Available on line www.jocpr.com

Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2010, 2(4):851-860

ISSN No: 0975-7384
CODEN(USA): JCPRC5

Applications of novel excipients in the allopathic and herbal formulations

Maneesh Kreer[1], Gaurav Swami[1*], Ravinder Kumar[1], Kapil Kanwar[1], Paramjot kaur[2], Preeti Singh[3] and Appramdeep Kaur[1]

[1]*CT Institute of Pharmaceutical Sciences, Jalandhar, Punjab, India*
[2]*Department of Pharmaceutical Sciences and Drug Research , Punjabi University, Patiala, India*
[3]*Saroj Institute of Management and Technology, Lucknow, India*

ABSTRACT

Excipients are additives used to convert active pharmaceutical ingredients into dosage forms suitable for administration to patients. New and modified excipients continue to emerge with better drug delivery performance. Synthetic polymers offer a broad range of properties that can be reasonably well "built-in" by design and modified by altering polymer characteristics. Excipients of natural origin are of particular interest to us for reasons of reliability, sustainability and avoiding reliance upon materials derived from fossil fuels. Plant products are therefore attractive alternatives to synthetic products because of biocompatibility, low toxicity, environmental "friendliness", and low price compared to synthetic products. Excipients from natural products are also generally non-polluting renewable sources for the sustainable supply of economical pharmaceutical products.

Keywords: Excipients, synthetic polymer, plant products, drug delivery system.

INTRODUCTION

The International Pharmaceutical Excipients Council defines excipients as "substances, other than the active drug substance of finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture; protect; support; enhance stability, bioavailability, or

patient acceptability; assist in product identification; or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use" [1].

An excipient is an inactive substance used as a carrier for the medication. Excipients are also sometimes used to bulk up formulations that contain very potent active ingredients, to allow for convenient and accurate dosage. In addition to their use in the single-dosage quantity, excipients can be used in the manufacturing process to aid in the handling of the active substance concerned. Depending on the route of administration, and form of medication, different excipients may be used. For oral administration tablets and capsules are used. Suppositories are used for rectal administration. Often, once an active ingredient has been purified, it cannot stay in purified form for long. In many cases it will denature, fall out of solution, or stick to the sides of the container. To stabilize the active ingredient, excipients are added, ensuring that the active ingredient stays "active", and, just as importantly, stable for a sufficiently long period of time that the shelf-life of the product makes it competitive with other products.
In brief these are inactive ingredients that help hold a dose of the active pharmaceutical ingredient (API) together and keep it stable for a long shelf life. Excipients also can serve to mask an unpleasant taste or texture and help ensure that the right amount of the API makes it to the right spot in the body at the right time. Whether it is a tablet, gel cap, liquid, cream, suppository, patch, injection, or inhalant, all medicines contain several excipients and every one of them is there for a good reason [2].

NEW AND NOVEL EXCIPIENTS

- New Chemical Entity
- New route of administration or higher use level for existing excipients
- Physical/Chemical modification of an existing excipient (family of different grades)
- Co-processed mixtures of existing excipients
- Food additive or GRAS substance used for the first time in a drug product (oral administration)

FDA PUBLISHED STATEMENTS FDA PUBLISHED STATEMENTS

"Any attempt by the manufacturer to justify a proposed human exposure to an excipient by discussing prior use of the excipient should consider differences between the proposed use and the prior use."[3]

The enhancements to the IPEC-Americas Significant Change Guide For Bulk Pharmaceutical Excipients bring the guideline up to current industry expectations. These revisions establish new excipient industry practices to meet changing drug product manufacturer requirements to address new consumer and regulatory concerns [4].

With the advent of FDA's process analytical technologies (PAT) initiative, a basic paradigm is proposed that better-controlled products will result from improving control over the process. This improved control, in turn, will rely on a better characterization and understanding of excipients and the characteristics that affect their performance in the formulation and the process [5].

Table 1: Natural Products, including naturally occurring polymers and derivatives

Name	**Use**
Squalene, squalane	Vaccine adjuvant
Phosvitin	Protein stabilizer
Phytic acid	Protein stabilizer
Phospholipids	Liposomes
Spermidine	Inhibitor of lipid peroxidation
Hyaluronic acid	Viscoelastic
Sphingomyelin	Component of liposomes
Biopolymer	Protective coating for liposome
Spermine: bile acids	DNA transfection agent
Deacylated saponin	Surfactant in intranasal or ocular delivery
Alpha Hemolysin	Increasing susceptibility of tumor cells to cytotoxic drugs
Galactosylated Histone H1	Liver gene delivery
Sialic acid	RES-avoiding drug delivery
Galacturonic acid or polygalacturonic acid	Contrast medium in MRI
N-Acetyl [Phe8(CH2-NH)Arg9] bradykinin	Transport across the blood brain barrier
Enoxaparin, heparin	Protein stabilizer
Cyclodextrins	Solubilizer for hydrophobic molecules
Phosvitin–galactomannan conjugate	Emulsifier
Pyridoxal phosphate or derivatives	Paramagnetic metal chelating agent in NMRI
Recombinant fusion streptavidin-mab protien	Transport across the blood brain barrier
Hyaluronic acid: cyclodextrin	Modification of depolymerization kinetics and Release
Palmityl-D-glucuronide	RES-avoiding liposomal drug delivery
Transferrin	Ligand in receptor-mediated gene delivery
Fibronectin	Protein stabilize

Table 2: Synthetic polymer or modification

Name	**Use**
Tyloxapol	Enhancement of dendrimer-mediated
Hydroxypropyl-methacrylamide	Drug targeting
Histidyl poly(lysine)	Endosomolytic, enhanced transfection
Polyfumaric, polysebacic acid	Enhancing bioadhesive properties of Polymers
Steryl poly(lysine)	Terplex nonviral DNA delivery
PLA–POE block	Modulated drug release, prevention of protein copolymer adsorption
PEG–poly(lysine) or polyaspartic acid block copolymer	Polymeric micellar drug carrier
PLGA	Sustained drug delivery
Polyaspartic acid or polyglutamic acid	Hydrophilic analogs of hydrophobic molecules
POE–poly(_-benzyl L-glutamate)	Nanoparticles for delivery of hydrophobic block copolymer drugs
Poly(amidoamine) dendrimers	Vaccine adjuvant, drug entrapment, Transfection

Table 3: Small molecules

Name	**Use**
DOTMA, polyquaternary ammonium salt lipid	DNA-transfecting agents
Mannosylglycerate	Enzyme stabilizer
Sucrose laurate	Solubilizer
DTPA	Chelating agent for paramagnetic metals in MRI
SAIB	High-viscosity liquid carrier for controlled depot delivery

Tranexamic acid	Solubilizer for nonglycosylated proteins
***N*-(-beta-Hydroxyethyl)-lactamide**	Solvent
***N*-Methyl pyrrolidinone**	Solvent
Dimethyl sulfoxide	Solvent
Dimethyl sulfoxide	Solvent for embolyzing composition

Table 4: Modifications of natural products with synthetic polymers

Name	**Use**
Tocopherol–PEG–succinate hepatocytes	Antioxidant or solubilizer
Polyrotaxanes	Drug delivery
Galactosylated poly(lysine)	Gene delivery vector
SP-B: poly(lysine)	Gene delivery vector
Alpha-2-Macroglobulin: poly(lysine)	Gene delivery vector
Carboxyphenoxypropane: sebacic acid copolymer	Implantable drug delivery system
Polyoxyethylated derivative of castor oil	Surfactant, emulsifier
Galactosylated Poly(ethyleneimine)	Lectin-mediated gene transfer to hepatocytes

Table 5: Modification of natural products or polymers with small molecules

Name	**Use**
Spermine: cholesteryl carbamate, fatty acids or alcohols	DNA transfection vectors
N-Octyl-glucoside	Proteoliposome preparation using detergent-mediated dialysis
Palmitoyl glycol chitosan	Controlled drug delivery
Glycated chitosan	Immunoadjuvant
N,*N*,*N*-Trimethyl chitosan	DNA complexing agent
Chlorogenic acid chitosan	Confer water solubility at basic pH
Digalactosyl glycerol	Component of liposomes
Sulfolipo cyclodextrin derivatives, Sulfobutyl ethers of cyclodextrins	Vaccine adjuvant Solubilizer with reduced hemolytic Potential
Polymers of acylated amino acidsb(Proteinoids)	Oral protein delivery
DOSPA: histamine- or protamine-derived peptides gene	Enhancing cationic lipid–mediated gene transfection
Acyl carnitines	Reduction of side effects
3-[(3-Cholamidopropyl)-dimethylammonio]-1-propane sulfonate	Solubilizer

Table 6: Modifications of synthetic polymers with small polymers

Name	Uses
Poly(ethyl acrylic acid), Poly(propylacrylic acid)	pH-dependent membrane lysis
Long-chain alkyl amine substituted poly(acrylic acid)	Solubilizer
Polypeptides, DTPA	Drug delivery

HERBAL EXCIPIENTS USED IN NOVEL DRUG DELIVERY SYSTEM

Excipients of natural origin are of particular interest to us for reasons of reliability, sustainability and avoiding reliance upon materials derived from fossil fuels. Plant products are therefore attractive alternatives to synthetic products because of biocompatibility, low toxicity, environmental “friendliness”, and low price compared to synthetic products. Excipients from natural products are also generally non-polluting renewable sources for the sustainable supply of economical pharmaceutical products.

A. Polysaccharides in pharmaceuticals

Natural polysaccharides are extensively used for solid form formulations. They are highly stable, safe, nontoxic, and hydrophilic and gel forming in nature. Pectin, starch, guar gum, amylase and karaya gums are a few polysaccharides commonly used in dosage forms. Non-starch, linear polysaccharides remain intact in the physiological environment of the stomach and the small intestine,but are degraded by the bacteria present in human colon which make them potentially useful in targeted drug delivery systems to the colon [6].

a) Pectins:

Pectin are non-starch.linear polysaccharides extracted from plant cell walls. They are predominantly linear polymers of mainly (1-4)-linked D-galacturonic acid resides interrupted by 1,2-linked L-rhamnose residues with a few hundred to about one thousand building blocks per molecule, corresponding to an average molecular weight of about 50,000 to about 1,80,000(2). Being soluble in water, pectin is not able to shield its drug load effect effectively during its passage through the stomach and small intestine. It was found that a coat of considerable thickness was required to protect the drug core in simulated *in vivo* conditions. Mixed films of pectin with ethylcellulose were investigated as a coating material for colon-specific drug delivery. Sungthongjeen et al investigated the high-methoxy pectin for its potential value in controlled-release matrix formulations [6]. The effects of compression force,ratio of drug to pectin, and type of pectin on drug release from matrix tablets were also investigated. A very low solubility pectin-derivative (pectinic acid, degree of methoxylation 4%) was found to be well suited as an excipient for pelletisation by extrusion/spheronisation. Pectin microspheres of piroxicam were prepared by the spray dying technique. In vivo tests in rabbits with dispersions of piroxicam-loaded microspheres also indicated a significant improvement of piroxicam bioavailbility in the aqueoushumuor (2.5-fold) when compared with commercial piroxicam eye drops [7].

b) Alginates:

Alginates are natural polysaccharide polymers isolated from the brown sea weed (Phaeophyceae). Alginic acid can be converted into its salts, of which sodium alginate is the major form currently used. A linear polymer consisting of D-mannuronic acid and L-guluronic acid residues arranged in blocks in the polymer chain, these homogenous blocks (composed of either acid residue alone) are separated by blocks made of random or alternating units of mannuronic and guluronic acids. Alginates offer various applications in drug delivery, such as in matrix type alginate gel beads, in liposomes, in modulating gastrointestinal transit time, for local applications and to deliver the bio molecules in tissue engineering application[8].

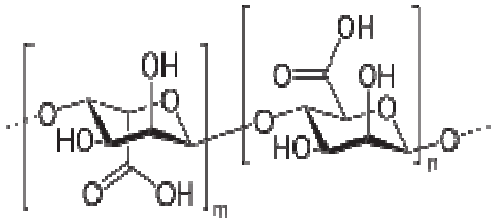

Fig. 1. Structure of alginic acid

In comparative study, alginate formulation appeared to be better than the polylactide-co-glycolide (PLG) formulation in improving the bioavailability of two clinically important antifungal drugs-clotrimazole and econazole [9].

c) Starches:

It is the principal form of carbohydrate reserve in green plants and especially present in seeds and underground plant organs. Starch occurs in the form of granules (starch grains), the shape and size of which are characteristic of the species, as it is also the ratio of the content of principal constituents, amylase andamylopectin. A number of starches are recognized for pharmaceutical use.These include maize(*Zeamays*),rice(*Oryza sativa*),wheat(*Triticum aestivum*) and potato(*Solanum tuberosum*) [10].

Modified starch was tested for general applicability of a new pregelatinized starch product in directly compressible controlled-release matrix systems.It was prepared by enzymatic degradation of potato starch followed by precipitation (retrogradation), filtration and washing with ethanol.The advantages of the material include ease of tablet preparation, the potential of a constant release rate(zero- order) for an extended period of time and its ability to incorporate high percentages of drugs with different physicochemical properties [11].

Acetylating of starch considerably decreases its swelling and enzymatic degradation. Thus, starch acetate (SA) based delivery systems were tested for controlled drug delivery [12].

B. Gums:

Gums are translucent and amorphous substances produced by the plants.Usually pathological products, gums are produced when the plants are growing under unfavorable conditions or when injured. Gums are plant hydrocolloids and may be anionic or non ionic polysaccharides. On hydrolysis gums yield sugar and salts of uronic acid [13].

a) New Plant Gum Obtained from Cissus refescence

The plant Cissus refescence F. Amplhelidaceae is a climbing stem widely distributed in many parts of Nigeria, especially within the guinea savannah region of Anambra, Kogi and Benue states. The Igala and Idoma ethnic groups refer to this plant as Okoho and use the mucilage from the stem as thickeners in soup. Although the gum obtained from Cissus refescence has been evaluated for its potential use as a dispersant in pharmaceutical liquid systems [14].

b) Guar gums:

Guar gums derived from the seeds of *cyamopsis tetragonolobus* (family Leguminosae) is naturally occurring galactomannan polysaccride.It is made up of linear chain of beta-D-mannopyranose joined by beta-(1-4) linkage with alpha-D-galactopyranosyl units attached by 1,6- links in the ratio of 1:2[6]. Guar gum is used in colon-delivery systems due to its drug release retarding property and suspectibility to microbial degradation in large intestine. Another water soluble drug,diltiazem HCl has given controlled release comparable with marketed sustained release diltiazem HCl tablets(D-SR tablets), which are prerared in the form of matrix tablets with guar gum using the wet granulation technique[15].

c) Gum acacia:
Gum acacia or gum Arabic is the dried gummy exudates obtained from stem and branches of *Acacia Senegal* (Linne) Willdenow and other related species of acacia (Family Leguminosae). The gum has been recognized as an acidic polysaccharide containing D-galactose , L-arabinose, L- rhamnose, and D- glucuronic acid. Acacia is mainly used in oral and topical pharmaceutical formulations as a suspending and emulsifying agent, often in combination with tragacanth. It is also used in the preparation of pastilles and lozenges and as a tablet binder [16].

Gum Arabic was used as an osmotic, suspending and expanding agent in the preparation of a monolithic osmotic tablet (MOTS) with two orifices on both sides surfaces [17].

d) Karaya gum:
Karaya gum is obtained from *Sterculia urens* (Family sterculiaceae) is partially acetylated polymer of galactose, rhamnose and glucuronic acid[16]. Swellable hydrophilic natural gums like xanthum gum and karaya gum were used as release-controlling agents in producing directly compressed matrices.Karaya gum displayed a much lower hydration capacity and a higher rate of erosion, both markedly affected by agitation speed.Both xanthan and karaya gums produced near zero order drug release with the erosion mechanism playing a dominant role, especially in karaya gum matrices [18].

e) Xanthun gums:
Xanthun gum is high molecular weight extra cellular polysaccharide produced by the fermentation of the gram negative bacterium *Xanthomonas campestries*. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (Beta-D-gulucose residues) and a trisaccharide side chain of beta-D-mannose-beta-D-glucuronicacid-alpha-D-mannose attached with alternate glucose residues of the main chain [16]. Xanthan gum showed a higher ability to retard the drug release than synthetic hydroxypropylmethylcellulos [19].

f) Gum from Moringa oleifera:
The gum from Morniga oleifera for its ability to retard the release of proranolol hydrochloride from tablets and effect of excipients of opposite solubility on the release of the drug.

g) Tragacanth:
This gum is obtained from the branches of *Astragalus gummifer* Family Leguminosae.Tragacanth when used as the carrier in the formulation of 1- and 3- layer matrices produced satisfactory release prolongation either alone or in combination with other polymers [13].

C. **Volatile oils**
Volatile oils are generally mixtures of hydrocarbons and oxygenated compounds derived from these hydrocarbons.Many oils are terpenoid in origin; some of them are aromatic derivatives mixed with terpens(e.g. cinnamon and carvacrol) although aromatic in structure, are terpenoid in origin [10].

a) Methanol:
Methanol is obtained by steam distillation of the flowering tops of *Mentha piperita* belonging to the family Labiatae. A membrane- moderated transdermal therapeutic system(TTS)of nimodipine using 2%w/w hydroxypropylmethylcellulose (HPMC) gel as a reservoir system containing menthol as penetration enhancer and 60%v/v ethanol- water as solvent system [13]. Methanol was tested for improving the bioavailability of poorly water-soluble ibuprofen in the rectum with poloxamer [15, 20].

b) *Caraway*:
Caraway fruit consists of the dried, ripe fruits of Carum carvi (Umbelliferae).The volatile oil consists of ketone carvone and the terpene limonene. In another attempt, a limonene- based transdermal therapeutic system (TTS) was prepared to study its ability to provide the desired steady-state plasma concentration of nicorandil in human volunteers [21].

CONCLUSION

In addition to conventional pharmaceutical excipients as bulking agents, substance use for masking taste/texture or as a substance use to aid during manufacturing process, Novel excipients offer broad range of additional properties suitable to preserve the integrity of active constituents of the formulation and enhances it's self life. New and modified excipients, irrespective of its source (synthetic or herbal) produces formulation that offer better drug delivery performance, reliability, negligible toxicity, enhances stability, improve bioavailability and patient acceptability. It also avoids dependence of pharmaceutical industry on rapidly perishing non renewable resources like fossil fuel.

The synthetic polymers can be designed or modified as per requirement of the formulation; by altering polymer characteristics and on the other hand herbal pharmaceutical excipients are biocompatible, non toxic, environment friendly and economical.

It seems conceivable that in the near future, kilogram quantities of fusion proteins, fibronectin, poly (lysine), or hemolysin could become available as off-the-shelf excipients or as designer excipient kits. This scenario is even more plausible considering that moieties that were unheard of a decade ago are now routinely available for use as excipients or in biochemical research (e.g., Lipofectamine, poly (lactide-co-glycolide), PAMAM dendrimers, tocopherol PEG succinate, etc.).

Excipients that have never been used before must pass formidable regulatory requirements before being incorporated into approved dosage forms. Such requirements include, but are not limited to, comprehensive toxicology (including acute, chronic, and reproductive) and pharmacokinetic and carcinogenic studies as outlined in the ICH S7, S3A, S3B, S2B, and S5A and the US Pharmacopeia

REFERENCES

[1] Shireesh P. Apte and Sydney O. Ugwu. A review and classification of emerging excipients in paranteral medications. *Pharmaceutical Tech.* **2003**; 46-60.
[2] Guidance for Industry, Drug Product. Chemistry, Manufacturing and Controls Information, U.S Dept. of Health and Human Services, FDA, CDER, CBER, **2003**; pp. 3-9.
[3] R. Osterberg and N. Sec., Toxicity of Excipients-A Food and Drug Administration Perspective. *International Journal of Toxicology*. **2003**; 1-7.
[4] Iewin silverstein. IPEC-Americans 'Updated significant change guide for bulk pharmaceutical excipients. *Pharm. Tech.* **2005**; 98-102.
[5] R. Christian Moreton.Excipient Functionality. *Pharm.Tech*. **2004**; 98-119
[6] Sinha VR, Rachana K. Polysaccharides in colon specific drug delivery. *Int. J.Pharm*. **2001**; 224: 19-38.
[7] Giunchedi P, Conte U, Chetom P, Saettone MF. Pectin microspheres as ophthalmic carriers for piroxicam: Evaluation in vitro and in vivo in albino rabbits. *Eur. J. Pharm. Sci*. **1999**; 9: 1-7.
[8] Tonnesen HH, Karlssen J. Alginate in drug delivery system *Drug Develop. Ind. Pharm*. **2002**; 28: 620-31.
[9] Pandey R, Ahmad Z, Sharma S, Khuller GK. Nano-encapsulation of azole antifungals: Potential applications to improve oral drug delivery. *Int. J. Pharm*. **2005**; 301: 268-76.
[10] Trease GE, Evans WC editors. Text Book of Pharmacognosy, 15th ed., **2002**. London, Balliere.
[11] Te-Wierik GH, Eissens AC, Bergsma J, Arends-Scholte AW, Bolhuis GK. A new generation starch product as excipient in pharmaceutical tablets III: Parameters affecting controlled drug release from tablets based on high surface area retrograded pregelatinized potato starch. *Int. J. Pharm*. **1997**; 157: 181-7.
[12] Tuovinen L, Peltonen S, Jarvinen K. Drug release from starch-acetate films. *J. Control Release*. **2003**; 91: 345-54.
[13] Kokate CK, Purohit AP, Gokhle SB, editors. Pharmacognosy. 22nd ed. Nrali Parkashan, India. **2003**; pp. 133-66.
[14] Alfa J, Chukwu A, Udeala OK. Cissus stem gum as potential dispersant in Pharmaceutical liquid systems, rheological characterization. *Boll. Chim. Farm*. **1999**; 140: 20-7
[15] Krishnaiah YS, Satyanarayana S, Prasad YV. Studies of guar gum compression-coated 5-aminosalicylic acid tablets for colon-specific drug delivery. *Drug Develop. Ind. Pharm*. **1999**; 25: 651-7.
[16] Bhardwaj TR, Kanwar M, Lal R, Gupta A. Natural gums and modified naural gums as sustained-release carriers. *Drug Develop. Ind. Pharm*. **2000**; 26: 1025-38.
[17] Lu EX, Jiang ZQ, Zhang QZ, Jiang XG. A water insoluble drug monolithic osmotic tablet system utilizing gum Arabic as an osmotic, suspending and expanding agent. *J. Control Release.* **2003**; 92: 375-82.
[18] Munday DL, Cox PJ. Compressed xanthan and karaya gum matrices: Hydration, erosion and drug release mechanisms. *Int. J. Pharm*. **2000**; 203: 179-92.
[19] Gohel MC, Amin AF, Patel KV, Panchal MK. Studies in relese behavior of diltiazem HCl from matrix tablets containing (hydroxypropyl) methyl cellulose and xanthan gum. *Boll Chim. Farm.* **2002**; 141: 21-8.
[20] Yong CS, Yang CH, Rhee JD, Lee BJ, Kim DC, Kim DD. Enhanced rectal bioavaility of ibuprofen in rats by poloxamer 188 and menthol. *Int. J. Pharm*. **2004**; 269: 169-76.

[21] Krishnaiah YS, Chandrasekhar DV, Rama B, jayaram B, Satvanarayana V, Al-Saidan SM. Invivo evaluation of limonene-based transdermal therapeutic system of nicorandil in healthy human volunteers. *Skin Pharmacol. Physiol*. **2005**; 18: 263-72.