Chapter 1

Introduction
INTRODUCTION

1.1. Novel excipients: Role in drug development

1.1.1. Basic purpose of novel excipient

Excipients are pharmacologically inactive substances included in drug products to improve efficiency of drug. They consist of large number of ingredients of natural, semi-synthetic or synthetic origin. They constitute major portion of the drug product or dosage form. In case of very potent drugs, this proportion may exceed 95% of the bulk of the formulation (Bharathi et al., 2013). The entire mechanism of drug delivery system depends on the types and concentration of excipients used in the formulation. They help in processing of formulation and confer stability to it. They also enhance bioavailability, increase specificity and selectivity in drug delivery. Overall, these excipients enhance safety and efficacy of drug leading to better patient acceptability. Novel excipients are new chemical entities manufactured by new innovative technology. They are either synthesized, mixed or co-processed excipients in which, the functionality of two or three excipients can be achieved in a single excipient.

The plain microcrystalline cellulose has poor flow property and poor binding capacity which may lay problem during direct compression of tablet formulation. So to improve the flow property, novel grade of microcrystalline cellulose is used which is called as Avicel PH grade, that provides better flow property to granules during direct compression (Thoorens et al., 2014; Gohel et al., 2012). Tablet formulations require that, the blend of tableting mixture must flow freely from the hopper of tableting machine into the tablet die. For that the blend should have a diluents, disintegrant, binder and lubricant in appropriate proportion. But the novel co-processed excipients in which dibasic calcium phosphate is co-processed with binder and disintegrant, provide the better compressibility and better dissolution properties (Deokar et. al., 2011).

1.1.2. Developing novel excipients: Methods, characterization, regulation

The development of excipients has three main goals;

- To demonstrate the advantage over existing materials for the target application.
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- To establish a reliable manufacturing process that leads to the desired product characteristics.
- To demonstrate the appropriate stability of the new grade.

Now a day, each and every manufacturer is working on the development of novel excipients. But, developing of novel excipients require long development timelines and high cost due to requirement for establishment of safety and efficacy of excipients.

1.1.2.1. Development of novel excipients may be carried out by two different ways:

1.1.2.1.1. Modification carried out on known excipient:

In this method generally some chemical modification is carried out on existing excipients, such as introduction of new functional group or chain enlargement. For example, cellulose can be functionally modified as cellulose acetate, cellulose nitrate, carboxymethyl cellulose and hydroxypropylmethyl cellulose. All these natural or processed excipients like starch and cellulose and the novel excipients which is derived from such natural excipients are also well established in Pharmacopoeia.

1.1.2.1.2. Completely New Excipients:

Novel excipient’s development is substantially similar to the non-clinical development of a new active ingredient. A very high R&D investment and a long development time are required for discovering completely new excipients. Development of novel excipients is the most challenging task for a researcher as many facts are taken into consideration including route of administration, function of excipients, regulatory requirement and the risk assessment. For development of novel excipients, different chemical structure classes (lead) are screened and selected structure optimized for particular characteristic. After that a long process of optimization, trial is carried out to evaluate new excipients moiety. Then, pharmacological and toxicological studies are carried out, which may take several years to establish suitability. In general development and approval of any novel excipient takes about 6 – 8 years.

1.1.2.2. Characterization of Novel excipients:

The novel excipients may be characterized in three ways.

a. Functionality including diluents, solubilizer, glidant etc.
b. Physicochemical property including solubility, pH, viscosity, crystallinity, melting point, optical rotation, specific gravity, assay etc.

c. Safety / Toxicological evaluation as per ICH M4S (R2) guidelines, ADME, chronic and sub chronic toxicity, genotoxicity, carcinogenicity, irritation study, skin allergy etc.

1.1.2.3. **Regulatory requirement for approval of novel excipients:**

As per the FDA and ICH guideline the excipients which is first time used in the human drug product is known as novel excipients. There is no special guideline for approval of any novel excipients. As per the current guidelines novel excipients are not approved independently, it is approved along with the drug dosage form in which it is used. There is no special regulatory approval process is available which can used for novel excipients as new chemical entity. Even ICH guideline which is well acceptable for whole world, does not have any specific guidance for approval of new excipients. Food and Drug administration (FDA) has guideline for safety efficacy approval for new excipients. FDA maintains Inactive ingredient database (IDD) which deals with the use of excipients in defined concentration as per respective dosage form. IDD may also known as IIG. American safety committee proposed and constitutes the IPEC in 2007 which is independent review process for evaluation of novel excipients. FDA guideline for evaluation of safety of novel excipients also cited by the ICH safety-testing guidelines (e.g. ICH S1A, S2B, S3A). ICH M3 guidelines also represent the nonclinical safety study for conducting human trial is also relevant to safety evaluation of novel excipients (Demerlis et al., 2009).

1.2. **Starch**

1.2.1. **Utility as Excipient**

Each day, one way or the other, our life is touched by one of our most plentiful renewable resources, corn starch. The ideal storage form of starch in plant is carbohydrate and it is one of the most important nutritional sources for human being. Apart from the significant role in human nutrition, it has many industrial applications including manufacturing of paper, textiles, pharmaceuticals, biodegradable polymers and additive in foods industry (Forssell et al., 1995; Ambily et al., 2012). Its utility in daily life cannot be overemphasized.
Chemically, it is a polysaccharide and assembled from the simple sugar glucose. Being a natural polymeric system the molecular mass of starch ranges from 50,000 to million.

The molecular structure of starch is formed by several units of glucose which may vary from five hundred to several hundred thousand units joined together by covalent bonds. In general starch constitutes of amylase plus amylopectin. Looking into the constituent of amylose and amylopectin, it can be established that d-glucose residues with \( \alpha-(1\rightarrow4) \) linkages is found in a linear amylose (Fig.1.1) and \( \alpha-(1\rightarrow4) \) linkages and \( \alpha-(1\rightarrow6) \) branch linkages in amylopectin, (Fig.1.2). Both combined in a water-insoluble granule that is partially crystalline and whose size, shape, and morphology are dependent on its biological source. The proportion of amylose and amylopectin in starch depends upon its sources from where they are derived (Singh et al., 2010). The special linkage in starch, results in the formation of a branched structure. This branched structure appears in a pattern to form tree like shape of starch.

![Fig.1.1: Structure of the amylose unit of starch](image_url)
1.2.2. Novelty is lacking in the starch and requirement for modification

In its nascent form it finds limited use in the food industry and pharmaceutical industries. This is because the nascent starch generates rubbery or cohesive paste while heating and on cooling it forms undesirable gels (Abbas et al., 2010). Due to above said reason, the food manufacturers and pharmaceutical sector generally prefers modified and treated starches which poses better behavioral characteristic than those provided by native starches. The properties of starches can be improved by a variety of modifications; few of them are listed here.

1.2.3. Modification of starch lay to improve formulation in drug delivery

There are several examples in which shows that modification of starch helps in improvement in drug delivery. E.g. The nascent starch acts as poor disintigrant while the modification of starch led to form phosphate starch which is the better disintigrant property in comparison to nascent starch (Jubril et al., 2012). The hydrolyzed starch may also acts as a good disintigrant (Lederer and Paganini et al., 2000; Te-Wierik et al., 1997).
Starch has poor gelling characteristic and its gel structure are also not stable so due to this reason it is difficult to form controlled drug delivery with nascent starch. In view to overcome such problem the acetylation and hydroxypropylation was carried out on nascent starch backbone. Thus it forms hydroxypropylated starch (Gon et al., 2002) and acetylated starch (Tuovinen et al., 2003), which are ideal ingredients for formulation of controlled drug delivery dosage form (El Khamsa et al., 2014).

### 1.2.4. Methods of starch modifications

Starch can be modified by following methods (Kavlani et al., 2012):

a. **Physical Methods:** Heat-moisture treatment, annealing, retro-degradation, freezing, ultra high pressure treatment, glow discharge plasma treatment, osmotic pressure treatment and gelatinization.

b. **Chemical Methods:** Etherification, esterification, oxidation, crosslinking and acid treatment.

c. **Enzymatic Methods:** Amylomaltases, break a 1,4 bond between two glucose units to subsequently make a novel a 1,4 bond producing modified starch. Cyclomaltodextrinase, isolated from alkalophilic Bacillus species is used to produce low- amylase starch by modifying rice starch.

Many more methods of starch modification have gained pace in this arena. One such chemical modification based method is co-polymer formation. In this method two or more than two different monomers are united together and are polymerized resulting in formation of co-polymer and process is called as co-polymerization. There are several techniques which are used for co-polymerization, among which graft co-polymerization is one of the unique technique to prepare the co-polymer.

Branched co-polymeric system having different side chain from the main polymeric chain is termed as graft copolymer (Maiti et al., 2010). Grafting is most convenient method for production of graft-copolymer in which the grafting is carried on synthetic or semi-synthetic polymer with natural polymer. By grafting, additional new properties are added to natural polymer with minimum loss of the initial properties of the substrate. Graft polymer has several advantages over natural polymer like its
biodegradability, good swelling property. Apart from these, graft polymeric material has other advantages like

- Heat Resistance (Shi et al., 2012).
- Thermosensitivity (Chen et al., 1996; Zhang et al., 2009).
- pH sensitivity.
- Antibacterial effect (Mizerska et al., 2010; Patil et al., 2012).