Appendices

EXCIPIENTS PROFILE

A. Cremophor® EL

Nonproprietary Names: Macrogolglycerol Ricinoleate Ph.Eur., Polyoxyl 35 castor oil USP

Synonyms: Cremophor EL, Cremophor ELP, PEG-35 castor oil, polyoxyethylene 35 castor oil

Chemical Name: Polyethoxylated castor oil

Empirical Formula: $C_{47}H_{51}NO_{14}$

Molecular Weight: 853.91

Functional Category: Solubilizer and Emulsifier

HLB: The hydrophilic-lipophilic balance (HLB) lies between 12 and 14.

Applications in Pharmaceutical Formulation or Technology: Polyoxyl 35 castor oil is used as emulsifying agent, solubilizer and permeation enhancer in the formulation of self microemulsifying drug delivery system, microemulsion, nanoemulsion etc.

Description: It occurs as a pale yellow, viscous liquid that is clear at temperatures above 26°C. It has a slight but characteristic odour. The critical micelle concentration (CMC) lies at approx. 0.02%.[1]

Melting point: 19-20°C

Solubility: Soluble in water, Chloroform, Ethanol, Fatty acids and fatty alcohols. Miscible with other polyoxyethylene castor oil derivatives.

Stability and Storage Conditions: It forms stable solutions in many organic solvents such as chloroform, ethanol and isopropyl alcohol; it also forms clear, stable, aqueous solutions. It should be stored in airtight container, protected from light, kept in cool and dry place.

Incompatibilities : Polyoxyl 35 castor oil (Cremophor EL and Cremophor ELP) is incompatible with mercuric chloride as precipitation occurs. Some organic substances may cause precipitation at certain concentrations, especially compounds containing phenolic hydroxyl groups, e.g. phenol, resorcinol, and tannins.

Method of Manufacture : Polyoxyethylene castor oil derivatives are prepared by reacting varying amounts of ethylene oxide with either castor oil or hydrogenated castor oil under controlled conditions. Polyoxyl 35 castor oil is produced in this way by reacting 1 mole of castor oil with 35–40 moles of ethylene oxide.

Handling Precautions: Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended.

Regulatory Status: Included in the FDA Inactive Ingredients Guide (IV injections and ophthalmic solutions). Included in parenteral medicines licensed in the UK. Included in the Canadian List of Acceptable Non-medicinal Ingredients. [2]

B. Capmul MCM C8 EP

Nonproprietary Name: Glyceryl Caprylate

Synonym: Glycerol monocaprylate (type I), Medium chain mono- & diglycerides, Glyceroli monocaprylas

Functional Category : Caprylic and capric mono-diglyceride esters function as very effective carriers and solubilizers of active compounds. Mono-diglyceride medium chain esters are recommended for the dissolution of some difficult compounds such as sterols and have also showed bacteriostatic activity.

Physical state and appearance: Liquid or soft solid, slightly brown in colour.

Description: It is a mono-, diglyceride of medium chain fatty acids (mainly caprylic acid). It is a mixture of monoacylglycerols, mainly mono-O-octanoylglycerol, containing variable quantities of di- and triacylglycerols, obtained by direct esterification of glycerol

with caprylic (octanoic) acid. It meets the requirements of the European Pharmacopoeia Monograph for "Glycerol Monocaprylate" Type I.

Application in Pharmaceutical formulation: Capmul MCM C8 is used as oil phase in the formulation of Self micro emulsifying drug delivery system, microemulsion, nanoemulsion etc.

HLB: The hydrophilic-lipophilic balance (HLB) is 5.

Boiling point: > 227 °C

Storage: Keep away from heat and flame. Keep container closed when not in use. Store in a dry area. Stainless steel storage tanks are recommended. Lined or unlined mild steel drums are suitable.

Storage temperature: (68°F) minimum to (77°F) Maximum

Regulatory Status: Meets the requirements of the European Pharmacopoeia Monograph for "Glycerol Monocaprylate" Type I, Mono- and diglycerides prepared from edible fats and oils or fat-forming acids are generally recognized as safe (GRAS) according to 21 CFR 184.150. [3]

C. Peceol

Nonproprietary Names: Glycerol monooleates (type 40) EP, Glycerol monooleates (type 40) NF

Synonym: Glycerol monooleate

Chemical description: Consists of mono-, di- and triglycerides of oleic ($C_{18:1}$) acid, highly purified diethylene glycol monoethyl ether

Physical Form: Liquid

Viscosity (mPa.s) : 220 (20°C)

Functional Category: Solubilizer for lipophilic APIs and bioavailability enhancer.

HLB: The hydrophilic-lipophilic balance (HLB) is 1.

Formulation techniques and dosage forms: Suitable for hard gelatin and soft gelatin capsules. Suitable for adsorption onto neutral carrier powders for use in tablets, capsule filling and sachets.

Applications in Pharmaceutical Formulation or Technology: Oily vehicle for use in self-emulsifying lipid formulations to obtain a coarse dispersion ie. emulsion (SEDDS) or a fine dispersion ie.microemulsion (SMEDDS). Bioavailability enhancer: increased oral bioavailability is potentially associated with the long chain fatty acids present in its composition and selective absorption of highly lipophilic active pharmaceutical ingredients by the lymphatic transport system reducing hepatic first-pass metabolism. Good solvent for lipophilic active pharmaceutical ingredients.

Regulatory Status:

Safety of use is inferred by GRAS status and precedence of use in approved pharmaceutical products.[4]

D. Transcutol HP

Nonproprietary Names: Diethylene glycol monoethyl ether

Chemical Name: Diethylene glycol monoethyl ether

Viscosity (mPa.s): 4.8 (20°C)

Functional Category: Solvent and powerful solubilizer.

Applications in Pharmaceutical Formulation or Technology:

A highly purified powerful solvent for poorly water soluble active pharmaceutical ingredients. Hydrophilic cosolvent for use in oral self-emulsifying lipid formulations to obtain a coarse dispersion ie. emulsion (SEDDS) or a fine dispersions ie. microemulsion (SMEDDS).

Description: Colorless, slight odour, Hydrophilic cosolvent.

Solubility: Water soluble

Boiling point: >198°C

Safety: Safety of use and low irritancy inferred by numerous toxicological studies and precedence of use in approved pharmaceutical products.[5]

REFERENCES

[1] Technical Information-Cremophor® EL Castor Oil, in, BASF SE - Care Chemicals Division - Pharma Ingredients & Services - 67117 Limburgerhof, 2008, pp. 8.

[2] Polyoxyethylene Castor Oil Derivatives, in: R. C. Rowe, P. J.Sheskey, S.C. Owen (Eds.) Pharmaceutical Excipients, pp. 1516-1531.

[3] Capmul MCM C8, in, Abitec USA, 2017.

[4] Peceol, in, Gattefosse, 2017.

[5] Transcutol-HP, in, Gattefosse, 2017.

PRESENTATIONS AND PUBLICATIONS

Patent Application

1. Piyush K. Mundada, Krutika K. Sawant, **Veenu P. Mundada**, 'Oral Compositions and Processes for Preparing Different Dosage Forms Comprising of Controlled Release Multi Unit Particulate System' Application No. 1625/MUM/2014., Date of filing of application: 12/05/2014, Publication Date : 27/11/2015, Journal No: 48/2015.

Publications

1. **V.P. Mundada** and K.K. Sawant, Enhanced oral bioavailability and anticoagulant activity of Dabigatran etexilate by self micro emulsifying drug delivery system: systematic development, *in vitro*, *ex vivo* and *in vivo* evaluation. J Nanomed Nanotechnol, 2018. 9(1): p. 480.

2. Sawant K.K, **Mundada V.P.**, Patel VJ. Development and Optimization of w/o/w Multiple Emulsion of Lisinopril Dihydrate Using Plackett Burman and Box-Behnken Designs. J Nanomed Nanotechnol. 2017;8:422.

3. Piyush K. Mundada, Krutika K. Sawant, **Veenu P. Mundada.** 'Formulation and Optimization of Controlled Release Powder for Reconstitution for Metoprolol Succinate Multi Unit Particulate Formulation using Risk Based QbD Approach'. Journal of Drug Delivery Science and Technology 41 (2017) 462-474.

4. **Mundada V**, Patel M, Sawant K. Submicron Emulsions and Their Applications in Oral Delivery. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2016; 33.

Poster Presentations

1. Mitali Patel, **Veenu Mundada**, Krutika Sawant. *'Fabrication and Optimization of Solid Lipid Nanoparticles to Enhance Intestinal Absorption and Bioavailability of Lurasidone hydrochloride'* presented poster in 2017 AAPS Annual Meeting & Exposition, held on November 12-15, 2017.

2. **Mundada Veenu** , Mundada Piyush, Patel Mitali, Dr. Sawant Krutika. '*Regulatory and Statutory Hurdles in Development, Approval and Marketing of Generic Drug Product'* presented poster in 3rd Nirma Institute of Pharmacy International Conference on Global Challenges in Drug Discovery, Development and Regulatory Affairs, held on January 21-23, 2016.

3. Piyush K. Mundada, **Veenu P. Mundada**, Krutika K. Sawant. '*Development and Optimization of Controlled Release Multi Unit Particulate Systems (MUPS) of Antihypertensive Drug by QbD Approach*' presented poster in International Conference on Advances in Formulation Development: Challenges and Applications, organised by Faculty of Pharmacy, Parul University, held on March 4-5, 2016.

Conferences/ Seminar/Workshop Attended

1. National Seminar on '*Recent Advances in Dermaceuticals NSRAD-2018'* organized by Faculty of Pharmacy, The M S University of Baroda on January 20, 2018.

2. A Two Day National Seminar & Workshop on '*Optimization and Screening of Variables by DoE- A Science-Driven, Systematic Approach for Drug Formulation Development'*, organized by Sumandeep Vidyapeeth on 17th-18th March, 2017.

3. International conference on '*Global Challenges in Drug Discovery, Development and Regulatory Affairs*' organized by Institute of Pharmacy, Nirma University on 21st -23rd January, 2016.

4. International conference on '*Advances in Formulation Development: Challenges and Applications'* organized by Parul University on 4th -5th March, 2016.

5. UGC sponsored national seminar on '*Fostering Innovations in Pharmaceutical Research: Planning to implementation'* organized by The M S University of Baroda on 20th March, 2015.

6. One day Workshop on "*Enhancing Drug Solubility and Bioavailability using Nanotechnology*" organized by Center of Excellence in Nanotechnology (CoE-NT), Confederation of Indian Industry, Ahmedabad in October 2014.

7. UGC sponsored national seminar on '*Protection of Intellectual Property Rights: Patent or Perish*', organized by Pharmacy Department, The M S University of Baroda on January 4, 2014.