Chapter 4: Bioactive and Excipients Profile

4.1: Cholecalciferol (Vitamin D3)

The deficiency of Vitamin D is gaining immense recognition as a serious health concern leading to a variety of health issues (Holick MF, 2012; Hossein-nezhad and Holick, 2012). This vitamin is synthesized in the skin following the exposure of sunlight or this micronutrient can also be obtained from food sources (Hickey and Gordon, 2004). The molecular structure of cholecalciferol is given in Fig. 4.1.

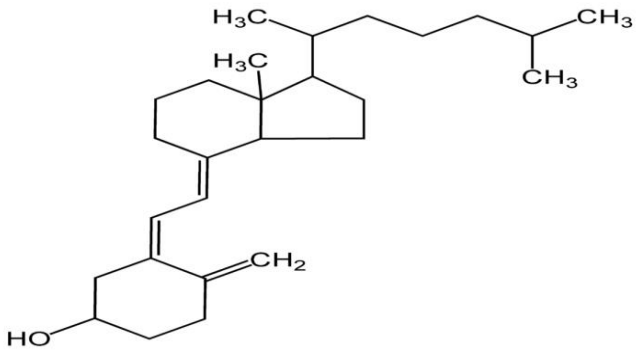

Fig. 4.1: Molecular structure of cholecalciferol

Various physicochemical properties and other aspect of cholecalciferol is given in Table 3.1.

Table 4.1: Physicochemical parameter and other aspect of cholecalciferol

Properties	**Description**
IUPAC name	(1*S*,3*Z*)-3-[(2*E*)-2-[(1*R*,3*aS*,7*aR*)-7*a*-methyl-1-[(2*R*)-6-methylheptan-2-yl]-2,3,3*a*,5,6,7-hexahydro-1*H*-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol
Molecular weight	384.648 g/mol
Molecular formula	$C_{27}H_{44}O$
Physical description	Cholecalciferol appears as fine colorless crystals
Log P	7.5
Melting point	84.5
Solubility	Insoluble in water ($1.3X10^{-5}$ mg/L at 25 ° C), Soluble in the commonly used organic vehicles, slightly soluble in vegetable oils.
Stability	Oxidized and inactivated by moist air within few days.
Optical Rotation	Specific optical rotation (1.6% in acetone): +84.8 deg at 20°C (1.6% in chloroform): +51.9 deg at 20 °C
Protein binding	50-80%

4.2: Excipient Profile

4.2.1 Hydroxypropylmethylcellulose Acetate Succinate (HPMC-AS)

HPMC-AS is a mixture of acetic acid and monosuccinic acid esters of hydroxypropylmethyl cellulose. Hydroxypropylmethylcellulose acetate succinate (HPMCAS), is an important enteric polymer and it is more stable than hydroxypropylmethylcellulose phthalate (HPMCP) (Nakamichi *et al.,* 2004). HPMCAS was originally developed as an aqueous enteric coating polymer. An important property of this polymer is that its dissolution profile at solution of various pH, can be controlled by varying the ratio of succinoyl and acetyl moieties. The structure of HPMC-AS is shown in Fig. 4.2 and its various properties are given in Table 4.2.

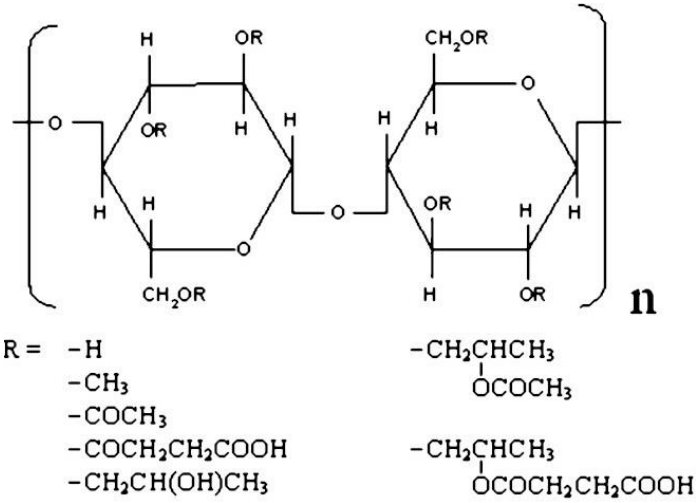

Fig. 4.2: Molecular structure of hydroxypropylmethylcellulose acetate succinate

Table 4.2: Properties of hydroxypropylmethylcellulose acetate succinate

Properties	**Description**
Molecular wight	55000 – 93000 Da
Density	1.27-1.30 gm/cm3
Appearance	white to off-white powder or granules.
Solubility	HPMCAS renders a clear/turbid solution in buffers having pH>4.5 depending on the ratio of acetyl or succinoyl substitution.

4.2.2 Polyvinylpyrrolidone (PVP)

Polyvinylpyrrolidone is commonly explored as a solubilizing agent in oral and injectable preparations. Additionally, there are reports for its application to improve dissolution of active pharmaceutical agents with low aqueous solubility (Iwata and Ueda, 1996). PVP is a synthetic polymer consisting of linear 1-vinyl-2-pyrrolidinone groups, which are having different degree of polymerization leading to polymers with different molecular weights. There are various grades of PVP which exhibited specific viscosity in aqueous medium. Based on this various grade of PVP are categorized as a K-value. PVP exhibited appreciable solubility profile in different organic vehicles and therefore it is of specific importance for fabrication of polymeric system including solid dispersions using solvent evaporation technique. Polyvinylpyrrolidone showed remarkable solubility profile in aqueous medium and it has capacity to augment the wettability of dispersed molecule leading to its solubility enhancement (Walking, 1994; Itai *et al.*, 1985). The molecular structure of polyvinylpyrrolidone is shown in Fig. 3.3 and its various properties are given in Table 4.3.

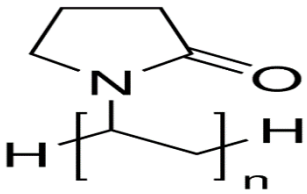

Fig. 4.3. Molecular structure of polyvinylpyrrolidone

Table 4.3. Properties of polyvinylpyrrolidone

Properties	**Description**
Molecular formula	$(C_6H_9NO)n$
Density	1.23-1.29 gm/mL
Appearance	White powder
Solubility	Soluble in water, ethanol, soluble chlorinated hydrocarbons, amines, nitro paraffins. Insoluble in ether.

4.2.2.1 Significance of chain length of polyvinylpyrrolidone

The dissolution profile of a drug is an important parameter influencing the in vivo fate of the molecule and in this regard polyvinylpyrrolidone chain length is critical factor determining the dissolution rate of the drug from the polymeric solid dispersion. Increase in the chain length of polyvinylpyrrolidone retard its water solubility and a high molecular weight polyvinylpyrrolidone is associated with higher viscosity (Walking, 1994). Approximate molecular weight of different grades of PVP is given in Table 4.4.

Table 4.4: Approximate molecular weight of various PVP grades

K-value	Molecular weight
12	2500
15	8000
17	10000
25	30000
30	50000
60	400,000
90	1000,000
120	3000,000

4.2.2.2 Ratio of bioactive molecule to polyvinylpyrrolidone

The ratio of bioactive molecule to polyvinylpyrrolidone affect solubility profile of bioactive molecule and polymeric solid dispersion with grater portion of polyvinylpyrrolidone showed enhanced drug solubility and drug release (Doherty and York, 1989).

4.2.2.3 Safety profile of polyvinylpyrrolidone

Polyvinylpyrrolidones has been traditionally used as plasma expanders since long and with the advent of dextran the role of polyvinylpyrrolidones gradually reduced. However, polyvinylpyrrolidones are commonly explored in the pharmaceutical industry as excipient. Following the oral administration of polyvinylpyrrolidones, their absorption is very limited due to their higher molecular weight and

polyvinylpyrrolidones are regarded as not being toxic. Only minor side effect including the formation of granulomas after intramuscular injection is reported (Walking, 1994).

4.2.3 Poloxamer

The poloxamer polyols represent a range of block copolymers of ethylene oxide and propylene oxide with molecular formula $HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$. Poloxamers are non-ionic polyoxyethylene–polyoxypropylene based polymers which are explored in formulations to improve emulsification or solubilization (Oh *et al.*, 2003; Mata *et al.*, 2005) The polyoxyethylene portion is hydrophilic whereas the polyoxypropylene moity is lipophilic. Poloxamers represent a class of compounds having propylene and ethylene oxides chains. However, they can be differentiated in terms of relative proportion of propylene and ethylene oxides unit which are incorporated in manufacturing stage. The molecular structure of poloxamer is shown in Fig. 4.4 and its various properties are given in Table 4.5.

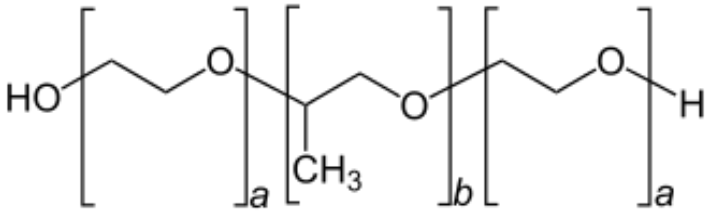

Fig. 4.4. Molecular structure of poloxamer

Table 4.5: Properties of poloxamer

Properties	**Description**
Molecular formula	$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$.
Density	1.06 gm/mL
Appearance	White, waxy, free-flowing granules
Solubility	Generally soluble in water, however, solubility profile is different poloxamer is different.
Application	Poloxamers are explored in a range of formulations given orally, parenterally, and topically. These excipients are considered as safe and non-irritant polymer.

4.2.4 Cremophor EL

Cremophor EL is Polyoxyl 35 castor. The reaction of ethylene oxide with castor oil or hydrogenated castor oil yield polyoxyethylene castor oil derivatives known as Cremophor. Cremophor EL is commonly utilized as emulsifying and solubility enhancing excipient. It is of particular importance for the development of aqueous preparations comprising volatile oils, and lipophilic molecules (Macek TJ, 1963; Webb NE 1976). There are examples of formulations of poorly water-soluble drugs with the application of Cremophor EL and this can be witnessed by the commercial formulation of cyclosporin A, (Ran *et al.,* 2001) paclitaxel (Gelderblom *et al.,* 2001) etc. Various other properties of Cremophor EL are shown in Table 4.6.

Table 4.6: Properties of Cremophor EL

Properties	**Description**
Synonyms	Polyoxyl 35 castor oil, polyoxyethylene 35 castor oil.
Functional category	Emulsifying agent; solubilizing agent
Appearance	It appears as a pale yellow, oily liquid
Specific gravity	1.05–1.06
Viscosity at 25ºC	600–850 cP s
HLB value	12–14
Melting point (ºC)	19–20
pH	6-8
Critical micelle concentration (%)	0.002
Refractive index at 20ºC	1.471

Cremophor EL is utilized in many formulations intended for administration via orally, topically, and parenterally. The toxicity studies (acute and chronic) in animal model have indicated this excipient to be nontoxic. However, there are reports of some side effects in human and animal model after parenteral administration of formulation containing Cremophor EL (Dye and Watkins 1980; Chapuis *et al.*, 1985; Verani R., 1986).

4.2.5 Oleic acid

Oleic acid has been explored in pharmaceutical formulations as an emulsifying agent. Also, it is used as a penetration enhancer in preparations for topical use (Lewis and Hadgraft 1990) and to improve the bioavailability of poorly aqueous soluble molecules in tablet dosage form (Tokumura *et al.,* 1987). In addition, this possesses potential for being used as excipient in capsules, in topical microemulsion formulations (Zhao *et al.,* 2006) and in self-emulsifying formulation for oral use (Quan *et al.,* 2007). This excipient has shown to be involved in the hypoglycemic effect of multiple emulsions comprising insulin for intestinal administration (Onuki Y., 2004). Oleic acid is recognized to functions as ileal 'brake' which causes retardation in movement of luminal stuff through large intestine (Dobson *et al.,* 2002). The molecular structure of oleic acid is shown in Fig. 4.5 and its various properties are given in Table 4.7.

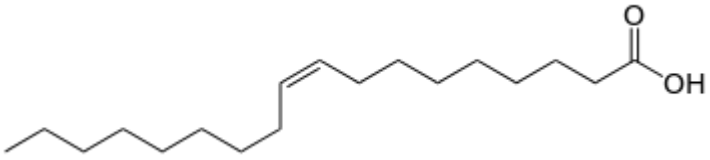

Fig. 4.5. Molecular structure of Oleic acid

Table 4.7: Properties of Oleic acid

Properties	**Description**
Synonyms	Emersol; 9,10-octadecenoic acid; oleinic acid
Chemical Name	(Z)-9-Octadecenoic acid
Functional category	Emulsifying agent; skin penetration enhancer
Appearance	It is a yellowish to pale brown, oily liquid
Specific gravity	0.889–0.895
Acid value	196–204
Melting point (ºC)	13–14C
Solubility	Miscible with ethanol (95%), chloroform and oils but insoluble in water
Acidity/alkalinity (pH)	4.4

4.2.6 Polyethylene glycol (PEG)

Polyethylene glycols are commonly explored in a various oral, parenteral, topical, ophthalmic, and rectal formulations. Also, they find application in polymeric formulations for controlled-release purpose (Mohl and Winter, 2004). PEGs are hydrophilic material which are non-irritant after external application. Their skin penetration capacity is poor and their removal from the skin is easy via gentle, which supports their application in ointment (Hadia *et al.,* 1989) PEGs in water also possess application as suspending aid to modulate the viscosity of other solubilizers. In combination with other emulsifying agent, PEGs find its application in stabilization of emulsion. Liquid PEGs are explored as aqueous miscible vehicle for the bioactive of soft gelatin capsules. PEG with molecular weight of 300 and 400 are widely utilized in the formulation for parenteral administration. PEGs are widely utilized as pharmaceutical aid to augment two important feature including solubility and dissolution of therapeutic agent in solid dispersion-based formulations (Miralles *et al.,* 1982). The molecular structure of oleic acid is shown in Fig. 4.6 and its various properties of PEG 400 are given in Table 4.8.

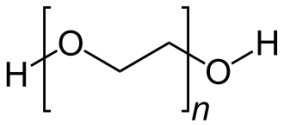

Fig. 4.6. Molecular structure of oleic acid

Table 4.8: Properties of PEG 400

Properties	**Description**
Average molecular weight	380–420
Freezing point (C)	4-8
pH (5% w/v solution)	4-7
Appearance	It appears as clear, colorless or slightly yellow-colored liquids
Density (g/cm3)	1.120
Hydroxyl value	264–300
Viscosity (dynamic) [mPa s (cP)]	105–130