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Drug-Excipient Interactions: An Overview on Mechanisms and Effects on Drug Stability and Bioavailability

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Abstract

Drugs are administered as medicines or drug products which are composed of active substance and excipients. Excipients are not inert materials, they can interact with the active substance or with other materials in the surroundings. In this review, drug-excipient interactions (DEI) will be reviewed in two parts. In this first part, a definition of DEI will be proposed. The classification systems will be reviewed, however, the main classes, namely, chemical, physical, and biopharmaceutical will be defined and subclassified accordingly. Physical interactions occur mainly in three forms: complexation, adsorption, or solid dispersions. Chemical interactions occur mainly as hydrolysis, oxidation, Maillard reaction, isomerization, or polymerization. Biopharmaceutical interactions occur after drug administration and mainly affect the pharmacokinetics of the drugs. All these interactions will be defined and explained through the many examples picked from the up-to-date literature. The impact of such interactions on drug release from dosage forms, drug stability in the dosage forms, drug dissolution, absorption, and bioavailability after administration to patients will be briefly explained.

Keywords: Drug-Excipients Interactions, Physical interactions, chemical interactions, adsorption, solid dispersion, complexations, hydrolysis, oxidations.

1- Introduction

Drugs are rarely administered as pure chemical substances alone and are almost always given as formulated preparations or medicines. These can vary from relatively simple solutions to complex drug delivery systems through the use of appropriate additives or excipients in the formulations[1].The term, excipients, came from the Latin word excipiens, present participle of the verb "excipere" which means to receive, to gather, to take out. This refers to one of the properties of an excipient, which is to ensure that a medicinal product has the weight, consistency, and volume necessary for the correct administration

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of the active principle to the patient[2].The USP NF defines excipients as substances, other than active drug substance or finished dosage forms, that have been appropriately evaluated for safety and are included in drug delivery systems 1) to aid in the processing of the drug delivery system during its manufacture; 2) to protect, support, or enhance stability, bioavailability, or patient acceptability; 3) to assist in product identification; or 4) to enhance any other attribute of the overall safety, effectiveness, or delivery of the drug during storage or use[3]. Asomewhat similar definition wasproposed by IPEC(International Pharmaceutical Excipients Council)states:Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceuticalproduct dosage form[4].

Excipients can be classified based on their origin, use in dosage form, and functions they perform[5]. On origin bases they can be either animal source like Lactose, Gelatin, Stearic acid, Beeswax, Lanolin..etc; Vegetable source like Starch, Peppermint, Guar gum, Acacia.. etc.; Mineral source like Calcium phosphate, Silica, Talc,Calamine, Kaolin, Paraffin, etc.; or Synthetic like Saccharin,Polyethylene glycols, Polysorbates, Povidone.. etc[5]. On the basis of their use include those used in solid dosage forms like diluents, binders, disintegrants, ..etc.; liquid dosage forms like solvents, buffering agents, suspending agents, ..etc. or semisolid dosage forms like ointment bases, gelling agents, suppository bases .. etc[6].;and on the bases of their functions excipients include diluents or bulking agents, binders, disintegrants, lubricants, anti-adherents, flavors, colors,.. etc. A complete list of excipient categories was mentioned in USP NF[7].

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[8].Physical and chemical interactions betweendrugs and excipients can affect the chemicalnature, the stability, and bioavailability of drugproducts, and consequently, their therapeuticefficacy and safety[9].Excipients may have functional groups that interact directly with active pharmaceuticalingredients. Alternatively, they may contain impurities or residues or form degradation products that in turncause decompositions of the drug substance[10].

In this review, drug excipient interactions will be defined and reviewed. Different classes of interactions will be defined and explored with examples from literature. The impact of these interactions on drug stability and bioavailability will be discussed.

2- Definitions and Classifications of Drug-Excipients Interactions:

2.1 Definitions

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There is no consensus on one definition to the term "drug-excipient interaction (DEI)". We herebyproposethe following:"It is the interaction, intentional (desirable) or unintentional (undesirable), that occur between drug substance (active pharmaceutical ingredients, API) and other non-drug substances (additives, excipients, impurities) during processing (Preformualtion, formulation, manufacturing), after processing (shelf storage) and/orafter administration of the dosage form (drug product) to the patient, which may lead to changes in drug and/ordrug product properties".
According to this definition,DEI can be divided into two main groups[11]:

a. Intentional (desirable) interactions: those which can be primarily planned, designed, controlled, and utilized to modify certain property or properties of the drug or pharmaceutical product to the desired direction. For instance, color, odor, and taste-masking by coating, increase or decrease dissolution rate, enhancement of absorption rate, … etc. These and other examples will be discussed later in this review[11].
b. Unintentional (undesirable) interactions: those are generally referred to as incompatibilities. They include physical, chemical, or biopharmaceutical processes that take place during the preparation, storage, or after administration of the drug product resulting in changes in physical, chemical, microbiological, or therapeutic properties of the dosage form[11, 12].

The first, intentional (desirable), most probably, are among physical type interactions while the latter, unintentional, could be both physical and chemical types.

2.2 Classification

Most of the literature references classify DEI into three classes: physical, chemical and biopharmaceutical. These will be discussed in the following sections.

2.2.1 Physical Interactions

Theyare quite commonbut are difficult to detect. A physical interaction doesn't involve any chemical changes. Physical interactions are frequently used in the manufacturing of dosage forms, for example, to modify drug dissolution[13].Many of such interactions canbe categorized as noncovalent. These may include van der Waalsattractions (or dispersion forces), hydrogen bonding, and electrostatic interactions(also called ionic bonding). All of these interactions involve an electrical chargedue to temporary dipoles or ion formation[14-16].
Physical interactions may include but are not limited to complexation, adsorption, and solid dispersions. These are explained in the following sections:

2.2.1.1 Complexation:

Crowley and Martinin[8], who are consideredpioneers in this field, stated: "although it is prudent to aware of functional groups associated with drugs and excipients when

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considering possibilities of interaction, it must be stated that interaction on paper may not always occur in practice, particularly in solid-state. Solution chemistry does not always translate reactions in the solid-state, particularly in terms of rate of reactionwhich may be an important consideration in dosage forms. Stoichiometry, local environment, degree of crystallinity or indeed drug excipient ratio can mean that some potential interactions are more aproblem in concept than in reality"[8].

Traditionally, amorphous drugs have been formulated as microscale solid dispersions prepared by spray-drying, freeze-drying, or hot-melt extrusion, where the drug is stabilized by polymer excipients such as hydroxypropylmethylcellulose (HPMC) and poly(vinylpyrrolidone) (PVP). The polymer stabilizer reduces the molecular mobility of the dispersed drug, thereby preventing recrystallization of the amorphous drug during storage[15]. Drug−polyelectrolyte complexation was employed as a strategy to prepare stable amorphous itraconazole nanoparticles using dextran sulfate as the polyelectrolyte[16]. Zier et al[17], in a recent study, found that the addition of maltodextrin before and during the spray drying processes has increased the stability of senna extract significantly. Ohnsorg , et al[18], used bottlebrush polymers to enhance the solubility of phenytoin significantly with the hydrophilicity of the end-group moiety induced. These polymers have great potential as vehicles to noncovalently sequester, stabilize, and deliver hydrophobic small molecule actives. The anticancer drug camptothecin is conjugated to form a hydrophobic prodrug that is subsequently encapsulated in biocompatible, poly(lactic acid)-block-poly(ethylene glycol) (PLA-b-PEG)-stabilized nanocarriers (NCs)[19]. The addition of a lipid excipient, like 1-palmitoyl-2- oleoyl-glycero-3-phosphocholine will control water access to the core of NCs,and hence the therapeutic conjugate release can be sustained over tens to hundreds of hours[19].

Cyclodextrins and their derivatives are the most well-known complexing agents used in pharmaceutical formulation due to their suitable physicochemical and biological properties[20].Many drug properties were studied using cyclodextrins such as solubility[21-23], permeability[24, 25],andstability[26].Drug complexation with cyclodextrins was a subject of many drug delivery systems such as ophthalmic[27-29], Nasal[30-32], rectal[33, 34], transdermal[34, 35], and oral[36-39].

2.2.1.2 Adsorption

Adsorption is the process in which atoms, ions, or molecules from a substance (it could be gas, liquid, or dissolved solid) adhere to a surface of the adsorbent. Adsorption is a surface-based process where a film of adsorbate is created on the surface while absorption involves the entire volume of the absorbing substance[40]. Ali et al, studied the adsorption of propranolol HCl on chitosan and cellulose acetate and found that the latter was a better adsorbent surface[41]. Activated charcoal (AC) is conventionally used as an antidote in case of drug poisoning[42, 43]. Activated charcoal adsorbs many noxious

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substances—medical drugs, phytotoxins, and poisonous chemicals—onto its surface, preventing its absorption from the gastrointestinal tract[44].Sah et al, found that administration of AC adsorbed a sufficient amount of diazepam and that a standard dose of 50 g of AC as provided in general poisoning cases is sufficient to prevent diazepam intoxication[45]. Other studies estimated that AC reduced citalopram bioavailability and increased total body clearance[46]. Comparable studies estimated that early administration of AC following overdose reducedthe absorption of quetiapine[47], sertraline[48], escitalopram[49],and venlafaxine[50].
In a recent study on nanosuspensions stabilization of poorly soluble drugs, Ferrar etal[51], demonstrate that amphiphilic excipients possessing long hydrophobic alkyl or polymer blockchains are the best choice. Such excipients, regardless of molecular weight, HLB value, or CMC, can adsorb on the surface of the hydrophobic drug crystal and prevent particle aggregation.

Wang et al[52], reported about the uptake of ranitidine on and released from palygorskite (Pal), kaolinite (Kao), and talc was evaluated under different physicochemical conditions. The results showed that the uptake of ranitidine on these minerals was limited to the external surface areas only. Cation exchange and electrostatic interactions were responsible for the drug uptake on Pal and Kao, resulting in monolayer sorption. In contrast, multilayer ranitidine uptake was found on the talc surfaces.

Ziprasidone solid self-microemulsifying drug delivery system (SMEDDS) was formulated by first making liquid SMEDDS using Oleic acid, Tween 80,and methanol as a penetrant, surfactant, and co-surfactant respectively. The liquid SMEDDS then is converted into a solid one by physicaladsorption of an adsorbent material[53].

2.2.1.3 Solid Dispersion

Solid dispersion is defined as ‘a dispersion of one or more active ingredients in an inert carrier at the solid-state, prepared by the melting, the solvent or the melting solvent method’. Nowadays, the term solid dispersion is mostly linked to glass solutions of poorly soluble compounds, using amorphous carriers with high glass transition temperatures[54]. Solid dispersions have been classified based on the distribution of
solute molecules within the carrier matrix as eutectic mixtures, solid solutions, and microfine crystalline dispersions. A eutectic mixture consists of two materials which, when mixed in a particular proportion, form a composition that has a single melting point lower than the melting points of the original components[55].
Amorphous drugs could be formulated asmicroscale solid dispersions prepared by spray-drying, freeze-drying,or hot-melt extrusion, where the drug is stabilized bypolymer excipients having high glass transition temperatures(Tg), such as hydroxypropylmethylcellulose (HPMC) andpoly(vinylpyrrolidone) (PVP)[16]. The polymer

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stabilizer reducesthe molecular mobility of the dispersed drug, preventing recrystallization of the amorphous drug during storage and inhibiting the solution-mediated nucleation and crystal growth of the dissolved drug, resulting in prolonged supersaturation[56].Ideally, the polymershould achieve such a job using noncovalent and stabilizing interactions[57]. This is usually represented by the concept of the "spring−parachute"analogy schematically illustrated in Figure-1[57, 58]. In this concept, amorphous drug molecules are the "sping"relative to their crystalline counterparts, while the stabilizingpolymer excipient acts as a "parachute". This is very beneficial upon drug dissolutionand supersaturation to increase the absorption ofdrugs across the gastrointestinal barrier[57]. Polymers, in this contest, slow the diffusion of the drugby delaying crystallization of drug molecules, and/or physically bind drug molecules through hydrophobic, hydrogen bonding, or other interaction sites on the polymer chain, thereby increasing the activation barrier for crystallization[59].

Other researchers classified solid dispersion into four generations, depending on the physical state of the carrier which is amorphous or crystalline [60]. Various drugs and drug products are formulated using one or more of these methods. Examples of such drugs and their research concept are listed in table 1.

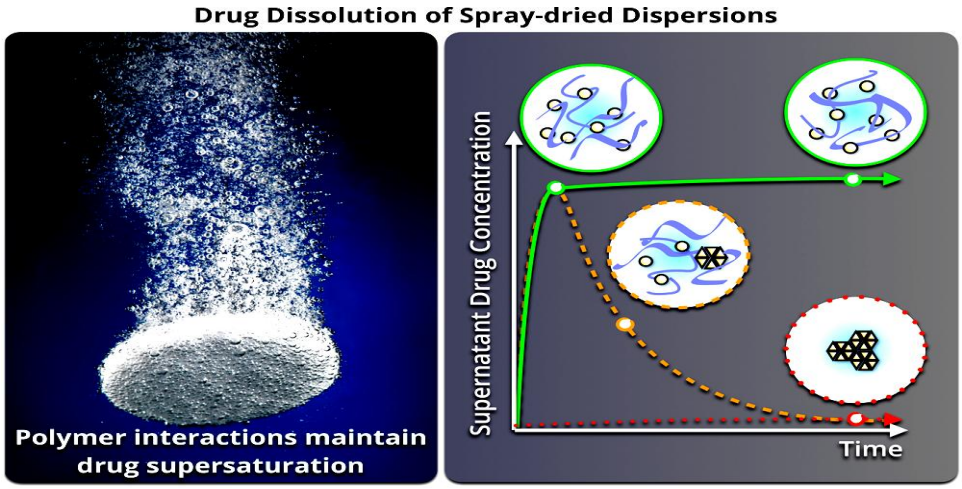

Fig 1: Spring- parachute concept illustrating how solid dispersions enhance the apparent drug solubility. In the plot, purple curves represent polymer, yellow circles depict amorphous drug molecules, and yellow hexagons denote crystallized drug molecules. With a precipitation-inhibiting polymer, the supersaturation of amorphizeddrug can be maintained (green curve, high concentration plateau). With a nonideal polymer, desupersaturation depletes suppressant drug content (orange dashed curve, decreasing concentration). For hydrophobic crystalline drug molecules, limited absorption across the gastrointestinal barrier can occur (red dotted curve, low concentration plateau).(with permission from Ref [57])

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Table 1: Examples of Drugs under research or ready formulated as a solid dispersion

Drug	**Polymer (carrier)**	**Concept**	**Ref No**
Biclotymol	α- & β- Pentaacetylglucose	Low mol wt excipients for stabilization, molecular mobility, and inclination to recrystallization of amorphous biclotymol	61
Probucol	Five diblock terpolymers consist of the first block of either: poly(ethylene-alt-propylene) (PEP), poly (Nisopropylacryl amide) or poly(N,N-diethylamino-ethyl Methacrylate and second hydrophilic block consisting of a gradient copolymer of N,Ndimethyl-acrylamide (DMA) and 2-methacrylamidotrehalose	Synthetic polymers offer tunable platforms to create new oral drug delivery vehicles (excipients) to increase solubility, supersaturation maintenance, and bioavailability of poorly aqueous soluble drugs (ex. Probucol)	62
Phenytoin	hydroxypropyl methylcellulose acetate succinate (HPMCAS)	HPMCAS with higher acetyl and lower succinyl content is more effective in promoting phenytoin solubility in dissolution media, and polymers become less effective when drug loading becomes high	59
lapatinib and gefitinib	polystyrene sulfonic acid	Potential of drug-excipient interaction on amorphous solid dispersion	63
Lapatinib	Soluplus, polyvinylpyrrolidone vinyl acetate (PVPVA), hydroxypropylmethylcellulose acetate succinate (HPMCAS), and hydroxypropyl-methylcellulose phthalate	The effect of polymer selection on the dissolution and physical stability the behavior of LB was examined	64
Ezetimibe	Hydroxypropylcellulose and Tween 80	effect of hydroxypropyl-cellulose and Tween 80 on the physicochemical properties	65

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		and oral bioavailability of ezetimibe-loaded solid dispersions	
Cyclosporine A	amphiphilic block copolymer, poly[MPC-co-BMA]	self-micellizing solid dispersion of cyclosporine A using an amphiphilic block copolymer, to improve the biopharmaceutical properties of Cyclosporine A	[66]
Indomethacin	Eudragit E	Ionic complex forms between indomethacin and Eudragit E in amorphous solid dispersions.	[67]
Ibuprofen	(poly(vinyl pyrrolidone) [PVP], poly(vinyl pyrrolidone/ vinyl acetate) [PVP/VA], poly(vinyl acetate) [PVA], or polystyrene [PST])	Hydrogen bonds (HBs) in amorphous solid dispersions may be monitored by molecular dynamics simulation. HBs influence physical stability through effects on both drug miscibility and mobility.	[68]
Levodopa	The a-cyclodextrin (aCD) and poly(vinylpyrrolidone) (PVP), Hydroxypropyl methylcellulose, poly (vinyl alcohol)(PVA), and D-mannitol	LEVO-containing binary nasal powders with different excipients by dry cogrinding process. The interactions between the components were examined. aCD and PVP had an intensive crystallinity degree reducing effect on LEVO measured by XRPD, and they functioned as cogrinding agents.	[69]
Loperamide	HPMCE50, HPMC-E15-LV, and PVA as film-forming polymer, propylene glycol as a plasticizer, Sodium starch glycolate (2-8%) as a super disintegrant,	Fast dissolving films as an alternative to fast-dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a	[70]

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		few seconds	
Furosemide	gelatin and carboxymethyl cellulose sodium (sodium CMC), sodium alginate and glycerin as a plasticizer, sodium hydroxide as solubility enhance	Drug-loaded polymeric film prepared by solvent casting method using different polymers. Floating Film enhances the bioavailability of Furosemide by prolonging its duration in the stomach via the floating	[71]
Brucine	PEG poly (lactic-co-glycolic acid) (PLGA)	Drug loaded nanoparticles were prepared by a modified solvent evaporation method with good entrapment percentage and significant reductions in tumor growth rate	[72]
Deferasirox	polyethylene glycol 4000 (PEG 4000) and polyvinylpyrrolidone K25	Solid Dispersions were made by the solvent evaporation technique with different drug-to-carrier ratios. Then, the dispersion was milled and mixed with other components, and the mixture layered on sugar-based cores by a pan coating technique	[73]
Zidovudine	PVP, PVA as patch forming, and Eudragit RL as a coating material	Transdermal patches were formulated using a permeation enhancer namely T-Anethole. Zidovudine patches were prepared by solvent casting method	[74]
Diosgenin	Soluplus is an amphiphilic polyvinyl caprolactampolyvinyl acetate-polyethylene glycol graft co-polymer	The purpose was to prepare Soluplus-mediated diosgenin amorphous solid dispersions (ASDs) to improve its solubility, bioavailability, and stability.	[75]
Thiamine Chloride HCl	pectin and PVP (poly[vinylpyrrolidone	Thiamine chloride HCl:polymer dispersions were prepared by	[76]

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		lyophilizing solutions containing thiamine and amorphous polymers (pectin and PVP (poly[vinylpyrrolidone]	
Enalapril maleate	sodium alginate, iota-carrageenan, sodium bicarbonate, calcium chloride	formulations of floating microspheres were prepared by ionotropic gelation using different concentrations of sodium alginate, iota-carrageenan, sodium bicarbonate, calcium chloride, and the drug.	[77]
biflavonoids from *Selaginella doederleinii* extract	polyvinylpyrrolidone K-30	Solid dispersions of TBESD with various hydrophilic polymers were prepared. Amorphous solid dispersion (TBESD-ASD) with polyvinylpyrrolidone K-30 was successfully prepared by the solvent evaporation method	[78]
Quercetin	chitosan oligosaccharide	an amorphous chitosan oligosaccharide was applied as a water-soluble matrix to form surfactant-free amorphous solid dispersion via the ball milling to vitrify quercetin and enhance the dissolution and bioavailability	[79]

2.2.2 Chemical Interactions

In general, the susceptibility of an API towards reactions with excipients is dependent on the existence of a possible chemical reaction pathway and upon the energy of the associated transition state, which acts as an energy barrier for the reaction. Depending on the electronic structure of the API molecule and the reaction mechanism, the height of this energy barrier can vary widely, and thus, influences how fast an API degrades[80].

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 8402 - 8429
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Crowley and Martini mentioned five modes of API degradation upon interaction with excipients or their impurities[81]. These modes are hydrolysis, oxidation, photolysis, physical transformation, and others and will be discussed in the following subsections with updated examples.

2.2.2.1 Hydrolysis

The most susceptible drugs are those containing carbonyl groups like esters, amides lactones,etc. with a good leaving group[82, 83].The reaction involves the addition of water molecules and splitting the parent drug into two parts (Figure-2).

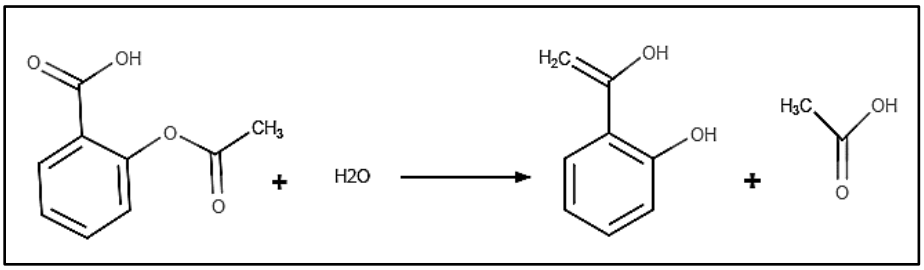

Figure 2. Hydrolysis of aspirin.

The presence of excipients may promote the reaction either directly or by altering the aqueous environment or affecting other parameters such as pH, ionic strength, or dielectric constant[81].Another important factor is water activity (availability)[83]as related toexcipient moisture contents wherethehydrolysis rate depends on the water activity around the drug.As an exampleof the influence of water availability on hydrolysis rates isaspirin compacts containing dibasic calcium phosphatedihydrate degrade approximately 10 times fasterthan formulations containing lactose and two-fold fasterthan formulations containing microcrystalline cellulose[82-84].

The physical state of the drug in the dosageform is also important. Crystalline state is more stable against hydrolysis than amorphous which is, in turn, more stable than liquid or solution state.As an example, the rate of aspirinhydrolysis is 10-fold greater in tablets containingpowdered vs. granular magnesium stearate, andfive-fold greater in tablets containing dibasic calciumphosphate dihydrate with a particle size of 10 vs. 40µm.[83, 85]Another example is lyophilized β-methyl carbapenem chloride which exhibits moisture-dependent β-lactam hydrolysis rates. Co-lyophilization with sucrose decreases the rate of the reaction while its crystalline benzenesulfonate trihydrate derivative exhibited improved stability in the solid-state relative to the amorphous form[86].
Tablet formulations of the maleate salt of an investigative basic drug showed a major loss in potency due to hydrolysis. A stable tablet formulation with shelf-life >3 years was successfully developed by lowering the microenvironmental pH of the tablet from 4.3 to <3.0 by adding citric acid to the formulation[87] The same can be said for ester hydrolysis of DMP 754, a methyl ester prodrug of a benzamidine derivative. The reaction was

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dependent on the‘pH’ in solid anhydrous lactose blends containing (citric or fumaric acids as pH modifiers) whichdepends on both the ionization constant (pKa) and aqueous solubility of such modifiers.Consequently, citric acid resulted in more significant ester hydrolysis (77% decomposition after 8 weeks at 40°C/75% RH) compared to 7% for the blend containing fumaric acid[88].

The release rate of the drug can be controlled using hydrolyzable polymers. Doxorubicin was encapsulated in vesicles prepared of a mixture of two diblock copolymers of polyethyleneglycol–poly-L-lactic acid (PEG–PLA) or polyethyleneglycol–polycaprolactone (PEG–PCL). The release rate was accelerated with an increased proportion of PEG but is delayed with a more hydrophobic chain (i.e. PCL)[89].
Also, release rate, as well as hydrolysis kinetics, can be controlled using certain types of excipients. Amorphous silica with different OH surface groups’ densities was used to adjust release rate and hydrolysis degradation of aspirin through hydrogen bond and/or dispersion forces formation[90].

Magnesium stearate is the most extensively used tableting lubricant. It exists in four hydration states, which contribute to its lubrication efficiency. However, a literature surveyrevealed numerous reports on magnesium stearate chemical interactions. It acceleratehydrolytic degradation of acetylsalicylic acid[91], accelerated degradation of the quinapril hydrochloride –excipient binary mixture in elevated relative humidity (RH) conditions[92],and enhances hydrolytic degradation at elevated RH of moexipril hydrochloride[93]. In a more recent study[94], the effect of magnesium stearate (MgSt) content on the chemical stability of acetylsalicylic acid was evaluated as a model system of drug–excipient compatibility studies. In the long-term stability study (25 °C/60% relative humidity, 6 months), there was good agreement in total between measured values and the new model-predicted values. It was inferred that the degradation rates were depended on MgSt content at the fixed temperature and humidity because the micro-environmental pH of the excipient was catalytically affected.

“Nucleophilic catalysis” by polyhydroxy excipients such as dextrose, sucrose, sorbitol, and mannitol hasbeen reported for ester hydrolysis. For example, the degradation of β-lactam antibiotics was enhanced in aqueous solutions of carbohydrates and polyhydric alcohols. Degradation of ampicillin, cephaloridine, and cefazoline in alkaline solutions was accelerated by glucoseand dextrans[95].
In a recent study, Peliglitazar is found to be capable of undergoing both base (an amine degradant and p-hydroxyanisole) and acid-catalyzed degradation (benzylic alcohol, and glycine carbamate) and is sensitive to excipients (HPMC, PVA, PEG, Triacetene) used in oral solid dosage form[96].

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Other examples of drugs undergoing hydrolysis affected by excipients include methylphenidate with glycerin in oral solutions[10], fosinopril sodium with Magnesium Stearate[10,97,] and nitrazepam with hygroscopic excipients[9].

2.2.2.2 Oxidation

Oxidation can be defined as a reaction thatincreases the content of more electronegative atoms in amolecule. With organic systems, these electronegativeheteroatoms are generally oxygen or halogens[98].Oxidation reactions can be catalyzed by oxygen, heavy metal ions, and light, leading to free radical formation (induction). Free radicals react with oxygen to form peroxy radicals which in turn interact with the oxidizable compound (propagation). Aldehydes, alcohols, alkaloids,and unsaturated fats are of most susceptible to oxidation[8](Figure-3).

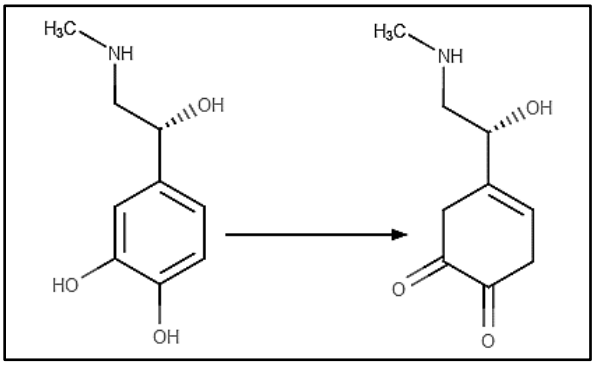

Figure 3. Oxidation of epinephrine.

Excipients can be a source ofoxidants and metals.Excipients can alsobe involved in generating mobile oxidativespecies such as peroxyl radicals, superoxide, andhydroxyl radicals[84].On the other hand, many excipients contain impurities like peroxides, aldehydes, organic acids, reducing sugars, etc. These impurities are reactive, such that even trace levels could cause drug degradation[99]. However, excipients (generally and antioxidants specifically)can be good stabilizers to drugs against oxidation[99-101].The followings are some examples.

The acidic NSAID AD-1590 undergoes auto-oxidation in suppository bases and converted inactive. Complexation with cyclodextrins improves the stability of this drug by decreasing solubility in this lipophilic bases[100].

Raloxifene hydrochloride underwent oxidation to the N-oxide derivative in the presence of povidone and crospovidone due toperoxide impurities. A rational limit test for peroxide content in these excipients should be adopted to limit the formation of the degradation product[102].

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Oxidation of a cyclic peptide drug in a lyophilized formulation occurs in the solid-state and depends on the presence of impurities in the pharmaceutical excipient (Mannitol) used in the formulation[103]

Fluphenazine Deaconate forms several N-oxides due to the oxidation of the phenothiazine group. This could be due to the peroxide present in the excipients or photo-oxidation of the active drug after accelerated conditions[104].

Biological products like proteins and hormones are oxidized through their methionine, tryptophan, and histidine residues. Surfactants such as polysorbates and poloxamers are used in these biological products can generate reactive oxygen species and aldehydes through autoxidation. The presence of transition metals like ferrous will aggravate the process[105, 106]. The oxidation of parathyroid hormone (PTH) catalyzed by ferrous ethylene-diaminetetraacetic acid (EDTA) is site-specific and localized primarily to the residues Methionine and Histidine[107]to minimize the risk of oxidation, polysorbates should be stored at low temperature and protected from light exposure. Besides, free methionine and tryptophan could be used to protect against peroxide and free radical oxidation[99].

Organoleptic agents such as coloring, flavoring, sweetening, and texturing formulations play a significant role in pharmaceuticals and cosmetics due to their ability to increase patient compliance. However, many of these agents are susceptible to oxidation and other chemical instabilities. For examples Beta-carotene colorant (isoterpenoid red-orange), Indigo carmine colorant (FD&C Blue No. 2), Furanone derivatives (flavor) in caramel, strawberry, grape..etc and Menthol and terpenoids in Mint flavors (peppermint and spearmint) are all susceptible to oxidation due to factors such as heat, light and pH change. These instabilities may result in at least,in color or flavor change and may lead to a more serious interaction with API or other dosage contents[108].
Also, the oxidation ofsensitive drugs that degrade by free radical mechanismscould be sensitive to the mechanically generated radicals.Thus, the use of high shear mixing increased the oxidativedegradation rate of an oxidatively sensitive drug, which
was attributed to the mechanoradicals generated from theexcipient like microcrystalline cellulose[109].

2.2.2.3 Maillard reaction

This reaction is so named after Louis Maillard, to form colored pigments from sugars and amines. Primary amines in the formulation with carbonyl compounds, basically reducing sugars, undergo Maillard reaction, to form Schiff's base (imine substances) and finallythe Amadori rearrangements[110] (Figure-4)0

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 4, 2021, Pages. 8402 - 8429
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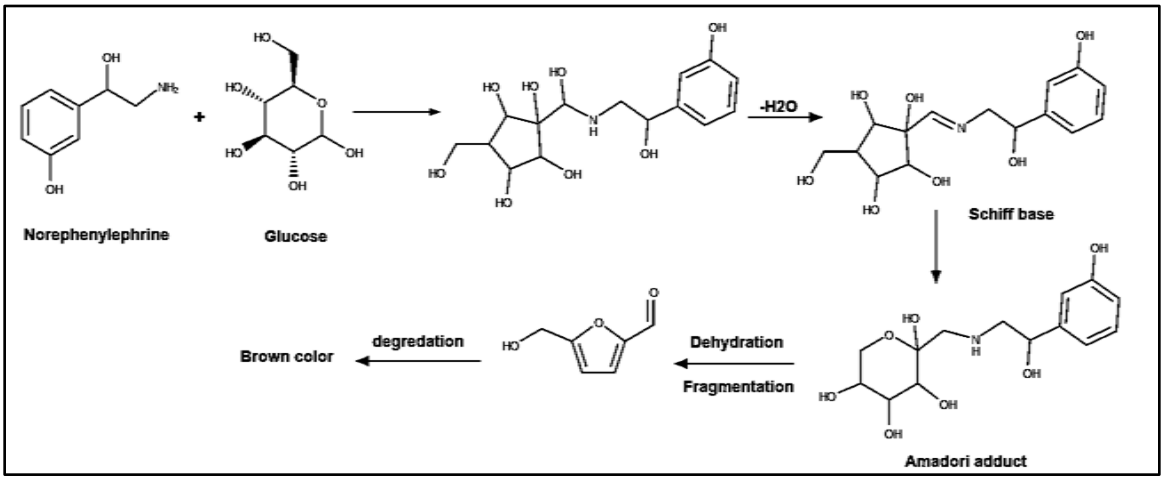

Figure 4. Example of Maillard reaction. Proposed mechanism for the discoloration of the sugar-coated tablets of norphenylephrine hydrochloride[111].

In their study of interactions of 2 model drugs, namely, metoprolol and diclofenac sodium, with excipients, Omari and Akkam[112] found that metoprolol tablets became deep yellow when coated with aqueous-based polymer while in those coated with dry powder (solventless), the color change was significantly lower. These color changes were due to interaction with lactose.

The outbreak due to phenytoin intoxication (1968, Australia) was attributed to its interaction with excipients[113]. When CaSO4 was used as a diluent, phenytoin absorption was decreased due tothe formation of calciumsalt and precipitate. However, when CaSO4 was replaced in the formulation by lactose, the amount of phenytoin absorbed was much higher, resulting in the observed intoxication[113].Silva et al, found that phenytoin sodium also interacted with lactose through Maillard reaction in an aqueous medium confirmed by the browning of the formulation. Phenytoin-free molecule did not undergo this reaction [113]. Levofloxacin[114] and methyldopa[115] were also found incompatible with lactose by the Maillard reaction mechanism.

2.2.2.4 Other Chemical Interactions

This may includeisomerization, photolysis, and polymerization. Isomerization involves the conversion of a chemical into itsoptical or geometric isomer. Isomers may have differentpharmacological or toxicological properties[116]. For example, theactivity of Levo (L) form of adrenaline is 15-20 times greaterthan for the Dextro (D) form. Another example where optical isomerization of an experimental compound was observed at an asymmetric carbon atom that linked the pyrrolobenzodiazepine ring to a heterocyclic ring through an amide bond. This was in a soft gelatin capsule dosage form which contained a

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mixture of PEG 400 and glycerol. The degradation of the active was accelerated by the formic acid in the formulation[117]. Yet another example is the conversion of E-type prostaglandins to A-type which are isomerized subsequently to B-type prostaglandins under alkaline conditions, therefore, the biological activities of E-type prostaglandins decrease. This degradation can be decelerated by the addition of cyclodextrin as an inclusion complex[20].

Polymerization reactions occur as a result of intermolecular reactions lead to dimeric and highermolecular weight species. Concentrated solutions ofampicillin, aminopenicillin, progressively form dimer,trimer, and ultimately polymeric degradation products[116].Some organoleptic agents also may undergo polymerization degradation. An example is the natural color Betalains which is susceptible to color fading or browning due to subsequent polymerization[118].

2.2.3 Biopharmaceutical Interactions

Theseare the interactions that are observedafter administration of the medication.Interaction within the body is betweenmedicine and body fluids whichinfluence the rate of absorption[5]Drug–excipient interactions have the potential to affect manyphysiological processes and factors, such as the pH of themicroenvironment, protein binding, GI transit time, stabilityin the GI tract, effects on gut flora, and so on. The potentialoutcome of all of these interactions might be to alter thebioavailability of the drug[119].Common examples are increasing gastric pH by antacids affecting enteric coat integrity, the interaction of tetracycline with calcium ions forming unabsorbable complex, and increasing GI motility by sorbitol and glycols whichaffect drug transit time and absorption[5].The extent to which drug bioavailability is affected by these interactions would vary on a case-by-case basis depending upon factors such as the potency and dose of the drug, therapeutic window, site of absorption, rate-limiting factor in drug absorption (e.g., permeability or solubility limited), or whether drug metabolism, efflux, complexation, or degradation at the site of absorption play a role in determining its bioavailability[120].

These interaction types are,most probably, categorized under the pharmacokinetic interactions, which occur when one compound alters the pharmacokinetics (i.e. the absorption, distribution, metabolism, and/or excretion) of another compound[121].

An example is aneffect of the surfactant sodium lauryl sulfate (SLS) on the bioavailability of risperidone and alendronate tablets, where 4 mg of SLS increases the bioavailabilityof the later more than 5-folds[122]. Another example is what has been reported about excipients induction of some changes to the tight junction and P-glycoprotein which can affect drug disposition[123]. In this study, they found that excipients like methyl-β-cyclodextrin, sodium carboxymethyl starch, low-substituted hydroxypropyl cellulose, and croscarmellose sodium significantly increased the membrane permeability

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of the model drug, (5(6)-carboxyfluorescein, 5-CF) in the jejunum but not in the ilium. On the other hand, in both the jejunum and the ileum, the membrane permeation of 5-CF has decreased with 0.02% (w/v) hydroxypropyl cellulose but significantly increased with it at 0.20% (w/v)[123].

Gerber et al reported about the effect of disintegrantson the absorption transport of a model compound, Rhodamine 123 (R123), across excised pig intestinal tissue[124]. The results showed that some of the selected disintegrants (e.g. Ac-di-sol® and Kollidon® CL-M) increased R123 absorptive transport due to inhibition of P-gp related efflux, while another disintegrant (e.g. sodium alginate) changed R123 transport due to inhibition of P-gp in conjunction with a transient opening of the tight junctions in a concentration-dependent way[124]. The permeability of celecoxib, an NSAID, was reported to be enhanced by a combination of magnesium stearate and colloidal silicon dioxide as tablet excipients[125]. In an article by Ashiru-Oredope et al, the solubility enhancing agent PEG 400 was found to enhance the bioavailability of ranitidine in male subjects but not females, with the most pronounced effect in males noted with the 0.75 g dose of PEG 400[126].This effect is related to the osmotic activity of this excipient. In the same regard, Chen et al, reported on the effect of sorbitol, another osmotically active agent, on the absorption of metoprolol and ranitidine. No significant effect of sorbitol (5 g) on the extent (AUC) and a 23% reduction in rate (C_{max}) of absorption of a single dose of metoprolol has been recorded, whereas a significant effect has been observed on both AUC and C_{max} (44% and 51% reduction, respectively) when sorbitol (5 g) and ranitidine (BCS class III) were administered concomitantly[127].

In a recent study[128], the effect of vitamin A palmitate and abietic acidas inhibitors ofP-glycoprotein (P-gp) and uridine diphosphate-glucuronosyl-transferase-2B7 (UGT2B7), respectively, was studied, applying machine learning methods. P-gp and UGT2B7 aretwo proteins that impact the pharmacokinetics of approximately 20% of FDA-approved drugs.Vitamin A palmitate was found to increase the permeability of P-gp substrates such as ranitidine, colchicine, and loperamide across porcine intestinal tissue while abietic acid (the main component of Gum Rosin) slowed the conversion of a proprietary UGT substrate[128].

In conclusion, for any drug formulation, both the type and concentration of the excipients as well as the drug properties are important, and in this regard, a combination of more than one excipient could be suggested to minimize the undesirable effects.

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3- Conclusions

Excipients are essential materials added to drugs (APIs) to form drug products and ensure that medicines possess proper weight, consistency, and volume for correct administration as well as bioavailability. However excipients are not inert materials, they can interact with the API and/or with other boundary materials (other excipients, solvents, biological tissues ..etc.) which may affect drug stability and effectiveness. In this review (Part I), a definition of the term "drug excipient interaction (DEI)" was proposed, different classes of DEI (physical, chemical, biopharmaceutical) were defined and explored and examples of these interactions was briefly explained.

Physical DEI is among the desirable "intentional" interactions and may occur in the form of complexation, adsorption, or solid dispersion. Such interactions involve noncovalent bonds like van Der Waal forces, hydrogen bonding, and ionic-electrostatic interactions. Chemical interactions may involve covalent as well as other bonding forces and occur as hydrolysis, oxidation, isomerization, or polymerization. These interactions most probably, are detrimental "undesirable" and referred to as incompatibilities. Biopharmaceutical interactions that occur after administration and most probably introduce changes in pharmacokinetic parameters (absorption, distribution, metabolism, and excretion) of the drug may affect its bioavailability and activity.

DEI should be taken into serious considerations and be assessed accurately so that any undesirable effect on the drug is avoided.

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