API) and excipients. Excipients are included in dosage forms to aid manufacture, administration or absorption (Crowley and Martini). The ideal excipients must be able to fulfill the important functions i.e. dose, stability and release of API from the formulation. Although considered pharmacologically inert, excipients can initiate, propagate or participate in chemical or physical interactions with drug compounds, which may compromise the effectiveness of a medication. Excipients are not exquisitely pure. In common with virtually all materials of minerals, synthetic, semi-synthetic or natural origin manufacture involves using starting materials, reagents and solvents. Residues invariably remain after isolation. Often, it is the multi-component nature of the excipient that drives many of the interactions with APIs. Even for the most commonly used excipients, it is necessary to understand the context of their manufacture in order to identify potential API interactions with trace components. Excipients may have functional groups that interact directly with active pharmaceutical ingredients. Alternatively, they may contain impurities or residues, or form degradation products in turn cause decomposition of the drug substance. For the development of proposed pharmaceutical dosage form, three main components which should be consider are (Moreton, 2006)

- a. Properties and limitation of API
- b. Properties and limitation of excipients
- c. Advantage and limitation of method(s) used

In term of development of dosage form, all three considerations are of equally important. Excipients are the substances other than API which are intentionally incorporated into

For Correspondence:
Nishath Fathima
*Department of Quality assurance,
Sultan-UI-Uloom College of Pharmacy,
Banjara Hills, Hyderabad, India.*

pharmaceutical dosage form for specific purposes (Bhattacharya, 2006) such as;

- a. Improvement of the stability of API in the dosage form
- b. Modulation of bioavailability of active pharmaceutical ingredients
- c. Maintain the pH of liquid formulation
- d. Maintain the rheology of semisolid dosage form
- e. Act as tablet binders, tablet disintegrant
- f. Act as antioxidant and emulsifying agents
- g. To allow the adequate administration
- h. To facilitate the manufacturing of dosage form
- i. For aesthetic reason
- j. For identification

Definition of excipients as developed by IPEC (International Pharmaceutical Excipients Council) America And IPEC Europe is, "These are the substance(s) other than the API which has been appropriately evaluated for safety and is included in a drug delivery system to either aid processing of the system during manufacturing or protect, support or enhance stability, bioavailability or patients compliances or assist in product identification and enhance any other attributes of overall safety and effectiveness of drug product during storage or use " (Blecher, 1995).

Excipients are classified according to their functions (Edward et al., 2005) as:

- Binders
- Disintegrants
- Fillers (diluents)
- Lubricants
- Glidants
- Compression aids
- Colors
- Sweeteners
- Preservatives
- Flavors
- Film formers/coatings
- Suspending/dispersing agents/surfactants

In pharmaceutical dosage form API are in intimate contact with one or more excipients. Moreover in most of dosage form the quantity of excipients are greater than the amount of API present in dosage form, for example typically a tablet contain binders, disintegrants, lubricants, and fillers, therefore excipients can have tremendous impact on the performance of API when present in dosage form. It can influence the safety and effectiveness of drug depending upon route of administration, for example in solid dosage form excipients can affect safety and effectiveness by promoting or delaying gastrointestinal release. Therefore, understanding of drug-excipients interactions is very important during selection of appropriate excipients for proposed dosage form.

Mode of drug decomposition

Medicinal agents invariably have structural features that

interact with receptors or facilitate metabolic handling. These inevitably confer some degree of lability, making them vulnerable to degradation (and interaction with other materials). Common modes of degradation are described below

Hydrolysis

Drugs with functional groups such as esters, amides, lactones or lactams may be susceptible to hydrolytic degradation. It is probably the most commonly encountered mode of drug degradation because of the prevalence of such groups in medicinal agents and ubiquitous nature of water. Water can also act as a vehicle for interactions or facilitates microbial growth.

Oxidation

Oxidative degradation is second only to hydrolysis as a mode of decomposition. In contrast to hydrolysis, oxidative mechanisms are complex, involving removal of an electropositive atom, radical or electron or, conversely, addition of an electronegative moiety. Oxidation reactions can be catalyzed by oxygen, heavy metal ions and light, leading to free radical formation. Free radicals react with oxygen to form peroxy radicals which in turn react with oxidizable compound to generate additional free radicals to fuel further reactions. Aldehydes, alcohols, phenols, alkaloids and unsaturated fats and oils are all susceptible to oxidation.

Isomerization

Isomerization involves conversion of a chemical into its optical or geometric isomer. Isomers may have different pharmacological or toxicological properties. For example, the activity of levo (L) form of adrenaline is 15-20 times greater than for the dextro (D) form.

Photolysis

Reactions such as oxidation-reduction, ring alteration and polymerization can be catalyzed or accelerated by exposure to sunlight or artificial light. Energy absorption is greater at lower wavelengths and, as many as drugs absorb UV light; degradation by low wavelength radiation is common. Exposure to light almost invariably leads to discoloration even when chemical transformation is modest or even undetectable.

Polymerization

Intermolecular reactions can lead to dimeric and higher molecular weight species. Concentrated solutions of ampicillin, an amino-penicillin, progressively form dimer, trimer and ultimately polymeric degradation products (Bundgaard, 1976). Table 1 lists examples of medicinal agents susceptible to such modes of degradation. Degradation may reflect vulnerability to environmental stresses such as heat, humidity, light or drug-drug interactions. Degradation may also be facilitated or promoted by excipients possessing the requisite functional groups for interaction, or containing residues that catalyze/participate in degradation processes. If excipients are also susceptible to change, this provides additional possibilities for the generation of species that participate in break-down processes.

Table 1 : Modes of degradation of medicinal agents

Hydrolysis	Oxidation	Isomerization	Photolysis	Polymerization
Methyl dopa Procaine Penicillins	Calcitonin Ascorbic acid isoprenaline	Tetracycline Vitamin A Adrenaline	Riboflavin Folic acid Nifedipine	Ceftazidime Ampicillin

Mechanism of drug-excipients interaction

Exact mechanism of drug excipients interaction is not clear. However, there are several well documented mechanisms in the literature. Drug-excipients interaction occurs more frequently than excipient-excipient interaction (Pifferi et al., 2003; Cavatur et al., 2004). Drug-excipients interaction can either be beneficial or detrimental, which can be simply classified (Moreton, 2006) as

1. Physical interactions
2. Chemical interactions

Physical interactions

It is quite common, but is very difficult to detect. A physical interaction doesn't involve any chemical changes. Physical interactions are frequently used in manufacturing of dosage form, for example to modify drug dissolution. However many of the physical interactions are unintended which usually causes the problems. Physical interaction can either be beneficial or detrimental to product performance.

An example of a physical interaction between an API and an excipient is that between primary amine drugs and microcrystalline cellulose. When dissolution is carried out in water a small percentage of the drug may be bound to the microcrystalline cellulose and not released. For high-dose drugs, this may not be a major issue, but for low dose drugs it can lead to dissolution failures. This has caused problems in the past, but the phenomenon can be remedied by carrying out dissolution using a weak electrolyte solution for the dissolution medium (e.g., 0.05 M HCl). Under these revised dissolution test conditions, adsorption onto the microcrystalline cellulose is very much reduced and 100% dissolution may be achieved even for low-dose APIs (Edge et al., 2003).

A general example of a physical interaction is interactive mixing. In this smaller particles (typically the APIs) interact with the surface of the larger carrier particles (typically the excipients) through physical forces. In this way we obtain a more homogenous powder blend. After the medicine, e.g., a tablet has been administered to the patient, the aqueous environment of the gastrointestinal tract (GIT) either causes the smaller API particle or other carrier particles to dissolve or causes the surface interactions to change to allow the smaller particles to be released from the larger carrier particles.

But as we have already stated, physical interactions can also be detrimental, and magnesium stearate is recognized within the pharmaceutical industry for causing problems such as reduced tablet "hardness" and dissolution from tablets and capsules.

Adsorption of drug molecules onto the surface of excipients can render the drug unavailable for dissolution and diffusion, which can result in reduced bioavailability. For example, antibacterial activity of cetylpyridinium chloride was decreased

when magnesium stearate was used as lubricants in tablet containing cetylpyridinium chloride; this was due to adsorption of cetylpyridinium cation by stearate anion on magnesium stearate particle (Mackay et al., 1996). In one of the investigation, it was observed that dissolution of drug was decreased due to adsorption of drug on the surface of microcrystalline cellulose. In a similar context, adsorption of novel k-opoid agonist by microcrystalline cellulose led to incomplete drug release from the capsules. Adsorption may also initiate chemical breakdown. Colloidal silica was shown to catalyze nitrozapam degradation in tablet dosage form, possibly by adsorptive interactions altering electron density in the vicinity of the labile azo group and thus facilitating attack by hydrolyzing entities (Czaja and Mielck, 1982).

Complexing agents usually bind reversible with drugs to form complex, which do not allow them to dissolve, complexing agent such as cyclodextrin are often used to increase the bioavailability of poorly water soluble drugs (Rajewski and Stella, 1997).

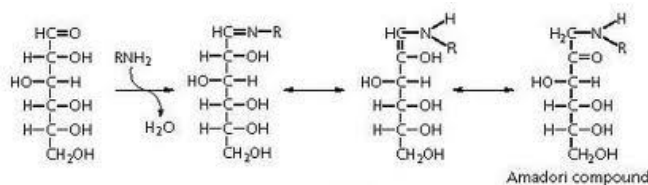
However, it was found that complexation of cyclodextrin with non-steroidal anti-inflammatory drug (NSAID) naproxen and tolbutamide (Hoffman et al., 1993) increased the dissolution, but there was no corresponding increase in bioavailability. Phenobarbital formed an insoluble complex with PEG-400, which resulted in slower dissolution and decreased absorption (Bhatia et al., 1996). In-vitro evaluation of complexation of steroids prednisolone with water soluble excipients, showed increased dissolution, but the complexes were having high molecular weight and might be too large to diffuse through GI membrane, therefore it may be possible that in-vivo bioavailability of prednisolone would be lower (Fincher et al., 1973)

Chemical interactions

Chemical interaction involves chemical reaction between drugs and excipients or drugs and impurities/ residues present in the excipients to form different molecules. Chemical interactions are almost detrimental to the product because they produce degradation products, different degradation product are classified as in ICH guideline ICHQ3B (ICH guideline ICHQ3B, 2008). Different types of chemical drug-excipients interaction have been reported in the literature.

Chemical interactions between drug and excipients.

Primary amine group of chlorpromazine undergoes Maillard reaction with glycosidic hydroxyl group of reducing sugar dextrose to form imine, which finally breakdown to form Amadori compounds (Horiuchi et al., 1997) (Figure 1).

**Fig 1:** Maillard reaction

In one another study it was observed that release of diclofenac sodium from matrix tablet was inhibited by polymer chitosan at low pH, most possibly via formation of ionic complex between diclofenac sodium and ionized cationic polymer (Block et al., 1997).

Secondary amines may also interact with reducing sugars. However, the reaction cascade does not proceed beyond the formation of the imine, and thus no coloration develops (Baertschi et al., 1998)

Primary amines may interact with double bonds in a reaction analogous to a Michael addition reaction (e.g., fluvoxamine maleate, where the fluvoxamine primary amine group can interact with the double bond in the maleic acid counterion). Examples of excipients that contain double bonds include sodium stearyl fumarate and sorbitan monooleate.

Certain APIs are susceptible to oxidation, e.g., atorvastatin and cytidine nucleoside analogues. Fumed metal oxides (e.g., fumed silica, fumed titania, and fumed zirconia) can promote such oxidation reactions.

These reactions are more complex in some ways, and less easy to predict. Lactone formation because of the close proximity of heteroatoms and an active hydrogen atom in the molecule, e.g., benazepril.

Suspending agents such as sodium alginate dissolve in water to form large negatively charged anions, co-formulation in aqueous systems with drugs such as neomycin and polymyxin (active moieties of which are positively charged) result in precipitation.

Silicon dioxide catalyzes oxidation of diethylstilbestrol to the peroxide and conjugated quinone degradation products. Air auto-oxidation of methyl linoleate to peroxides with subsequent decomposition to aldehydes has been shown to be accelerated in the presence of colloidal silicon dioxide (Tischinger et al.). Interaction between chloramphenicol stearate and colloidal silica during grinding leads to polymorphic transformation of the chloramphenicol, demonstrating that unwanted effects of excipients are not restricted to chemical transformations (Forni et al., 1988).

Interaction of drug with excipient residues/ impurities

Excipients are not exquisitely pure. In common with virtually all materials of minerals, synthetic, semi-synthetic or natural origin manufacture involves using starting materials, reagents and solvents. Residues invariably remain after isolation. Low levels of residues may have a greater impact than might be expected, however- particularly where the ratio of excipient to drug is very high, or where the residue has low molecular weight or acts as a catalyst.

Table 2 illustrates how reactive chemical entities are commonplace in widely used excipients. The list is not comprehensive, perhaps reflecting the absence of such information in most pharmacopoeial monographs, as well as the reluctance of excipient providers to be forthcoming about modes of manufacture and types of residues in their products.

Table 2 : Impurities found in common excipients

Excipient	Residue
Povidone, crospovidone, polysorbates	Peroxides
Magnesium stearate, fixed oils, lipids	Antioxidants
Lactose	Aldehydes, reducing sugars
Benzyl alcohol	Benzaldehyde
Polyethylene glycol	Aldehydes, peroxides, organic acids
Microcrystalline cellulose	Lignin, hemicelluloses, water
Starch	Formaldehyde
Talc	Heavy metals
Dibasic calcium phosphate dihydrate	Alkaline residues
Stearate lubricants	Alkaline residues
Hydroxypropylmethyl/ethyl celluloses	Glyoxal

Dextrose is widely used as tonicity modifier in the parenterals dosage form and it is used as nutrition solution. Sterilizations by autoclaving of such parenteral preparations containing dextrose can cause isomerization of dextrose in fructose and formation of aldehyde(5-hydroxymethyl furfuraldehyde), which can react with primary amino group to form Schiff base and colour development (Almond and Janicki, 1974). Wirth et al showed that Maillard reaction product was also found in capsule containing lactose and antidepressant Fluoxetine (Baertschi, 1998). Lactose is a disaccharide of glucose and galactose. These reducing sugars have been found in spray-dried lactose (Brownley et al., 1963) as has the hexose degradation product, 5-hydroxymethylfurfural, probably generated by heat encountered during spray-drying (Brownley et al., 1964). As an aldehyde, 5-hydroxymethylfurfural can participate in addition reactions with primary amino groups, resulting in Schiff base formation and colour development (Almond et al., 1974).

The presence of pH-modifying residues can accelerate hydrolytic degradation or have more esoteric effects. Most medicinal agents are salts of organic acids or bases. Residues that modify pH may lead to free base or acid formation during long-term storage. Such products may be volatile and lost by sublimation from the dosage form. This 'disappearance' without concomitant formation of degradation products can be mystifying and requires much time and effort to elucidate. Thorough characterization of the drug substance and awareness of residues in excipients may help resolve or obviate such mysteries. For example Oxazolam degrades in the presence of microcrystalline cellulose may be attribute to carboxylic acid groups on the cellulose surface in addition to effect of water.

Several studies with drug substances have shown that process operations such as grinding and drying can release bound water, which is then 'free' to participate in hydrolytic reactions (Puttipathkachorn et al., 1990; Nakagawa, 1982; Takahashi et al., 1984). Such process stresses can also be expected to loosen bound water in excipients, which may then degrade moisture sensitive drugs with which they are formulated. Such possibilities make it easy to understand why testing simple drug-excipient mixtures in excipient screening studies may not predict interactions in formulated product. Compression, attrition or other crystal disrupting stresses may be the catalyst for interaction but these are rarely mentioned as meriting investigation. For example high moisture content of polyvinyl pyrrolidone and urea enhances

aspirin hydrolysis (Figure 2). Excipients can form hydrates may enhance drug degradation by giving up their water of crystallization during grinding. Lactose hydrate enhances degradation of 4-methylphenylamino acetate hydrochloride upon grinding.

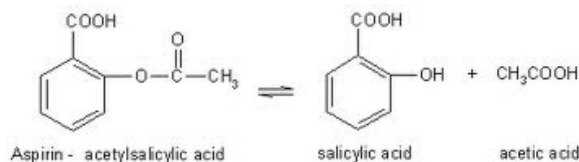


Fig 2: Hydrolysis of Aspirin.

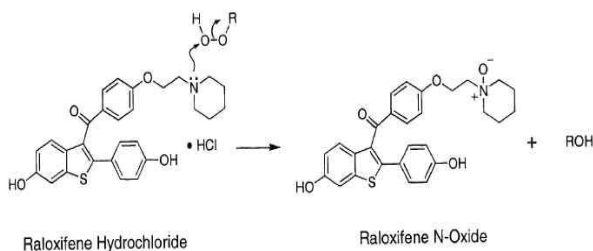


Fig 3: Degradation of Raloxifene Hydrochloride

Peroxide residues in povidone (binder) and crospovidone (disintegrant) were shown to be responsible for the enhanced formation of the N-oxide degradation product of the oestrogen receptor modulator, raloxifene (Figure 3).

A number of food industry publications provide useful insights into how processing can lead to impurity formation in food additives that are also pharmaceutical excipients. High temperatures and low moisture contents can induce caramelization of sugars and oxidation of fatty acids to aldehydes, lactones, ketones, alcohols and esters (Aidrian, 1982; Danehy 1986). Such degradation products may also be present in the same materials used in pharmaceutical dosage forms. Unfortunately, pharmacopoeial monographs rarely list such organic contaminants.

Biopharmaceutical products

The relative fragility of the proteinaceous materials in biopharmaceutical products and the frequent need for more sophisticated systems for their delivery places constraints and demands on excipients. The physical state of most biopharmaceutical products can favor interaction. The amorphous nature of most lyophiles means that destabilizers such as residual moisture are not held in a structured milieu. This amorphous state also affords greater molecular flexibility and consequent opportunities for reactions. Constant vigilance and rigorous screening are required if physical and chemical interactions that compromise quality, performance or safety are to be avoided. The reducing sugars in mannitol, an excipient widely used in parenterals, have been reported as responsible for the oxidative degradation of a cyclic heptapeptide (Dubost et al., 1996).

Non-ionic surfactants have traditionally been used as emulsion formers in topical and oral products, and more recently as

solubilizers and stabilizers in biotechnology products. They are susceptible to hydrolysis (Bates et al., 1973) and auto-oxidation (Azaz et al., 1978). Peroxide levels in polyethylene glycol solutions have been shown to increase with concentration in solution and storage time (Ding, 1993). Continuing generation of powerful oxidizing agents could be very damaging to protein structures containing cysteine, histidine, methionine or other terminal groups susceptible to oxidation.

Lipid excipients may be used to form micro-emulsions or other drug targeting systems. Most food grade lipids contain peroxides that decompose under the influence of heat and UV radiation. This can lead to free radical formation, which can in turn oxidize unsaturated groups leading to deterioration of the delivery system and also, possibly, the active ingredient (Decker et al., 1999). Storage conditions use periods and limits for residues need to be established for such excipients. Such information needs to be generated by rigorous and suitably controlled investigative studies. An antioxidant butylated hydroxyl toluene (BHT) has been shown to inhibit peroxide formation in Tween 20 during storage (Jaeger et al., 1994). It is common to include such stabilizers in oxidizable excipients. Inadvertent removal, or replacement by the excipient provider, could precipitate a stability crisis in a product where the additive was unknowingly stabilizing the active ingredient as well. Such possibilities make it imperative that change control and notification agreements are in place between provider and pharmaceutical manufacturer, particularly for biopharmaceutical products, as these cannot be subject to the same definitive analytical characterization as small molecule medicinal agents.

Excipients may be an indirect cause of degradation in biopharmaceutical products. Succinate buffer was shown to crystallize during the freezing stage of a lyophilization cycle, with associated pH reduction and unfolding of gamma interferon (Lam et al., 1996). Human growth hormone, lyophilized in the presence of sodium chloride, showed severe aggregation and precipitation, as well as accelerated oxidation and deamidation (Pikal et al., 1991). Such examples of chemical and physical stability of excipients re-enforce the desirability of performing process-simulating stress testing.

CONCLUSION

Many stability problems encountered during development and post-commercialization can be ascribed to inadequate matching of the ingredients in dosage forms, lack of awareness of the complexities of chemical and physical interactions, or the unheralded presence of a residue in one of the excipients. Many such issues concern low levels of novel entities formed by drug-excipient interactions that pose questions concerning safety or tolerance. Such incidents have probably been increased by the growing sophistication of analytical techniques to detect, identify and quantitate low level impurities.

Drug-excipient interactions may take a long time to be manifested in conventional stability testing programmes, and are not always predicted by stress and pre-formulation studies. They can complicate and compromise a development programme or the viability of a commercial product. It is possible to reduce the

probability of such undesirable and costly scenarios by allaying knowledge of the propensity of a drug to undergo degradation reactions with an awareness of excipient reactivity and of the residues that they may contain. Such awareness may help to anticipate undesirable interactions and avoid their occurrence. A judicious choice of excipients or control of their quality will exclude or limit residues promoting degradation. It is surprising, therefore, that there is a paucity of information in compendia or other publications on potentially damaging residues in even the most common excipients. It is a sphere of activity that groups attempting to harmonize excipient monographs do not seem to have addressed, and it is to be hoped that 'least common denominator' considerations in harmonization initiatives do not exacerbate the situation. Perhaps it could be a subject for a future initiative.

In summary, knowledge of drug–excipient interactions is a necessary prerequisite to the development of dosage forms that are stable and of good quality. It is hoped that this review provides some perspective of this important area of pharmaceutical technology.

REFERENCES

- Aidrian J. (1982). The Maillard Reaction. In M. Rechcigl (Ed.) Handbook of the Nutritive Value of Processed Food, Vol. 1 (pp 529-608). Boca Raton, Florida, USA.
- Almond HR., Janicki CA., Jr. Reaction of Haloperidol with 5 (Hydroxymethyl)-2-Furfuraldehyde, an Impurity in Anhydrous Lactose. *J. Pharm. Sci.* 1974; 63: 41–43.
- Azaz E., Donbrow M., Pillersdorf AM. Autoxidation of Polysorbates. *J. Pharm.Sci.* 1978; 67(12): 1676–1681.
- Baertschi SW, Johnson RA, Wirth DD, et al. Maillard reaction of lactose and fluoxetine hydrochloride, a secondary amine. *J Pharm Sci* 1998; 87(1): 31-39
- Baertschi SW., Gregg SM., Hallenbeck DK., Johnson RA., Maple SR., Miller MS., Wirth DD. Maillard reaction of lactose and fluoxetine hydrochloride, a secondary amine. *J.Pharm, Sci.*1998; 87: 31-39
- Bates TR., Dixon E., Nightingale CH. Kinetics of Hydrolysis of Polyoxy-ethylene (20) Sorbitan Fatty Acid Ester Surfactants. *J. Pharm. Pharmacol.* 1973; 25(6): 470-477.
- Bhatia VN., Benet LZ., Guillory JK., Singh P., Sokoloski TD. Effect of inert tablet ingredients on drug absorption. I. effect of PEG 4000 on intestinal absorption of four barbiturates. *J. Pharm. Sci.* 1996; 55:63-68.
- Bhattacharya L. Excipients quality in Pharmaceutical development: Understanding their function benefits process control. *Contract pharma*, article, June 2006.
- Blecher L. Excipients-the important components. *Pharm process.* 1995; 12(1): 6-7.
- Block LH., Pankaj Reg, Sabnis S. Use of chitosan in compressed tablets of Diclofenac sodium: inhibition of drug release in an acidic environment. *Pharm. Dev. Technol.* 1997; 2: 243–255.
- Brownley CA., Jr, Lachman L. Browning of Spray-Processed Lactose. *J. Pharm. Sci.* 1964; 53: 452–454.
- Brownley CA., Jr, Lachman L. Preliminary Report on the Comparative Stability of Certified Colorants with Lactose in Aqueous Solution. *J. Pharm. Sci.* 1963; 52: 8–93.
- Bundgaard H. Polymerization of Penicillins: Kinetics and Mechanism of Di- and Polymerization of Ampicillin in Aqueous Solution. *Acta Pharma. Suec.* 1976; 13(1): 9–26.
- Cavatur R., Chrzan Z., Vemuri NM. Use of isothermal microcalorimetry in pharmaceutical Preformulation studies Part III. Evaluation of excipients compatibility of a new chemical entity. *J Therm Anal Cal.* 2004; 78: 63-72.
- Crowley PJ and Martini LG. Excipients in Pharmaceutical Products: Encyclopedia of Pharmaceutical Technology. New York: Marcel Dekker Inc.
- Czaja J.and Mielck JB. Solid-State Degradation Kinetics of Nitrazepam in the Presence of Colloidal Silica. *Pharm. Acta. Helv.* 1982; 57(5–6): 153–155.
- Danehy JP. Maillard Reactions: Non-Enzymic Browning in Food Systems with Specific Reference to the Development of Flavour. *Adv. Food Res.* 1986; 30: 77–138.
- Decker EA., Mancuso JR. and McClements JD. Ability of Iron to Promote Surfactant Peroxide Decomposition and Oxidize Alpha Tocopherol. *J. Agri. Food.Chem.* 1999; 47: 4146–4149.
- Ding S.Quantitation of Hydroperoxides in the Aqueous Solutions of Non-Ionic Surfactants using Polysorbate 80 as the Model Surfactant. *J. Pharm. Biomed. Anal.* 1993; 11(2): 95–101.
- Dubost et al. Characterization of a Lyophilized Formulation of a Cyclic Solid-State Reaction Product from a Heptapeptide. A Novel Example of an Excipient-Induced Oxidation. *Pharm. Res.* 1996; 12: 1811–1814.
- Edge S, Moreton RC, Staniforth JN. Adsorption of an amine drug onto microcrystalline cellulose and silicified microcrystalline cellulose samples. *Drug Dev Ind Pharm* 2003; 29 (4): 475-487.
- Edward M., Rudnic, Schwartz JB (2005). Oral solid dosage forms. Remington Science and Practice of Pharmacy, (Ed 21) Williams and Wilkins. (pp889-928). Baltimore, USA.
- Fincher JH., Lach JL., Northern RE., Dissolution–dialysis method of assessing in vitro drug availability of prednisolone tablets. *Am. J. Hosp. Pharm.* 1973; 30:622-7.
- Forni et al. The Grinding of the Polymorphic Forms of Chloramphenicol Stearic Ester in the Presence of Colloidal Silica. *Acta Pharma. Suec.* 1988; 25(3): 173–180.
- Hoffman M., Kedzierewicz F., Maincent P., Zinutti C. Bioavailability study of tolbutamide β- cyclodextrin inclusion compounds, solid dispersion and bulk powder. *Int J.Pharm.* 1993; 94:69-74.
- Horiuchi S., Ikeda K., Kayashima K., Mizutari K, Ono T. Photo-Enhanced Modification of Human Skin Elastin in Actinic Elastosis by N-(Carboxymethyl)lysine, One of the Glycoxidation Products of the Maillard Reaction. *J. Inve. Dermatology.* 1997; 108: 792-802.
- ICH guideline ICHQ3B (2008). [http:// www. ich. org/ LOB/ media/MEDIA421.pdf](http://www.ich.org/LOB/media/MEDIA421.pdf).
- Jaeger J., Sorensen K. and Wolff SP. (1994). Peroxide Accumulation in Detergents. *J. Biochem. Biopharm. Methods.* 1994; 29: 77–81.
- Lam et al.(1996). Replacing Succinate with Glycollate Buffer Improves the Stability of Lyophilized Gamma Interferon. *Int. J. Pharm.* 1996; 142: 85–95.
- Mackay KM., Michael R., Richards E., Xing JZ. Excipients interaction with Cetylpyridinium chloride activity in tablet based lozenges. *Pharm. Res.*1996; 13: 1258-1264.
- Moreton RC (2006). Excipients interactions. In: Ashok Katdare, Mahesh V. Choubal (Ed.) Excipients Development for Pharmaceutical, Biotechnology and Drug Delivery System (pp.93-108). New York: Informa Health Care.
- Nakagawa H., Sugimoto I., Takahashi Y. The Effects of Grinding and Drying on the Solid State Stability of Sodium Prasterone Sulfate. *Chem. Pharm. Bull.* 1982; 30(1): 242–248.
- Pifferi G., Restani P. The safety of pharmaceutical excipients. *II Farmaco.* 2003; 58: 541-550.
- Pikal et al. The Effects of Formulation Variables on the Stability of Freeze-Dried Human Growth Hormone. *Pharm. Res.* 1991; 8(4):427–436.
- Puttipipatkachorn et al. Effect of Grinding on Dehydration of Crystal Water of Theophylline (accelerated by mechanical impact and heat during drying). *Chem. Pharm. Bull.* 1990; 38(8): 2233–2236.
- Rajewski, RA., Stella VJ. Cyclodextrins: their future in drug formulation and delivery. *Pharm. Res.* 1997; 14: 556–567.
- Takahashi et al . Effects of Grinding and Drying on the Solid-State Stability of Ampicillin Trihydrate. *Chem. Pharm. Bull.* 1984; 32(12): 4963–4970.
- Tischinger H.,Wagner et al. Oxidative Degradation of Linoleic Acid Methyl ester in Suspensions of Inorganic Excipients. Part I. *Pharmazie* 42: 320–324.