Modified Excipients in Novel Drug Delivery: Need of the Day

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Abstract
Drug products not only contain “actives” that confer the intended therapeutic benefits such as pain relief or act on particular part of the body, but contain other materials that are also “functional” with respect to the drug product. These are known as excipients and specific functionality which they confer to a particular product is independent upon the process used to add the excipient to the formulation and its exact location within the final dosage form. Introduction of novel drug delivery systems and new drug moieties lead to the need for new excipients with varied characteristics. Development of new excipient entities and their evaluation is a costly procedure; modification of existing excipients is very easy, more economical and less time consuming. The development of excipients that are capable of fulfilling multifunctional roles such as enhancing drug bioavailability and drug stability as well as controlling the release of the drug according to the therapeutic needs is one of the most important prerequisites for further progress in the design of novel drug delivery systems. The main focus of this article is on synthetic novel excipients that perform multiple functions in pharmaceutical formulations.

Keywords: excipients, functionality, synthetic, stability, bioavailability

1 INTRODUCTION

Therapeutic moieties cannot be administrated as such, so they are modified to various dosage forms for the reasons of patient compliance, dose accuracy and consistency, improving bioavailability, aesthetics and reduction of side effects (Prasanna et al., 2011). Excipients are the fundamental requirements to these modifications allowing formulation scientists to achieve their objectives. Excipients in brief can be defined as “The components of a formulation other than the active ingredient” (Parker et al., 2009). As compounds become more challenging to formulate, new excipients are needed to enable the delivery, manufacture and development of these compounds. Conventional excipients have been replaced with sophisticated compounds that fulfill multifunctional roles in modern pharmaceutical dosage forms such as improvement of the stability and bioavailability of the active ingredient, enhancement of patient acceptability and performance of technological functions that ensure ease of manufacture (Steinberg et al., 1996 and Pifferi et al., 2003).
1.1 Need of novel excipients

The excipients industry to date has been an extension of the food industry (Steinberg et al., 2001). Moreover, excipients are products of the food industry, which has helped maintain a good safety profile. Increasing regulatory pressure on purity, safety, and standardization of the excipients has catalyzed the formation of an international body, the International Pharmaceutical Excipients Council (IPEC) (http://www.ipecamericas.org). IPEC is a tripartite council with representation from the United States, Europe, and Japan; and has made efforts to harmonize requirements for purity and functionality testing (Blecher, 1993). The development of new excipients to date has been market driven (i.e., excipients are developed in response to market demand) rather than marketing driven (i.e., excipients are developed first and market demand is created through marketing strategies) and has not seen much activity as shown by the fact that, for the past many years, not a single new chemical excipient has been introduced into the market. The primary reason for this lack of new chemical excipients is the relatively high cost involved in excipients discovery and development. However, with the increasing number of new drug moieties with varying physicochemical and stability properties, there is growing pressure on formulators to search for new excipients to achieve the desired set of functionalities. The reasons to develop new excipients are following:

a. **Effective use of existing excipients**: Identification of new applications for the existing excipients is a relatively inexpensive and less time involving process as compared to an entirely new development. Chitosan is one of such existing excipients, which has found new applications in recent years. Modified chitosan with silicon dioxide is a new excipient developed based on coprecipitation of chitosan and silica which can be used as a superdisintegrant (Rashid et al., 2008) with improved flow and compaction properties. It also acts as filler (El-Barghouthi et al., 2008).

b. **Excipients with desirable properties**: There are a number of existing excipients which lack some of the desirable properties required in some formulations, viz., soluble tablets, in which an ideal lubricant should be water soluble with effectiveness similar to that of magnesium stearate. (http://www.fda.gov/cder/guidance/index)

c. **Drugs developed by genetic engineering**: As new drugs are being developed, their compatibility with the existing excipients sometimes poses a big question. Hence, new excipients will be necessary to overcome these problems. The drugs of protein and peptide class require stabilizers of a different nature when compared to that of conventional oral solid dosage forms.
d. **Advances in production process and equipment:** The developments or improvements in pharmaceutical process and equipments, particularly increase in production rates at low cost, lead to the need for new excipients. The newly developed tablet machines require materials with better compressibility because they operate with shorter dwell and contact times, as compared to early machines that require materials with good flow properties.

e. **Patient or subject compliance:** Some excipients, which are used nowadays, are unacceptable for the reasons of patient safety and comfort. Lactose intolerance occurs in persons, who are deficient in the enzyme lactase, leading to abdominal cramps, diarrhea, distension and flatulence.

f. **Specialized drug delivery systems:** The development of novel or specialized drug delivery systems requires the use of special excipients. Metered dose inhalation devices require excipients of a particular size grade and development of mucoadhesive preparations necessitated the utilization of new bio adhesive polymers (Buckton, 2008; Veillard, 1991).

### 1.2 Advances in formulations and drug delivery systems

The advances in formulations and drug delivery systems lead to development of new or modified forms of existing excipients. The various areas exploring the development are classified into (a) improvements to immediate and controlled release dosage forms; (b) nanotechnology; (c) specialized delivery systems; (d) biologics (www.meggle-pharma.com)

a. **Improvements to immediate and controlled release dosage forms:** New excipient grades, with better performance or tighter controls are also developed for pharmaceutical use. Hydroxypropyl methylcellulose (HPMC) is a commonly used hydrophilic polymer to achieve matrix based controlled release. However, direct compression of HPMC-based formulations is challenging because HPMC may impart poor flow properties to the formulation, causing problems during high-speed tablet manufacturing (Sheskey *et al*, 1996). Thus, granulation of HPMC-based formulations is usually required. Granulation process variables can exert a significant impact on the dissolution characteristics of HPMC based tablets. Huang *et al* found that when HPMC K15M matrix tablets were prepared by wet-granulation; the tablet hardness, distribution of HPMC within the tablet (intergranular and intragranular), and the amount of water added in the wet granulation step, all have a significant impact on dissolution and release profiles of the drug from the tablets (Huang *et al*, 2003). Recently, new grades of HPMC K4M and K100M DC have been
designed to possess properties such as larger particle sizes and better flow properties to facilitate direct compression, thus avoiding the need for granulation. Tableting trials with the new HPMC DC grades showed lower tablet weight variability with similar release using model drugs compared to the CR grades (Ender et al, 2007).

b. **Nanotechnology:** Recent advances in nanotechnology for drug delivery are divided into 4 areas. Firstly, advances to improve manufacturability and robustness of existing technologies (e.g. liposomes, nanoparticles and nanocrystals). Secondly, strategies to improve stability of the nanoscale systems *in vivo* and *in vitro* are researched. For example, PEGylation and alternatives to PEGylation to improve *in vivo* stability and reduce immunogenicity are explored. Thirdly, new materials are designed to obtain improved properties, such as derivatization of existing polymers like poloxamer to optimize drug solubilization or customized drug release at targeted sites. Fourthly, numerous new targeting functionalities have been designed by many to improve specificity to target organs. As many drug candidates are either poorly water soluble or challenging to deliver, there is a need for new solubilizers and specialized drug delivery systems to enable solubilization and bioavailability. Polyoxyl 15 Hydroxystearate is an example of a new solubilizer that also exhibits good tolerability over traditional solubilizers like polysorbate 80. It is also the first new excipient to be evaluated under the new IPEC Novel Excipient Safety Evaluation Procedure, established in 2007 (Velagaleti, 2009). Cyclodextrins are also used to achieve drug solubilization by complexation. To date, cyclodextrins have been used in the formulations of 34 marketed products (Brewster et al, 2007). Recent advances in cyclodextrins research are focused on designing new derivatives with “customized” substitutions, substitutions to increase solubility and lower toxicity, and scale-up of the inclusion complexes manufacturing.

c. **Specialized Delivery Systems:** Solid dispersions are also a hot research field because they have shown much promise to improve the dissolution and bioavailability of poorly water soluble drugs. The introduction of new polymeric carriers such as Hypermellose acetate succinate (HPMCAS), copolymers based on dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate, poly (vinylpyrrolidone-vinyl acetate) (PVP-VA), lauroyl macrogol glycerides (polyoxylglycerides) have further advanced this field. These excipients provide thermoplastic and thermal stability to solid dispersions and have also improved manufacturability. Taste masking is important in the development of paediatric formulations and dosage forms like rapidly disintegrating tablets containing bitter drugs.
One mechanism of taste masking is to prevent dissolution of the drug in the mouth and contacting the taste buds, and only releasing drug in the stomach or beyond in the gastrointestinal tract. A newly available methyl methacrylate diethylaminoethyl methacrylate (6:4) copolymer dispersion with macrogol cetosteareylether and sodium lauryl sulfate included as stabilizers in the formulation which is based on this principle. The copolymer being pH-sensitive effectively prevents drug dissolution under neutral conditions in the saliva, with immediate release under acidic conditions of the stomach (www.pharma-ingredients.basf.com).

**d. Biologics:** Recent advances in biologics are focused primarily on parenteral routes of administration. Materials have been investigated for greater stabilization (*in vitro* and *in vivo*), reduced frequency of administration, achievement of high doses and improved manufacturability of biologic formulations such as maintaining protein activity on scale-up. Major classes of delivery systems used in biologics formulation include microspheres (PLGA-based, Chitosan-based), liposomes (PEGylated lipids) and hydrogels (modified dextran and starch-based). In the area of sIRNA delivery systems for systemic administration, three major groups of systems based on material are used (David *et al.*, 2010). The first are the lipid systems, including neutral liposomes composed of dioleyl-glycerophosphatidylcholine (DOPC) and cationic liposomes composed of 1, 2-Dioleoyl-3-trimethylammonium-propane (DOTAP). The second are the systems that use polymers, such as natural polymers (e.g. atelocollagen and cyclodextrins) and synthetic polymers (e.g. Polyethyleniemine (PEI). Lastly, peptides and proteins, like antibody-protamine fusion proteins are also used to formulate sIRNA.

### 1.3 Synthetic excipients

Synthetic excipients are used in the manufacture of tablets to bind the tablet together, reduce die wall friction between the tablet and the tableting press, control pH balance, and to disintegrate the tablet in the stomach once it has been ingested. In parenterals, synthetic excipients are used as solubilization agents to make actives more soluble, and therefore, more deliverable (Russell, 2004).

The advancements in the area of synthetic excipients are discussed under coprocessed, multifunctional and high functionality excipients.

### 1.4 Coprocessed Excipients

A coprocessed excipient is a combination of two or more compendial or non compendial excipients designed to physically modify their properties in
manner not achievable by simple physical mixing, and without significant chemical change. Coprocessed excipients are used mainly in solid dosage forms such as tablets, capsules, powder and in liquid dosage forms such as emulsions, suspensions, injections and in semisolid dosage forms such as creams, ointments and pastes (Chaudhary et al, 2012).

**Principle of coprocessing:** Basic fundamental of coprocessing is based on particle engineering. Solid substances are characterized by three levels of solid state- molecular, particle, and bulk level. These levels are closely linked to one another, with the changes in one level reflecting in another level. The molecular level comprises the arrangement of individual molecules in the crystal lattice and includes phenomena such as polymorphism, pseudo-polymorphism, and the amorphous state. Particle level comprises individual particle properties such as shape, size, surface area, and porosity. The bulk level is composed of an ensemble of particles and properties such as flow ability, compressibility, and dilution potential, which are critical factors in the performance of excipients. Coprocessing based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvements as well as masking the undesirable properties of individual excipients. The availability of a large number of excipients for coprocessing ensures numerous possibilities to produce tailor-made “designer excipients” to address specific functionality requirements (Marwaha et al, 2010).

**Coprocessing of excipients:** The actual process of developing a coprocessed excipient involves the following steps (Bansal et al, 2004):

- Identifying the group of excipients to be coprocessed by carefully studying the material characteristics and functionality requirements.
- Selecting the proportions of various excipients.
- Assessing the particle size required for coprocessing. This is especially important when one of the components is processed in a dispersed phase. Post processing the particle size of the latter depends on its initial particle size.
- Selecting a suitable process of drying such as spray or flash drying.
- Optimizing the process (because even this can contribute to functionality variations).

**Advantages of coprocessing**

e. **Improved Flow Properties and compressibility:** Controlled optimal particle size and particle-size distribution ensures superior flow properties of co-processsed excipients without the need to add glidants. The
volumetric flow properties of SMCC were studied in comparison with MCC. The particle-size range of these excipients was found to be similar to those of the parent excipients, but the flow of coprocessed excipients was better than the flow of simple physical mixtures. A comparison of the flow properties of cellactose was also performed. The angle of repose and the Hausner’s ratio were measured, and cellactose was found to have better flow characteristics than lactose or a mixture of cellulose and lactose (York, 1992). These have been used mainly in direct compression tableting because in this process there is a net increase in the flow properties and compressibility profiles and the excipient formed is a filler-binder. (Marwaha et al., 2010)

f. **Better dilution potential:** Dilution potential is the ability of the excipient to retain its compressibility even when diluted with another material. Most active drug substances are poorly compressible, and as a result, excipients must have better compressibility properties to retain good compaction even when diluted with a poorly compressible agent. (Flores et al, 2000).

<table>
<thead>
<tr>
<th>Co-processed Excipient</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Added advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose, 3.2% Kollidon 30, Kollidon CL</td>
<td>Ludipress</td>
<td>Basfag, Ludwigshafen, Germany</td>
<td>Low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed</td>
</tr>
<tr>
<td>Lactose, 25% cellulose</td>
<td>Cellactose</td>
<td>Meggle gmbh &amp; co. Kg, Germany</td>
<td>Highly compressible, good mouth feel, better tableting at low cost</td>
</tr>
<tr>
<td>Sucrose 3% dextrin</td>
<td>Dipac</td>
<td>Penwest pharm. Company</td>
<td>Directly compressible</td>
</tr>
<tr>
<td>Microcrystalline cellulose, Silicon dioxide</td>
<td>Prosolv</td>
<td>Penwest pharmaceuticals company</td>
<td>Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability</td>
</tr>
<tr>
<td>Microcrystalline cellulose, Guar gum</td>
<td>Avicel ce-15</td>
<td>Fmc corporation</td>
<td>Less grittiness, minimal chalkiness, overall palatability</td>
</tr>
<tr>
<td>Calcium carbonate, Sorbitol</td>
<td>Formaxx</td>
<td>Merck</td>
<td>Controlled particle size distribution</td>
</tr>
<tr>
<td>Microcrystalline cellulose, Lactose</td>
<td>Microlela</td>
<td>Meggle</td>
<td>Capable of formulating high dose, small tablets with poorly flow able active ingredients</td>
</tr>
</tbody>
</table>
g. **Fill weight variation:** In general, materials for direct compression tend to show high fill weight variations as a result of poor flow properties, but coprocessed excipients, when compared with simple mixtures or parent materials, have been shown to have fewer fill weight variation problems. The primary reason for this phenomenon is the impregnation of one particle into the matrix of another, which reduces the rough particle surfaces and creates a near optimal size distribution, causing better flow properties. Fill weight variation tends to be more prominent with high-speed compression machines.

h. **Reduced lubricant sensitivity:** Most coprocessed products consist of a relatively large amount of brittle material such as lactose monohydrate and a smaller amount of plastic material such as cellulose that is fixed between or on the particles of the brittle material. The plastic material provides good bonding properties because it creates a continuous matrix with a large surface for bonding. The large amount of brittle material provides low lubricant sensitivity because it prevents the formation of a coherent lubricant network by forming newly exposed surfaces upon compression, thus breaking up the lubricant network. Various examples of coprocessed directly compressible excipients and application of these excipients are depicted in Table 1 and 2 respectively.

**Table 2:** Application of Coprocessed excipients (Chaudhary et al., 2010)

<table>
<thead>
<tr>
<th>Excipients</th>
<th>Drug</th>
<th>Approach used</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludiflash</td>
<td>Risperidone</td>
<td>Direct compression</td>
<td>Disintegration time of 27 sec</td>
</tr>
<tr>
<td>Pharmaburst</td>
<td>Famotidine</td>
<td>Taste masking microsphere using spray drying</td>
<td>Disintegration in 30 seconds with improved taste.</td>
</tr>
<tr>
<td>F-MELT</td>
<td>Acetaminophen</td>
<td>Direct compression using 10% to 65% w/w</td>
<td>Good mouth feel and excellent oral disintegration time below 30 sec</td>
</tr>
<tr>
<td>Orocell 200 &amp; Orocell 400</td>
<td>Ibuprofen</td>
<td>Direct compressible</td>
<td>Disintegration time of 5 sec</td>
</tr>
<tr>
<td>Pearlitol SD</td>
<td>Metformin</td>
<td>Wet granulation</td>
<td>Disintegration time of 85 s, 100% drug release in 10 min</td>
</tr>
<tr>
<td>GalenIQ 720 and 721</td>
<td>Placebo</td>
<td>Direct compression</td>
<td>Even without superdisintegrants, tablets containing both isomalt grades disintegrated within 200–500 s</td>
</tr>
<tr>
<td>Polacrilitin potassium</td>
<td>Sumatriptan</td>
<td>Direct compression</td>
<td>Disintegration time of 45 sec, 100% drug release in 10 min</td>
</tr>
</tbody>
</table>

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Technologies used for coprocessed excipients

a. Roller compaction: In the roller compaction process, powder blends first pass a feeding zone, where most of the rearrangement occurs (Chougule et al., 2012). The dense powders then go through a compaction zone, where increasing force is being exerted by two counter rotating rolls. As the pressure goes up further into the compaction zone, the particles deform, fragment, and bond to form ribbons. Roller compaction is widely applied to dry granulation. It offers many superior characteristics e.g. good control of process and cost advantages compared to wet granulation. As no liquid or drying is involved, this process is more suitable for water or heat sensitive drugs (Reynolds et al., 2010). Compared to direct compression, roller compaction can handle high drug loading, improve flow and content uniformity and prevent segregation. Like any other processes, dry granulation has its own issues, such as loss of compactibility of dissolution problem. A systematic approach of formulation and process development is the key to high quality drug products. At high drug loading, the compactibility and flow ability of drug substance will be critical for roller compaction and tableting processes (Miller, 1997). Different excipients need to be evaluated in formulation development to achieve desirable chemical stability, tablet properties, and process control.

b. Wet granulation: Wet granulation is a process still widely used in the pharmaceutical industry. It has not been replaced by direct compression technology, partly because of development cost considerations and habits, and partly because it remains in some cases an attractive technique. The process continues until all the powder has been agglomerated, and it needs to be stabilized as far as moisture balance is concerned. The equilibrium may not be constant, however, as the moisture content of the granules could be increasing slightly throughout the process, and the trajectories of the particles may change with changes in the density of the agglomerated powder bed. Complete drying is quickly achieved in the hot air stream when binder spraying is stopped (Hapgood et al., 2009). The drying step traditionally takes place after transferring the damp mass into another piece of equipment (fluid bed dryer), but the use of single-pot technology (drying in place) is now spreading. The granules formed are understandably denser than those obtained in fluid bed granulation (York et al., 2009).

c. Spray drying: This technique enables the transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium. It is a continuous particle processing drying operation. The feed can be a solution, suspension, dispersion or emulsion. The dried product
can be in the form of powders, granules or agglomerates depending upon the physical and chemical properties of the feed, the dryer design and final powder properties desired (http://www.ich.org/LOB/media). Spray drying process (Gohel, 2005) mainly involves five steps:

i. **Concentration:** Feedstock is normally concentrated prior to introduction into the spray dryer.

ii. **Atomization:** The atomization stage creates the optimum condition for evaporation to a dried product having the desired characteristics.

iii. **Droplet-air contact:** In the chamber, atomized liquid is brought into contact with hot gas, resulting in the evaporation of 95% of the water contained in the droplets in a matter of a few seconds.

iv. **Droplet drying:** Moisture evaporation takes place in two stages: during the first stage, there is sufficient moisture in the drop to replace the liquid evaporated at the surface and evaporation takes place at a relatively constant rate. The second stage begins when there is no longer enough moisture to maintain saturated conditions at the droplet surface, causing a dried shell to form at the surface. Evaporation then depends on the diffusion of moisture through the shell, which is increasing in thickness.

v. **Separation:** Cyclones, bag filters, and electrostatic precipitators may be used for the final separation stage. Wet Scrubbers are often used to purify and cool the air so that it can be released to atmosphere. Spray drying process have advantages that can be designed to virtually any capacity required. Feed rates range from a few pounds per hour to over 100 tons per hour. Operation is continuous and adaptable to full automatic control. It can be used with both heat resistant and heat sensitive products. Nearly spherical particles can be produced. There are some limitation that includes limited versatility in producing particles or structures with the complex morphologies, and rapid drug release rates often exhibiting a burst effect (Patel et al, 2009).

d. **Co-spray drying:** Incorporation of ingredients under dry or solid form during drying process, by atomizing active compounds in solution or under the form of emulsion. The process is advantageous in many ways such as- Possibility to associate non-miscible products in continuous operation, Possibility to blend and dry simultaneously soluble and insoluble compounds, Possibility to fix and protect sensitive active compounds on neutral carrier (Patel et al, 2009). This leads to improved hardness and compressibility, better uniformity than granulated in actives,
enhanced machine tableting speed, lesser disintegration time, consistent physical parameters of excipients ensuring sturdy formulation, no need to maintain inventory of various excipients, cost saving due to elimination of wet granulation production steps, productivity increase due to increased machine speed and cost saving in rework expenses. But there are some limitation that includes limited versatility in producing particles or structures with the complex morphologies, and rapid drug release rates often exhibiting a burst effect.

e. **Solvent evaporation:** This process is carried out in a liquid manufacturing vehicle. The coating excipient is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core excipient material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated (if necessary) to evaporate the solvent. Once all the solvent is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if required) with continued agitation. At this stage, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders. The core materials may be either water-soluble or water-insoluble materials.

f. **Melt extrusion:** Melt extrusion is a process of formation of small beads/pellets from the molten mass which is extruded through extruder (http://www.Zeusinc.com). This technique is reproducible, less time consuming and moreover, complicate and intricate shapes are possible. But equipment and die costs are high.

g. **Crystallization:** Crystallization is the (natural or artificial) process of formation of solid crystals precipitating from a solution, melt or more rarely deposited directly from a gas. Crystallization is also a chemical solid–liquid separation technique, in which mass transfer of a solute from the liquid solution to a pure solid crystalline phase occurs (Blecher, 1993). For crystallization to occur from a solution it must be supersaturated. This means that the solution has to contain more solute entities (molecules or ions) dissolved than it would contain under the equilibrium (saturated solution). This can be achieved by various methods such as: solution cooling, addition of a second solvent to reduce the solubility of the solute (technique known as antisolvent or drown-out), chemical reaction and change in pH being the most common methods used in industrial practice.

h. **Agglomeration:** Agglomeration is the act or process of forming or crystallizing into grains. Granules typically have a size range between
0.2 to 4.0 mm depending on their subsequent use. Agglomeration of powders is widely used to improve physical properties like: wettability, flowability, bulk density and product appearance (Blecher, 1993). Two types of granulation technologies are employed, namely, wet granulation and dry granulation. Wet granulation is the more preferred method for coprocessing.

1.5 Multifunctional Excipients

Multifunctional excipients are a class of excipients that includes preprocessed and coprocessed excipients that provide added functionalities to the formulation (for example, Silicified Micro-Crystalline Cellulose, which is a processed combination of MCC and colloidal silicon dioxide). These functionalities include flowability, compressibility, particle size distribution, shape, porosity, etc. The term multifunctional excipient is also extended to products that serve multiple roles in the formulation e.g. Ludipress, which is co-processed product containing lactose, Kollidon and Kollidon-CL, serves the role of directly compressible diluent with binder and disintegrant properties (www.contractpharm.com).

Multifunctional excipients can be obtained by developing a new excipient (such as cross-linked polymers) or by developing new grades of existing excipients; modification in the processing leads to changes in the particle size distribution, particle shape and morphology and porosity. Traditionally, industry stays away from developing a new excipient altogether, due to the cost involved and problems faced in getting regulatory approvals. The change in the manufacturing process of an excipient along with addition of minor amount of another known excipient results in a product that has enhanced physical characteristics leading to added functionality. Combining of known excipients at sub-particle level (also known as co-processing) leads to excipients with modified properties like enhanced surface area, increased porosity, enhanced compressibility, good flowability etc. Co-processed excipients are also suitable for direct compression and thus help in simplification of tablet manufacturing. The reason for enhanced compressibility can be drawn from the fact that most of the co-processed excipients primarily consist of a large amount of brittle material and a smaller amount of plastic material. Thus, a co-processed material displays the property, which is a combination of plasticity as well as brittleness.

1.5.1 Recent Studies Using Multifunctional Excipients

a. Rice Germ Oil (RGO) as multifunctional excipient: Self-microemulsifying drug delivery system (SMEDDS) of tacrolimus (TAC) was formulated with RGO, an indigenous source of gamma-oryzanol.
Being the same biological source, RGO and rice bran oil (RBO) were compared and it was found that RGO have more solubilization potential for TAC (2.2-fold) as well as higher antioxidant activity (8.06-fold) than the RBO. TAC-SMEDDDS was prepared using RGO/Capmul PG8 (2:3) as an oil phase, Cremophore EL as a surfactant, and Transcutol P as a cosurfactant. The in vitro dissolution studies showed complete and rapid drug release in 30 min compared to a plain drug (<5%) and marketed capsule (<50%). Thus, gamma-oryzanol-enriched RGO acts as a potential multifunctional excipient for lipid formulations (Pawar et al., 2012).

**b. Sugar end-capped Poly-D, L-lactides as excipients:** Sugar end-capped poly-D, L-lactide (SPDLA) polymers were investigated as a potential release controlling excipient in oral sustained release matrix tablets. The SPDLA polymers were obtained by a catalytic ring-opening polymerization technique using methyl α-D-glucopyranoside as a multifunctional initiator in the polymerization. Polymers of different molecular weights were synthesized by varying molar ratios of monomer/catalyst. The matrix tablets were prepared by direct compression technique from the binary mixtures of SPDLA and microcrystalline cellulose, and theophylline was used as a model drug. The drug release was the fastest with the lowest molecular weight SPDLA grade, and the drug release followed zero-order rate. In conclusion, SPDLAs are a novel type of drug carrier polymers applicable in oral controlled drug delivery systems (Vuorinen et al., 2009).

**c. O-Phospho-L-Serine, multi-functional excipient:** Factor VIII (FVIII) is an important cofactor in the blood coagulation cascade. A deficiency or dysfunction of FVIII causes hemophilia A, a life-threatening bleeding disorder. FVIII circulates in plasma as a heterodimer comprising 6 domains (heavy chain, A1-A2-B and light chain, A3-C1-C2). Replacement therapy using FVIII is the leading therapy in the management of hemophilia. This research work investigated the effect of O-phospho-L-serine (OPLS), which binds to the lipid binding region, on the immunogenicity of B domain deleted recombinant factor VIII (BDDrFVIII). Sandwich enzyme-linked immunosorbent assay (ELISA) studies showed that OPLS specifically bind to the lipid binding region. Overall, the study demonstrated that specific molecular interaction of BDDrFVIII occurs with OPLS resulting in less protein aggregation and less immunogenicity (Miclea et al., 2007).

**d. Modification of the permeability of starch by processing with magnesium silicate:** Starch processed with magnesium silicate, using co-precipitation or dry granulation, can be used as a multifunctional excipient with the required binding and disintegration properties. Powder
compression using Kawakita analysis confirmed the higher plasticity and lower degree of rearrangement of starch- magnesium silicate resulting from co-precipitation compared to dry granulation. In addition, co-precipitation imparts high surface micro-irregularities as evidenced by SEM analysis. Formulation of a high strength model drug with starch- magnesium silicate illustrated the efficiency of the highly permeable starch- magnesium silicate in attaining quick drug release when compared to formulations with commercially available modified starch (Rashid et al, 2011).

e. **Co-processed MCC-Eudragit® E excipients for extrusion-spheronization:** This study investigates the extrusion–spheronization performance of some mixtures of co-processed microcrystalline cellulose and Eudragit® E (as excipients) and sorbitol (as soluble filler-disintegrant. The pellets prepared with co-processed MCC-Eudragit_ E and sorbitol show a drug dissolution rate dependent on the content of Eudragit_ E in the co-processed excipient and on the proportion of sorbitol incorporated. Furthermore, the pellets made with co-processed MCC-Eudragit®E incorporating the higher proportion of sorbitol (50%) show a very high dissolution rate of hydrochlorothiazide (HCT) and undergo rapid disintegration in the dissolution medium (Goyanes et al,2011).

f. **Modified celluloses- Multifunctional excipients:** The assessment of different celluloses (native cellulose, powdered cellulose, UICEL B UICEL S, Microcrystalline cellulose, UICEL XL) with respect to their suitability as excipients in rapidly dissolving immediate release tablets was the main scope of this research work. Based on different models six celluloses were evaluated. All tested materials were suitable for rapidly dissolving immediate release tablets independent of the relative density and drug load (Medina et al, 2006).

g. **Chitin metal silicate (CMS) co-precipitate:** The CMS co-precipitates have the potential to be used as a single filler tablet excipient with a multifunction action. This might make the formulation simpler by introducing one excipient with double or triple function instead of two or more excipients with less probability of incompatibility between formulation ingredients. The compressibility of poorly compressible drugs like Metronidazole and spironolactone was highly improved using CMS co precipitates (Rashid et al, 2008).

h. **Selected polysaccharide hydrogels:** Polysaccharide hydrogels from the seeds of Tamarindus indicia and from the trunk of Prunus Amygdalus were selected for physicochemical characterization and microbial load determination to establish them as pharmaceutical excipients. The
pharmaceutical properties such as density, porosity, packing arrangement, flow was found to be good for using them as pharmaceutical excipients. It was concluded that selected hydrogels had promising properties for application as multifunctional excipients (Rohokale et al., 2012).

1.5.2 Examples Of Innovative Multifunctional Excipients

a. galenIQ™- The smart excipient: GalenIQ™ combines a multitude of outstanding characteristics and is suitable for a wide range of pharmaceutical applications. galenIQ™ can be used as more than just a bulk excipient. It also serves as an anti-caking agent, anti-humectant, stabilizer or oral care and taste agent to mention just a few additional functions. galenIQ™ (pharmaceutical grade isomalt) is a filler/binder, tablet & capsule diluent, coating agent & it complies with the isomalt monographs of the current Ph. Eur., BP, USP-NF and is approved for use in Japan and China. galen IQ™ is manufactured under cGMP guidelines for pharmaceutical excipients (IPEC-PQG) & under its generic name „isomalt‘, galenIQ™ is listed in all major reference books for pharmaceutical excipients and in the US FDA/CDER Inactive Ingredient Database (www.galenIQ.com).

Physicochemical properties of galenIQ™

Different solubilities, very low hygroscopic, highly resistant against enzymatic and acidic degradation, heat stable; melting range: 145 to 150 °C, no reaction with amino groups, no incompatibilities with API’s faced, unique morphology, equilibrated sweetness, non-carcinogenic.

b. MCC SANAQ®burst: MCC SANAQ®burst consists of 100% pure MCC (with no additional excipients). The fast disintegration is kept even after spheronization and extrusion. It is a unique multifunctional excipient act as binder, filler and superdisintegrant.

c. NEUSILIN: Neusilin® is a synthetic, amorphous form of Magnesium Aluminometasilicate (MAS). It is a multifunctional excipient that can be used in both direct compression and wet granulation of solid dosage forms. Neusilin® is widely used for improvement of the quality of tablets, powder, granules and capsules. Neusilin® does not develop gels with aqueous solutions unlike other magnesium aluminium silicates (www.Neusilin.com). Neusilin® occurs as a fine powder or as granules of Magnesium Aluminometasilicate. Neusilin® is represented by an empirical formula Al₂O₃·MgO·1.7SiO₂·xH₂O. Neusilin® is amorphous, possesses very large specific surface area and has high oil and water adsorption capacity. It is superior in compressibility. It makes hard tablets at low compression force and in addition, at low concentrations can improve the hardness of other
Kanojia, N.
Kaur, L.
Nagpal, M.
Bala, R.

filler and binder excipients. Compounding with Neusilin® helps to stabilize moisture sensitive as well as lipophilic API’s. It is stable against heat and has a long shelf life. It is available in various grades. The grades differ in their bulk density, water content, particle size and pH (Chakraborty et al, 2010).

It is used as excipient for direct compression, oil adsorption of poorly water soluble actives, improves powder flowability, anti-caking agent for hygroscopic powders, stabilization of deliquescent drugs, low friability and less tablet rejections and smaller tablets with relevant hardness.

d. SYLOID® FP Multifunctional excipients: SYLOID® FP silica is efficient in many pharmaceutical applications due to its unique morphology. It has a highly developed network of meso-pores that provide access to the large surface area that defines its performance. The result is a product that is easy to incorporate, providing more uniform dispersion of actives and improved content uniformity and high adsorptive capacity - both for hydrophilic and hydrophobic compounds (Parker et al, 2009).

It act as effective desiccant to increase the stability of moisture-sensitive active pharmaceutical ingredients (APIs), efficient conditioner for powder formulations used in suspensions, capillary wetting agent for better release and disintegration, contribution to the controlled release of active pharmaceutical ingredients and enhanced bioavailability. It is used as glidant, carrier for active ingredients, moisture scavenger/protector and used in tabletting as well as Coating.

e. UNI-PURE™ WG Multifunctional Excipient: The optimum performance of UNI-PURE WG depends on several factors, including the physicochemical properties of the drug, the type of filler and the process used to make granules and tablet. In a given formulation, tablet performance is determinedly processing conditions (www.excipients.com). It Improves solid dosage formulations and simplifies processing, multifunctional excipient swells in cold water for better processing, improves compressibility, wet granulation binder, reduce disintegration time and enhanced tablet properties.

f. Pharmaburst™ “Quick Dissolve”: Pharmaburst is a coprocessed excipient system with specific excipients, which allows rapid disintegration and low adhesion to punch faces. It is also said to be a “Quick Dissolve” delivery system (www.SPIPharma.com). It is highly compactable, high loading in small tablet, smooth mouth feel, standard temperature humidity and cooling, rapid disintegration, uses USP/EP excipients, produced under cGMP, cost effective.
g. **Recombinant Albumin- rAlbumin:** A multifunctional excipient, rAlbumin acts to stabilize the drug product by reducing aggregation, oxidation, and surface adsorption. Particularly valuable for liquid formulations, rAlbumin can significantly decrease the attrition rate in formulation development and provides increased freedom to choose the best candidate for further development. Novozymes has developed a range of recombinant human albumins (rAlbumins) specifically for the pharmaceutical industry. Manufactured in an animal-free process to the highest quality standards, Novozymes’ rAlbumins act as multifunctional excipients. Their use reduces the requirement for multiple excipients, such as SADs, and delivers a safe and consistent product that enhances the stability and performance of the customer’s drug product. The functional properties of rAlbumin as an effective excipient in three areas commonly affecting product stability are: Aggregation, Oxidation and Nonspecific adsorption. It also provides a comparison of the physiochemical properties of a range of commercially available albumins through detailed product analysis (Bharate et al., 2010).

1.6 **High Functionality Excipients (Hfe)**

HFE are inactive ingredients that meet four unique criteria. Firstly, they are multifunctional. They do not perform a single function, like glidants, lubricants, anti-adherents, binders or disintegrants. HFE combine two or more functions through a single ingredient. Secondly, HFE have high inherent functional performance allowing for increased batch sizes and higher drug-loading, even at low usage levels. Thirdly, HFE require no complex processing, making them ideal for direct compression processes. Lastly, HFE impart their high inherent performance characteristics to the overall formulation. This last criterion is critical and separates HFE from other multi-functional excipients or conventional specialty excipients (Zeleznik et al., 2004).

**PROSOLV SMCC (Silicified microcrystalline cellulose):** Silicified microcrystalline cellulose – combines 98% microcrystalline cellulose (MCC) and 2% fumed colloidal silicon dioxide (CSD) in a patented coprocessed intimate mixture. PROSOLV provides significant functional performance and may be utilized in development of unique dosage forms for the branded generic market segment, providing substantial economic benefits with regard to revenue streams (Sherwood et al., 1998). It is accepted by US FDA, high drug loading and gives better flow, compatibility and disintegration.
1.7 Recent Advancements in Synthetic Excipients

a. Starch 1500 (Partially pregelatinized maize starch): Starch 1500 is a unique pharmaceutical excipient combining several properties in a single product. Only Starch 1500 performs the multiple functions of a binder, disintegrant, flow-aid and self-lubricant. It is extremely versatile, being effective in a variety of processing methods for solid oral dosage forms. Starch 1500 also exhibits synergy, enhancing the functionality of other commonly used excipients in formulations (www.colorcon.com). Starch 1500 is manufactured exclusively for the pharmaceutical industry in dedicated cGMP facilities. The process involves a physical modification of the starch (no chemical additives or surfactants are used), resulting in the combined benefits of the soluble and insoluble functionality of Starch 1500. Maize starch is composed of two polymers, amylose and amylopectin which are tightly bound in a specific sphaero crystalline structure. Through partial pregelatinization, the bond between portions of the two polymers is broken, providing Starch 1500 with its unique properties. The process results in partial solubility, increased particle size, improved flow properties and compactibility. Colorcon’s unique manufacturing process results in the most effective functional balance for Starch 1500, providing good cold water binding and granulation properties, yet retaining effective tablet disintegrant properties. The physical structure of Starch 1500 also imparts good compactibility, flow and lubrication capability. These multifunctional properties can be utilized in a variety of applications, including direct compaction, wet granulation, fluid bed granulation and capsule plug formation. The distinct benefits of Starch 1500 can bring significant process flexibility to solid dosage forms.

b. C*Pharm DC 9300 directly compressible starch: C*Pharm DC 9300 combines the two main properties of both pregelatinized and native starch: strong binding and fast disintegration (Michaud et al., 2002). This new directly compressible starch appears as a white free-flowing powder composed of partly gelatinized agglomerated starch granules. One of the other very interesting properties of directly compressible starch is its aptitude to demonstrate synergies with other excipients such as lactose and microcrystalline cellulose. These two products are certainly some of the most widely used excipients in pharmaceutical formulations besides starch (Manudhane et al., 2010). The classification of modified starches is given in Table 3.

c. Captisol (Modified beta cyclodextrin): Captisol® was invented by scientists at the University of Kansas Higuchi Biosciences Center for use
Table 3: Classification of modified starches

<table>
<thead>
<tr>
<th>Type of modification</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Chemical modification (cross-linking, Substitution, Conversion)</td>
<td>Distarch phosphate Starch esters: Acetylated starch, starch phosphate, octenylsuccinate-treated starch. Starch ether: hydroxypropylated starch, carboxy methylated starch, cationized starch etc. Acid converted starch, oxidized starch, bleached Starch. Pyroconversion (dextrinization): dextrin, British gum, etc.</td>
</tr>
<tr>
<td>3. Enzymatic Modification</td>
<td>Maltodextrins, cyclodextrin, amylose etc.</td>
</tr>
</tbody>
</table>

Figure 1: Chemical structure of Captisol (www.Captisol.com)

in drug development and formulation. Captisol® is a patent protected, uniquely modified cyclodextrin, whose chemical structure was rationally designed to maximize safety and optimize interaction to improve the solubility, stability, and bioavailability; to lessen the volatility, irritation, smell or taste. Captisol is a polyanionic beta-cyclodextrin derivative with a sodium sulfonate salt separated from the lipophilic cavity by a butyl ether spacer group, or sulfobutylether (SBE). Captisol is the trade name for CyDex’s SBE7 BETA –CD-preparation. The chemical structure of captisol is shown in Figure 1.
d. Benefits of captisol over parent cyclodextrins

i. Straight forward biodistribution and elimination: Upon administration, the Captisol-drug complex rapidly dissociates. Captisol formulations are biocompatible and can be administered by numerous routes including parenteral and oral route. Captisol exhibits limited plasma protein binding and distributes to extracellular fluid.

ii. Pharmacologically inactive: Captisol produced no pharmacological effect on the cardiovascular system; autonomic or somatic functions; respiratory capacity; or fluid or electrolyte excretion upon I.V. administration in a variety of animal models (www.Captisol.com)

iii. Ease of use: Compared to other drug delivery technologies, Captisol is easy to use in your laboratory. Neutral, cationic and anionic drugs have been effectively complexed by Captisol. In contrast to other solubilisation technologies, the feasibility of Captisol can be rapidly assessed with a few simple experiments.

e. Marketed products using Captisol technology

i. Captisol-enabled® Propylene Glycol-Free Melphalan

a. Ligand’s Captisol-enabled® Melphalan program is a new IV formulation of Melphalan that has the potential to offer multiple advantages for clinicians and patients in the multiple myeloma transplant setting. Ligand’s formulation completely avoids the use of propylene glycol, which is used as a co-solvent in the current formulation of Melphalan (sold as Alkeran® for Injection), and has been reported to cause renal and cardiac side-effects that limit the ability to deliver higher quantities of intended therapeutic compounds. The use of Captisol® technology to reformulate Melphalan is anticipated to allow for longer administration durations and slower infusion rates, potentially enabling clinicians to safely achieve a higher dose intensity of per-transplant chemotherapy (www.Cydexinc.com).

ii. CyDex : Captisol-Enabled Propofol Injectable Solution- New Anaesthetic Formulation

a. The solubility of Propofol in water is low, approximately 0.154 mg/mL. Both marketed formulations are prepared as oil-in-water emulsions, with most of the Propofol being solubilised in the lipid phase. Emulsion formulations are problematic because the lipid components readily support microbial growth. Captisol-Enabled Propofol uses the novel solubilising agent, Captisol® (sulphobutyl ether-ß-cyclodextrin) to provide a true aqueous solution. This formulation minimises the
potential for an allergic reaction, reduces microbial growth potential and eliminates the need for a lipid component in the formulation. The new formulation is fat free with equivalent pharmacokinetics and pharmacodynamics as the currently marketed products (www.Cydexinc.com).

iii. Captisol-Enabled Sertraline oral solution - The First Aqueous Oral Sertraline Solution for the treatment of depression

a. CyDex, Inc., a leader in innovative drug delivery technologies, has developed an aqueous formulation of this widely-used SSRI, Captisol-Enabled Sertraline Oral Solution. It is complexed with Captisol in an aqueous based formulation. Captisol effectively solubilises and taste-masks sertraline HCl in water at the concentration present in the marketed formulation (equivalent to 20 mg/mL sertraline). The Captisol-Enabled formulation is a pleasant tasting solution. Captisol-Enabled® Sertraline oral solution is the first aqueous oral solution of sertraline (www.Cydexinc.com).

iv. CyDex Licenses Captisol® to Proteolix - Promising Oncology Compound

a. CyDex granted Proteolix global rights to Captisol for a formulation of PR-171 – a novel proteasome inhibitor derived from the natural product epoxomicin. PR-171, also known as carfilzomib, is potent on heme tumor cell lines and induces programmed cell death in multiple myeloma cells taken from patients, including those that are resistant to current therapies. The compound is currently in Phase I clinical trials at six leading oncology centres in the United States and Canada. These trials are designed to measure the safety and tolerability of PR-171 in multiple myeloma and lymphoma patients and to describe preliminary evidence of anti-tumor responses (www.Cydexinc.com).

f. Silicones: Silicones belong to broad family of specialty chemicals that is not limited to the well-known cyclomethicone, dimethicone and simethicone. Silicones include volatile liquids and nonvolatile siloxane fluids of different viscosities, as well as siloxane copolymers (emulsifiers), siloxane elastomeric gels and siloxane waxes (Sene et al., 2002). The diversity of these materials is reflected by the variety of benefits provided and the versatility of silicone formulations. Silicone polymers provide a number of unique attributes that are due to their distinct physicochemical properties. As silicone polymers have unique properties, they are used in pressure sensitive adhesive (PSA) applications and as a matrix in transdermal drug delivery systems (TDDS) and wound care. They are also useful as additives in solid dosage forms,
as process aid or hydrophobisation agent for tablets. More recently, a new class of excipient based on silicone has been introduced in topical formulation. Silicones meet the increasing demand of pharmaceutical industry for novel synthetic excipients. Although silicone excipients do not contain preservatives, organic plasticisers, antioxidants, tackifiers or stabilizers (which make their composition simpler compared with other types of polymer), their polymeric structure must be fully characterized to support pharmaceutical use (Sene et al, 2002).

1.8 Recent Patents On Novel Excipients

Joan cucala Escoi published a patent (US20050031862 A1 10, Feb, 2005) entitled modified calcium phosphate excipient. The present invention is based on the discovery that calcium phosphate can be modified with a fatty acid wax and further such a modified calcium phosphate can provide advantageous properties. Accordingly, a first aspect of the invention relates to an excipient composition comprising calcium phosphate modified with a fatty acid wax, wherein a weight ratio of calcium phosphate to wax is within the range of 50:50 to 95:5, respectively. The excipient composition is generally provided in a free flowing particulate form and the fatty acid wax is generally selected from palmitic acid, behenic acid, stearic acid, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil, and mixtures thereof. The particles generally have an average size in the range of 20 to 1000 microns, typically 50 to 500 microns, and in some embodiments from 125 to 250 microns. The calcium phosphate is normally an anhydrous dibasic calcium phosphate (Joan Cucala Escoi et al, 2005).

Gorgegoan published a patent (EP1697050A2, Sep 6, 2006) entitled Fiber rich fraction (FRF) of trigonella foenum-graceumseeds and its use as a pharmaceutical excipient. The present invention relates to a novel solvent free process of obtaining an insoluble fiber rich fraction from Trigonella Foenum-graceum seeds. The invention further relates to the fraction obtained from Trigonella Foenum-graceum seeds, having at least 50% of dietary fiber with a ratio of insoluble dietary fiber to soluble dietary fiber greater than 0.8 and a protein content not more than 10 weight % with a viscosity greater than 10000 cps at 2% w/v concentration. The invention also relates to the process of purifying the fiber rich fraction to obtain a highly purified fiber rich fraction. The invention further discloses use of FRF or highly purified FRF as a pharmaceutical excipient in various pharmaceutical dosage forms (Gorgegoan et al, 2006).

Vincent green published a patent (US 2006/0008521 A1, Jan, 2006) entitled Tablet excipient. This invention relates to a composition comprising physically
modified, partially pregelatinized starch, which is useful as a multi-functional excipient for solid dosage forms, a method of making such composition, and solid dosage forms prepared using the composition. The starch composition according to this invention is a multi-functional excipient, which possesses excellent binding, disintegrating, and flow properties. It is also capable of accelerating drug dissolution from a solid dosage form (Vincent green et al, 2006).

Romain Callaird published a patent (US20110076326, March 31, 2011) entitled modified protein excipient for delayed-release tablet. The present invention relates to the delayed release of molecules when formulated in a compressed tablet that is protein-based of which the protein’s isoelectric point has been modified in order to reduce solubility and swelling. Particularly, the invention relates to tablets that comprise an excipient comprising chemically-modified food proteins such as soy proteins or β-lactoglobulin useful for delaying release of an active ingredient, namely a pharmaceutical drug or a probiotic (Romain Callaird et al, 2011)

Gordon Bardley published a patent (US8226967 B2, July 24, 2012) entitled Surface active proteins as excipients in solid pharmaceutical formulations. The invention provides a method for utilising surface active proteins as excipients in pharmaceutical technology, particularly in galenics. The hydrophobins may be used either by admixture to pharmaceutically utilized polymers and compounds, by incorporation into/formation of a matrix or by coating of galenic forms to achieve a modulation of release kinetics. The pharmaceutical form to be treated with the method according to the present invention can be designated for oral application or other routes of administration (e.g. rectal application). Examples for galenic forms according to the present invention are capsules, pills, tablets, matrix tablets, microgranules and suppositories, but not limited to these (Gordon Bardley et al, 2012).

2 CONCLUSION

The world of excipients has moved well beyond just improving the stability of drugs, to creating a total solution for manufacturers and ultimately, patients. Synthetic excipients represent a versatile class of materials that have been utilized in the development of different pharmaceutical formulations. Coprocessing could hold the key to a successful future for synthetic excipients by ushering in a new class of multifunctional compounds. Excipients can be physically modified to enhance its properties and to improve its performances. It can also be chemically modified to obtain a very wide range of new properties that can play an important role in the formulation of smart drug delivery systems.

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REFERENCES


Retrieved from <URL http://www.colorcon.com>

Retrieved from <URL http://www.Cydexinc.com>


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