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International Journal of Pharmaceutics 187 (1999) 1–15

international journal of pharmaceutics

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Review

Studies of beneficial interactions between active medicaments and excipients in pharmaceutical formulations

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Received 24 November 1997; received in revised form 7 April 1999; accepted 6 May 1999

Abstract

A review of "up to date" research findings leading to new concepts of the pharmaceutical formulations and their interactions has been presented. The rational approaches to the excipients choice as well as to their interactions with medicaments have been shown as a basis for modern modelling of pharmaceutical formulations. The importance of complexation, hydrogen bonding, ion–dipole, dipole–dipole and van der Waals attractions as the tools which can modify the physicochemical, pharmacological or pharmacokinetical behaviour of the medicaments has been emphasised. In vivo studies (carried out in healthy human subjects—volunteers, in beagle dogs, in rats etc.) and in vitro studies (on excised human skin, hairless mouse skin etc.) as well as studies of chemical stability and bioavailability serve also as a proof of these interactions. Therefore, excipients are important components of pharmaceutical formulations and they can take an active part in the improvement of the characteristics of formulations (but they may also reduce the effectiveness of some preparations). In this context, the so called active and inactive ingredients in pharmaceutical formulations are inexact, old and "out-of date". Their further use is only conventional. In conclusion, among the various modern techniques applied the combination of infrared spectroscopy and X-ray diffraction has been estimated as the most successful in proving the interactions between drugs and excipients. Finally, pharmaceutical formulations and their interactions have constituted a diverse and rapidly expanding field of Pharmacy (Pharmaceutical Technology, Pharmaceutical Industry and Pharmaceutical Sciences) which covers a wide range of numerical topics within an unified framework.

Keywords: Interactions; Active medicaments; Excipients; Pharmaceutical formulations; Bioavailability; Therapeutic activity; Infrared spectroscopy; X-ray diffraction patterns; Crystalline structures

1. Introduction

Numerous papers dealing with studies of interactions between active medicaments and excipi-

* Fax: +359-2-973386.

0378-5173/99/$ - see front matter
PII: S0378-5173(99)00176-3

ents have been published in the last two decades. The aims of many of these investigations are connected with the optimisation of pharmaceutical formulations which ensure: the improvement of the solubility of poorly soluble drugs (Takahashi et al., 1990; Green et al., 1991; Imai et al., 1991; Guyot et al., 1995; Oguchi et al., 1995; Sigurðardottir and Loftsson, 1995; Singla and Wadhwa, 1995; Vandelli et al., 1995; Veiga et al., 1996); increased dissolution rates (Kedzierewicz et al., 1990; Lee et al., 1991; Ammar and El-Nahhas, 1995a; Guyot et al., 1995; Holgado et al., 1995; Hosny and Al-Angary, 1995; Singla and Wadhwa, 1995; Vandelli et al., 1995; Veiga et al., 1996); stability (Takahashi et al., 1990; Green et al., 1991; Adeyeye et al., 1995; Ammar and El-Nahhas, 1995b; Ammar et al., 1995; Kedzierewicz et al., 1995; Sigurðardottir and Loftsson, 1995); increased rate of drug release (Kawashima et al., 1985; Lee et al., 1991; Adeyeye et al., 1995; Ammar and El-Nahhas, 1995a,b,c; Holgado et al., 1995; Preiss et al., 1995; Sigurðardottir and Loftsson, 1995; Tirkkonen et al., 1995; Torrado-Santiago et al., 1995a,b; Büyüktimkin et al., 1996; Wolf et al., 1996); alteration of therapeutic activity (Kalinkova and Krasteva, 1989; Ammar et al., 1995; Cserháti, 1995; Czejka et al., 1995; Singla and Wadhwa, 1995; Valentova et al., 1995; Büyüktimkin et al., 1996); increase of bioavailability (Kawashima et al., 1985; Ammar et al., 1995; Hosny and Al-Angary, 1995; Neubert et al., 1995; Büyüktimkin et al., 1996; Veiga et al., 1996) and a decrease of unwanted side effects (Kawashima et al., 1985; El-Monem et al., 1991; Cserháti, 1995; Nokhodchi et al., 1995; Singla and Wadhwa, 1995).

2. Medicaments (included in pharmaceutical formulations)

This section has been conventionally denominated so because of two reasons: first, to accentuate mainly on the medicaments selected from a definite pharmacological group; and second, to represent the medicaments taking part in various interactions with excipients in different pharmaceutical formulations aiming at their improvements.

2.1. Antimicrobial and antiviral agents

Amoxicillin trihydrate granules (Gasheva et al., 1984) and nystatin plaque (Kalinkova and Krasteva, 1989) have shown a prolonged release and increased therapeutic effect compared to active medicaments alone. This is due to the intermolecular H-bond interactions of the former with hydroxyl groups of the excipient ethylcellulose and the latter—the nystatin's OH groups with the excipients pectin and glycerin. The amorphous state of the ethylcellulose (as a factor favouring the H-bonds formation) as well as the unaltered crystalline structure of the amoxicillin trihydrate in the granules have been established. The so called nystatin plaque is a formulation (Bulgarian product) for a local treatment of the oral candidomycoses.

The interaction between chloramphenicol stearate and the excipient colloidal silica in a grinding process have been observed (Forni et al., 1988). Grinding in the presence of the colloidal silica has turned drug crystal polymorph A into polymorph B (biologically active) and has decreased its crystallinity. The ratios of pro-drug and colloidal silica as well as the grinding time have influenced the effect of the colloidal silica. The increased in vitro enzymatic hydrolysis rate was explained as being caused both by crystallinity alteration (its decrease) and drug interaction with silica silanoic groups.

The antimicrobial agent norfloxacin is widely used in urinary-tract-infections treatment. Guyot et al. (1995) have obtained inclusion complexes of norfloxacin with cyclodextrins (CYDs) and polyvinylpyrrolidone (PVP) solid dispersions. These have significantly increased water solubility and dissolution rate in comparison with norfloxacin alone.

2.2. Anticancer and antitumour agents

The Platinum (II) complexes of four-substituted *o*-phenylenediamine derivatives for antitumour activity against P-388 leukaemia have been tested (Kidani et al., 1979). The authors have connected the antitumour activity of the complexes with the three important facts—the formation of the so

called in chemistry chelate rings; the strength of these formations as well as with the high values of the stretching vibrations of the chemical band Pt-N in the complexes IR spectra. The influence of different substituting groups on the antitumour activity have been also estimated. Among them the two substituting groups (–COOH and $–SO_3H$) have caused a decrease of the activity because of their ionic species and unfavourable penetration into cell membranes. On the basis of the above mentioned facts Kidani et al. (1979) have concluded that they can predict the relative stability of the Pt(II) complexes with various substituting groups.

The effects of different cyclodextrins (α-, β-,γ-) and hydroxy-propyl-β-cyclodextrin (HP-β-CYD) on *N*-trifluoroacetyldoxorubicin-14-valerate (AD-32) stability and solubility in aqueous media have been investigated (Bekers et al., 1991). AD-32 shows greater antitumour activity (in experimental in vitro systems as well as in animals) compared to those of doxorubicin. (AD-32 is a derivative of doxorubicin). AD-32 is almost insoluble in water and it shows also a totally different mode of cytotoxic action. The stabilising effects of the two CYD and the acetonitrile (the latter included in a system 1:1 v/v with water) on the degradation of AD-32 have been estimated to be the same.

The excipient HP-β-CYD has the greatest effect on the solubility of AD-32 and this observation will be of importance in optimising AD-32 formulations for pharmaceutical purposes (Bekers et al., 1991).

Solid complexes formed between chlorambucil and heptakis (2,6-di-*O*-methyl)-β-cyclodextrin, β-cyclodextrin have been isolated (Green et al., 1991). This complexation leads to chemical stabilisation of the drug. The authors have concluded that these complexes will be useful in the preparation of solid dosage forms with an extended shelf life.

Data of interaction between anticancer medicaments and carboxymethyl-β-cyclodextrin (CM-β-CD) have been published (Cserháti, 1995). An alphabetical list of anticancer drugs studies is presented in Table 1 for reader's information.

The author has observed that among the 23 anticancer drugs investigated 13 formed inclusion complexes with (CM-β-CD). The complexation depends on drug chemical structures, hydrophobic forces (form the apolar drug substructures to inner wall of excipient's cavity), polar and steric factors etc. The hydrophilic parameters of drugs (specific hydrophobic surface area and hydrophobicity) exert the greatest influence on the stability of inclusion complexes studied. Author's discussion has concluded that the elucidation of the inclusion complexes formation between anticancer drugs and CM-β-CD may promote the development of new, more effective agents with lower toxic side effects.

2.3. Antidiabetics

Tolbutamide is employed as an oral hypoglycemic agent. The drug alone is practically in-

Table 1
Anticancer drugs investigated for interaction with carboxymethyl-β-cyclodextrin (Cserháti, 1995) listed in alphabetical order

Commercial name	Country-manufacturer	Commercial name	Country-manufacturer	Commercial name	Country-manufacturer
Adriblastine[a]	Italy	Farmorubicin	Italy	Provera	UK
Alexan	Germany	Ftorafur	Russia	Taxol	Germany
Bleogin	Japan	Leukeran	UK	Vinblastine	Hungary
Bicnu	France	Methotrexate	Czech Republic	Vincristine	Hungary
Cytoxan	Germany	Mitomycin C	Japan	Vumon	Germany
Deticene	France	Myelobromol	Hungary	Zitazonium	Hungary
Elobromol	Hungary	Natulan	Switzerland	Zitostop	Hungary
Estracyt	Sweden	Paraplatin	Germany		

[a] Doxorubicin

soluble in water. Tolbutamide as an inclusion complex with β-CYDs has shown a very rapid in vitro dissolution rate (Kedzierewicz et al., 1990, 1995). The authors have concluded that the three systems studied (tolbutamide-β-cyclodextrin inclusion complex, tolbutamide-PEG 6000 comelt, and tolbutamide-PEG 6000 coprecipitate) are candidates for further incorporation into tablets and hard capsules.

Tolbutamide interactions with both cyclodextrins (β-CD and HP-β-CD) have been observed (Veiga et al., 1996). The experimental results have shown that the complexes studied possess increased dissolution rates as a function of excipient concentrations.

2.4. Anti-inflammatories/antirheumatics

Indomethacin is a frequently prescribed acidic non-steroidal anti-inflammatory drug with serious side effects—gastrointestinal ulceration and haemorrhage.

Effects of complexation of this drug with calcium glycerophosphate have been studied (El-Monem et al., 1991), it results in: increased water solubility, enhanced bioavailability (significant increase in plasma levels in rats), marked reduction in gastric ulcerogenic activity and comparable anti-inflammatory activities compared with the drug on its own.

The interaction of indomethacin with chitosans of low molecular weight has been investigated (Imai et al., 1991). In vivo absorption studies using these complexes orally administered in beagle dogs show clearly the improvement of the absorption rate due to the rapid dissolution rate of indomethacin in the gastrointestinal fluid (in comparison with drug alone).

The hydrogen bonding interaction between indomethacin and polycarbophil has been observed (Hosny and Al-Angary, 1995). Rectal administration of indomethacin suppositories containing polycarbophil to healthy beagle dogs results in an increase in drug release with a sustained blood level for at least 12 h. The polycarbophil concentrations have been determined as important factors influencing bioavailability and plasma levels of indomethacin.

Zinc-indomethacin complexation has been reported (Singla and Wadhwa, 1995). The complex showed doubling in solubility, an increased dissolution rate (at pH 6.0), and an anti-inflammatory activity three-times greater, compared to the parent drug. (Zinc is known to exhibit anti-inflammatory activity of its own through various mechanisms). The ulcerogenic effects are negligible (when administered at 1.5-times its own ED_{50}, in rats) and this indicates that the dose of the drug may be reduced significantly by complexing, without affecting its therapeutic action.

The interaction between indomethacin and dodecyl 2-(*N*,*N*-dimethylamino) propionate (DDAIP) has been examined (Büyüktimkin et al., 1996). The existence of preferential H-bonding and dipole–dipole interactions have been demonstrated. The investigations suggest that an interaction mechanism may also be effective on the transport of indomethacin. It is well known that the stratum corneum layer of the skin is an excellent barrier to most chemicals and also that relatively few drugs can be transported through this layer to deliver an adequate therapeutic dose. The formation of new structures with DDAIP can increase the drug's penetration through the stratum corneum. The authors have shown DDAIP as a very effective biodegradable penetrating enhancer and facilitating the permeation of the drug through the skin (indomethacin's transport was found to be 430 times higher than the control). They have also demonstrated that the DDAIP interacts with stratum corneum proteins by breaking –S–S-bonds of keratin structure. Further investigations are required concerning these actions to prove the absorptive capacity of indomethacin.

2.5. Antihistaminics

The interactions of promethazine hydrochloride and dextrans or pectins have been investigated (Rachnev et al., 1986). The recent concepts about the tranquilliser action of phenothiazine's derivates are connected with the flexibility of their molecules. The results (IR spectroscopy, X-ray diffraction, UV spectroscopy) have shown an absence of complex formation with H-bonds, polymorphic alterations were also excluded and

changes in band's intensity in UV spectra have been observed (hypochromic effects). The degree of binding has correlated with the concentrations of dextrans. The citrus pectin has shown a minimal advantage as compared with other pectins used.

These results are in good agreement with the literature data for the low values of ionisation potentials of phenothiazine which determines them as moderate electron donors (Ratajczak and Orville-Thomas, 1984). Dreiding models (a three dimensional research) of promethazine hydrochloride have also shown that the molecule deformation were similar to the crystallographic data published for the complexes of phenothiazine The interactions of promethazine hydrochloride and dextrans or pectins are realised by forming of complexes with charge transition. Hydrophobic and insignificant dipole interactions are also possible. The complex formation has been confirmed by some investigations for bioavailability.

2.6. Analgesics/antipyretics (including narcotics)

Acetylsalicylic acid (aspirin) is the most widely used oral drug (Tsunematsu et al., 1991). Its effects as an analgetic, antipyretic and anti-inflammatory agent have been very well known for a long time. Today aspirin is used as antithrombotic drug as well as an agent comparable with the narcotic analgesics administered (intramuscularly/intravenously) in the postoperative period. Some respiratory depressant effects of aspirin has been observed (Tsunematsu et al., 1991).

The chemical stability of aspirin in ground mixtures with α-, β-, γ-CYDs has been reported (Nakai, 1986). The author has found a good correlation between the decomposition rate constants and the state of the acetoxyl groups of aspirin samples observed in their IR spectra. The great intensity of the absorption band at 1748 cm^{-1} has been connected with the high degree of interaction and the strength of hydrogen bonding between aspirin and β-cyclodextrin. The results observed have been explained mainly by small cavity size of the α-cyclodextrin (without including aspirin molecules) and the large diameter of γ-cyclodextrin'n cavity (allowing the aspirin molecules to move in it). The enhancement of aspirin hydrolysis has been due to the above mentioned processes.

The author has noted that β-, and γ-cyclodextrins have a different influence on the stability of aspirin in their inclusion compounds. The decomposition rate of the γ-cyclodextrin inclusion compound was 40 times greater than that of the β-cyclodextrin inclusion compound. Aspirin rapidly decomposes in the α-cyclodextrin/aspirin system. The author has concluded that aspirin molecules are dispersed in the networks of cyclodextrin or cellulose molecules which are intermolecularly hydrogen bonded.

The effects of particle size and (−)-α-bisabolol on the gastrotoxicity of acetylsalicylic acid (AAS) in rats have been studied (Torrado-Santiago et al., 1995a,b). The gastrotoxicity of AAS includes a double mechanism-local and systemic toxicity. The first is produced by direct contact of the drug with the gastric mucosa. This can be avoided by using coated formulations or parenteral administration of AAS. The systemic toxicity of AAS is produced by inhibition of prostaglandin production. Low concentration of prostaglandins I_2 and E_2 in the gastric mucosa causes vasoconstriction and reduction of the blood flow. The administration of different protective agents (histamine H_2-receptor antagonists, prostaglandins, omeprazole and sucralfate) has decreased the AAS ulcerogenicity. (−)-α-Bisabolol (obtained from camomile oil) is an antioxidant with anti-inflammatory activity and low toxicity. (It has also a protective effect on the indomethacin ulcerogenicity.) The authors have found a significant protective effect of (−)-α-bisabolol oral administration with AAS. Torrado-Santiago et al. (1995a,b), have concluded that the possible inclusion of (−)-α-bisabolol in AAS formulations should be considered.

Different hydrophilic excipients on the release of acetylsalicylic acid matrix tablets prepared from pellets have been studied (Torrado-Santiago et al., 1995a,b). Microcrystalline cellulose (MCC), wheat starch and dextrose monohydrate have been evaluated. It has been found that the different excipients increased drug dissolution due to their characteristics and the percentages of the excipients.

Among the three excipients, the greatest increase was obtained by addition of MCC and wheat starch. MCC is an excipient with a higher compression protect effect on the pellets during tablet compaction. In vitro drug release depends on the MCC content of the tablets.

2.7. β-adrenergic blockers

Propranolol hydrochloride (Inderal®, Obsidan®, Propranolol) interacts with a methacrylic acid copolymer (Eudragit L) Lee et al. (1991) as well as with pectin (Neubert et al., 1995). It is well known, that some drugs containing amino/imino groups can form water-insoluble complexes with Eudragit L. In the gastrointenstinal tract, the drugs are released from complexes slowly by an ion-exchange process. (Lee et al., 1991) have characterised the complex as sparingly soluble (slow releasing of propranolol) which may be due to hydrogel formation when the tablet is exposed to the dissolution medium. Neubert et al. (1995) have remarked that the bioavailability of drugs can be changed by interaction with food components. The authors have studied the influence of pectins on the transport of the β-blocking agent propranolol across artificial membrane. They have concluded that the arrangement of continuous regions of free carboxyl groups of pectins is the major factor which influences in vitro results.

Carteolol polymeric complexes with Eudragit L in order to obtain controlled release dosage forms have been prepared (Holgado et al., 1995). Carteolol hydrochloride has a potent β-adrenergic blocking action. The results obtained show intermolecular associations of a saline bond type between drug and excipient.

2.8. Corticosteroids

Various vehicle excipients, so called penetration enhancers, can affect the skin barrier (stratum corneum) and thereby influence the permeability of drugs into or through the skin.

The effect of polyvinylpyrrolidone (PVP) on the ability of CYDs to form complexes and its permeability through hairless mouse skin have been studied (Sigurðardottir and Loftsson, 1995). It is well known that CYDs (cyclodextrins) are generally poorly absorbed through the skin.

The authors conclude that CYDs can be used as skin penetration enhancers. The type of CYDs used, the correct concentration to dissolve the drug (addition of more CYDs than is needed will result in a decreased flux of the drug) have been shown as important factors. PVP acted as a co-enhancer for the CYD enhanced transdermal delivery of hydrocortisone.

Experiments about penetration of hydrocortisone (as inclusion compounds with cyclodextrins-β-CD or HP-β-CD) into excised human skin have been provided (Preiss et al., 1995). The authors conclude that the preferred penetration route for the easily soluble inclusion compounds is a transappendageal diffusion rather than a transdermal one. A good correlation between the penetration results in the dermis (but not in the other skin layers) and the release results obtained by using an ointment liberation model has been observed.

2.9. Radioprotective agents

Radioprotective agents have a very important role in radiotherapy (of neoplastic diseases). The cells and healthy tissues can be injured by free radicals and oxygen produced in the organism during the radiation. A decrease of these side effects is possible with the use of the enzyme superoxide dismutase (SOD).

The radioprotective effect in mice of six copper complexes have been studied (Valentova et al., 1995). The authors have remarked the effects depending of the structure as well as that the complexes are not only the source of copper ions.

The complexes including in their structure glutamic acid, β-alanin, DL-phenylalanine, respectively, have shown a good radioprotective activity. (The latter was determined by the survival of mice to the 30th day after exposure).

Schiff's base copper complexes which are prepared from salicylaldehyde and different amino acids possess effects similar to those of SOD. Valentova et al. (1995) have found a significant discrepancy in the activity of the two complexes investigated as a result of the different amino group positions.

The structure changes of chelate rings influence the oxidative-reductive properties of these complexes which are responsible for the effects in agreement with the SOD-like activity.

3. Excipients (included in pharmaceutical formulations)

Excipients used often in the drug formulations studied include: β-(CYDs) or their derivatives, celluloses (Gasheva et al., 1984; Oguchi et al., 1995; Tirkkonen et al., 1995; Wolf et al., 1996), pectins (Rachnev et al., 1986; Kalinkova and Krasteva, 1989; Neubert et al., 1995), dextrans (Rachnev et al., 1986), chitosans (Imai et al., 1991) and other excipients. Comparatively very little data are available on the application of α-cyclodextrins (Oguchi et al., 1990) as well as of dextrans.

3.1. Characteristics of β-cyclodextrins (CYDs)

The CYDs are the first choice because of their ability to form inclusion complexes, to stabilise unstable drugs (Green et al., 1991; Ammar and El-Nahhas, 1995a,b,c; Kedzierewicz et al., 1995), to change the pharmacological and pharmacokinetic behaviour of the original drug (Cserháti, 1995), their commercial availability and economical convenience (Giordano et al., 1990).

CYDs are cyclic non-reducing oligosaccharides containing six (α-cyclodextrin), seven (β-cyclodextrin) or eight (γ-cyclodextrin) α-1,4-linked glucopyranose units, with a hydrophilic outer surface and a hydrophobic cavity in the centre (Cserháti, 1995; Sigurðardottir and Loftsson, 1995; Zeng et al., 1995; Veiga et al., 1996). Many drugs form non-covalently bonded complexes as a guest whole drug molecule or some part of it (Sigurðardottir and Loftsson, 1995; Zeng et al., 1995; Veiga et al., 1996) penetrated into the cavity. β-Cyclodextrin's cavity has inside diameter of about 7 Å (enough large for an aromatic ring accommodation). α-Cyclodextrins are generally too small to include the majority of drugs. γ-Cyclodextrins are more suitable, but they have a prohibitive price for its use in pharmaceutical manufacturing (they are a by-product of α- and β-CYDs preparation).

Many papers have reported the stabilisation of different drugs with β-cyclodextrins: vitamins A and D_3, clefibrate, guaizulene, colchicine (Ammar and El-Nahhas, 1995b), hydrocortisone (Sigurðardottir and Loftsson, 1995), theophylline (Adeyeye et al., 1995), tolbutamide (Kedzierewicz et al., 1995; Veiga et al., 1996), chlorambucil (Green et al., 1991) and fostedil (Takahashi et al., 1985).

3.2. Characteristics of celluloses

Valuable information about celluloses as well as about their important IR spectral behaviour is described by many authors (Gasheva et al., 1984; Oguchi et al., 1995; Tirkkonen et al., 1995; Wolf et al., 1996). Oguchi et al. (1995) underlined also the practical importance and the fundamental interest in cellulose particularly in pharmaceutical technology (Kochhar et al., 1995) due to its excellent utility.

3.3. Pectins

The interactions between pectin and different active medicaments has not been discussed sufficiently in literature. Results have been published (Rachnev et al., 1986; Kalinkova and Krasteva, 1989; Neubert et al., 1995) for the interactions observed between apple, citrus pectins and drugs promethazine hydrochloride, nystatin and propranolol, respectively. The results obtained are discussed in Sections 2.5 and 2.1 and Section 2.7, respectively.

Evaluations about pectins as valuable excipients in pharmaceutical technology have been given (Rachnev et al., 1986; Neubert et al., 1995). It is also well known that they are used in food products. Pectins consist of long chains of galacturonic acid residues interrupted by some high-branched rhamnogalacturonan regions. The different properties and effects of pectins as well as the activity of pectinesterase and polygalacturonase, the gelation or binding of cations are influenced mainly in their structural parameters (degree of esterification and conformation).

3.4. Chitosans

Data on chitosans and the results obtained with four kinds of chitosans (with different molecular weights and different degrees of deacetylation) in the complexation use with indomethacin have been described (Imai et al., 1991).

Good biocompatibility and biodegradability are the important characteristics which have contributed to this attention in pharmacy towards natural polymers as polysaccharides and proteins. The chitosans (deacetylated products of alkaline treatments of chitin) are the most useful natural polymers. These basic polysaccharides interact with acidic drugs. They enhance the dissolution rates of poorly water-soluble drug.

3.5. Other excipients

Many other excipients are included in the studies of interactions with active medicaments. Some of them are presented in Table 2 and here they are only mentioned as follows: calcium glycerophosphate (El-Monem et al., 1991), colloidal silica (Forni et al., 1988), dicalcium phosphate dihydrate (Landin et al., 1995), dodecyl 2-(*N*,*N*-dimethylamino) propionate (Büyüktimkin et al., 1996), Eudragit L (Holgado et al., 1995), methacrylic acid (Lee et al., 1991), polycarbophil (Hosny and Al-Angary, 1995), PEG (Guyot et al., 1995).

4. IR-spectroscopy and X-ray diffraction—the basic methods of studies of interactions between active medicaments and excipients in pharmaceutical formulations

IR-spectroscopy and X-ray diffraction are well known methods of drug analysis and have an exclusively great significance in investigations of interactions between drugs and excipients in pharmaceutical formulations. Many authors successfully use the combination of these two methods (Kawashima et al., 1983, 1985; Gasheva et al., 1984; Forni et al., 1988; Kedzierewicz et al., 1990; Oguchi et al., 1990; Green et al., 1991; Imai et al., 1991; Guyot et al., 1995; Vandelli et al., 1995; Büyüktimkin et al., 1996). Data from additional investigations is also available in literature about the following methods: DSC (Forni et al., 1988; Imai et al., 1991; Guyot et al., 1995; Singla and Wadhwa, 1995; Vandelli et al., 1995; Veiga et al., 1996; Wolf et al., 1996; Büyüktimkin et al., 1996), NMR (Imai et al., 1991; Holgado et al., 1995; Singla and Wadhwa, 1995; Vandelli et al., 1995; Büyüktimkin et al., 1996), UV spectroscopy (El-Monem et al., 1991; Ammar and El-Nahhas, 1995b; Ammar et al., 1995; Neubert et al., 1995; Singla and Wadhwa, 1995; Büyüktimkin et al., 1996), Raman spectroscopy (Veiga et al., 1996), TG (Giordano et al., 1990), SEM (Wolf et al., 1996).

Of course, the complex use of recent instrumental methods ensures the most complete information but it is not absolutely obligatory for drug control in pharmaceutical industry and is not economically justified.

Usually, IR spectroscopy precedes X-ray diffraction studies. The realised interactions between drug(s) and excipients are discovered and proved by IR spectroscopy with the following important characteristics: appearance of new IR absorption band(s); broadening of band(s); alteration in intensity. The comparison of the four IR spectra—of the drug alone, of the excipient alone, of the complex and of the simple physical mixture (prepared in the same stoichiometry as the complex from both drug and excipient(s)) secures the greatest precision of the analysis. Here, IR spectroscopy applied mainly as identifying technique is also based on the up-to-dated principles, procedures, standards and requirements assisting both manufacturers and drug regulators in their control. X-ray diffraction studies require an analogous comparison of the X-ray diffractogrammes.

The recent IR techniques (FTIR-microscopy, FTIR photoacoustic, etc.) have been estimated an applied in successful solutions of various pharmaceutical problems. IR spectroscopy and IR techniques have well known advantages in comparison with other analytical methods.

Important IR spectral data on Fourier transform infrared spectroscopy-attenuated total reference method (FTIR-ATR) identification of

Table 2
Studies of interactions between active medicaments and excipients in pharmaceutical formulations

Active medicament/ excipients	Stoichiometry (molar ratios percentages)	Therapeutic activity (drug administration)	Pharmaceutical formulations	Results of interactions	Notes	References
Acetylsalicylic acid (ASA)/ microcrystalline cellulose (MCC) Avicel[R] PH-101	Different proportions—5, 10, 15, 25%	Analgesic antipyretic	Matrix-tablets	The release rate of ASA is dependent on proportions of the excipients 0–25% MCC		Torrado-Santiago et al. (1995a,b)
Acetylsalicylic acid/ (methacrylate copolymers Eudragit[R] RS) wheat starch Dextrose monohydrate	Different proportions—5, 10, 15, 25%	Analgesic antipyretic	Matrix-tablets	Poor drug release		Torrado-Santiago et al. (1995a,b)
Amoxicillin trihydrate/ethylcellulose	9:1 and 1:1	Antibiotic	Sirup granulae	Increased drug activity and drug prolonged release		Gasheva et al. (1984)
Allopurinol β-Cyclodextrin	1:1 complex	By anti hyperuricemia treatment	A paste (vacuum dried at 40°C by kneading method)	Improvement of dissolution rate	Complex	Ammar and El-Nahhas (1995a)
Bromhexine hydrochloride/β-cyclodextrin (β-CD)	1:1 complex	A potent mucolytic agent	A paste (vacuum dried at 40°C by kneading method)	Increased solubility; improvement in the release properties of the drug from transdermal delivery systems	Complex	Ammar and El-Nahhas (1995c)
Carteolol hydrochloride/Eudragit L	22% carteolol	A potent β-adrenergic blocking action	Dosage forms	Type ammonium salt interactions	Polymeric complex	Holgado et al. (1995)
Chlorambucil (CHL)/ Heptakis (2,6-di-*O*-methyl) β-cyclodextrin, β-cyclodextrin	1:1 complex molar ratio	Antitumor agent		Preparation of solid dosage forms with extended shelf life	Complex H-bonding interactions	Green et al. (1991)
Chloramphenicol stearate/colloidal silica		Antibiotic	Powder	In vitro higher enzymatic hydrolysis rate (value)		Forni et al. (1988)
Chlorpromazine hydrochloride/β-cyclodextrin	1:1 complex	Antipsychotic agent		Improvement of: bioavailability; increased intensity of drug action; photochemical stability	Effect of complex measured by a single oral dose in volunteers	Ammar et al. (1995)

Table 2 (*Continued*)

Active medicament/excipients	Stoichiometry (molar ratios percentages)	Therapeutic activity (drug administration)	Pharmaceutical formulations	Results of interactions	Notes	References
Colchicine/β-cyclodextrin	Inclusion complex 1:1			Marked stability of the drug and its protection against photo-degradation	Complex	Ammar and El-Nahhas (1995b)
Fostedil/Microcrystalline Cellulose or Corn Starch	1:3, 1:1, 3:1	Ca^{++} antagonist coronary vasodilator, hypotensive actions	Tablet	Excipients showed a polymorphic transformation-accelerating effects	Form I suitable for pharmacology preparation	Takahashi et al. (1985)
Hydrocortisone (HC)/cyclodextrins, β-cyclodextrin hydrohypropyl-β-cyclodextrin	1% (w/w)	Corticosteroid	Cream (O/W), gel	Increased drug release results in enhanced penetration into dermis		Preiss et al. (1995)
Hydrocortisone/cyclodextrins, polyvinylpyrrolidone (PVP)		Transdermal delivery (stratum corneum)	Suspension	Chemical stability, solubility in water		Sigurðardottir and Loftsson, 1995
Indomethacin/Calcium glycerophosphate	1:1 molecular complex	Antiinflammatory drug (agent)	Various dosage forms	5-fold increase in water solubility, enhanced bioavailability, reduced ulcerogenicity		El-Monem et al., (1991)
Indomethacin (IM)/chitosans (low molecular weight)	16:1		Aqueous solution	Rapid absorption and dissolution rates	Oral administration to beagle dogs	Imai et al. (1991)
Indomethacin/dodecyl 2-(*N*,*N*-dimethylamino) propionate (DDAIP)	Equimolar amounts (1 mmol) of drug and DDAIP	Transdermal delivery	Model	Formation of new structure which increases penetration through the stratum corneum		Büyüktimkin et al. (1996)
Indomethacin/epirizole	Molecular ratio 2:1		Spherically agglomerated crystals	Possible reduced adverse effects of indomethacin and improved therapeutic action		Kawashima (1984)
Indomethacin/ethylcellulose			Microcapsules; suppositories	Increases extent of release		Tirkkonen et al. (1995)
Indomethacin/polycarbophil	5, 6 and 8% polycarbophil		Three different dosage forms	Increased plasma levels and bioavailability improved significantly (determined in dogs)	Complex, potential candidates for further incorporation into hard capsules or tablets	Hosny and Al-Angary (1995)

Table 2 (*Continued*)

Active medicament/ excipients	Stoichiometry (molar ratios percentages)	Therapeutic activity (drug administration)	Pharmaceutical formulations	Results of interactions	Notes	References
Indomethacin/zinc	2:1 0.05 mol/200 ml water; 0.025 mol/200 ml water	Anti-inflammatory activity; anti-ulcerogenic activity		Increased stability and dissolution rate; zinc reduced ulcerogenic effects	Complex; biological evaluation in rats	Singla and Wadhwa (1995)
Interferon-α-2b (INF) and 5-Fluorouracil (5FU)		Gastrointest. antitumour agent	Model drugs	An accumulation of 5FU in the serum of patients	During continuous infusion	Czejka et al. (1995)
Norfloxacin/cyclodextrins (β-CD or HP-β-CD) and PEG	Ratios 1:1 and 1:2	Antimicrobial agent; urinary tract infection		Concerning storage bioavailibility, increased dissolution rate	Inclusion complex	Guyot et al. (1995)
Nystatin (NYS)/glycerin pectin	1% (NYS); 13%	Antibiotic	Plaque for stomatology	Increased activity, prolonged drug release	H-bonding interactions	Kalinkova and Krasteva (1989)
Promethazine.HCl/dextran Promethazine.HCl/ pectin	1:1	Antihistaminic agent	Models	Complexes with transition of charge		Rachnev et al. (1986)
Propranolol HCL / Methacrylic acid Copolymer (Eudragit L)	68% in complex 1:1	β-blocking agent	Tablets	Potential mechanism for prolonged release of active drug		Lee et al. (1991)
Propranolol HCL/ pectin	Solutions of 1 mmol (375 mg/ml) and 0,5 mmol (187,5 mg/ml)	β-blocking agent		The results obtained in vitro show the different effects of pectins on the lipid-membrane transport of the drug		Neubert et al. (1995)
Sulfamethoxazole/ polysaccharide gum and colloidal silica	5% drug 5% coloidal silica 0.5% gum	Chemotherapeutic	Spray-dried microcapsules	Increased particle size and increased flowability and packability		Kawashima et al. (1983)
Theophylline/ethylendiamine		Diuretic saluretic cardiakum	Spherically agglomerated crystals	Free flowing and directly compressible agglomerated crystals	See Japanese Pharmacopoeia X	Kawashima (1984)
Tolbutamide/β-cyclodextrin	1:2	Oral hypoglycemic agent		Increased solubility, 100% drug released inclusion complex	Inclusion complex	Kedzierewicz et al. (1990)
Tolbutamide (TBM)/β-cyclodextrin and hydroxypropyl-β-cyclodextrin (HP-β-CD)	1:2	Oral hypoglycemic agent	Coprecipitate	Increase of solubility and dissolution rate for the drug, bioavailability	Possible enhancement of bioavailability	Veiga et al. (1996)
Tolbutamide/β-cyclodextrins			Comelt, coprecipitate	Complex is very stable regardless of the storage temperature	Inclusion complex	Kedzierewicz et al. (1995)
Ursodeoxycholic acid (UDCA)/2-hydroxypropyl-β-cyclodextrin	1:1	Biliary cirrhosis	Suspensions	Increased stability and bioavailability of UDCA	Inclusion complex	Vandelli et al. (1995)

excipients as pure monosubstances in mixtures or as drug formulations have been published (Peters et al., 1995). The authors considered that the method is excellent for rapid control by manufacturing drug formulations. An electronic library for computer search of absorption and transmission spectra of excipients and drugs has been established.

FTIR microscopy has been used both to study qualitatively the structure of emulsions (from cetrimide, cetostearyl alcohol, etc.) and to analyse quantitatively the oil droplets for the latter (Louden and Rowe, 1990). The results in industrial context are particularly of interest in the preparation of antiseptic creams. The authors have evaluated FT-IR microscopy as potential relatively rapid, non-destructive technique in the quantitative analysis of the complex emulsions as well as in the understanding of the mechanisms of their formation. They have also concluded that the technique could be used in optimisation of processing conditions to eliminate batch to batch variation.

The foregoing facts confirm that among the various modern techniques applied the combination of infrared spectroscopy and X-ray diffraction has been estimated as the most successful in proving the interactions between drugs and excipients.

5. Peculiarities of studies of interactions between active medicaments and excipients in pharmaceutical formulations

Studies of interactions between active medicaments and excipients in pharmaceutical formulations are characterised with specific peculiarities. Here, they are summarised in three basic groups:

- the pharmaceutical formulations as multicomponent systems including various drugs and excipients with their specific behaviours;
- the complex physico-chemical character (mechanism, type) of the interactions;
- numerous methods of analysis (physico-chemical, biological etc.), their use, choice, combination and data interpretation.

Two important factors have been also taken into account—the crystallinity and the presence of water molecules. The crystalline states (of drugs, excipients and complexes) have been screened and considered: (Kawashima et al., 1983; Gasheva et al., 1984; De Taeye and Zeegers-Huyskens, 1985; Kawashima et al., 1985; Nakai, 1986; Rachnev et al., 1986; Forni et al., 1988; Oguchi et al., 1990; Imai et al., 1991; Adeyeye et al., 1995; Kedzierewicz et al., 1995; Oguchi et al., 1995; Tirkkonen et al., 1995; Torrado-Santiago et al., 1995a,b; Vandelli et al., 1995).

The recent IR techniques (FTIR microscopy, FTIR photoacoustic, etc.) have been applied in successful solutions of these pharmaceutical problems.

The possibilities of photoacoustic FTIR and ^{13}C cross polarisation-magic angle spinning (^{13}C CP/MAS) NMR in investigating crystallinity in the tablet bulk and at the tablet surface, respectively, have been offered (Ek et al., 1995). Authors have concluded that photoacoustic FTIR is a well suited method for surface layer studies. Ek's paper has shown the beginning of the investigations of the microcrystalline cellulose in the literature using photoacoustic FTIR technique. Data reported have been of interest for the pharmaceutical industry.

A very important fact is that the quality of pharmaceutical formulations can be connected also with the possible different interactions with water molecules. Many authors have thoroughly discussed these very important problems in their papers (De Taeye and Zeegers-Huyskens, 1985; Ahlneck and Zografi, 1990; Giordano et al., 1990; Adeyeye et al., 1995; Griesser and Burger, 1995; Nokhodchi et al., 1995). The review article (Ahlneck and Zografi, 1990) gives an excellent basis for the better understanding of these problems.

The effects of varied moisture conditions on drug release stability of theophylline matrix tablets have been reported (Adeyeye et al., 1995). Above 52% relative humidity storage changes the anhydrous theophylline to monohydrate and the excipient magnesium stearate (Müller, 1977) to its polymorph.

The water molecules in the caffeine hydrate are bound to N_9 atom of the imidazole ring have been

observed (De Taeye and Zeegers-Huyskens, 1985). These typical OH–N bonds (distances 2.85 A) take part in the arrangement of drug crystal packing and show tunnels of water molecules approximately parallel to the long crystal direction.

At least one third of the solid crystalline substances of the European Pharmacopoeia have been estimated and the formation of different associates with water has been reported (Griesser and Burger, 1995). They have studied caffeine 4/5-hydrate (0.807 mol water per mol caffeine) desolvation. The authors have concluded that this process is very complex dependent on vapour pressure conditions, temperature and crystal dimensions. Caffeine 4/5-hydrate is extremely unstable and it is necessary to be stored at 75% relative humidity. This fact has been known for 50 years but has not been adequately considered in today's pharmacopoeias.

The effect of moisture on energies (plastic, elastic, ejection force) in ibuprofen compaction has been examined (Nokhodchi et al., 1995).

The inclusions of active medicaments in cyclodextrins is unable to sustain drug release in the lungs, which may be due to the premature breakdown of drug–cyclodextrin conjugates in vivo (Zeng et al., 1995). The authors have established that none of the previous reports has confirmed the in vivo stability of the drug-cyclodextrin complex and it is still hard to rationalise the potential of cyclodextrin complexes as pulmonary controlled release systems.

Really, pharmaceutical formulations and their peculiarities have constituted a diverse and rapidly expanding field of Pharmacy which covers a wide range of numerical topics.

6. Conclusions

The above described studies of interactions between active medicaments and excipients in pharmaceutical formulations have been presented as proofs for their importance in Pharmacy. The beneficial possibilities of these interactions have been estimated in successful solutions of various specific pharmaceutical problems—the improvement of the solubility of poorly soluble drugs, of increased dissolution rates, stability, increased drug release, therapeutic activity, increase of bioavailability and decrease of unwanted side effects. The significant role of excipients in these interactions and their behaviours as active ingredients in the pharmaceutical formulations have been emphasised.

Some peculiarities of these basic studies have been summarised in three groups (pharmaceutical formulations as multicomponent systems; complex character of the interactions; numerous methods of analysis). Crystalline states (of drugs, excipients and complexes) as well as the presence of water molecules have been considered as two important factors.

Among the various modern techniques applied the combination of infrared spectroscopy and X-ray diffraction has been estimated as the most successful in proving the interactions between drugs and excipients.

It is quite true that the paradigms of drug research have changed significantly (Kubinyi, 1995). The chances of finding new structures obtained by interactions (between active medicaments and excipients), with less effort than by dedicated syntheses are increasing. Many bodies (Dibner, 1985) collaborate in the two fields—applied and basic research of this important pharmaceutical area.

Finally, the studies of interactions between active medicaments and active excipients will be greatly developed in the future due to the three basic factors—the care of high quality drugs, the pharmaceutical industry growth and the continuous progress in instrumental technique developments for recent standardised drug control.

Acknowledgements

The author is grateful to Professor P.F. D'Arcy for his kind advice and valuable instructions suggested in preparing this review article. Special thanks are expressed to Professor A.T. Florence for the critical review of this manuscript, for the numerous excellent ideas suggested and for his invaluable time devoted to the improvement of this manuscript. The author thanks Mrs. M. Alex-

ieva and Mr. K. Hill for the valuable help in English translation. The study is entirely supported by the personal devices of the author's modest financial income. This is the author's human and civil position in the present difficult period of the severe economic state of this country when many ill children and old people need help.

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