Dextran: A Promising Macromolecular Drug Carrier

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Over the past three decades intensive efforts have been made to design novel systems able to deliver the drug more effectively to the target site. The ongoing intense search for novel and innovative drug delivery systems is predominantly a consequence of the well-established fact that the conventional dosage forms are not sufficiently effective in conveying the drug compound to its site of action and once in the target area, in releasing the active agent over a desired period of time. The potential use of macromolecular prodrugs as a means of achieving targeted drug delivery has attracted considerable interest in recent years. Macromolecules such as antibodies, lipoproteins, lectins, proteins, polypeptides, polysaccharides, natural as well as synthetic polymers offer potential applicabilities as high molecular weight carriers for various therapeutically active compounds. Dextrans serve as one of the most promising macromolecular carrier candidates for a wide variety of therapeutic agents due to their excellent physico-chemical properties and physiological acceptance. The present contribution attempts to review various features of the dextran carrier like its source, structural and physico-chemical characteristics, pharmacokinetic fate and its applications as macromolecular carrier with special emphasis on dextran prodrugs.

The ongoing intense search for novel and innovative drug delivery systems is predominantly a consequence of the well-established fact that the conventional dosage forms are not sufficiently effective in conveying the drug to its site of action and once in the target area, in releasing the active agent over a desired period of time. In order to achieve controlled and site-specific drug delivery two approaches have been attempted. One of these approaches is pharmaceutical approach, which involves coating the drugs with pH-dependent polymers, time-dependent delivery systems, biodegradable coatings and embedding the drugs in therapeutic systems like liposomes or microspheres[1]. The other approach involves chemically based delivery systems like prodrug approach, in which a latentiated drug derivative is prepared, which is inactive as such but yields active drug after activation in mammalian systems by chemical or enzymatic pathway[2]. The potential use of macromolecular prodrugs as a means of achieving targeted drug delivery has attracted considerable interest in recent years. Macromolecules such as antibodies, lipoproteins, lectins, proteins, polypeptides, polysaccharides, natural as well as synthetic polymers offer potential applicabilities as high molecular weight carriers for various therapeutically active compounds.

BASIC CONCEPT

Since the 1950s, a variety of drugs have been covalently attached to many natural and synthetic polymers. Initially, the only rationale was that converting the drug into macromolecular prodrug might reduce renal excretion and hence increase the duration of activity. At that time there was little concern about the cellular uptake and processing of these conjugates. In 1975, Ringsdorf[3] proposed a more rationalized model for macromolecular prodrugs (fig. 1). He upgraded the potential of this concept by calling attention to the possibility of introducing onto the polymer carrier not only the drug moiety but also groups that can influence the solubility properties as well as groups that can alter the body distribution and promote cell selectivity.

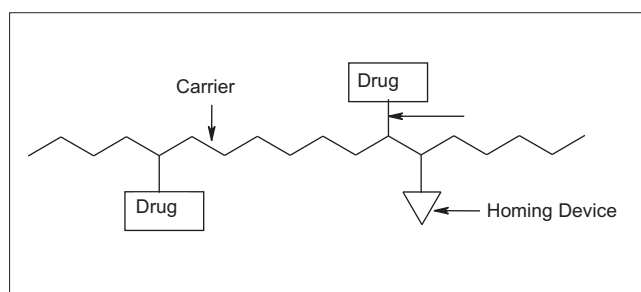In this model, the polymeric carrier can be either an

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Fig. 1: Ringsdorf model for macromolecular prodrug

inert or a biodegradable polymer. The drug can be fixed directly or via spacer group onto the polymer backbone. If the polymeric conjugate is pharmacologically active as a whole, the product can be regarded as polymer drug. Conjugates that are active after release of parent drug are termed as macromolecular prodrugs. Proper selection of the spacer provides the possibility of controlling the site and rate of release of active drug from conjugate by hydrolytic or enzymatic cleavage. The most interesting aspect of this model is the possibility of altering body distribution and cell uptake by attaching cell specific or non-specific uptake enhancers (homing device). This model has been an important milestone in the history of polymeric prodrug design.

Dextrans, which belong to the group of polysaccharide macromolecular carriers devoid of selective transport properties, may serve as one of the most promising carrier candidates for a wide variety of therapeutic agents due to their excellent physico-chemical properties and physiological acceptance. The important objectives that may be achieved by utilizing these soluble drug carrier conjugates include drug targeting, improvement of circulation time, stabilization of therapeutic agent, solubilization of drugs, reduction of side effects, sustained release action and depot properties[4].

Origins of dextran:
Dextrans of different chemical composition are synthesized by a large number of bacteria confined to the family *Lactobacillaceae* and mainly from *Leuconostoc mesenteroids, Leuconostoc dextranicum* and *Streptobacterium dextranicum.* The medium for synthesis contains low molecular weight dextran, sucrose or other carbohydrates containing anhydro-D-glucopyranose units[5]. Of particular pharmaceutical interest are dextrans derived from *Leuconostoc mesenteroids* NRRL B-152. These are characterized by their content of 95% α-1,6-glucopyranosidic linkages and 5% 1,3-linkages. The product of microbiological synthesis is termed 'native-dextran'. Clinical dextrans are obtained from high molecular weight native dextrans after their partial depolymerisation by acid hydrolysis and fractionation[6].

Physical properties:
Dextrans obtained from different sources differ in their structure and properties i.e. molecular weight, degree of branching, relative quantity of particular type of glycosidic links, solubility, optical activity and physiological action. Dextrans are soluble in water, formamide and dimethylsulfoxide and insoluble in alcohol and acetone.

Native dextran is a polymer of high molecular weight ranging between 10^7 to 10^8. Its molecular weight can be reduced by acid hydrolysis irrespective of the nature of acid used. Native dextran also possesses high degree of polydispersibility. The value of optical rotation for aqueous solutions of various dextrans varies from +199° to +235°. The intrinsic viscosity is affected by the nature and pH of solvent, degree of branching, number of intermolecular bonds and temperature[7].

Chemistry:
Dextran (fig. 2) is the generic name applied to a large class of α-D-glucans with anhydro-D-glucopyranose units as a part of their main molecular chain. The predominance of α-1,6-linkages is a common feature of dextrans[8]. Pharmaceutically, the most important dextrans are composed of 95% α-1,6-glucopyranosidic linkages and 5% 1,3-linkages. The 1,3-linkages are points of attachment of side chains, of which about 85% are 1 or 2 glucose residues in length and the remaining 15% of side chain may have an average length of 33 glucose residues, which may not be uniformly distributed in the molecule. Dextrans may also contain variable quantities of α-1,2-, α-1,3- and α-1,4-glycosidic bonds, by means of which side chains are usually attached to the main chains. Being very reactive towards chemical reactions, dextran can be extensively exploited as a carrier for attaching the drugs. With alkali and alkaline earth metals, dextrans form alkoxides dextranate[9]. Oxidation products of dextrans are useful in preparation of several new derivatives of dextrans. Periodic acid and lead tetraacetate in DMSO can be used to oxidize dextran partially[10]. A water-soluble chlorodeoxydextran has been prepared by treating dextran with thionyl chloride in DMF. Aminodeoxy derivatives have been obtained by
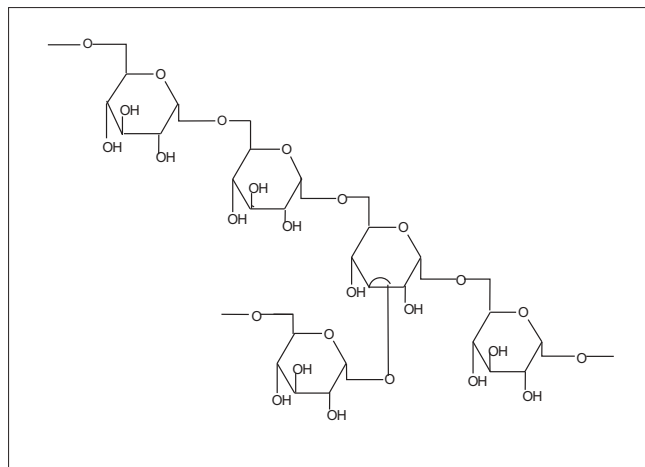

Fig. 2: Structure of dextran

nucleophilic substitution[10]. A deoxymercapto derivative has been obtained by pyrolysis of oxidation-product of dextran-xanthate with sodium nitrite followed by treatment of resulting polymer with alkali[11].

Pharmacokinetic fate of dextran:

Several physico-chemical properties like molecular size and shape, flexibility, charge, hydrophilic lipophilic balance are determinants for pharmacokinetic fate of dextran[12]. When given parenterelly, intravascular persistence of dextran varies dramatically with molecular weight. Dextrans of the molecular weight less than 70,000 have rapid elimination rates during the first hour after injection followed by a slower decrease in concentration[13]. Dextrans with molecular weight in the range 70,000-2,50,000 show prolonged survival in circulatory system. The high polarity of dextrans excludes their transcellular passage and their size prevents their passage through gastrointestinal tract. Dextrans are depolymerised by the enzyme dextranase present in intestine.

DEXTRAN CONJUGATES

Dextran conjugates can either be irreversibly linked or reversibly linked. Irreversibly linked dextran conjugates are obtained by immobilization techniques and include dextran enzyme conjugates, dextran hormone complexes and dextran metal complexes. Reversible dextran conjugates include dextran esters, dextran ethers and dextran amides.

IRREVERSIBLE DEXTRAN CONJUGATES

Dextran derivatives, in which the ligand is irreversibly linked to the carrier, have been employed extensively in experimental medicine and find wide applications in the field of biotechnology and related areas[14]. Some examples are summarized below:

Dextran enzyme conjugates:

Enzymes are natural regulators of biochemical processes and the potential of enzyme therapy is now accepted in almost every field of medicine. In order to couple enzymes to dextran polymers, number of mild reactions have been adapted that were initially developed for immobilization of enzymes on insoluble polysaccharide support. This approach has been useful in obtaining soluble dextran conjugates of various enzymes, which offer various advantages like improvement of enzyme stability at physiological pH, increase in the biological half-life of

enzyme, better thermal stability, lowered risk of emergence of allergic reactions on repeated administration[15]. Important enzymes that have been linked to dextran are α-amylase, arginase, asparaginase, carboxypeptidase, catalase, β-galactosidase, hyaluronidase, NAD+, streptokinase, papain, α-chymotrypsin and trypsin[16].

Dextran small molecule complexes:

Carboxymethyl dextran (fig. 3 (a)), dextran sulphate (fig. 3 (b)), and diethylaminoethyl dextran (DEAE) (fig. 3 (c)) are the charged dextran derivatives that form complexes with various chemical entities. Various hormones like oxytocin and vasopressin have been linked to dextran so as to increase their water solubility along with retention of their activity[17]. Attempts to enhance the lymphatic uptake of bleomycin[18] by complexation with dextran sulphate after i.m. and oral administration have been reported. Improved therapeutic efficiency of isometamidium[19] and reduced nephrotoxicity of gentamicin[20] has been reported when these drugs were administered in the form of dextran sulphate complexes. Enhancement of uptake of proteins and nucleic acids by cells[21] and of interferon production[22] has been reported by complexation with DEAE dextran.

Dextran metal complexes:

Complexes of dextran with heavy metals like iron and antimony are relatively easily obtained by reacting metal salts with the polymer in aqueous solution followed by precipitation of the macromolecular derivatives with alcohol. Parenteral iron-dextran has been used for the rapid regeneration of the red cell mass in anemia and in patients, intolerant of oral forms of iron[23]. Pentavalent antimonials are quite effective in the treatment of leishmaniasis, but they are rapidly excreted in urine and have short duration of action. So, antimony has been complexed with dextran, which after intramuscular injection is slowly absorbed from injection site and hence sufficient blood levels are maintained so as to suppress the *Leishmania donavani* infection effectively[24]. Cis-platinum (II) has been complexed with carboxymethyl dextran and is reported to be cytotoxic *in vitro* against 5 murine and 2 human derived tumor cell lines[25].
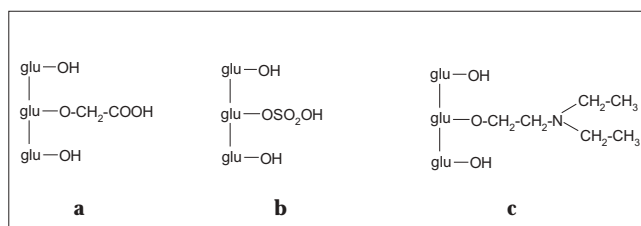

Fig. 3: Irreversible dextran complexes

REVERSIBLE DEXTRAN CONJUGATES (PRODRUGS)

Dextran fulfils many of the ideal characteristic features of a good carrier candidate. It is nontoxic, nonimmunogenic and nonantigenic. It contains huge number of carbohydrate hydroxyl groups available for drug fixation. Even though this restricts the number of drugs that might be directly liganded to the matrix, by application of spacer arm technique drugs possessing diverse functional groups can be linked to dextran. Dextrans can be autoclaved and are stable to chemical manipulations. Dextran conjugates are easy to characterize due to homogenous structure of dextran. Even at excessive ligand incorporation high water solubility is restored.

Models for covalent drug fixation to dextran (fig. 4):

Dextran can be attached to the drug to form a prodrug by various techniques like direct linkage, attachment through intercalated spacer arm, use of modulator ligand and tissue specific receptor ligand[26]. In Direct linkage model, drug is directly linked to dextran, which would release the active agent in a predictable manner. The regeneration of the parent drug would be exclusively governed by the pH dependent hydrolysis, as the bulky dextran matrix would be inaccessible to enzymatic attack. Intercalation of a spacer arm between the drug and the carrier may serve three purposes. First, the terminal functional group of the spacer arm can be varied, thus allowing covalent drug fixation to be established through a variety of chemical bonds. Second, steric hindrance of enzyme activation of the liganded drug might be circumvented by augmenting the distance between the drug and the dextran backbone. Third, sequentially labile
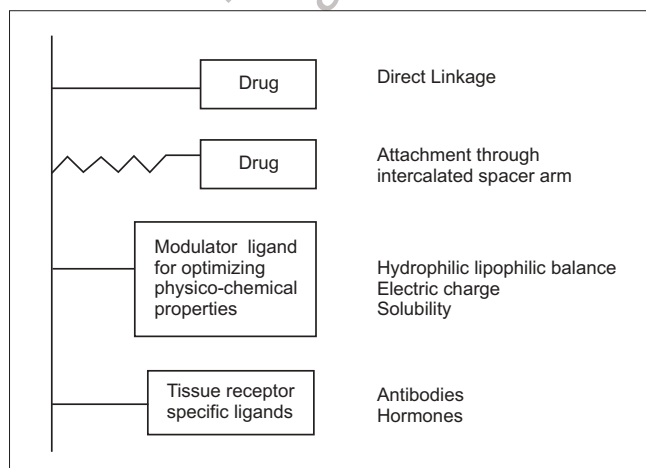

Fig. 4: Models for covalent drug fixation to dextran

dextran prodrugs can be constructed in such a way that the pH dependent hydrolysis only liberates the spacer-drug derivatives (the corresponding low molecular weight prodrug), which after extravasation or diffusion from the site of injection is activated at the diseased tissue. The physico-chemical properties of the dextran conjugates like solubility, electric charge, partition coefficient can be optimized by linking inactive chemical entities as modulator ligands to the polymer chain. This would alter/improve the disposition and persistence of dextran conjugates. In order to guide the conjugate selectively to the targeted site, a homing device or target specific moiety like antibody or hormone can be incorporated in the model.

MECHANISM OF ACTIVATION FOR DEXTRAN PRODRUGS

The active drug is released from the dextran prodrug by the cleavage of the covalent bond existing between drug and the carrier moiety (dextran) that can be pH dependent or enzymatic[27]. If the drug contains a hydrolysable chemical bond, it might deteriorate while still attached to the polymer backbone. The ability of bulky dextran molecule to suppress catabolism of attached drug/enzyme has been exploited extensively[27]. Enzymatic partial disrupture of the main chains of dextran prodrugs (without affecting the carrier drug bond) will change the molecular weight distribution of the originally administered prodrug, thus making it susceptible to the attack of various hydrolases[28].

SYNTHESIS OF DEXTRAN CONJUGATES

Direct esterification[29]:
The dextran ester prodrugs of several drugs like nicotinic acid, naproxen, aspirin, ketoprofen, ibuprofen, diclofenac and indomethacin have been synthesized with the aim of achieving prolonged release properties. Various techniques of direct esterification are shown in fig. 5.

Carbonate ester method[30]:
Drugs containing a hydroxyl group can be coupled to dextran in the form of carbonate ester linkages either by activating the carrier hydroxyl group by phosgene followed by addition of alcoholic drug [fig. 6, Scheme I] or by preparing chlorocarbonate dextran esters of the drug which are further used as intermediates in the construction of enzyme conjugates [fig. 6, Scheme II].
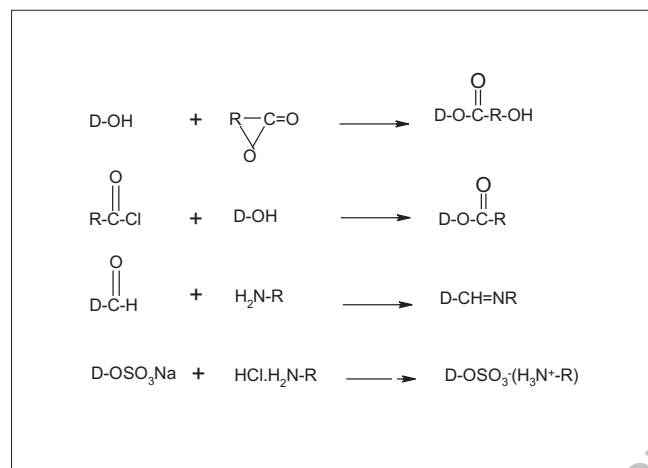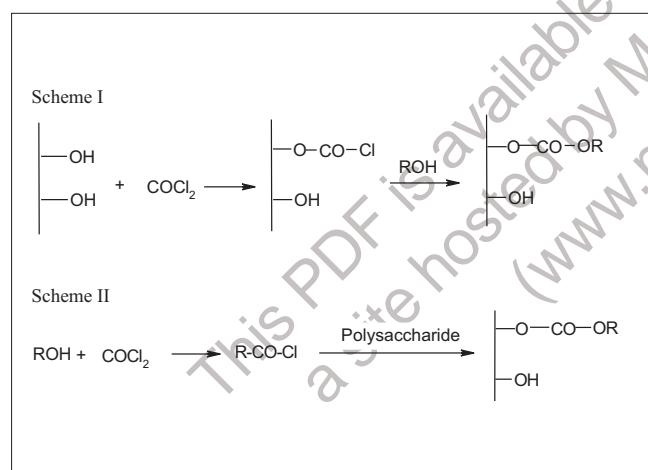
Periodate oxidation method[31] (fig. 7):

Dialdehyde dextran is obtained by periodate oxidation of dextran, which is condensed with amino compounds yielding schiff bases. The subsequent reduction with sodium borohydride is performed in order to stabilize the conjugate.
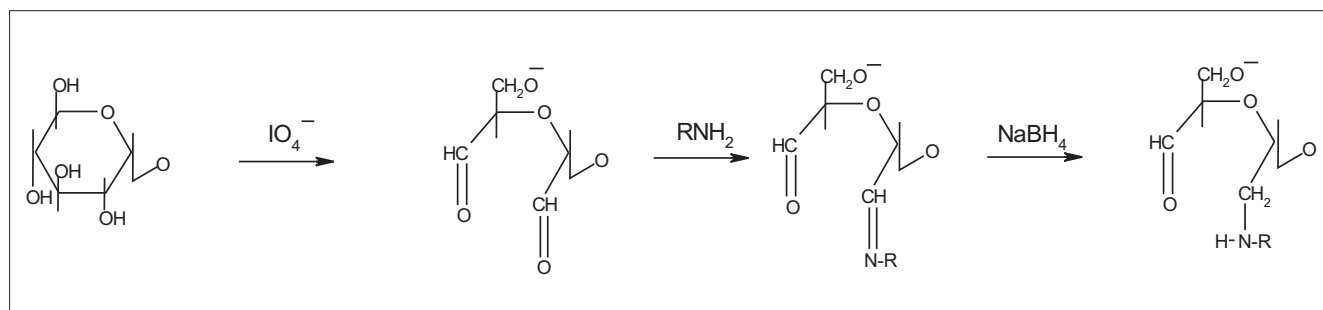
Carbamate ester method[32]:

The carbamate ester liganded conjugates exhibit

Fig. 5: Synthesis of dextran conjugates: Direct esterification

Fig. 6: Synthesis of dextran conjugates: Carbonate ester method

prolonged duration of activity and reduced toxicity in proportion to the free drug. The principal routes to obtain dextran carbamate ester linkages are depicted in fig. 8.
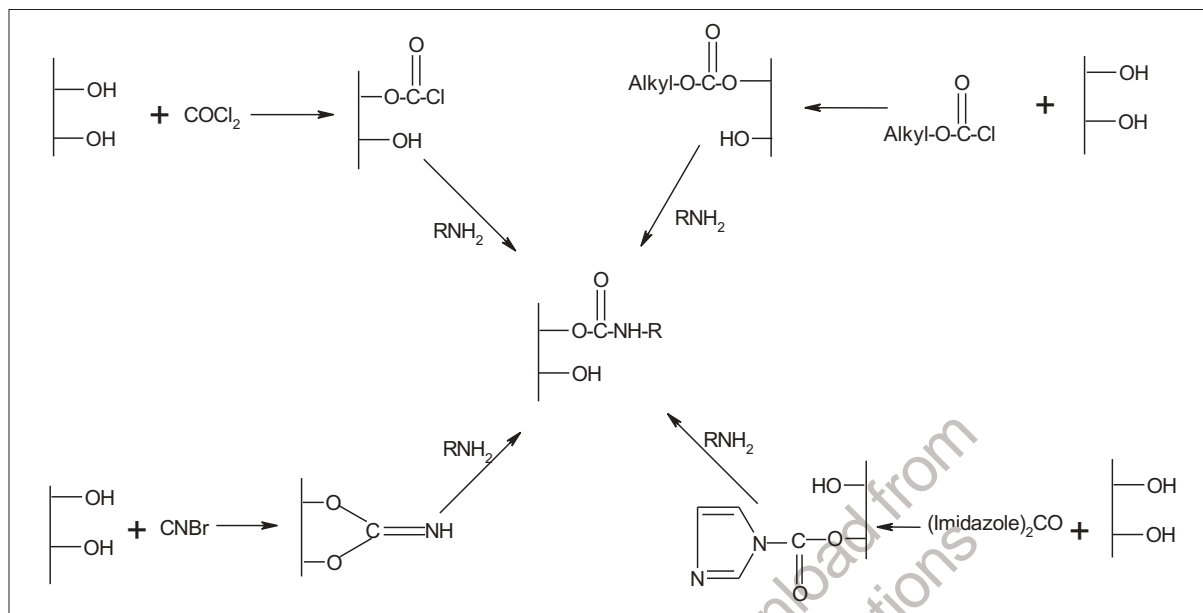
Cyanogen bromide activation method[33]:

The cynogen bromide activation of dextran is probably the most widely used reaction to achieve covalent attachment of compounds possessing an amino function to dextran (fig. 9).

APPLICATIONS OF DEXTRAN CONJUGATES

### Improved *in vitro* Physico-chemical properties:

The tendency of enzymes to undergo autolytic degradation and thermal lability might be partly circumvented by coupling them with dextran. Thermal stability of various enzymes like adenosine deaminase[34], α-amylase[35], epoxide hydrolase[36] and α-chymotrypsin[37] has been increased by their conjugation with dextrans of molecular weight 80,000, 1,000,000, 70,000 and 10,000 respectively. Possibly other bioactive peptidic agents might be stabilized in the same way. Several carboxylic acid drugs like NSAIDs are insoluble in water in the free acid form. Dextran prodrugs of such drugs may constitute an alternative approach to provide reproducible bioavailability of water insoluble drugs by releasing the active agent in soluble state in the gastrointestinal tract[38]. The water solubility of naproxen is increased by a factor of 500 when it is conjugated to dextran[39]. Various conjugates of metronidazole have been prepared with dextran, like dextran metronidazole monomaleinate ester conjugate, dextran metronidazole monoglutarate ester conjugate, and dextran metronidazole monosuccinate ester conjugate in order to improve physico-chemical properties of metronidazole[40].

Site-specific drug delivery; colon-directed drug delivery:

Natural polysaccharides have been extensively used for

Fig. 7: Synthesis of dextran conjugates: Periodate oxidation method

Fig. 8: Synthesis of dextran conjugates: Carbamate ester method
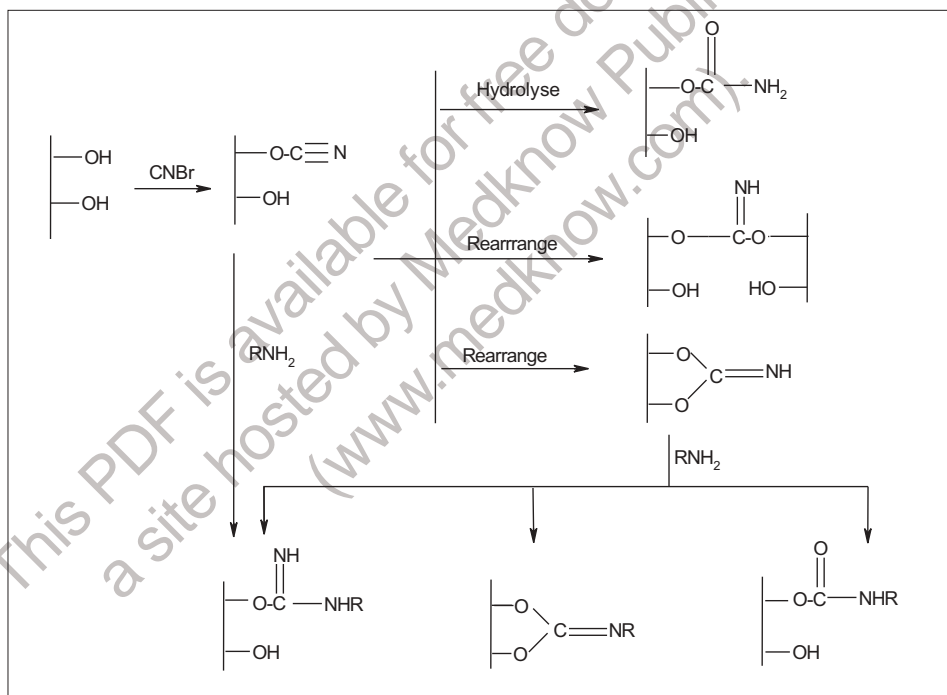
Fig. 9: Synthesis of dextran conjugates: Cyanogen bromide activation method

the development of solid dosage forms for delivery of drugs to colon, as it is inhabited by a large number and variety of bacteria, which secrete many enzymes like β-D-glucosidase, β-D-galactosidase, amylase, pectinase, xylanase, β-D-xylosidase and dextranase[41]. So formulation of a drug-saccharide conjugate (prodrug) is an important approach for targeting drugs to colon. Among the various polysaccharides, dextran is an important carrier for delivery of drugs to colon[42]. 5-Aminosalicylic acid (5-ASA) is an effective drug for

inflammatory bowel disease, but absorbed rapidly in stomach and small intestine so that only a negligible amount reaches to colon. To overcome this problem a number of azo-coupled dextran-5-ASA prodrugs (fig. 10) have been synthesized[43], which effectively deliver 5-ASA to colon. Dextran-nalidixic acid ester (dextran-NA) was developed as colon specific prodrug[44]. When release studies were performed in HCl buffer (pH 1.2) and phosphate buffer (pH 6.8) at 37° NA was not detected during 6h of the incubation period, which

indicated that dextran-NA might be chemically stable during the transit through the gastrointestinal tract. When dextran-NA was incubated with cecal contents of rats at 37°, the extent of NA released in 24 h was 41% of the dose. Dexamethasone-succinate-dextran (DSD) was synthesized by attaching dexamethasone to dextran (Molecular mass 70,400 Dalton) using succinic anhydride as a spacer. It was found to deliver dexamethasone specifically to colon[45,46]. Methylprednisolone has been covalently attached to dextran using succinic acid and glutaric acid as the linkers[47,48]. The hydrolysis kinetic studies show that conjugation with dextran helps to deliver the drug to large bowel.

Targeting to tumor cells:
Even though number of agents effective in killing neoplastic cells are available, their utility in the treatment of cancer is often limited by their cytotoxicity towards proliferating normal cells as well. Numerous studies over the past 40 years have reported an apparent passive targeting of soluble macromolecules to solid tumors due to enhanced permeation and retention (EPR effect) of macromolecules by tumors. Additionally, macromolecular drug carrier systems have been developed in an attempt to enhance the selectivity of action of cytotoxic drugs by coupling them to carriers with expected affinity for the target tissue. Large molecular weight polysaccharides with molecular mass greater or equal to 40 kD have low clearance and relatively long plasma half-life, resulting in accumulation in tumor tissues[12].

For antitumor agents introduced directly into the intracranial space, the extent of penetration into the tissue and hence the effectiveness of the therapy depends on the rate of drug elimination from the tissue. To test the hypothesis that slowly eliminated agents would penetrate

further through tissues, methotrexate (MTX)-dextran conjugates have been synthesized by covalently linking MTX to dextran through a short-lived ester bond (MTX-ester-dextran) and a longer-lived amide bond (MTX-amide-dextran). The ability of these agents to kill cells and to penetrate through tissue has been evaluated. The cytotoxicity of MTX-ester-dextran and MTX-amide-dextran was found equivalent to unmodified MTX. Intracranial polymeric delivery of MTX or MTX-amide-dextran to rats with intracranial 9L gliosarcoma produced modest but significant increases in survival; conjugation of MTX to dextran appeared to shift the dose-response curve to a lower dosage[49].

Synthesis of dextran conjugate of sodium phenylacetate (NaPA) with substituted dextrans like dextran- methyl-carboxylate- benzylamide (LS17-DMCB) has been reported, which shows better tumor inhibition effect against human tumor melanoma 1205LU cells than NaPA alone[50]. A dicarboxymethyl-dextran conjugate of cisplatin has been synthesized by immobilizing cisplatin to dextran through six-membered chelate type coordination bond, which shows significantly longer half life and better tumor growth inhibitory activity than plain cisplatin in colon 26 cancer cells[51]. A macromolecular prodrug of cisplatin using dextran carrier, having branched galactose units has been synthesized for targeting to hepatoma cells with successful results[52].

Clinically available camptothecins (CPTs) like irinotecan (CPT-11) and topotecan represent one of the most promising classes of antitumor agents. In order to improve their pharmacological profile, a new macromolecular prodrug denoted T-0128 was synthesized which consists of a novel CPT analogue T-2513 conjugated to carboxymethyl dextran via a triglycine spacer[53]. This conjugate shows better specificity and ten times better activity than parent T-2513. The conjugate of paclitaxel with carboxymethyl dextran via an amino acid linker has been shown to produce better antitumor activity than paclitaxel alone[54]. The pharmacokinetic and therapeutic studies of mitomycin- dextran conjugate shows better activity and prolonged action than plain mitomycin against walker-256-carcinoma in rats[55]. The effect being more pronounced in case of cationic conjugate which is attributed to the presence of a high load of negatively charged sialic acid residues on cancer cell surface accomplishing effective cationic conjugate absorption[56]. Over-expression of the epidermal growth factor receptor (EGFR) has been reported in bladder cancer
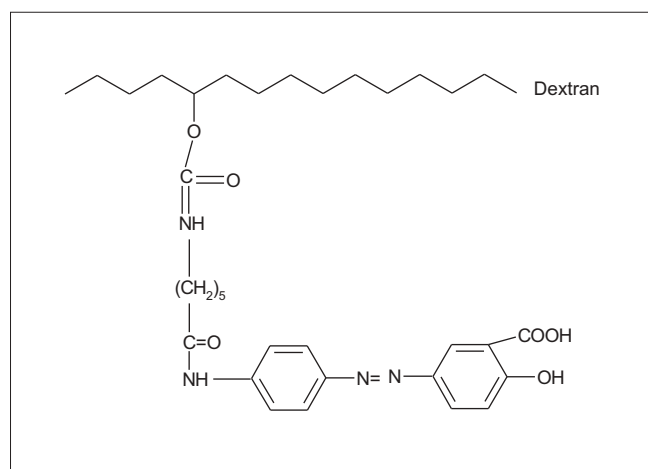

Fig. 10: Azo-coupled dextran-5-ASA prodrug

and is a potential target for therapy with radionuclides. The intravesically administered EGF-dextran conjugate EGF-dextran-^{99m}Tc selectively accumulates in the tumor tissue and shows better activity than ^{99m}Tc alone[57].

Targeted antimycobacterial therapy:

The treatment of tuberculosis requires long-term antibiotic therapy. Targeted antibiotic therapy improves the efficacy of treatment by concentrating the drugs close to mycobacterium. For this purpose, norfloxacin has been linked to mannosylated dextran using peptide spacer arm. This conjugate shows more efficacy against mycobacterium than plain norfloxacin[58].

Antileishmanial targeted therapy:

Pyrimethamine is effective in antileishmanial therapy due to its ability to inhibit both the enzymes of leishmanial folate pathway, but *in vivo* this effect occurs only at high concentration, which is associated with toxicity. To overcome this problem, a prodrug of pyrimethamine namely carboxymethyldextran thiomannopyrannoside pyrimethamine has been synthesized, which shows approximately 50% destruction of intracellular amastigotes with no detectable toxicity to macrophage cells[59].

Pharmacokinetic application; systemic sustained drug action:

The profile of plasma concentration of drugs is an important determinant of their quantitative access to peripheral targets. The plasma concentration is usually measured as the area under the curve (AUC). In general, slow renal elimination and metabolic inactivation promote better access of drugs to remote targets. The effectiveness of various drugs is limited due to their rapid renal excretion. Conjugation of drugs to hydrophilic macromolecular carriers like dextran can prevent rapid renal excretion and restrict the drug entry into cells, thus prolonging their plasma circulation time[60]. Insulin dextran complex when injected intraperitoneally in diabetized rabbits maintains blood glucose levels at normal value over several days[61]. Design of dextran prodrugs with the goal of affording prolonged systemic concentration of the liberated drug after oral administration has been reported for quinidine[62], ursodeoxycholic acid[63], ibuprofen[64] and analogues of aspirin[65]. Isoniazid has been conjugated to dextran to form dextran-isoniazid complex, which exhibits prolonged persistence in circulation and reduced acute toxicity in the guinea pigs as compared to the parent drug[26]. Nicotinic acid is an effective hypolipidemic agent, but suffers from the disadvantage

of being rapidly eliminated from the systemic circulation. When it is conjugated with dextran, the drug is gradually released from the polymeric support leading to a prolonged presence of the active substance in the body, which lowers triglyceride levels[66].

pH-controlled intracellular drug release:

Polymers like dextran on entering the endosomal or lysosomal compartment are exposed to an acidic medium (pH 4.5-5.5). Using acid cleavable spacers (fig. 11) like hydrazon spacer and N-cis-aconityl spacer between the drug and the carrier, a pH controlled intracellular drug release can be obtained[67]. Streptomycin has been linked to dextran via carboxylic hydrazone linkage for its intracellular delivery[68].

Pharmacodynamic applications; modification of immunogenecity of peptides:

When proteins or peptides are conjugated to macromolecules, the resulting conjugate takes form of a colloid in most cases and the protein core gets protected from interaction with other macromolecular plasma components by a hydrophilic polymer shield. Thus conjugation decreases the immunogenecity of the protein component and permits repeated administration of foreign proteins. This approach is particularly useful when the protein is an enzyme with a low molecular weight substrate found in plasma. The antigenecity of L-asparaginase[69] and catalase[70] was substantially suppressed when they were conjugated to oxidized dextran and dextran with molecular weight of 40,000, respectively. Spacer linked dextran derivatives of pancreatic RNase showed decreased antigenecity[71].

Overcoming multidrug resistance:
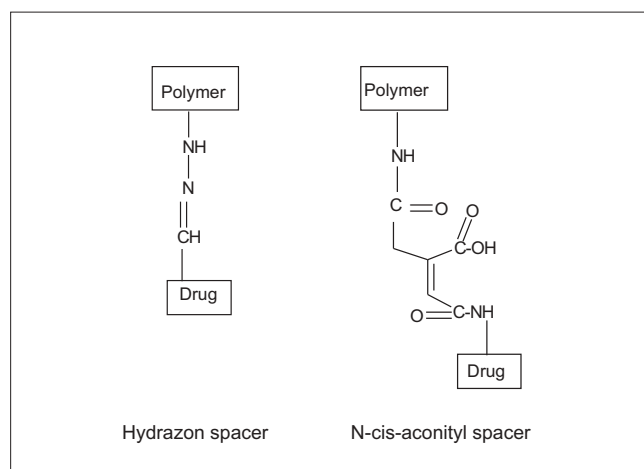
A major problem of using antitumor agents in cancer

Fig. 11: Acid cleavable spacers

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chemotherapy is multidrug resistance, which occurs mainly due to over-expression of the P-glycoprotein (Pgp). This transmembrane glycoprotein encoded by the mdrl gene, functions as an energy dependent efflux pump reducing the intracellular accumulation of anticancer drugs[72]. When the free drugs are administered, they enter the cell by diffusion through the plasma membrane and are recognized by the Pgp pumps. On the other hand when these drugs are conjugated to macromolecular carriers, the drug in the form of polymeric prodrug is taken up by endocytosis and subsequently efflux pumps are circumvented in turn reducing the multidrug resistance. The antitumor antibiotic doxorubicin was conjugated with polymeric dextrans of various molecular weights and the cytotoxicity of the conjugates against human carcinoma KB-3-1 cells and its multidrug-resistant subclone KB-V-1 cells was measured. The conjugates were found to be much less toxic to the KB-3-1 cells than the free doxorubicin. Furthermore these conjugates could act synergistically with other cancer drugs[73].

Reduction of toxicity:
The detrimental effects on normal cells exerted by antineoplastic agents necessitate administration of relatively low doses of the drugs[74]. Improved chemotherapy might arise from drug delivery systems using polymers, providing the maintenance of prolonged moderate body levels of the drugs. In contrast to plain daunomycin, the dextran daunomycin conjugate does not show side effects like atrophy of spleen and bonemarrow, damage to the heart and liver[75]. In comparison to parent daunomycin, the LD_{50} of the conjugate is enhanced by a factor of approximately 3.

Gastrointestinal side effects constitute the most frequent of all the adverse reactions of nonsteroidal antiinflammatory drugs. Flurbiprofen causes gastrointestinal disturbances, peptic ulceration and GIT bleeding. Conjugation of flurbiprofen with dextrans of different molecular weights (40,000, 60,000, 1,10,000, and 2,00,000) has shown a remarkable improvement in physico-chemical properties, colon specificity and gastrointestinal side effects[76]. Conjugates of suprofen have been synthesized by preparing their acylimidazol derivatives, which are condensed in situ with dextrans of different molecular weights (40,000, 60,000, 1,10,000 and 2,00,000). The ulcerogenic index of the conjugates shows a remarkable reduction as compared to the parent suprofen[77]. The nephrotoxicity of gentamycin is substantially reduced when it is conjugated with dextran sulphate[23].

CONCLUSION

Even though dextran prodrug approach is still in its infancy, the results from a number of reports lead to optimism concerning the utility of dextran conjugates to provide feasible drug delivery systems. In recent years, a great deal of knowledge has been accumulated about dextran conjugates, but several properties of dextran prodrugs are still partly recognized. A great deal of progress in this field might arise through identification of the drug target and mode of action, by exploiting intrinsic properties of the dextran carrier like protection of the liganded drug from unwanted biodegradation and control of the degradability of the dextran backbone.

REFERENCES
1. Chourasia, M.K. and Jain, S.K., **J. Pharm. Sci.,** 2003, 6, 33.
2. Chien, Y. W., **Drug Dev. Ind. Pharm.,** 1983, 9, 1291.
3. Schacht, E.H., Winne, K.D., Hoste, K. and Vansteenkiste, S., In; Wermuth, C.G., Eds., The Practice of Medicinal Chemistry, 2nd Edn., 2004, 587.
4. Vert, M., **CRC Crit. Rev. Ther. Drug Carr. Syst.,** 1986, 2, 291.
5. Botham, R.L., **Adv. Carbohydr. Chem. Biochem.,** 1974, 30, 371.
6. Murphy, P.T. and Whistler, R.L., In; Industrial Gums, 2nd Edn., Academic Press, New York, 1973, 513.
7. Jeanes, A., In; Encyclopedia of Polymer Science and Technology, Vol.IV, John Wiley and Sons, New York, 1966, 805.
8. Aspinall, G.O., In; The Polysaccharides, Vol.I, Academic Press, New York, 1982, 35.
9. Cohen, E. and Zilkha, A., **J. Polymer Sci.,** 1969, 7, 1881.
10. Zitka, V. and Bishop, C., **Can. J. Chem.,** 1966, 44, 1749.
11. Timmell, D., Sharka, B.S., Doane, W.M. and Russell, C.R., **J. Appl. Polymer Sci.,** 1973, 17,1607.
12. Mehvar, R., **Curr. Pharm. Biotechnol**., 2003, 4, 283.
13. Basedow, A.M., Ebert, K.H. and Ederer, H.J., **Macromolecules**, 1978, 11, 774.
14. Yalpani, M., **CRC Crit. Rev. Biotech.,** 1986, 3, 375.
15. Marshall, J.J., **Trends Biochem. Sci.,** 1978, 3, 79.
16. Torchilin, V.P. and Illina, E.V., **Adv. Drug Dev. Rev.,** 1987, 1, 87.
17. Snell, C.R. and Smyth, D.G., **Biochem. J.,** 1977, 165, 43.
18. Muranishi, S., Takahashi, Y., Hashida, M. and Sezaki, H., **J. Pharm. Biodyn.,** 1979, 2, 383.
19. Allu, Y.O. and Chineme, C.N., **Toxicol. Appl. Pharmacol.,** 1980, 53, 196.
20. Kikuchi, S., Inaba, A., Takahashi, M., Aramaki, Y. and Tsuchiya, I., **Int. J. Pharm.,** 1988, 42, 193.
21. Ryser, H.J.P., **Nature,** 1967, 215, 934.
22. Pitha, P.M. and Carter, W.A., **Virology,** 1971, 45, 777.
23. Porter, K.A., Blackburn, G.L. and Bistrian, B.R., **J. Amer. Coll. Nutr.,** 1988, 7, 107.
24. Mikhail, J.W., Mansour, N.S. and Khayyal, M.T., **Exp. Parasitol.,** 1975, 37, 348.
25. Schechter, B., Pauzner, R., Wichek, M. and Arnon, R., **Cancer Biochem. Biophys.,** 1986, 8, 289.
26. Wood, D.A., **Int. J. Pharm.**, 1980, 7, 1.
27. Yalpani, M., **Tetrahedron,** 1987, 41, 2957.
28. Sturgeon, G.M., In; Carbohydrate Chemistry, Vol. XIV, The Royal Society of Chemistry, Burlington House, London, 1983, 375.
29. Groff, J.L., Cherniak, R. and Jones, R.G., **Carbohydr. Res.,** 1982,

101, 168.

30. Kennedy, J.F. and Tun, H.C., **Carbohydr. Res.,** 1973, 26, 401.

31. Painter, T. and Larsen, B., **Acta Chem. Scand.,** 1970, 24, 2366.

32. Weiner, B.Z., Tahan, M., and Zilkha, A., **J. Med. Chem.,** 1972, 15, 410.

33. Axen, R. and Ernback, S., **Eur. J. Biochem.,** 1971, 18, 351.

34. Rosemeyer, H., Kornig, E. and Seela, F., **Eur. J. Biochem.,** 1982, 122, 375.

35. Marshall, J.J, **Carbohydr. Res.,** 1976, 49, 389.

36. Ibrahim, M., Hubert, P., Dellacherie, E., Magdalou, J., Muller, J. and Siest, G., **Enz. Microb. Technol.,** 1985, 7, 66.

37. Vegarud, G. and Christensen, T.B., **Biotechnol. Bioeng.,** 1975, 17, 1391.

38. Fini, A., Zecchi, V. and Tartarini, A., **Pharm. Acta Helv.,** 1985, 60, 58.

39. Harboe, E., Johansen, M. and Larsen, C., **Science,** 1988, 16, 73.

40. Larsen, C. and Johansen, M., **Int. J. Pharm.,** 1987, 35, 39.

41. Sinha V.R. and Kumria, R., **Int. J. Pharm.,** 2001, 224, 19.

42. Vandamme, T.F., Lenourry, C., Charreau, M and Chaumeil, J.C., **Carbohyd. Polym.,** 2002, 48, 219.

43. Schacht, C.E., **Macromol. Chem.,** 1990, 191, 529.

44. Lee, J.S., Jung, Y.J., Doh, M. and Kim, Y.M., **Drug Dev. Ind. Pharm.,** 2001, 27, 331.

45. Zhou, S.Y., Mei, Q.B., Zhou, J., Liu, L., Li, C. and Zhao, D.H., **Yao Xue Xue Bao.,** 2001, 36, 325.

46. Pang Y.N., Zhang, Z.R., Pang, Q.J. and Li, T.L., **Yao Xue Xue Bao.,** 2001, 36, 625.

47. Pang, Y.N., Zhang Y. and Zhang, Z.R., **World J. Gastroenterol.,** 2002, 15, 8, 913.

48. McLeod, A.D., Friend, D.R. and Tozer, T.N., **J. Pharm. Sci.,** 1994, 83, 1284.

49. Dang, W., Colvin, H.B. and Saltzman, W.M., **Cancer Res.,** 1994, 54, 1729.

50. *Gervelas, C., Avramoglou, T., Crepen, M. and Jozefonvicz, J.,* **Anti-Cancer Drug.,** 2002, 13, 37.

51. Ichinose, K., Tomiyama, N., Nakashima, M., Ohya, Y., Ichikawa, M., Ouchi, T. and Kanematsu, T., **Anti-Cancer Drug.,** 2000,11, 33.

52. Ohya, Y., Oue, H., Nagatomi, K. and Ouchi, T., **Biomacromolecules,** 2001, 2, 927.

53. Sezaki, H. and Hashida, M., **Crit. Rev. Ther. Drug Carr. Syst.,** 1984, 1, 1.

54. Sugahara, S., Kajiki, M., Kuriyama, H. and Kobayashi, T.R., **Biol. Pharm. Bull.,** 2002, 25, 632.

55. Nomura, T., Saikawa, A., Morita, S. Sakaeda, K.T., Yamashita, F., Honda, K, Takakura, Y., and Hashida, M., **J. Control. Release**, 1998, 52, 239.

56. Marre, A., Soyez, H. and Schacht, E., **J. Control. Release,** 1994, 32, 129.

57. Bue, P., Halmberg, A.R., Marquez, M., Westlin, J.E., Nilsons, S., and Malmstrom, P.U., **Eur. Urol.,** 2000, 38, 584.

58. Roseeuw, E., Coessens, V., Balazuc, A.M., Micheline, L., Chavarot, P., Pessina, A., Neri, M.G., Schacht, E., Marchal, G. and Domurado, D., **Antimicrob. Agents Chemother.,** 2003, 47, 3435.

59. Carvalho, P.B., Ramos, D.C., Cotrim, P.C. and Ferreira, E.I., **J. Pharm. Sci.,** 2003, 92, 2109.

60. Maeda, H., Seymour, L.W. and Miyamoto, Y., **Bioconj. Chem.,** 1992, 3, 351.

61. Singh, M., Vasudevan, P., Ray, A.R. and Guha, S.K., **Macromol. Chem.,** 1980,181, 2433.

62. Astinotti, D., Lapicque, F. and Dellacherie, E., **Macromol. Chem.,** 1985, 186, 933.

63. Ghedini, N., Ferruti, P., Andrisano, V. and Scapini, G., **Synth. Commun.,** 1983, 13, 707.

64. Cecchi, R., Rusconi, L., Tanzi, M.C. and Dannuso, F., **J. Med. Chem.,** 1981, 24, 622.

65. Grimova, J. and Hrabak, F., **J. Biomed. Mater. Res.,** 1978, 12, 525.

66. Flip, C., Ungureanu, D., Gheorghita, N., Mocanu, G. and Nechifor, M., **Rev. Med. Chir. Soc. Med. Natl. Iasi.,** 2003, 107, 179.

67. Kratz, F., Beyer, U. and Schutte, M.T., **Crit. Rev. Ther. Drug Carr. Syst.,** 1999, 16, 245.

68. Coessens, V., Schacht, E. and Domurado, D., **J. Control. Release,** 1996, 38, 141.

69. Wileman, T., Bennett, M. and Lilleymann, J., **J. Pharm. Pharmacol.,** 1983, 35, 762.

70. Marshall, J.J. and Humphreys, J.D., **J. Appl. Biochem.,** 1979, 1, 88.

71. Kurinenko, B.M., Kashkin, A.P., Kalacheva, N.V., Neringovo, O.F. and Nekhoroshkova, V., **Biochem. USSR,** 1985, 50, 488.

72. Moscow, J.A. and Cowan, K.H., **J. Natl. Cancer,** 1988, 80, 14.

73. Lam, W., Leung, C.H., Chan, H.L. and Fong, W.F., **Anti-Cancer Drug.,** 2000, 11, 377.

74. Arnon, R. and Sela, M., **Immunol. Rev.** 1982, 62, 5.

75. Hurwitz, E., Wilchek, M. and Pitha, J., **J. Appl. Biochem.** 1980, 2, 25.

76. Shrivastava, S.K., Jain, D.K. and Trivedi, P., **Pharmazie,** 2003, 58, 389.

77. Shrivastava S.K., Jain D.K. and Trivedi, P., **Pharmazie,** 2003, 58, 804.