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Complexes: Role in Pharmaceutical Formulation

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Complexation is a frequent form of interaction between drugs and excipients. Complexation has beneficial as well as deleterious effects. This is a review of research findings reporting complexation as a tool to overcome problems such as stability, safety, bioavailability and dissolution. The information on important complex types, material and applications is included in this review.

Key Words: Ion exchange resin, Tannic acid complex, Polymer drug conjugate, Inclusion complex.

INTRODUCTION

Complexes are result of a donor acceptor mechanism between two or more different chemical constituents. Complexes are classified in two categories based on chemical bonding: (1) Metal ion complexes (coordination complexes) and (2) molecular complexes which is further classified depending on type of bonding or interaction such as charge transfer complexes, hydrogen bonding complexes, hydrophobic interaction and stacking interaction[1]. Complexation is one of the important formulation tools. Examples of chelating agent such as EDTA used for stabilization, complexes with polymers such as polyethylene glycol, polystyrene, tannic acid, carbowaxes and povidone are available in literature.

Following discussion deals with important complexes, complexing agents used in formulation, mechanisms involved and applications in pharmaceutical formulation.

Ion exchange resins: Ion-exchange resins contain positively or negatively charged sites within a polymer matrix and are accordingly classified as either cationic or anionic exchanger[2]. They are further classified as strong or weak depending on their affinity for soluble counter-ions. The ion-exchange resins, which are commonly used in pharmaceutical preparations, are given in Table-1. The drug-resin complex formation and drug releases mechanism are given in Table-1.

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Resinates are prepared by two methods: (a) batch method in which drug solution or dispersion is stirred with ion exchange resin till equilibrium and uncomplexed drug is estimated and (b) column method in this the drug solution is passed through column packed with resin particles till equilibrium. Equilibrium is approached when concentration of percolate of drug solution doesn't change. Various applications of ion exchange resins include taste masking, improvement of stability, sustained release, targeted drug delivery of anticancer drugs. Pharmaceutical applications of ion exchange resins are adequately reviewed[3].

TABLE-1
ION EXCHANGE RESINS COMMONLY USED IN PHARMACEUTICAL FORMULATIONS

Resin type	Exchange species	Polymer type	Commercial Resin
Strong anion	$-NR_3$	Polystyrene divinyl benzene	Amberlite IR400, DOWEX1
Weak anion	$-NR_2$	Polystyrene divinyl benzene	Amberlite IR4B, DOWEX2
Strong cation	$-SO_3H$	Polystyrene divinyl benzene	Amberlite IR20, DOWEX50
Weak cation	-COOH	Methacrylic acid divinyl benzene	Amberlite IRC50, DOWEX1

The complex of cationic drug and the weak cation-exchange resin does not break at pH 6-7 of saliva with cation concentration of 40 meq/L. But at high cation concentration in stomach and pH of 1-3, free drug is immediately released[4] *viz.* rodec decongestant tablet containing pseudoephedrine[5]. Taste masked ciprofloxacin complexes using Indion 234 a commercially available weak cation exchange resin[6], non bitter complexes of chloroquine with ion exchange resins are reported[7]. Taste masking of sparfloxacin is reported with improvement in dissolution rate[8].

Pennkinetic system by Pennwalt corporation, USA is commercially available sustained release formulation[9].

The use of polymeric film coating has been employed to effect further control on diffusion of drug and pre-treatment with PEG-4000 helped retain geometry and coating of particles during dissolution[10]. Several techniques are reported using ion exchange resin as sustained release drug delivery system. Drug has been loaded on the resin, which dissociates slowly in GI fluids to give sustained release[11]. Resinates have been used in matrix[12]. Physical mixture of drug and ion exchange resin was allowed to form complex *in situ* which released drug with same rate as resinates[13], attempts to coat resinate with rate controlling barrier have successfully obtained by controlled release of drugs[14,15].

Complexing active ingredients with ion-exchange resins prevents harmful interaction with other components like vitamin B_{12} and carboxylic acid - this complex is as effective as free drug[16]. Ion-exchange resins may have inherent bioadhesive properties similar to those of highly charged polyanions[17].

Hence ion-exchange resins may be useful mucoadhesive systems for topical treatment of stomach such as in *H. pylori* infection for prolonging the gastric residence of amoxycillin and cimetidine[18].

Tannic acid complexes: Tannins comprise a large group of complex substances that are widely distributed in plant kingdom possessing astringent action and ability to precipitate proteins and alkaloids. Tannins can be broadly defined as derivatives of polyhydroxy benzoic acid, which are widely distributed in vegetable kingdom and are capable of combining with proteins[19]. The official tannic acid is believed to be mixture of digallic acid ester of D (+)-glucose of which the most important is penta di galloyl glucose. Amine drugs can be treated with tannic acid to form poorly soluble complexes. Such complexes can be obtained by simple acid base reaction on mixing together solution of individual compounds. Similarly if an alcoholic solution of a basic drug and tannic acid are mixed in 5:1 ratio, tannate complexes containing one amine per digallyl moiety are precipitated. These complexes are split by hydrolysis in gastric and intestinal fluid. Break down of the tannate complex depends on the pH, hydrolysis being faster in acidic medium than basic. Chlorpheniramine, phenylephedrine, ephedrine tannates bear sustained release claims. Long acting narcotic antagonists like naltrexone and cyclozocine form complexes with tannate salt of zinc or aluminium and are used in treatment of narcotic dependence[20]. Cynocobal-amine tannate complex show sustained release of the drug[21]. Non-bitter chloroquine formulation using tannic acid to mask the taste of drug by using the principles of complexation with tannic acid has been formulated[22]. It has been reported that cellulose acetate phthalate can be used as a material for sustained release preparation with an added advantage of enteric coating property[23].

Polymer drug conjugates: Polymeric prodrug or polymer drug conjugates (PDCs) (Fig. 1) are the systems in which drug moiety is covalently bonded to either natural or synthetic polymer which may or may not be biodegradable. This involves the use of an active substance and possibly a targeting moiety, both linked *via* spacers to a water-soluble polymeric backbone[24]. In comparison with the low molecular weight prodrug, a polymer-drug conjugate can generally be expected to overcome the problems of side effects and to have prolonged duration of action. In addition, the polymer-drug conjugate may possibly show an affinity for tumor cells[25]. A number of polymerdrug conjugates have been synthesized for cancer

chemotherapy, which includes polymeric prodrugs of mitomycin[26], adriamycin[27] cisplatin[28]. Polymer conjugates have been widely employed in controlled drug delivery. The rate of drug release from a polymeric conjugate can be controlled either physically or chemically[29,30].

Physically regulated drug delivery systems: The drug is physically entrapped in the polymeric network forming reservoir systems, with the rate of drug release being controlled by the diffusion of the drug through a polymeric barrier and/or degree of cross linking.

Chemically regulated drug delivery systems: The drug is attached to the polymeric carrier by a covalent bond (PDC), the enzymatic or chemical hydrolysis of the covalent linkage is utilized to release the free drug.

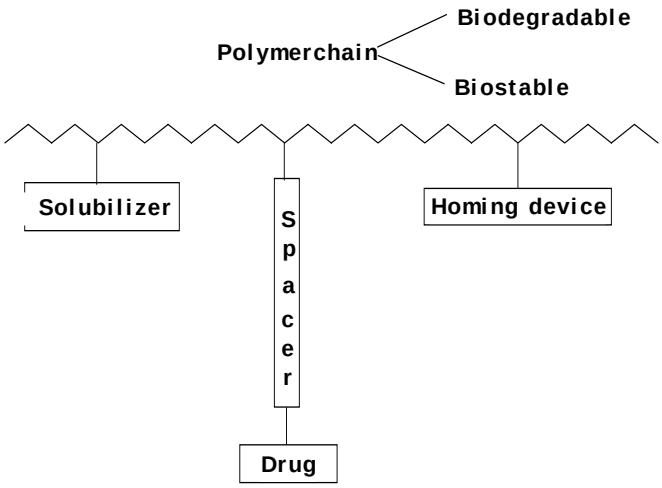

Fig.1. Generalized structure of a polymer drug conjugate

Types of polymer drug conjugates: Polymer-drug conjugates can broadly be classified into two types on the basis of their solubility in biological fluids like blood, lymph and interstitial fluid.

Soluble polymer drug conjugates: These are meant for systemic administration, where the polymer functions as a carrier for the transport of the drug to target cells.

Insoluble polymer drug conjugates: These are suitable for the local release of the drug after implantation such as insoluble films, microspheres or nanocapsules, which then release drug slowly in systemic circulation. *e.g.* gentamycin-sodium alginate conjugate[31].

Targeting may be accomplished by linking a receptor-specific moiety such as an antibody, lectin, hormone or carbohydrate to a soluble polymer-drug conjugate. The polymer functions as an intermediate carrier between the drug and the homing device to increase the amount of transported drug.

Currently the targeting of drugs with the aid of cell-specific molecules in the treatment of cancer and other diseases is attracting more interest. A marked example is the presence of the recognition system on certain cells for exposed carbohydrate residues of serum glycoproteins, synthetic polymers *e.g.* polyethylene glycol, *etc*.

Various other excipients are described to form complexes with different drug moieties giving specific advantages. Indomethacin polycarbophil complex improved significantly bioavailability of indomethacin in dogs[32]. Water soluble alginate salts and organic acid admixture is described for sustained drug delivery of poorly soluble basic drug[33]. Formulation of morphine polymer complex with Eudragit L has been shown to possess good flow and other granullometric properties with improved dissolution[34].

Inclusion complexes: This involves host guest relationship, host include the guest (drug molecule) into the cavity formed in molecular structure. These complexes are formed by geometry of host molecule. These complexes are best represented by cyclodextrins. Cyclodextrins have lipophilic inner cavity and hydrophilic outer surface and can interact with a large variety of guest molecules to form non-covalent inclusion complexes (Fig. 2). Chemically they are cyclic oligosaccharides containing at least six D-(+) glucopyranose units attached by α-(1,4) glucosidic bonds.

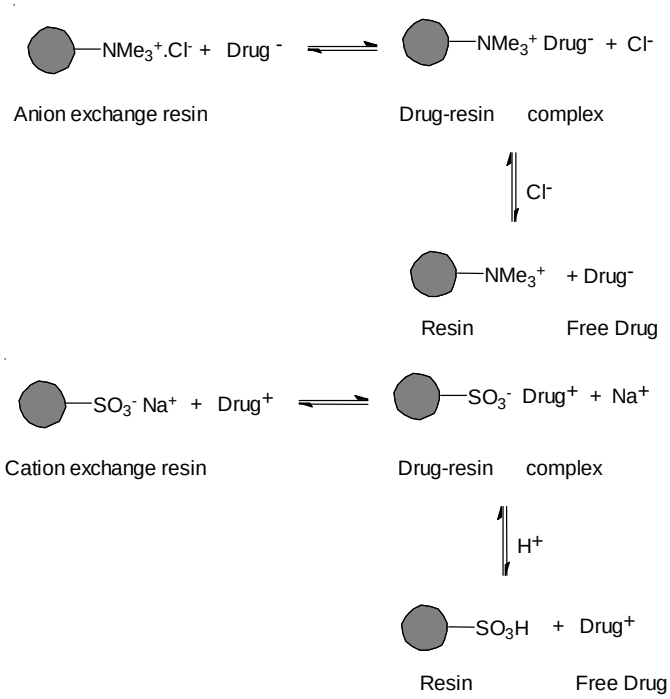

Fig.2. Equilibrium phenomenon and drug release mechanism for resinate

The three natural cyclodextrins (CDs) *i.e.*, α-, β- and γ-CDs (with 6, 7 or 8 glucose units, respectively) differ in their ring size and solubility (Table-2).

TABLE-2
SOME CHARACTERISTICS OF α-, β -, γ- and δ-CD[35,36]

Type of CDs	Cavity diameter (Å)	m.w.	Solubility (g/100 mL)
α-CD	4.7-5.3	972	14.50
β-CD	6.0-6.5	1135	1.85
γ-CD	7.5-8.3	1297	23.20
δ-CD	10.3-11.2	1459	8.19

Chemical modifications of cyclodextrins (Fig. 3) improve the physicochemical properties and inclusion capacity of parent cyclodextrins. Cyclodextrins improve availability of poorly water-soluble drugs by improvement of dissolution through inclusion complexation or when incorporated as solid dispersion. Reduction of drug crystallinity on complexation or solid dispersion with cyclodextrins also contributes enhanced dissolution rate[37]. Increase in the permeability of insoluble, hydrophobic drugs is brought about by making the drug available at the surface of the biological barrier. Cyclodextrins can bring about reduction in the irritation caused by drugs[38]. The improvement of drug safety may be due to increased potency of drug making it effective at low dose and entrapment of drugs at molecular level preventing their direct contact with biological membranes. Piroxicam/β-cyclodextrin inclusion complex showed better tolerance with lower incidence and severity of gastrointestinal side effects compared to the free drug[39]. Cyclodextrins can improve the stability to hydrolysis, oxidation and photodecomposition and thus increase the shelf life of drugs. This may be due to inhibition of drug interaction with vehicles and/or inhibition of drug bioconversion at the absorption site[38]. Cyclodextrin complexation encapsulates labile drug molecules at molecular level and thus insulates them against various degradation processes. Photostability of amlodipine was improved by inclusion complexation with β-cyclodextrin[40]. Cyclodextrins enhance the mucosal drug permeability mainly by increasing the free drug availability at the absorptive surface[41]. Complexation can also mask the unpalatable taste of drugs[42]. The use of β-cyclodextrin as a pelletization agent in the extrusion/spheronization process is also reported[43].

Chitosans are useful natural polymers. They are deacetylated products of alkaline treatment of chitin. Chitosans are basic in nature and interact with acidic drugs. They are used for enhancing dissolution rates of poorly

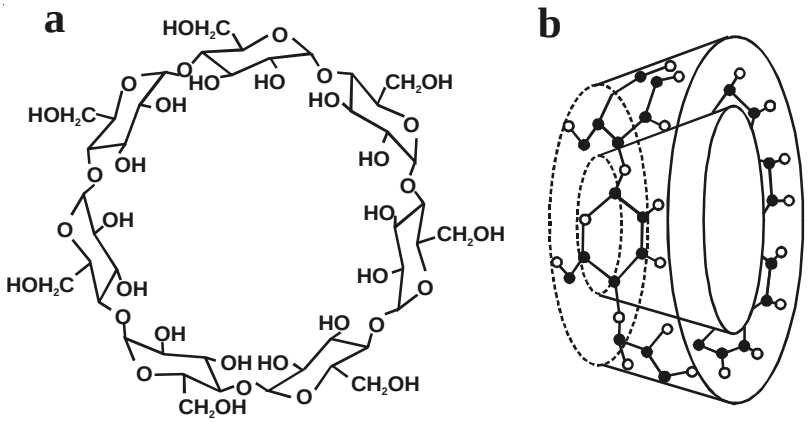

Fig. 3. (a) The chemical structure and (b) the toroidal shape of the â-cyclodextrin molecule

water-soluble drugs[43]. Chitosan-based mucoadhesive microspheres of clarithromycin to provide prolonged contact time for drug delivery of antibiotics to treat stomach ulcers[44].

Thus, in conclusion the complexation forms a beneficial interaction in drug formulations. Use of this technique can be done to improve drug release, dissolution, safety, controlled release and improving bioavailability and formulation properties[45].

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