CHAPTER-2

REVIEW OF LITERATURE

2.1 Malaria

Roe *et al.* (2022) highlighted that malaria affects many countries, and it has been reported that the incidence of the disease in 2021 was between 350 and 500 million cases. Over two billion people, around 40% of the world's population, are at risk of malaria. The number of malaria deaths worldwide has been estimated at 1.1–1.3 million per annum in World Health Organization (WHO) reports 2022.

Chan *et al.* (2022) in their report concluded that malaria has a broad distribution in both the subtropics and tropics, with many areas endemic to the disease. The countries of sub-Saharan Africa account for most malaria cases, with the remainder primarily clustered in India, Brazil, Afghanistan, Sri Lanka, Thailand, Indonesia, Vietnam, Cambodia, and China.

Dharmawardena *et al.* (2022) reported that malaria is estimated to cost Africa more than $12 billion annually and accounts for about 25% of all deaths in children under five on that continent. In many temperate areas, such as western Europe and the USA, public health measures and economic development have been successful in achieving near- or complete elimination of the disease, other than cases imported via international travel.

Forgie *et al.* (2022) discussed that *P. falciparum* has exerted more significant selective pressure on human evolution than any other pathogen. Despite *P. falciparum's* presence throughout the tropics, the health impact is far from even, with the large majority of the world's parasitized individuals in Asia and South Asia (reflecting the significant human population) and 90% of deaths occurring in Africa, mostly in children.

Chaudhry *et al.* (2022) outlined the significant features and recent developments in understanding malaria's biology, epidemiology, and clinical consequences that will be critical in developing new approaches for prevention and treatment of malaria.

Al-Awadhi *et al.* (2021) Antimalarial combination therapy, which has been widely explored, involves the simultaneous use of two or more blood schizontocidal drugs with independent modes of action against distinct biochemical targets in the malarial

parasite.

Vashist *et al.* (2016) described that malaria is a life-threatening disease caused by *Plasmodium* parasites transmitted to people through the bites of infected *Anopheles* mosquitoes. Consequently, their investment in antimalarial research is declining, and also increasing resistance to existing drugs coupled with the scarcity of new drugs/drug combinations, the onus of malaria control lies primarily on the wise use of available antimalarials through the design of nanotechnology-based drug delivery systems and combination therapy.

Aditya *et al.* (2013) described malaria as 'bad air,' from the early association of the disease with marshy areas. Towards the end of the 19th century, Charles Louis Alphonse Laveran, a French army surgeon, noticed parasites in the blood of a patient suffering from malaria. Dr. Ronald Ross, a British medical officer in Hyderabad, India, discovered mosquito-transmitted malaria. The Italian professor Giovanni Battista Grassi subsequently showed that human malaria could only be transmitted by Anopheles mosquitoes.

2.2 History of malaria

Oleinikov (2022) underlined that Laveran, a French military surgeon, first observed parasites in the blood of malaria patients, and for that discovery, he received the Nobel Prize in 1907.

Yang *et al.* (2021) outlined that the history of malaria outbreaks goes back to the beginnings of civilization. It is the most widespread disease due to which many people have lost lives and is even thought to have been the cause of major military defeats and the disappearance of some nations. The first descriptions of malaria are found in ancient Chinese medical records of 2700 BC and 1200 years later in the Ebers Papyrus.

Talapko *et al.* (2019) in their research described that malaria is the most widespread African disease. The causative agent of malaria is a small protozoon belonging to the *Plasmodium* species group, consisting of several subspecies.

Macintyre *et al.* (2018) discussed the ancient people frequently faced malaria and its symptoms, the fever that would occur in patients was attributed to various supernatural forces and angry divinities.

2.3 Treatment of malaria

Attama (2011) discussed that WHO has banned monotherapy and recommended a few rational combinations, and the artemether-lumefantrine combination is one of them. The rationale for combining these two antimalarials with different modes of action was to couple the synergistic fast onset of action of artemether with the long duration of action of lumefantrine.

Arshad *et al.* (2022) in their research described that 5artemether is essential for the rapid clearance of parasitemia and immediate resolution of symptoms.

Arora *et al.* (2021) reported that artemether is effective against drug-resistant malaria, and additionally, it reduces gametocyte carriage. However, the drug exhibits a short half-life of 2-3 h. It was combined with lumefantrine, which acts slowly and has a longer half-life. The long-acting effect of lumefantrine may prevent recrudescence and the development of resistance.

Alven & Aderibigbe (2019) discussed artemisinin which is a sesquiterpene lactone isolated from the plant *Artemesia annua L* and its derivatives were initially developed in China. These agents are the most potent antimalarial drugs available today, safe and well-tolerated. These compounds have a very short half-life; thus, a multiple-dose regimen is required to avoid recrudescence and achieve an acceptable cure rate. Artemisinin-based combination therapies are the preferred treatment for malaria today.

Marques-da-Silva *et al.* (2020) discussed that parenteral quinine as an intravenous infusion should be carried out over four hours to avoid cardiotoxicity. Therefore, it is often not a practically suitable treatment. It requires three times daily administration and has several adverse effects, including hypoglycemia, vomiting, headache, and tinnitus.

Lei *et al.* (2020) discussed that artemisinin and its derivatives, dihydroartemisinin (DHA), artesunate, and artemether represent a new class of antimalarial drugs with potent activity against *Plasmodium falciparum.* They also discussed various novel formulations feasible for the treatment of malaria.

Different drugs used for treatment of malaria are given in Table 2.1

Table 2.1: Frequently used drugs for the treatment of malaria.

Drugs with the mode of action	Advantages	Disadvantages	Clinical indications
Chloroquine (CQ) phosphate ✓ Accumulation of the toxic heme in the parasite by preventing the conversion of toxic heme into nontoxic hemozoin ✓ Lysosomotropic	✓ Fast action in RBC stages ✓ High volume of distribution ✓ Oral dosage forms ✓ Very low in toxicity ✓ High bioavailability	✓ Widespread development of resistance ✓ Macular retinopathy ✓ 1–2 months of half-life (long)	✓ Uncomplicated malaria ✓ *P. falciparum* (CQ sensitive) ✓ *P.vivax* (CQ-sensitive) ✓ *P. malariae*
Quinine (QN) sulfate ✓ Accumulation of cytotoxic heme within the parasite by acting on the heme detoxification pathway	✓ Fast action in RBC stages ✓ Oral route formulation ✓ High oral bioavailability ✓ Resistance is uncommon	✓ Less potent than CQ ✓ Cause cinchonism ✓ Hypoglycemia ✓ Serious hematologic disorders ✓ Small therapeutic index ✓ Drug association is needed ✓ Neurotoxicity dose-dependent ✓ i.v. bolus is forbidden	✓ Severe malaria ✓ P. vivax and *P. falciparum* ✓ CQ-resistant uncomplicated malaria ✓ Association with doxycycline, tetracycline, or clindamycin
Artemisinin ✓ Inhibits PfATP6 outside the parasite's food vacuole ✓ Acts as a gametocytocidal and schizontocidal	✓ Safe and well-tolerated ✓ Potent and fast action in blood stages ✓ Gametocytocidal effects ✓ No widespread resistance	✓ Poor water solubility ✓ Unavailable i.v. dosage form ✓ Low bioavailability by oral route ✓ Very short-elimination half-lives ✓ Expensive drug	✓ Severely complicated malaria management ✓ P. falciparum CQ-resistant

Primaquine (PQ) phosphate ✓ It acts by inhibiting the formation of functional transport vesicles in the golgi apparatus ✓ Interference with ubiquinone	✓ The only hypnozoites and transmission-blocking drugs for *P. vivax* and *P. ovale* ✓ Prophylactic action	✓ Must not be used during pregnancy ✓ Limited oral availability ✓ Hemolytic anemia ✓ Methemoglobinemia ✓ Hemolysis in patients with glucose6- phosphate dehydrogenase (G6PD) deficiency	✓ Uncomplicated malaria ✓ *P. vivax* and *P. ovale* (radical cure)
Mefloquine (MQ) ✓ Heme metabolism ✓ Blood schizontocide	✓ Potent action against erythrocytic stages ✓ *P. vivax (*gametocidal)	✓ Causes severe neuropsychiatric reactions ✓ Expensive drug ✓ Long half-life	✓ Uncomplicated malaria ✓ *P. falciparum* malaria ✓ *P. vivax* CQ-resistant ✓ *P. Malariae*
Atovaquone (AT) ✓ Inhibits mitochondrial respiration of the parasite	✓ Used as a prophylactic for treating P. falciparum malaria	✓ Long elimination half-life (50–70 h) ✓ Poor and variable absorption	✓ Uncomplicated malaria ✓ *P. falciparum* (CQ resistant ✓ Chemoprophylaxis

Singh *et al.* (2019) discussed that artemeether is the most researched derivative of this class and is available in parenteral dosage forms. According to the outcomes of the study, the WHO recommended ART as the drug of choice for treating severe malaria in low transmission areas and the second and third trimesters of pregnancy.

Zhang *et al.* (2018) discussed that parenteral or rectal dosage forms are essential for efficient and effective antimalarial treatment in severe malaria. However, parenteral chloroquine is no longer recommended for treating severe malaria because of widespread resistance.

Deshmukh (2023) highlighted that the arteemether-loaded NLCs were characterized, and tested against a cerebral malaria-induced mice model. It has shown better anti-malarial activity in *P. berghei* ANKA-infected C57BL/6 mice without any toxic adverse effects compared with free arteemether.

The potential parameters of artemisinin derivatives are given in Table 2.2.

Table 2.2: Potential parameters of various artemisinin derivatives.

Parameters	Artemisinin	Artemether	ART	Dihydroartemisinin	Artesunate
Water solubility (mg/mL)	1.27	3.16	0.176	3.16	0.678
Log P	2.52	2.52	3.52	2.52	2.35
Log S	-2.4	-2	-3	-2	-2.8
P_{Ka}	-4.4	12.11	-3.9	12.11	3.77
Physiological charge	0	0	0	0	-1
Hydrogen acceptor count	4	5	5	5	7
Hydrogen donor count	0	1	0	1	1
Polar surface charge (Å)	53.99	57.15	46.15	57.15	100.52
Refractivity	68.68	69.91	79.41	69.91	89.95
Polarizibility	29.43	30.02	34.08	30.02	39.46
Number of rings	4	4	4	4	4
Rule of five	Yes	Yes	Yes	Yes	Yes

2.4 Arteether (ART)

Tripathi *et al.* (2021) in their research discussed that ART is preferred rather than artemether because ART would be more lipophilic, and its metabolic breakdown

gives ethanol and not methanol, which would avoid the problems of methanol toxicity that can arise from the metabolic formation of formaldehyde and formic acid. Also, artemether cannot be given alone and the possible combinations of artemether are also discussed in this study.

Kumar *et al.* (2021) emphasized that ART has limitations as it has poor solubility and low bioavailability as 40% of the drug degrades in the stomach. ART falls under the BCS Class II category. As there is a solubility limitation, there is a need to increase the solubility of the drug, which ultimately leads to an increase in the drug's bioavailability. Degradation of the drug in the stomach may be prevented by forming enteric-coated formulations.

Iribhogbe & Emordi (2020) in their study reported the dose regimens of oral and intravenous ART in severe and uncomplicated malaria have been modeled according to the dose response. The study also suggested the amount of dose required to treat the disease. Further, the study highlighted the use of ART other than malaria and the amount of dose required to treat that disease. Although there was considerable inter-individual variation, the lowest oral dose was 2 mg/kg to give the maximum effect. Various routes that can be used to administer ART are also discussed in this study.

Van Baarle *et al.* (2020) highlighted that clinical resistance to artemisinin and its derivatives in malaria parasites collected from patients has not yet been confirmed. Still, specific sporadic reports have claimed clinical failures of artemisinin therapy. In western Thailand, India, and Sierra Leone, a few cases with reduced response were observed and reported for artemisinins.

Singh *et al.* (2019) described ART, which is an oil-soluble ethyl ether derivative of dihydroartemisinin, an efficient erythrocytic schizonticidal drug for treating multi-drug resistant falciparum malaria. It is available as an injection for intramuscular use only. ART shows rapid schizonticidal action and brings about quick clinical improvement in *falciparum* malaria with a low recrudescence rate. It also has some gametocidal action, which aids in cutting down the falciparum malaria transmission.

Q. Li & Pybus (2019) mentioned ART is extensively hydrolyzed to DHA in the gastrointestinal lumen before first-pass metabolism in the gut wall and liver occurs. The pH-dependent hydroxylation rates dictate ART and its metabolite profiles with esterases. *In-vitro,* data have indicated that the $t_{1/2}$ for hydroxylation of ART in the

stomach at pH 1.20 is 10 min.

Nontprasert *et al.* (2019) recommended an oral dose is 4 mg/kg/day of ART in combination therapy corresponding to an intravenous dose of 2.4 mg/kg. The median ART C_{max} occurred within 20 min of injection with an elimination $t_{1/2}$ of 30 minutes. Monotherapy ART treatment should be continued for at least 5 to 7 days to prevent recrudescence, while combination therapy with mefloquine allows ART to be administered over three days or less, with a satisfactory clinical results.

Magbool & Hussein (2018) discussed the pharmacokinetic data of ART and its metabolite DHA in healthy volunteers receiving a single daily oral administration of 200 mg ART for five consecutive days were measured using a liquid chromatography-mass spectrometry method. There were no differences in pharmacokinetic parameters for either ART or DHA between Day 1 and 5. The C_{max} and AUC_{∞} for DHA were 10 times and 20 times higher than those for ART. DHA reached maximum steady-state concentration at two hours ($t_{ss\text{-}max}$) following the dosage, with a short half-life of one hour and a once-dose regimen, while the mean $C_{ss\text{-}max}$ value was 703 ± 94 ng/ mL over five days.

Sheth *et al.* (2018) investigated that the t_{max} was longer convalescent than in acute phase patients (30–60 min) following 200 and 100 mg of ART, respectively. The bioavailability of the pro-drug ART was low (15%), but the relative bioavailability of DHA was high (82%).

Dawre *et al.* (2018) highlighted high solubility of ART in oil and more lipophilic nature, it would also readily cross the blood-brain barrier and effectively control cerebral malaria, primarily caused by parasites' blockade of cerebral microcapillaries.

Gunjan *et al.* (2018) discussed the pharmacokinetics parameters of ART. Absorption of intramuscular ART is rapid, with a maximum concentration of DHA in serum being achieved in less than one hour in most children. The t_{max} of ART following oral administration in healthy adult volunteers varies between an average of 15 min and 39.6 min, and 1.7 h in children with *Falciparum* hyper parasitaemia.

Carrara *et al.* (2009) observed parasite clearance delayed response, associated with a high risk of gametocytaemia. Although the argument is sought that failures in treatment resulted from mefloquine resistance (increased copy number of pfmdr1) compared to artemisinin resistance, caution should be observed that sensitivities to

both drugs are often correlated.

Noedl *et al.* (2008) used 7-day regimen for artesunate therapy (4 mg/kg b.w per day) to explore the potential emergence of artemisinin resistance along the Thai Cambodian border. Out of 60 *P. falciparum* patients, only two were classified as artesunate-resistant and had prolonged parasite clearance time with recrudescence between 21 and 28 days despite adequate drug plasma concentrations. Parasites from these two patients have a fourfold increased IC_{50} to dihydroartemisinin when compared to cured patients. It was evident from this study that clinical resistance of *P. falciparum* to artemisinin does exist.

Chen *et al.* (2003) indicated French Guiana and Senegal, excluding Cambodia, and some parasite isolates with IC_{50} to AMR were observed (30 nM in parasite populations). Reduced artesunate-mefloquine efficacy was reported on the Thai–Cambodian border based on three efficacy trials conducted in Cambodia and Thailand, with 15–20% recrudescence rates.

2.5 Solubility of arteether

Khan *et al.* (2022) described the pH of the solution is regarded as an essential factor in influencing the solubility of a drug depending on the pKa of the drug and hence the chemical structure of the drug molecule. Therefore a buffer solution may be employed to keep the pH value constant to maintain solubility. Changing the temperature of the answer may also affect the solubility of any drug.

Bareford & Swaan, (2007) discussed that ART is insoluble in water (17µg/mL) and 40% of the drug degrades in stomach. It is also more lipophilic than artemether, a possible advantage for accumulation in brain tissues.

Newton & Krishna (1998) represented solubility of a compound depends upon the physical and chemical properties of the solute and the solvent's factors such as temperature, pressure, pH of the solution, and pKa of the solute.

2.6 Solubility enhancement techniques

Khan *et al.* (2022) highlighted that solid dispersion is a collection of solid products manufactured of at least two or more different components; the most usual are a hydrophilic matrix and a hydrophobic drug.

Liw *et al.* (2022) stated that increasing the drug-carrier molar ratio to one-to-three and

one-to-six showed an amorphous FBP constituent in the system. DSC analysis revealed the melting point depression of FBP by the carrier, which signifies interaction between the drug and polymer. The dissolution study showed that the solid dispersion of FBP improves the drug solubility and release compared to the pure drug.

Lalge *et al.* (2022) employed the Flory Huggins theory to compute the interaction parameter and construct phase diagrams. In Soluplus, NIF was shown to be more miscible than FEL. Fourier transform infrared spectroscopy (FTIR) and solid-state nuclear magnetic resonance spectroscopy was used to investigate drug-polymer interactions (NMR). Both drugs reacted with Soluplus through hydrogen bonding interactions, according to findings from spectroscopic analysis.

Kaur *et al.* (2021) reported that fasted condition simulating gastric juice at pH 1.6, the solubility of physical mixture of doxorubicin was increased up to 12 times, while freeze-dried mixtures were enhanced to 15 times.

Sarpal & Munson (2021) prepared solid dispersions of nifedipine (NIF) and felodipine (FEL) as amorphous solid dispersions (ASDs) with an amphiphilic polymer Soluplus and also highlighted the need to consider thermodynamic and kinetic mixing when preparing ASDs to understand phase mixing between drug and polymer. For the two systems, thermodynamic miscibility was investigated using a melting point depression technique.

Dalmat *et al.* (2019) focused on the updated overview of commonly used macro and nano-drug delivery systems and techniques such as micronization, solid dispersion (SD), supercritical fluid (SCF), hydrotropic, co-solvency, micellar solubilization, cryogenic process, inclusion complex formation-based techniques, nanosuspension, solid lipid nanoparticles, and nanogels/nano matrices explored for solubility enhancement of poorly soluble drugs

Pawar *et al.* (2016) conducted research in which they produced solid dispersions of artemether characterized using Fourier transform infrared spectroscopy and differential scanning calorimetry. It was revealed that spray-dried solid distributions exhibit lower crystallinity and dissolving rates. According to solubility experiments, the optimal drug/soluplus ratio was 1:3. In 1.2 pH and 6.8 pH buffers, solid dispersion dissolution experiments revealed more drug release than pure drug. As a result, the author concluded that amorphous solid artemether dispersion might be a better option

for increasing the drug's dissolution.

Santos *et al.* (2021) developed solid dispersions of β-lap using poly (ethylene glycol) (PEG-6000) and polyvinylpyrrolidone (PVP K-30) as hydrophilic polymers and evaluated the dissolution rate in an aqueous medium. Solvent evaporation was used to make solid dispersions with various weight ratios of β-lap and hydrophilic polymer (1:1, 1:2, and 1:3). The dissolving profile of β-lap of paclitaxel as solid dispersions generated in both PVP and PEG was improved *in vitro* dissolution studies, with the former showing better results. The drug: polymer ratio influenced the -lap dissolving rate, with a more hydrophilic polymer resulting in faster drug dissolution.

Ansari *et al.* (2015) prepared solid dispersions of artemether and polyethylene glycol 6000 (PEG-6000) in a ratio of 12:88. Polyethylene glycol 6000, Cremophor-A25, olive oil, Transcutol, and hydroxypropyl methylcellulose (HPMC) in the ratio 12:75:5:4:2:2 was also used to make self-emulsified solid dispersions of artemether. Poloxamer-188 was used instead of Cremophor-A25. The solubility of freeze-dried combinations improved by up to 15 times in group 1, 121 times in group 2, and 135 times in group.

Madgulkar *et al.* (2016) explored the enhancement of solid dispersions with succinic acid utilizing drug-carrier ratios of 1:1, 1:4, 1:6, 1:8, and 1:10 by solvent evaporation and freeze-drying procedures to improve the solubility, dissolution profile, and bioavailability of artemisinin. Solubility was enhanced using the solvent evaporation method, and the maximum solubility was achieved using freeze-dried solid dispersions.

Yuvaraja & Khanam (2014) studied the enhancement of aqueous solubility of carvedilol (CV) by reliable dispersion technique by using a wide variety of carriers such as β- cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD), tartaric acid (TA), polyvinyl pyrrolidone K-30 (PVP K-30) and Poloxamer-407 (P-407). TA enhances cyclodextrin binding effectiveness while altering the microenvironment's pH in the dissolution medium.

Kim *et al.* (2011) described different types of solid dispersions and contemporary techniques for their preparation. Solid dispersions are typically prepared using the solvent technique, melting method, melting-solvent method, solvent wetting, spray drying, freeze-drying, low-temperature melting method, dropping method,

supercritical fluid (SCF) technology, hot-melt extrusion, melt agglomeration process. Solid dispersion technologies can also be applied in industrial production.

Sinha *et al.* (2010) stated that polyvinylpyrrolidone, sugar alcohols, sugars, Poloxamers, cellulose derivatives, polyethylene glycols, and amphiphilic polymers are the most often used hydrophilic carriers for solid dispersion preparations. The efficiency of solid dispersions depends on selecting appropriate excipients with suitable structural and required physicochemical parameters.

Oduola *et al.* (1992) described that ionization technique was employed to boost the drug's apparent inherent solubility.

2.7 Inclusion complexation using cyclodextrin for improved solubility

Utzeri *et al.* (2022) highlighted that the fermentation of carbohydrates undergoes enzymatic degradation, forming a mixture of monosaccharides, disaccharides, and various oligosaccharides, such as linear and branched dextrins and, under certain conditions, small amounts of cyclodextrins or cyclodextrins. Thus, CD production results from the enzymatic action of carbohydrates.

Tannous *et al.* (2021) mentioned that the complex formation between the drug and cyclodextrin improves the drug molecules' physical, chemical, and thermal stability. Including drugs within the cyclodextrin cavity prevents drug molecules' exposure to light, oxygen, water, and the surrounding elements that degrade the drug. Thus this strategy improves the stability of the drug. Few drugs irritate the mucosal linings on the stomach, intestine, eyes, and skin. The complexation of these drugs with cyclodextrin reduces the irritancy by lowering the local exposure of the free drug to the mucosal linings and the skin. The drug is released from the complex and gets absorbed into the body. Thus the local concentration of the free drug is low, thereby reducing the irritation to the mucosa. Incompatibility is the primary concern during the formulation of the dosage form of a drug. The incompatibility can be between two active ingredients or between an active and inactive ingredient. Encapsulation of medicine in cyclodextrin enables the physical separation of medication with the incompatible component, thus tackling the incompatibility issues within the formulations.

Santos *et al.* (2021) represented that the unpleasant odor and taste of the drug decrease patient compliance. The complexation of the drug with cyclodextrin can

mask the drug's undesirable taste and odor. This complexation decreases drug exposure to the saliva and thus hides the drug from the sensory receptors. This results in improving patience compliance as well reduce the drug toxicity. They also discussed that the complexation of drug enhanced the therapeutic effect of the drug.

Wahyuni *et al.* (2017) highlighted that the cyclodextrin's inner cavity is lipophilic due to its lining with skeletal carbons and ethereal oxygen. The polarity of the cyclodextrin cavity is similar to that of the aqueous ethanolic solution, owing to drug molecules entering into this lipophilic cavity of cyclodextrin (Fig. 2.1)

Favuzza *et al.* (2020) reported that CDs consist of glucose monomers arranged in a donut shape ring. Three naturally occurring CDs are α- CDs, β- CDs, and γ- CDs. CDs are useful pharmaceutical excipients made up of carbohydrates as the structural units. The three derivatives of cyclodextrin with their different use and the physical properties of all the derivatives is also discussed in the study.

Bautista *et al.* (2012) mentioned the enzymatic degradation of starch by cyclodextrin glycosyltransferase (CGT) produces cyclic oligomers. The study also emphasized that CDs are non-reducing, crystalline, water-soluble, cyclic oligosaccharides. Also, CD and its derivatives are useful in enhancing the drug solubility as well permeability by encapsulating drug in their cavity. Table 2.3 shows the physicochemical properties of different derivatives of CDs.

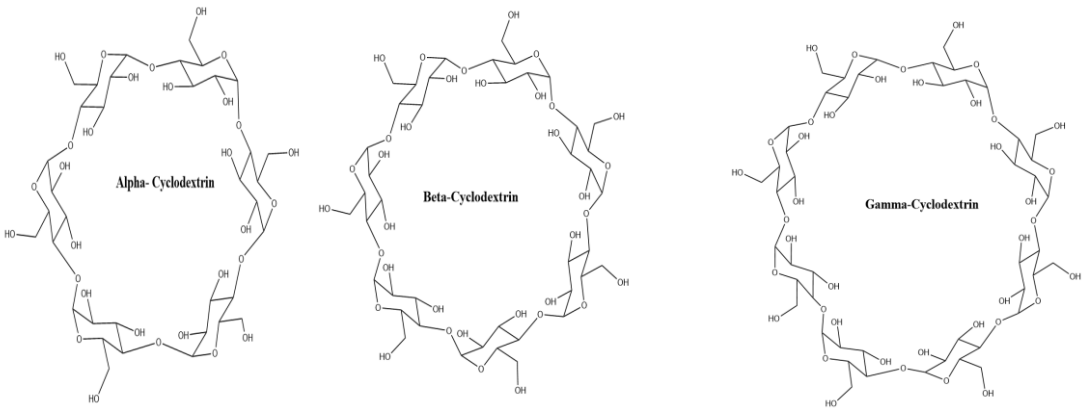

Figure 2.1: Chemical structures of alpha, beta, and gamma cyclodextrins.

Table 2.3 Physicochemical properties of three main types of cyclodextrins.

Types	α- CD	β- CD	γ- CD
No glucopyranose unit	Six	Seven	Eight
Cavity size	174Å (104 mL)	262 Å (157 mL)	427Å (256 mL)
Solubility in water (%w/v)	130	18.4	249
Uses	Used in the food industry as the soluble fiber	Improves solubility, bioavailability, and physical and chemical stability	Used as adjuvant, carrier, solvent stabilizer

Leemhuis *et al.* (2010) underlined that besides characteristics of CD, it also aids in handling the liquid drug by converting it into microcrystalline powders, reducing incompatibility between different medications and equally between drugs and excipients. In addition, it masks the taste and smell and diminishes ocular and gastrointestinal irritations. CDs cyclic oligosaccharide holds the drug molecule inside its cavity, called the formation of inclusion complex. The pharmaceutical applications of CD are highlighted in Fig. 2.2.

Viguera *et al.* (2001) highlighted that the altered properties include protection of the drug from the light and oxygen of photosensitive and oxygen-sensitive drugs, respectively, altering the chemical reactivity, enhancing solubility, masking odor, and taste, protecting against microbial degradation, etc.

Szejtli (1998) highlighted that the CD is a cyclic oligosaccharide, is a truncated cone with a hydrophobic exterior surface and a hydrophilic inner cavity where the drug molecules can occupy. The drug molecules interact with the CD within the cavity, forming an inclusion complex. Furthermore, the interaction between the drug and cyclodextrin is noncovalent and is more advantageous than the drug alone.Different derivatives of cyclodextrin with their application in drug delivery systems in enhancing solubility and bioavailability are illustrated in Table 2.4.

Table 2.4: Different cyclodextrin used for enhancement of drug water solubility.

Drug	pKa	Log P	Water solubility	Fold enhancement in solubility	Complex formation method	Dose (mg)	CD: Drug	CD type	Binding constant	Reference
Aceclofenac	4.7	2.17	-	-	Kneading	100 mg	1:1	HP-β-CD	-	(Rao *et al.*, 2010)
Acyclovir	2.27	-1.56	1.62 mg/mL	-	-	200 mg	10:1	HP-β-CD	-	(Zielenkiewicz *et al.*, 2010)
Amisulpride	9.37	1.10	16.89 µg/mL	3.74	Kneading	200 mg	1:1	γ-CD	1166.65	(Negi & Singh, 2013)
Artemether	4.8	3.02	-	1.8	Freeze-drying	20 mg	1:1	HP-β-CD	220	(Yang *et al.*, 2009)
Albendazole	10.26	2.7	1.37 µg/mL	53.4	Physical mixture	200 mg	1:1	β-CD, HP-β-CD	1266	(Moriwaki *et al.*, 2008)
Atorvastatin	11.82	5.7	20.4 µg/mL	-	Freeze drying	80 mg	1:1	β-CD	-	(Palem *et al.*, 2009)
Amiodarone	8.47	7.57	0.2-0.5 mg/mL	-	Freeze drying	200 mg	1:1	β-CD	1957	(Riekes *et al.*, 2010)
Cefdinir	3.2	-0.2	0.46 mg/mL	-	Kneading	300 mg	1:1	HP-β-CD, β-CD	-	(Aleem *et al.*, 2008)
Colchicine	1.85	1,3	45 µg/mL	-	-	1 mg	-	HP-β-CD	0.31	(Chauhan *et al.*, 2013)
Chloramphenicol	5.5	0.7	2.5 mg/mL	2.24	Co-evaporation	250 mg	1:1	(2,6,-di-o-methyl)-β-CD	493	(Shi & Zhou, 2011)
Darifenacin	9.2	4.5	2.98 mg/mL	-	Co-evaporation	7.5 mg	1:1	HP-β-CD	465.301	(Shi & Zhou, 2011)
Daidzein	7.39	2.51	0.15 mg/mL	9.4	Freeze drying	-	1:1	HP-β-CD	-	(Borghetti *et al.*, 2011)
Docetaxel	12.02	2.4	0.0019 mg/mL	5000	-	20 mg	1:33	M-β-CD	-	(Mazzaferro *et al.*, 2012)
Etodolac	4.65	2.5	16 µg/mL	-	Freeze drying	400 mg	-	HP-β-CD	-	(Ibrahim *et al.*,

										2010)
Flurbiprofen	4.22	3.8	10.45 µg/mL	15	-	50 mg	1:1	β-CD	-	(Li *et al.*, 2010)
Fenofibrate	-	5.3	5.5 µg/mL	20.53	Spray-drying	120 mg	1:1	HP-β-CD	124.60	(Bhise & Nand, 2013)
Fexofenadine	13.2	5.6	3.6 mg/mL	-	-	180 mg	1:1	β-CD, HP-β-CD	1139, 406	(Al Omari *et al.*, 2007)
Gliclazide	5.98	2.6	55 mg/mL	20.31	Kneading	80 mg	2:1	β-CD	691.45	(Hiremath *et al.*, 2008)
17-α-Hydroxy progesterone	17.6	3.17	6.48 µg/mL	-	Co-evaporation	-	2:1	HP-β-CD	-	(Manosroi *et al.*, 2008)
Isoquercitin	-	2.92	5.6 mg/mL	12.3	-	200 mg	1:1	DM-β-CD	783	(Wang *et al.*, 2009)
Itraconazole	3.7	5.66	~1 ng/mL	12	-	100 mg	2:1	HP-β-CD	-	(Taupitz *et al.*, 2013)
Josamycin	13.5	3.47	0.35 mg/mL	13.14	Co-precipitation	-	1:1	γ-CD	3060	(El Harti *et al.*, 2012)
Meloxicam	4.08	1.9	7.15 µg/mL	-	-	15 mg	1:1	β-CD	-	(Snor *et al.*, 2009)
Naringenin	9.46	2.47	475 µg/mL	400	-	-	1:16	HP-β-CD	-	(Kim *et al.*, 2011)
Nifidepine	≤ 1.01	2	7.12 µg/mL	395.36	Freeze drying	90 mg	1:1	β-CD	139.23	(Jagdale *et al.*, 2012)
Omeprazole	4.77	2.23	82.3 µg/mL	-	Freeze drying and spray drying	40 mg	1:1	M-β-CD	77.4	(Figueiras *et al.*, 2007)
Oxaproxin	4.3	3.7	-	60	Co-grounding	600 mg	1:1	RandomLy M-β-CD	2340	(Maestrelli *et al.*, 2011)
Piroxicam	6.3	3	23 µg/mL	-	Supercritical carbon dioxide	20 mg	2:1	β-CD	-	(Sauceau *et al.*, 2008)
Repaglinide	4.01	3.97	34 µg/mL	-	-	2 mg	1:1	HP-β-CD	377.4	(Nicolescu *et al.*, 2010)
Rapamycin	13.37	4.3	2.6 µg/mL	61	Freeze drying	2 mg	1:1	M-β-CD	579	(Abdur Rouf *et*

										al., 2011)
Rhein	4.55(acidic)	3.13	<0.1 mg/mL	-	-	-	1:1	HP-β-CD	350	(Petralito *et al.*, 2009)
Rofecoxib	19.7	3.2	-	-	Kneading	-	1:1	β-CD	769	(Rawat & Jain, 2003)
Rifampicin	8.25	2.7	1.4 mg/mL	22	-	300 mg	1:1	RandomLy M-β-CD	73.4	(Tewes *et al.*, 2008)
Rutin	8.45	0.15	0.125 mg/mL	-	-	500 mg	1:1	HP-γ-CD	405.3	(Nguyen *et al.*, 2013)
Raloxifene HCl	9.55	5.2	0.25 µg/mL	-	Kneading	60 mg	1:1	HP-β-CD	4.59	(Patil *et al.*, 2013)
Tadalafil	15.17	1.7	~2 µg/mL	-	Freeze drying	20 mg	5:1	HP-β-CD, DM-β-CD	-	(Badr-Eldin *et al.*, 2008)
Telmisartan	4.45	7.7	0.09 µg/mL	-	Physical mixture	80 mg	1:1	β-CD	644.56	(Sangwai & Vavia, 2013)
Vanillin	7.78	1.21	10 mg/mL	-	Freeze drying	-	1:1	β-CD	5.3	(Karathanos *et al.*, 2007)
Valdecoxib	9.8	3.2	10 µg/mL	-	Kneading	-	2:1	HP-β-CD	1.63	(Rajendrakumar *et al.*, 2005)
Sulfamethoxazole	5.8	0.7	610 µg/mL	-	Co-precipitation	160 mg	1:1	β-CD	122.3	(Özdemir & Erkin, 2012)

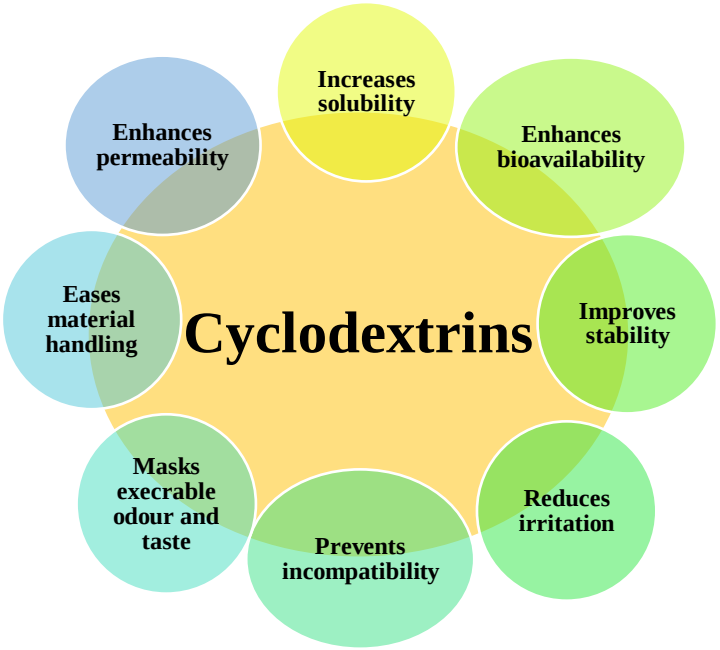

Figure 2.2: Pharmaceutical and biopharmaceutical applications of cyclodextrins.

Anderson (2011) highlighted that characteristic features of cyclodextrins and their derivatives make them potential candidates in agriculture, analytical chemistry, food technology, and the pharmaceutical industry. CD encapsulates the drug molecule within the cavity-forming an inclusion complex with the aid of interactions of the functional groups.

Dinge & Nagarsenker (2008) stated that these inclusion complexes is hydrophobic inside and hydrophilic outside, the drug within the cyclodextrin cavity. This results in little or no exposure of drug molecules to the aqueous environment making it a water-soluble drug-cyclodextrin complex (Fig. 2.3).

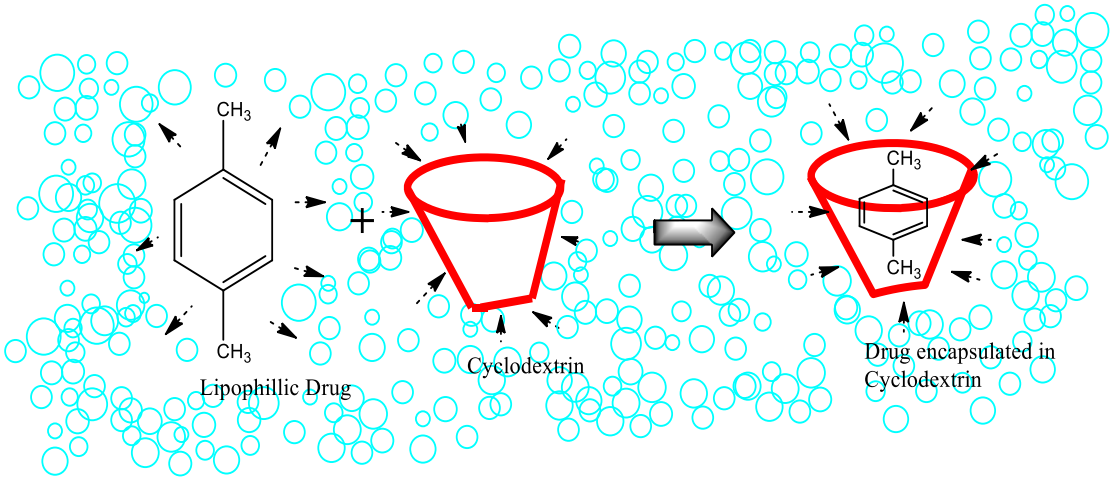

Figure 2.3: Enhanced aqueous solubility of drugs by complexation with CD.

Welliver & McDonough (2007) underlined that the most of the drugs have poor bioavailability due to their poor aqueous solubility (Fig. 2.4). For better absorption of a drug molecule, it should be released from the dosage form and be in the dissolved form When the drug forms a complex with cyclodextrin, its aqueous solubility is enhanced due to its masked hydrophobicity and increased absorption rate. It also improves the percutaneous and rectal absorption of drug molecules and thus aids in enhancing bioavailability. In addition, cyclodextrin abrupt the crystallization of drug molecules by preventing the self-assemble of the drug molecule into a crystal lattice.

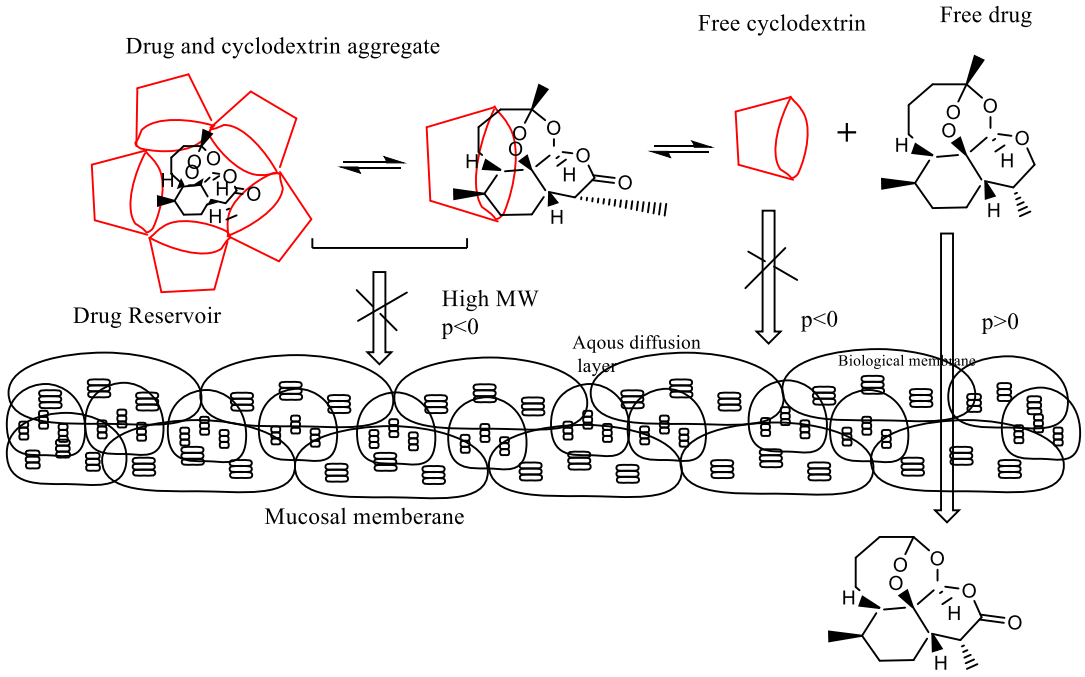

Figure 2.4: Drug permeation from cyclodextrin complexation through a biological membrane.

2.8 Nano-formulations for solubility enhancement

Qiao *et al.* (2022) highlited that the poor pharmacokinetic profile of drugs effective against specific diseases due to water solubility and toxicity and low bioavailability limits their use in related pharmacotherapy; however, nano-carriers are valuable tools that can help improve this problem in the pharmacokinetic profiles of drugs (Fig. 2.5).

Lu *et al.* (2022) described that nano-carriers are a proposition in malaria diagnosis and treatment as well as in vaccine formulations. An important factor in developing drug resistance in Plasmodium strains is the ineffective and non-rational use of pharmaceutical dosage forms of antimalarials. Nanotechnology-based systems thus

provide a better solution and afford an improved therapeutic outcome by drug targeting the specific site of action. Systematic development of drug resistance in malaria parasites also results from administering low drug concentrations when the parasitic count is high.

Carcaboso *et al.* (2003) highlighted that nanotechnology potentially restores the use of old drugs which were relatively toxic by varying and modifying their bio-distribution and thereby minimizing their toxicity. This is particularly advantageous in malaria therapy since novel dosage forms developed for delivering drugs to specific sites, i.e., parasite-infected cells, are urgently needed, especially for the antimalarials in clinical use. Various novel nano-formulations with its advantages and limitations are demonstrated in Table 2.5.

Table 2.5: Different nano-formulations with their advantages and disadvantages

Type of nano-carriers	**Advantages**	**Limitations**
Liposomes	Both hydrophilic and hydrophobic drugs can be carried, highly stable, biodegradable, non-toxic, can be administered by parenteral and cutaneous routes, enhanced therapeutic index, possibilities of surface functionalization	Highly expensive, short half-life, encapsulated drugs may leak into the systemic circulation
Polymeric nanoparticles	Biocompatible, affordable, avoid reticular endothelial system, flexible for ligand specific interaction, avoids leakage of the drug	Difficult to scale up
Solid lipid nanoparticles (SLNs)	Biocompatible, easy to scale up and sterilize, highly stable, can be administered by oral, parenteral, and cutaneous routes, avoidance of organic solvents, encapsulation of both lipophilic and hydrophobic	Drug loading efficacy is low, and chances of initial burst and drug explosion due to its crystalline structure, short half-life, and

	drugs	surfactant toxicity
Nanostructured lipid carriers (NLCs)	Improved stability and drug loading compared to SLNs, long shelf life, easy scale-up and sterilize	Toxicity related to surfactant
Nanoemulsions, SNEDDS	Easy to prepare, long shelf life, both lipophilic and hydrophobic drugs can be carried, used for oral, parenteral, and cutaneous routes of administration, thermodynamically stable, can be sterilized by filtration	Huge amount of surfactants are used, hence causing a risk of toxicity.
Metallic nanoparticles	Antibacterial, highly stable, and uniform in structure	Toxic adverse reactions

2.9 Solid Lipid Nanoparticles (SLNs)

Scioli *et al.* (2020) highlighted that SLNs are enticing formulation scientists globally owing to their benefits such as cost and safety compared to other colloidal nanoparticles (liposomes, emulsions, and polymeric nanoparticles). In SLNs, the matrix is a composition of high-melting solid lipids, different from the liposome and emulsion, where the vesicles and droplets are made up of low-melting phospholipids and liquid oil, respectively.

Rajpoot (2019) suggested that SLNs offer unique characteristics such as small size, large surface area, high drug loading, and the interaction of phases at the interfaces, and are attractive for their potential to enhance the activity of nutraceuticals, pharmaceuticals, and other materials. Lipid-based formulations can decrease drug toxicity and improve bioavailability due to their unique physiological and biodegradable properties. Dihydroartemisinin SLNs have shown enhanced anti-plasmodial activity *in vitro* (IC_{50} 0.25 ng/mL) and *in vivo* (97.24% chemo suppression at 2 mg/kg/day).

Mirchandani *et al.* (2021) prepared primaquine-loaded SLNs by a modified solvent emulsification evaporation method based on a water-in-oil-in-water (w/o/w) double emulsion with the aim to limit the severe toxic events (hematological and gastrointestinal) induced by primaquine. Primaquine-loaded SLNs has 20% more efficacythan conventional oral dose and at the dose of 2 mg/kg/ day, has effectively

treated (chemo suppression of 93.5%).

Mendoza-Muñoz *et al.* (2021) reported SLNs-encapsulated lumefantrine and artemether have shown enhanced efficacy and safety with high clearance of parasitemia and no report of recrudescence. Transferrin-conjugated SLNs encapsulated quinine dihydrochloride has also been formulated for effective delivery to the brain to treat cerebral malaria. The solubility and bioavailability of artemisnin derivatives enhanced by SLNs are highlighted in Table 2.6.

Table 2.6: The solubility and bioavailability of artemisinin derivatives are enhanced by SLNs.

Artemisinin derivatives	Application	References
ART	Improves antimalarial activity, increases relative bioavailability	(Dwivedi *et al.*, 2014)
Artemether	Enhance antimalarial activity	(Joshi *et al.*, 2008)
Artemisinin	Affect tubulovasicular network, antimalarial activity	(Zhu *et al.*, 2022)
Artemether	Improve sustain release	(Jain *et al.*, 2015)
DHA	Enhanced stability, improved efficacy by 24%	(Omwoyo *et al.*, 2015)
ART (anticancer)	Enhanced solubility	(Khatri *et al.*, 2019)
ART	Enhanced bioavailability	(Chadha *et al.*, 2012)

2.10 Nanostructured Lipid Carriers (NLCs)

Bajwa *et al.* (2022) prepared NLCs drug delivery system to enhance the solubility and bioavailability of ART. The Pharmacokinetic parameters of optimized formulation enhanced the oral bioavailability to 18.45%.

Gujjari *et al.* (2022) reported NLCs were principally deliberated for the delivery of parasite epidemiology and control lipophilic drugs but their appropriateness for hydrophilic drugs is now well documented. NLCs are extensively explored and gaining importance due to their unique characteristics like biological compatibility, non-toxic, and non-immunogenic nature.

Salvi & Pawar (2019) reported that NLCs were encapsulated, synthesized, characterized, and tested against the *P. berghei*-infected rodent malaria model.

Artemether-loaded NLCs have shown protection in malaria-induced mice models with enhanced oral bioavailability compared to free artemether.

Rashidzadeh *et al.* (2019) highlighted that the NLCs-loaded curcumin had been formulated and characterized for overcoming the problems (poor bioavailability, enhanced metabolism, and chemical instability) associated with free curcumin. NLCs-loaded curcumin has shown a better anti-plasmodial effect against *P. berghei*-infected mice compared to free curcumin.

Prabhu *et al.* (2016) reported that NLCs-encapsulated artemether-lumefantrine was prepared to improve oral efficacy and bioavailability using the microemulsion template technique. NLCs-encapsulated artemether-lumefantrine treatment (16 mg artemether and 96 mg lumefantrine, given once a day at 1/5 of the therapeutic dose) had shown complete clearance of parasitemia and a 100% survival rate in *P. berghei* infected mice.

Fang *et al.* (2013) described that lipid nanocarriers are introduced as an alternative to emulsions, liposomes, and polymeric nanoparticles. Additionally, nanostructured lipid carriers (NLCs) are the second-generation lipid carriers established to correct the complications accompanying with SLNs and are utilized in numerous therapeutic applications.

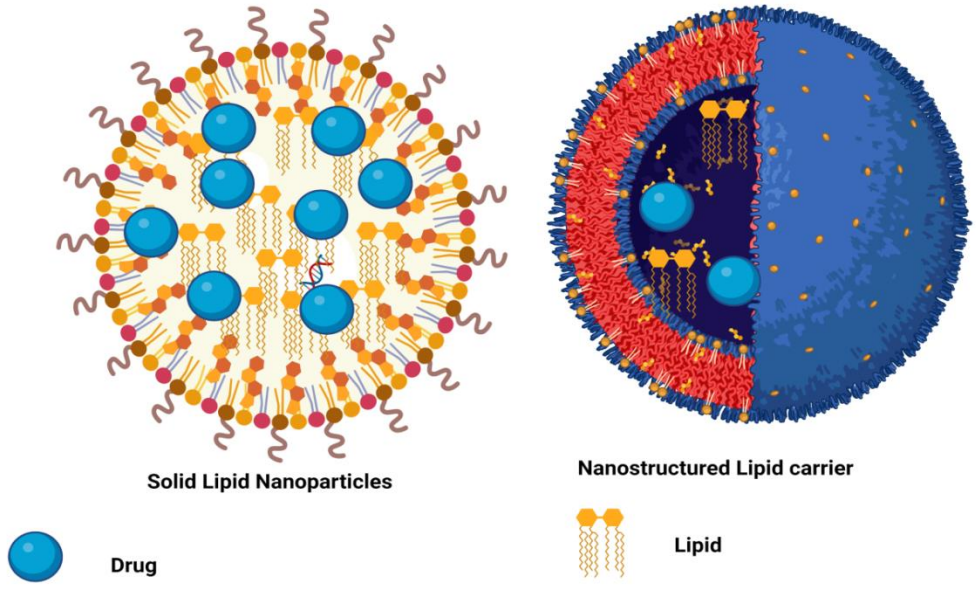

Figure 2.5: Schematic representation of solid lipid nanoparticles and nanostructured lipidic carriers.

The advantages and disadvantages of different nano drug delivery systems are illustrated in Table 2.7.

Tables 2.7: Merits and demerits of nanocarriers

Type of Nanocarrier	Merits of nanocarriers	Demerits of nanocarriers
Liposomes	Ease of manufacture. Biocompatibility of lipids. Can incorporate both hydrophilic and lipophilic drugs. Controlled release.	Susceptible to physical instability. Polymorphic changes due to lipid crystallization. Variable distribution kinetics. Rigid membrane.
FLVs and EEVs	Biodegradability and low toxicity. Ease of manufacture. Soft and malleable nature. High membrane flexibility. Targeted delivery can be achieved.	Prone to oxidative degradation. Phospholipids are expensive. Use to surfactants.
Nanoparticles (SLNs & NLCs)	Made up of biodegradable materials like lipids and oils. Multiple preparation methods. Avoid the immune system owing to their nano size. Both hydrophilic and lipophilic drugs can be incorporated. High drug loading.	Scale-up is the concern. Costly procedures. Toxicity is the primary concern due to the small size.

2.11 Self Micro Emulsifying Drug Delivery Systems (SMEDDS)

Khan *et al.* (2019) highlighted that the primaquine acts precisely on the liver stage parasites (pre-erythrocytic schizonts) and causes relapse after proliferation; nonetheless, this compound's main disadvantage is lower blood dissolution to achieve a therapeutic effect. To overcome these drawbacks, primaquine oral lipid nanoemulsion (10–200 nm particle size) was successfully prepared to target relapsing malaria. The liver freely absorbs primaquine by>45% more than previously

artemether nanoemulsions.

Puttappa *et al.* (2017) reported that the artesunate and quercetin capsulated self emulsifying drug delivery systems were successfully prepared and tested in preclinical models for their bioavailability, safety, and efficacy. As observed from pharmacokinetic experiments, these formulations showed higher oral bioavailability in Wistar rats, and enhanced parasite clearance was observed in *P. berghei*- infected Swiss mice without showing any toxic side effects.

Kumar & Seth (2013) highlighted that the emulsomes (nanoemulsions) are novel colloidal nanocarriers. An internal solid fat core is surrounded by a phospholipid bilayer and is stabilized by a high concentration of lecithins in the form of oil/water emulsion. Formulating emulsions is easy and advantageous in encapsulating aqueous and fat-soluble drugs.

Borhade *et al.* (2012) represented that these emulsomes are commonly prepared by emulsion solvent diffusive extraction or melt expression method. Also the study indicated that the clotrimazole nanoemulsions effectively cleared the blood-stage parasites in *P. berghei*-infected Swiss mice with enhanced efficacy and safety

Laxmi *et al.* (2015) mentioned that the nano-emulsion was formulated by ultrasonication using the internal oil phase (artemether dissolved in coconut oil and span 80) and external aqueous phase (tween 80 and ethanol in H_2O) and tested for *In - vivo* oral bioavailability. Artemether nanoemulsions showed 2.6 times higher oral bioavailability than free artemether, as noticed from pharmacokinetic experiments

Jain *et al.* (2012) highlighted that the nanoemulsions consisting of artemether-curcumin were formulated by an aqueous titration technique to target cerebral malaria via the olfactory delivery system to reach the brain. These nanoemulsions showed promising results in the *P. berghei* ANKA-infected murine model of cerebral malaria

Cole *et al.* (2008) listed the liquid/semisolid lipophilic vehicles compatible with hard capsules. The simple process of manufacturing; convenience for low-dose high potency drugs with high drug loading potential (approximately 50%) are the few advantages of capsule filling.

Caliph *et al.* (2000) highlighted that the administration of lipophilic drugs with lipids stimulates lymphatic transport and enhances drug absorption into the portal blood compared to non-lipid systems. mentioned that the oral bioavailability of a drug may

be altered by changing the bio-pharmaceutical properties like increased dissolution rate and solubility in the intestinal fluid, protection against chemical and enzymatic degradation in the oil droplets, and lipoproteins formation that promotes lymphatic transport of highly lipophilic drugs; hence it is noteworthy that lipids (triglycerides) affect the oral bioavailability of drugs concerning these points.

2.12 EXTRUSION/ SPHERONIZATION

Xu *et al.* (2021) reported that the formulation of pellets exhibits sustained-release controlled-release delivery systems. The study also described the quality of pellets as highly influenced by the process parameters associated mainly with the extrusion stage. Parameters such as morphology, size distribution, porosity, sphericity, etc. affect the release profile and stability of pellets, while the formulation parameters such as presence and absence of soluble or insoluble fillers, surface-active agents, pH adjusters, drug load, the ratio of filler and drug influences release profile.

Tang *et al.* (2008) mentioned the simplest and most commonly used technology for encapsulating liquid/semisolid formulations (for the oral route) is capsule filling. It has an osmotic layer, which expands when in contact with water and pumps the drug formulation via an orifice in the soft/ hard capsule. The compatibility between the capsule shell and excipients is a significant consideration in capsule filling.

Iqubal *et al.* (2015) highlighted that the extrusion spheronization is multiple processes of wet mass extrusion followed by spheronization to produce uniform size spherical particles, called spheroids, pellets, beads, or matrix pellets depending upon the material as the process used for extrusion spheronization. This technique can overcome limitations related to bioavailability and site-specific drug delivery. They also mentioned the simplest and most commonly used technology for encapsulating liquid/semisolid formulations (for the oral route) is capsule filling. It has an osmotic layer, which expands when in contact with water and pumps the drug formulation via an orifice in the soft/ hard capsule. The compatibility between the capsule shell and excipients is a significant consideration in capsule filling (Fig. 2.6).

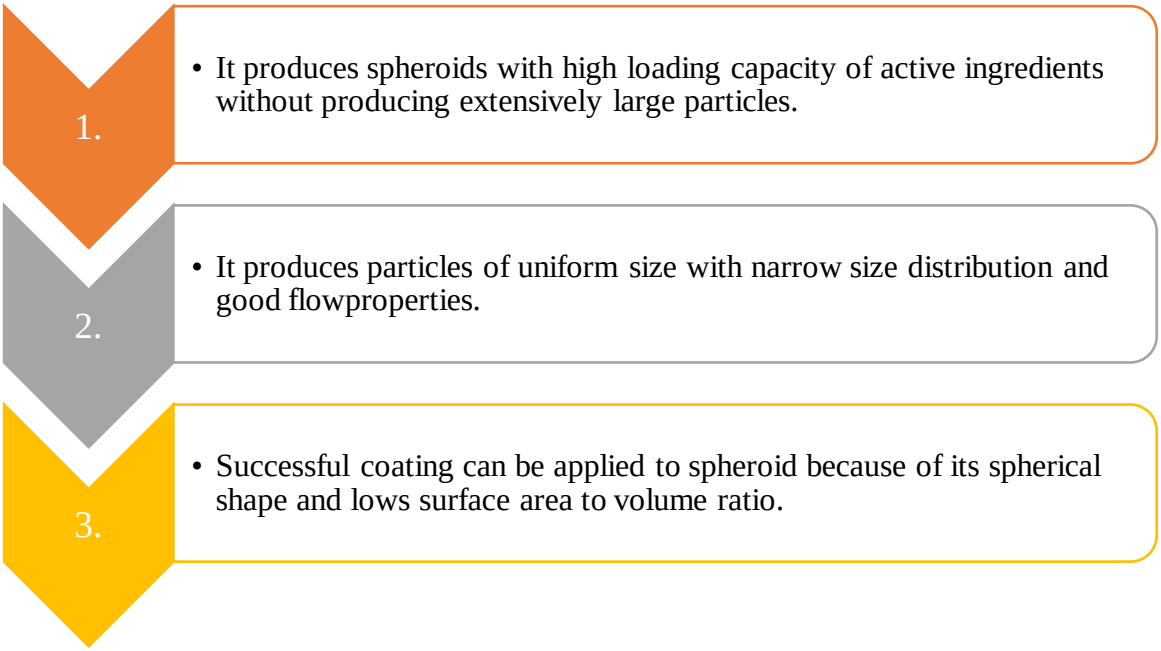

Figure 2.6: Advantages of spheroids produced by extrusion spheronization.

2.13 Enteric coated tablets/capsules

Wu *et al.* (2022) correlated *in vitro* properties of drug formulation to its *in vivo* performance and elucidated deciding properties of oral absorption of enteric coated capsules. Gastrointestinal simulation technology (GST) was used to simulate the *in vivo* plasma concentration-time curve and was implemented by GastroPlus^{TM} software to see the effect of absorption of drug when encapsulated in enteric coated capsules.

Amidon *et al.* (2015) stated that the enteric polymers are becoming very popular due to their property of being intact in the stomach but will dissolve and release the contents once it reaches the small intestine; their prime intention is to delay the release of drugs, which are inactivated by the stomach contents or may cause bleeding or nausea by the irritation of gastric mucosa. The enteric coating contains a pH-sensitive polymer, which means it remains intact in the stomach's acidic environment (pH 1.5 - 3.5), protecting the tablet's contents. After passing through the stomach, the coating disintegrates in the small intestine (duodenum), which has an alkaline environment (pH 6.5 - 7.6). The enteric coating is inert and simply passes through your system without any effect. Apart from the protection this coating offers, it also prevents any irritation of the gastric mucosa in the stomach.

Pang (2018) formulated a rosiglitazone sodium enteric-coated tablet by single punch tablet press, replacing hydroxypropyl cellulose and polyvinylpyrrolidone (PVP). The

release rate from the enteric-coated tablet of rosiglitazone sodium was characterized. The release rate study displayed that few rosiglitazone sodiums were released from enteric-coated formulation within 2 hours in simulated gastric juice. In contrast, it released more than 80% of the labeled amount in 30 min in simulated intestinal juice. The preparation method for rosiglitazone sodium enteric-coated tablets was simple and had good reproducibility. The release environment and determined methods could be used for the routine determinations of rosiglitazone sodium enteric-coated tablets.

2.14 Design of Experiment (DoE) and total quality management using quality by design

Pradhan *et al.* (2022) described various designs involved in screening and optimization which include factorial designs, fractional factorial design, Box-Behnken design, Plackett- Burman designs (for screening of critical attributes), optimal design, central composite designs (for optimization), taguchi designs, equirdial designs, and mixture designs.

Bonaccorso *et al.* (2021) used QbD technique to ensure the quality of pharmaceutical products and advance the process of turning laboratory-based research into effective therapies. This study discussed a variety of fundamental concepts, historical overviews, and applications of QbD in nanomedicine. Response Surface Methodology and Artificial Neural Network techniques in general, as well as their use in the creation of nanomedicine to monitor process parameters and achieve optimised systems while guaranteeing its quality profile, have received particular attention.

Aboushady *et al.* (2020) discussed various qualification elements used in the validation of the pharmaceutical product. Design qualification (DQ) is performed before the equipment purchase. User requirements like capabilities (e.g., speed, capacity, and several stations, etc. for a tablet press), requirements (e.g., voltage, size limitations, operational specifications, and requirements to work with the existing equipment), and features (e.g., ease of cleaning, etc.) should be considered when deciding on the specific design of a system or equipment. Installation qualification (IQ) studies establish confidence that the process equipment and ancillary systems can consistently operate within specified limits and tolerances. Operational qualification (OQ) systems and equipment should operate correctly and be verified following an active qualification protocol. The purpose of the Performance qualification (PQ) is to

verify that the equipment or system produces the required output. The PQ protocol will be specific to the equipment or system.

Nureye & Assefa (2020) stated that a quality management system is an integrated part of process validation. It is conducted in the context of a system, including design and development control, quality assurance, process control, and corrective and preventive measure.

Zheng *et al.* (2019) investigated the importance of validation including assurance of quality, less time, process optimization, reduction of quality cost, nominal mix-ups and bottlenecks, minimal batch failures, improved efficiency and productivity, reductions in rejections, increased output, avoidance of capital expenditures and fewer complaints about process-related failures.

Erath *et al.* (2019) in their study stated that the product should be designed in such a manner so that it withstands variations in the manufacturing process, and the manufacturing process should be capable and stable, assuring to give a quality product for the whole life cycle.

Osonwa & Hu (2018) discussed the statistical DoE as a valuable tool to establish in mathematical form the relationships between CPPs and CQAs. Experimental design can be used at the point of leverage to reduce design costs by speeding up the design process**,** reducing late engineering design changes, and reducing product material and labor complexity. Designed experiments are also a powerful tool to achieve manufacturing cost savings by minimizing process variation and reducing rework, scrap, and the need for inspection.

Bhoop *et al.* (2013) discussed that the DoE optimization techniques are becoming practically global, designing and developing an assortment of new dosage forms and modifying the existing ones. DoE is frequently sought after in drug discovery and development. Further, it includes the qualification of systems and equipment. It is a requirement for good manufacturing practices and other regulatory requirements. The purpose of validation is to ensure that the product's user needs and intended uses can be fulfilled consistently. The components are represented in Fig. 2.7.

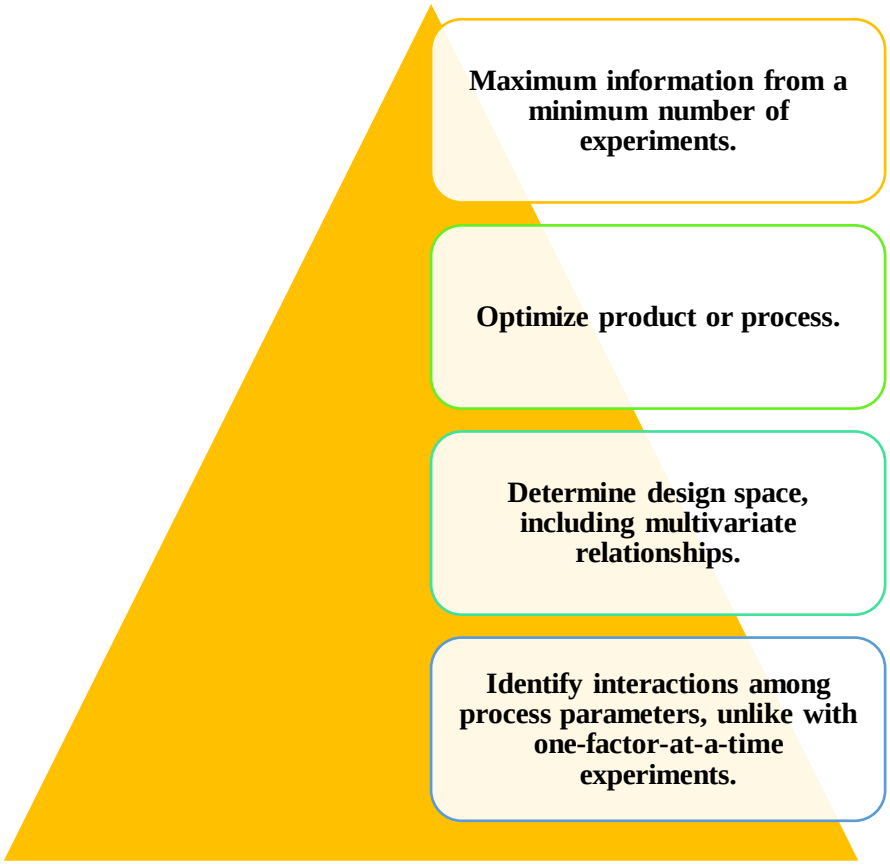

Figure 2.7: Role of design of experiment.

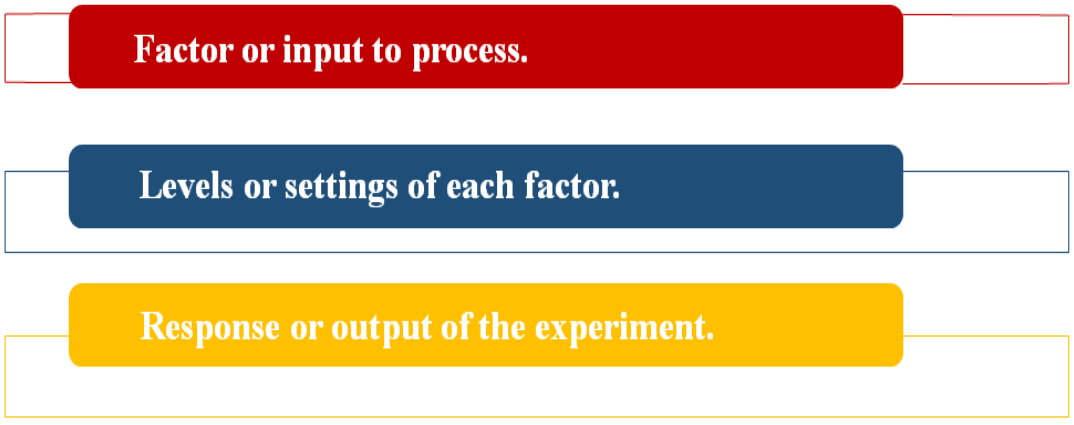

Figure 2.8: Common aspects of the process analyzed by a design experiment.

Oechslein & Lazar (2012) discussed process validation as the collection and evaluation of data from the process design stage through commercial production, which establishes scientific evidence that a process can consistently deliver a quality

product. Process validation involves a series of activities taking place over the product and process lifecycle. They also described the Placket Burman design is also known as a saturated design as all information in those designs is used to estimate the parameters, leaving no degrees of freedom to evaluate the error term for the ANOVA. Because the added factors are created by equating (aliasing) the "new" aspects with the interactions of a complete factorial design, these designs always will have 2**k runs (e.g., 4, 8, 16, 32, and so on). The common aspects to be considered for process analyzing using QbD approach are given in Fig. 2.8. The steps to be followed for optimizing drug delivery systems are illustrated in Fig. 2.9.

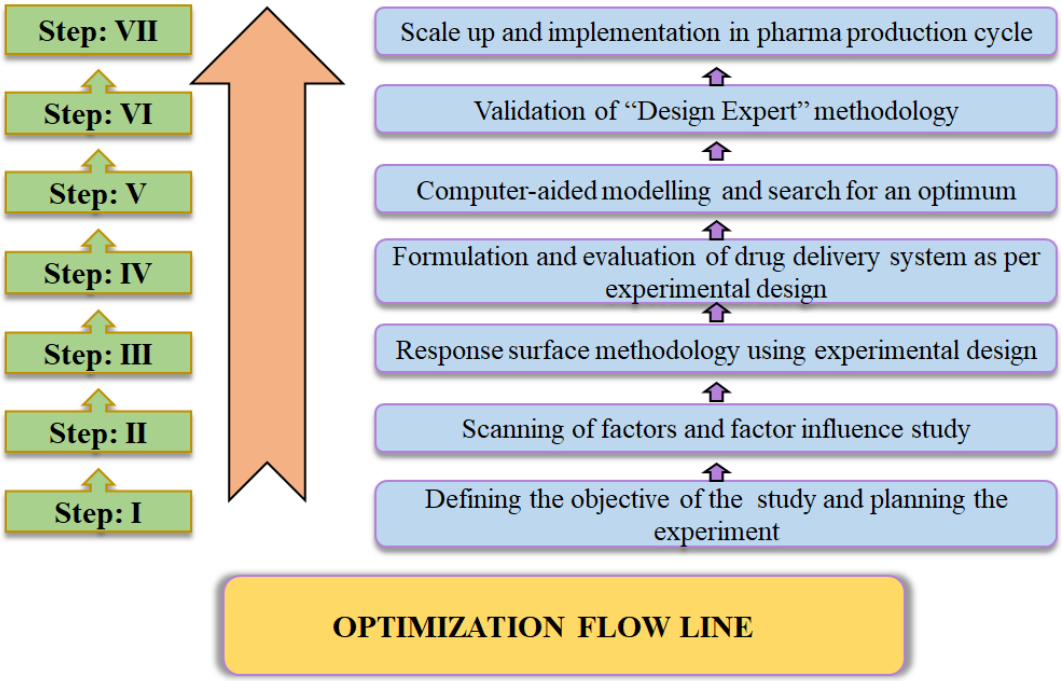

Figure 2.9: Seven-step ladder for optimizing drug delivery systems.

Nair *et al.* (2011) discussed the interactive effect of microspheres using 3^2 full factorial designs. Two variables were optimized for desired drug release and entrapment efficiency: the stirring speed and concentration of ethylcellulose. A statistical model with significant interaction terms and surface plots was derived to predict the drug release pattern. Acceptable batches were identified with the help of experimental design. As discussed in the book different types of validation and different elements of validation are illustrated in Fig. 2.10 and Fig. 2.11.

Late & Banga (2010) discussed Response Surface Methodology (RSM), which was applied to optimize novel fast disintegrating tablets using ß-cyclodextrin as the diluent by investigating the main and interactive effects of formulation variables such as diluent super disintegrant and direct compression aid. A good correlation between the predicted values and experimental data of the optimized formulation validated the prognostic ability of RSM.

Zhong *et al.* (2007) described the formulation of pro cationic liposomes–protamine–DNA complexes were optimized using a three-factor, five-level RSM design in terms of the weight ratio of protamine/DNA, molar percent of CHETA [(Cholest-5-en-3beta-yl[2[[4-[(carboxymethyl)dithio]-1-iminobutyl] amino] ethy-l] carbamate)] and the weight ratio of CHETA/DNA as independent variables.

Singh *et al.* (2006) prepared tablets by direct compression and evaluated them for bioadhesive strength and *in-vitro* dissolution parameters. In formulation and optimization of controlled release, mucoadhesive tablets of atenolol were formulated using carbopol 934P and sodium carboxymethylcellulose by central composite design for two factors at three levels to apply to optimize drug release profile and bioadhesive strength. In their study they highlighted various othe aspects to use QbD approach in pharmaceutical industry.

Kumar *et al.* (2013) described that Plackett and Burman designs are also known as Hadamard matrix designs. Also, in their findings discussed central composite and non-factorial response surface designs. The 2** (k-p) and 3** (k-p) designs require that the factors' levels are set; for example, 2 or 3 levels. In many instances, such designs are not feasible because, for example, some factor combinations are constrained in some way (e.g., factors A and B cannot simultaneously be set at their high levels). It is often desirable to explore the experimental region of interest at particular points that cannot be represented by a factorial design.

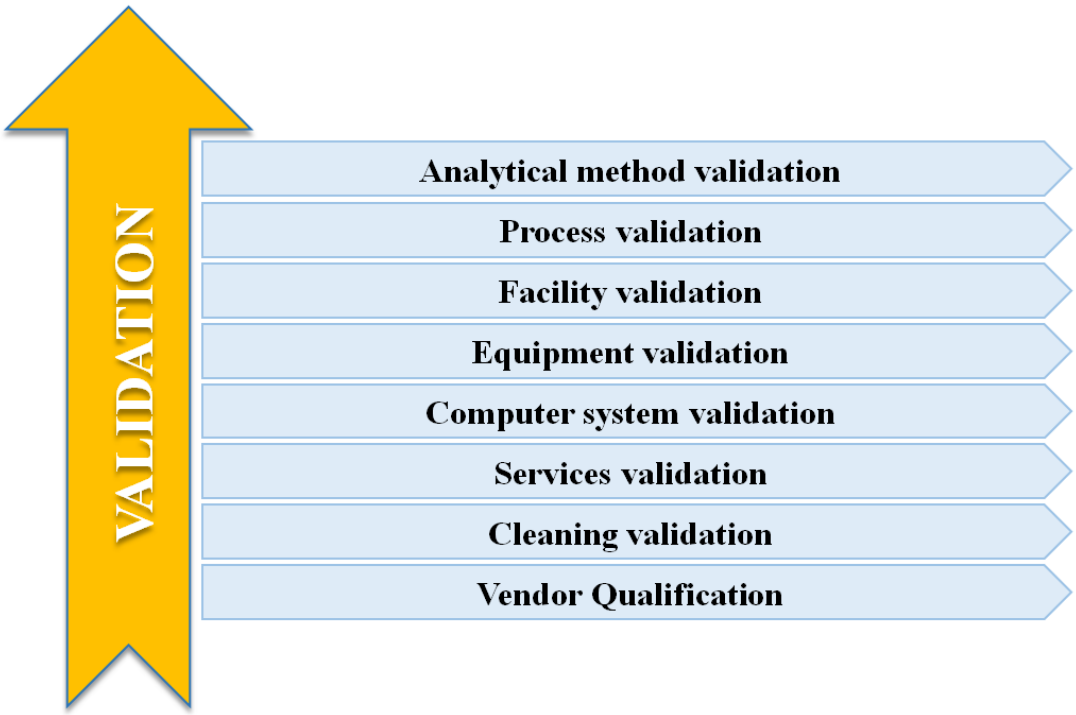

Figure 2.10: Various types of validation.

Process validation establishes written evidence that provides confidence that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

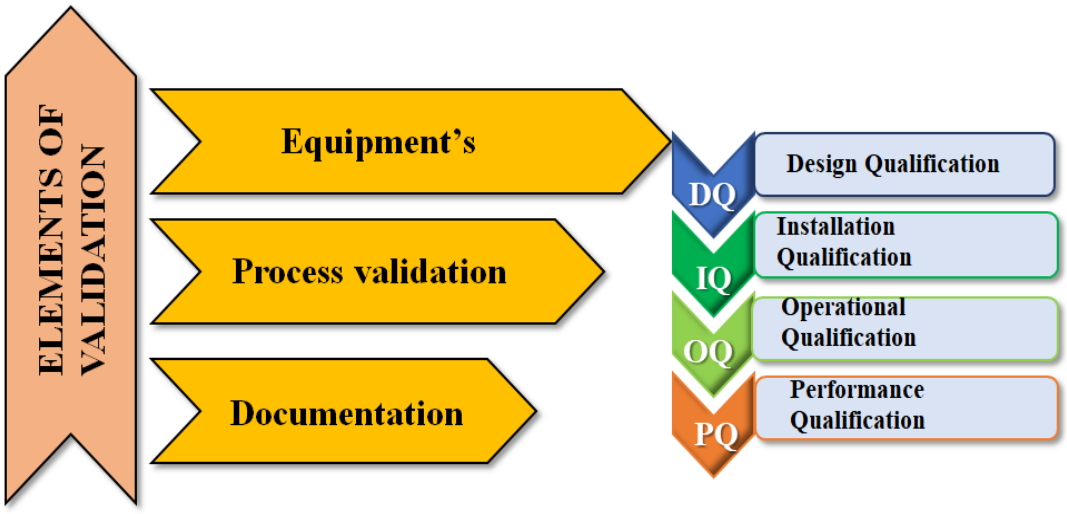

Figure 2.11: Elements of validation.

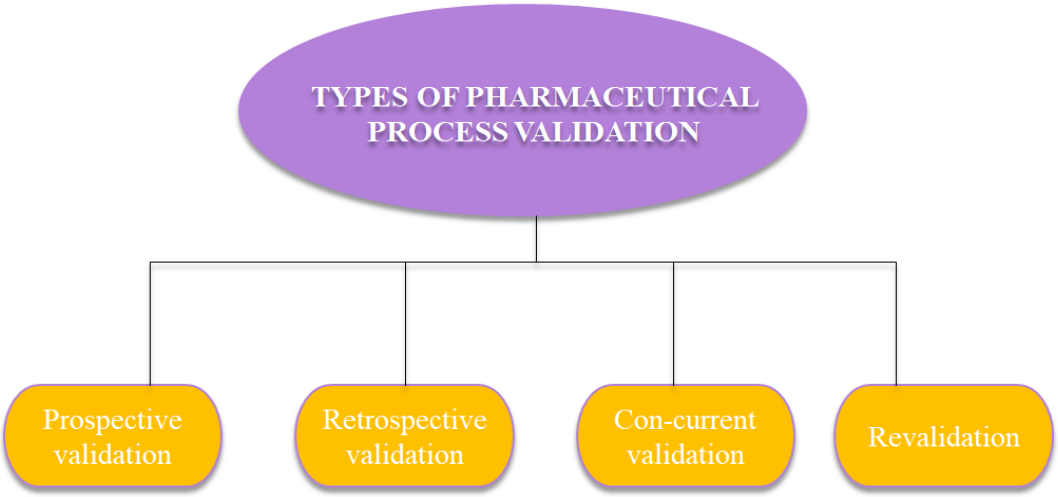

Figure 2.12: Types of process validation

Nash (2003) discussed that before commercial use, the forthcoming assurance should be conducted for the development process of a formulation. Critical process parameters are identified in prospective validation, the risk is evaluated, all the parameters are investigated, and the values are set. Further Nash in his book described that the most compelling reason for validation is to guarantee, as far as possible, that all processes and machinery in the pharmaceutical manufacturing process are being used to ensure the safety, integrity, quality, and strength of a dosage form. Validation is critical if there is a significant change to the premises, the facilities, the equipment, or the process, which may affect the quality of the product, directly or indirectly, should be validated. Different types of process validation are illustrated in Fig. 2.12.

Trubinski (2003) discussed that revalidation must be performed before any changes in manufacturing or changes in standard operating procedure. It provides evidence that changes in a process introduced intentionally/unintentionally do not adversely affect process characteristics and product quality. Every change should be reviewed and identified so that it does not affect the finished product directly or indirectly.

Montgomery (1999) discussed that DoE is an essential statistical tool in optimizing the formulation. It is a structured, organized method for determining the relationships among factors affecting a process and the response of the process. They also discussed in their study that Plackett and Burman showed how to complete factorial design could be fractionalized differently to yield saturated designs where the number

of runs is a multiple of 4 rather than a power of 2.

Related studies at mentor's lab

Sharma *et al.* (2016) in their review highlighted the properties of different cyclodextrin derivatives. Also, they emphasized on the recent advancement in drug delivery systems by conjugating drug with cyclodextrin derivatives.

Dadwal *et al.* (2018) in their research highlighted the importance of nanoparticles in enhancement of oral bioavailability, permeability and solubility of drugs.

Ali *et al.* (2016) in their research highlighted the role of NLCs in enhancing solubility, permeability and oral bioavailability of poorly aqueous soluble drugs. Moreover they also emphasized on the application of NLCs to prevent drug from acid degradation.

Rawat *et al.* (2023) highlighted the role of solid dispersion in solubility enhancement of hydrophobic drugs. In their research they highlighted how solid dispersion enhanced the stability, solubility and therapeutic effect of cholecalciferol.

Saroch *et al.* (2022) discussed the potential drug delivery systems for flavours and fragrances, several delivery systems such as microparticles, nanoparticles, and liposomes are being investigated. In addition, the selected nanoformulations have a thorough comprehension of several elements of Quality-by-Design principles, such as the determination of critical materials, process parameters, and quality attributes.

Dharwal *et al.* (2022) enhanced the permeability and oral bioavailability of pyrostigmine bromide by SMEDDS which may reduce the dose frequency.

Naman et al. (2021) developed oral disintegrating mini tablet of paracetamol employing quality by design approach. Quality target product profile and critical quality attributes for paracetamol oral disintegrating mini tablet were identified.

Bhandari et al. (2014) discussed the role of total quality management with special emphasis on recent advancements in online production monitoring, sophisticated analytical tools and anti-counterfeiting technologies in pharmaceutical industries.

Paudwal *et al.* (2019) discussed the recent advancement in solid dispersion to enhance the solubility of poorly water soluble drugs.