REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Strategies to Improve Solubility of Oral Drugs

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Abstract

One of the most common routes for drug administration is the oral route. It has many advantages like patient compliance, non-invasiveness and drug administration convenience. Oral administration accounts for over 60% of all established small-molecule medication products on the market. Oral drug absorption may be governed by many factors such as mucosal permeability, drug solubility and stability in the gastrointestinal tract. The trials to overcome these factors depend on understanding the biochemical, physicochemical, biological and metabolic barriers which affect the overall bioavailability of a drug. Enhancement of oral drug absorption can be achieved by many drug delivery systems and pharmaceutical technologies such as lipid-based carriers, micelles, nanocarriers, salt formation, solid dispersion, and complexation techniques using cyclodextrins. The strategies to improve the oral drug delivery will be discussed in details especially cyclodextrin complexation which is considered one of the most common strategies having great role in enhancing the oral drug delivery.

Keywords: oral drugs, solubility; complexation; cyclodextrins.

Introduction

Oral dosage forms are considered the most widely used form of drug administration due to their numerous advantages such as ease of drug administration through the oral route, individuals' preference, cost-effectiveness, and convenience of large-scale manufacturing. Oral administration accounts for over 60% of all established small-molecule medication products on the market.

According to current estimates, oral formulations account for around 90% of the global market share of all pharmaceutical formulations intended for human use. Moreover, orally administered pharmaceutical items account for about 84 percent of the best-selling pharmaceutical products, which are currently valued at $35 billion and growing at a 10% yearly pace. **(Prasad *et al.*, 2017)**.

1. Factors affecting drug absorption from the gastrointestinal tract:

Oral formulations have many problems, most of which can be ascribed to medication physicochemical features such as poor water solubility and membrane permeability. Furthermore, medication absorption can be hampered by its poor chemical and biological stability, as well as physiological obstacles such as pH, efflux transporters, and metabolic enzymes **(Table 1)**. Additionally, some medications can induce local irritation and nausea. **(Rubbens *et al.*, 2018).**

2. The Biopharmaceutical Classification System (BCS), and the Biopharmaceutics Drug Disposition Classification System (BDDCS)

The BCS classified drugs according to two critical physicochemical parameters: Drug solubility, and drug permeability **(Table 2)**. These two factors were selected as the most orally administrated drugs are absorbed via passive diffusion along the small intestine, where the extent of oral absorption is largely affected by a drug's membrane permeability and solubility. The BCS has a key flaw in that it does not provide an in-depth understanding of how drug metabolism and drug transport can affect drug product pharmacokinetics.

In 2005 Wu and Benet suggested a modified version of the categorization system (BDDCS) **(Table 3)** which provide a useful framework for predicting the effects of food, enzyme transporter interplay, and drug-drug interactions on drug pharmacokinetic performance. **(Wu and Benet, 2005)**.

3. Strategies to Improve Oral Drug Delivery

Considering the development of oral formulations, drugs with poor aqueous solubility need the understanding of barriers. Drug solubility is a key factor in the low oral bioavailability of hydrophobic drugs **(Boyd et al., 2019)**. Other elements related to the low bioavailability of hydrophobic drugs are food effect, gastric irritation, slow onset of action, lack of dosage proportionality, and high intra- and inter-subject variability (Singh and Kim, 2002). As a result, a variety of procedures are used to improve drugs' water solubility.

Careful screening of formulation considerations such as selection of the surfactant, particle size reduction, and salt selection, is essential regarding developing the formulations of poorly soluble drugs.

Typically, a mixture of surfactants has been used to improve medicine oral absorption. **(Wong *et al.*, 2006)**.

Surfactants have a hydrophilic head and a hydrophobic tail, in which both hydrophilic and lipophilic groups aid in drug molecule localization at the interface, lowering interfacial tension. Surfactants can improve the bioavailability of drugs through many mechanisms, including the enhancement of the solubility and permeability of drugs by temporarily opening tight intracellular junctions. On the contrary, the usage of surfactants at higher concentrations can turn into a safety concern that requires careful consideration **(Lawrence, 1994)**.

Other procedures, such as micronization, can also significantly improve drug bioavailability **(De Villiers *et al.*, 2008; Liu, 2018)**. In these techniques, the particle size of pharmaceuticals is lowered significantly, which increases their surface area and subsequently increases the dissolution rate.

3.1 Chemical modification

the prodrug concept is a popular chemical manipulation to enhance drug properties, including aqueous solubility, lipophilicity, stability, mucosal membrane permeability, and therapeutic index. The most common prodrug types include ester, amide, carbonate, carbamate, azo, glucuronide, and glycosidic bonds. In addition, polar moieties such as polyethylene glycol (PEG) are commonly included in drug molecules **(Greenwald *et al.*, 2000; Basit *et. al.*, 2001)** The prodrugs should be inactive, safe, and metabolizable. The prodrug planning can work on the oral bioavailability of medications by improving their water solvency and gastrointestinal penetrability and bypassing first-pass metabolism. Prodrugs can further develop the carrier-mediated absorption of charged or polar medications with insignificant passive absorption **(Shah *et al.*, 2020).** Further, they can target explicit bioactivation systems or colon bacterial microflora to accomplish site-explicit medication conveyance **(Schacht *et al.*, 1996)**. Roughly 7% of the advertised medications are assessed to be prodrugs **(Rautio *et al.*, 2008**) Lipophilic esters are the most ordinarily utilized for oral prodrugs; they can upgrade drug retention by further developing layer penetrability and intake through the lymphatic course **(Charman and Porter, 1996)**. Some representative examples of oral prodrugs are listed in **Table 4**.

3.2 Salt Formation

The pH solubility profile can be used to enhance the aqueous solubility of a drug by adjusting the pH. Moreover, because the micro-environmental conditions in the diffusion layer have been proven to play a significant role in improving the dissolution rate of drug molecules, the capacity of salt to adjust the total medium pH is critically important **(Yang *et al.*, 2014).**

In contrast to an acidic chemical, a basic drug with a higher pKa, maximal intrinsic solubility, and lower salt solubility has been found to prefer salt formation under increased pH. However, an error and trial process are required to identify and select the most suitable salt form for drugs.

3.3 Solid Dispersions

Solid dispersion shows the scattering of at least one medication in an inactive excipient or framework, in the solid state. It is usually formulated utilizing the melting (fusion), solvent evaporation, co-precipitation, melting–extrusion, or spray drying technique **(Serajuddin, 2018).** Solid dispersions are commonly designed using a hydrophilic polymer and water-insoluble drug. In solid dispersions, the physical condition of the active medicinal constituent is eminently changed from the crystalline to undefined state **(Serajuddin, 1999).**

The melting technique is widely utilized for designing versatile amounts of pharmaceutical formulations, but it is not suitable for heat sensitive compounds **(Serajuddin, 2018).** general pharmaceutical materials reasonable for solid dispersions incorporate cellulosic compounds such as hydroxypropyl cellulose (HPC) or hydroxypropyl-methylcellulose, PEG, polyvinylpyrrolidone, polyvinyl alcohol, and crospovidone **(Serajuddin, 1999; Newman, 2015).**

3.4 Drug Complexation

Incorporation complex formation with drug particles is another way to enhance their aqueous dissolution; it allows to control the release rates of lipophilic medications; cover the flavor of bitter drugs; and maximize the resilience of oral drug formulations by limiting the irritation of the drugs after oral intake **(Loftsson and Brewster, 1996).** There are many drugs prepared by various complexation techniques as shown in **(Table 5).**

In addition, it enjoys the additional benefit of working on the stability of medications, especially esters, by protecting artificially labile substances from possibly cruel natural circumstances and diminishing their enzymatic debasement.

In common, cyclodextrins are considered as expected transporters to work on oral conveyance of medications, albeit different kinds of complexing compounds for example sodium benzoate, niacin, caffeinate, and salicylate can be utilized **(Loftsson and Duchêne, 2007)**. Cyclodextrins are chains of cyclic oligomers encasing 6, 7, and 8 d-glucopyranose structures named alpha, beta, and gamma-cyclodextrins, simultaneously **(Figure 1).** Discs are fit for framing incorporation edifices with many medications by taking up an entire medication particle, or some piece of it, into the cavity. Such molecular encapsulation will influence a considerable lot of the physicochemical properties of drugs, like their water solubility and rate of dissolution As of now, in excess of 85 distinct oral medication formulations in view of complexation are accessible on the lookout **(Choudhury et al., 2018).**

3.4.1 Cyclodextrins:

Cyclodextrin is known to be the most practical of the three types of CDs because its cavity diameter is the best for guest molecules, its production technique does not require specialized technology, and it is less expensive **(Challa et al., 2005).**

The aqueous solubility of hydroxy-propyl chemical derivatives of -cyclodextrin is significantly higher than that of native cyclodextrins. To understand complexation mechanism CDs can be considered as cylinders with hydrophobic inside and hydrophilic outside. The hydrophobic cavity provides an ideal sanctuary for low water-soluble compounds to conceal their most hydrophobic portions or entire molecules from the surrounding atmosphere. In the presence of water, these hydrophobic molecules that can fit in the CD cavity are incorporated in it.

Table 1: factors affecting drug absorption from the gastrointestinal tract

Physiological factors	Physicochemical factors	Formulation factors	Miscellaneous
I. Physiology of GIT a. Presence or absence of food b. Esophageal motility c. Esophageal transit time d. pH of various segments II. Mode of transport across the GI tract a. Active transport b. Passive diffusion III. Metabolism	i. Ionization constant ii. Drug stability in the GI fluid iii. Lipophilicity of the drug iv. Crystal properties v. Drug solubility vi. Salt form vii. Dissolution rate viii. Protein binding ix. Adsorption x. Complex formation	i. Tablets ii. Capsules iii. Suspensions iv. Solutions v. Coated tablets	i. Gender ii. Smoking & Alcohol abuse iii. Age iv. Other drug use

Table 2: The biopharmaceutics classification system.

Class I	Class II
High solubility High permeability	Low solubility High permeability
Class III	**Class IV**
High solubility Low permeability	Low solubility Low permeability

Table 3: The Biopharmaceutics Drug Disposition Classification System.

Class I	Class II
High solubility extensive metabolism	Low solubility extensive metabolism
Class III	**Class IV**
High solubility Poor metabolism	Low solubility Poor metabolism

Table 4: Some representative examples of oral prodrugs

Prodrug type	Oral Applications	Commercial examples
Esters	**Enhancing aqueous solubility**	**Etoposide phosphate (Vepesid®)**
Oxides		**Sulindac (Clinoril®)**
Esters		**Enalapril maleate (Vasotec®), Olmesartan minoxidil (Benicar®)**
Ester salts	**Improving lipophilicity and intestinal permeability**	**Valacyclovir (Valtrex®)**
Amides		**Midodrine (Amatine®)**
Carbamates	**Carrier-mediated absorption**	**Gabapentin enacarbil (Horizant®)**
Azo prodrugs	**Colon-specific targeting**	**Sulfasalazine (Azulfidine®)**

Table 5: Dissolution enhancement by various complexation techniques.

Drug	Technique	Cyclodextrins	Mechanism	Reference
Piroxicam	Steam-Aided Granulation	*β*CD	Increased surface area	**(Cavallari *et al.*, 2002)**
Glipizide	KG	*β*CD&HP**β**CD	Inclusion complexes	**(Patel *et al.*, 2002)**
Ziprasidone Hydrochloride	KG, SE	*β*CD&HP*β*CD	Inclusion complexes	**(Deshmukh *et al.*, 2002)**
Gliclazide	Neutralization	*β*CD	Increased wettability	**(Lo *et al.*,2006)**
Glyburide	KG, SE	*β*CD, HP*β*CD & Chitosan	Inclusion complexes	**(Zerrouk *et al.*, 2006)**
Carbamazepine	KG	*β*CD	Increased solubility	**(Suresh *et al.*, 2006)**
Satranidazole	KG	*β*CD	Reduction in crystallinity	**(Derle *et al.*, 2006)**
Nimesulide	KG	*β*CD	Inclusion complexes	**(Mahapatra *et al.* 2020)**
Celecoxib	KG	*β*CD	Inclusion complexes	**(Rawat *et al.*,2005)**
Piroxicam	FD	*β*CD	Inclusion complexes	**(Jug *et al.*,2005)**

Norfloxacin	KG	*β*CD	Inclusion complexes	**(Aithal *et al.*, 2005)**
Meloxicam	FD	*β*CD&HP*β*CD	Increased wettability	**(Musuc, *et al.*, 2021)**
Nicardipine	KNG, SE, FD, SD	*β*CD&HP*β*CD	Improved wettability.	**(Patel and Purohit, 2009)**
Gliclazide	RC	*β*CD	Inclusion complexes	**(Özkan *et al.*, 2000)**
Carbamazepine	SE	*β*CD	Inclusion complexes	**(El-Zein *et al.*, 1998)**
Norfloxacin	FD	*β*CD&HP*β*CD	Reduction of particle size	**(Guyot *et al.*,1995)**
Naproxen	KG, SE	*β*CD	Inclusion complexes	**(Bettinetti and Mura, 1994)**
Efavirenz	KG, SE	*β*CD	IC	**(Kumar *et al.*, 2013)**
sulforaphane	co-precipitation method	HP-*β*-CD	enhance stability	**(Wu, *et al.*, 2010)**
thymol	electrospinning technique	(HP*β*CD) & (HP*γ*CD) &(M*β*CD)	Inclusion complexes	**(Celebioglu, *et al.*, 2018)**
Idebenone	FD	HP-*β*-CD	Inclusion complexes	**(Venuti, *et al.*, 2019)**
Carvacrol	FD	*β*CD	Inclusion complexes	**(Trindade, *et al.*, 2019)**
Carbamazepine	SE	*β*CD	Inclusion complexes	**(Musuc, *et al.*, 2021)**
docetaxel	SE	DM-*β*-CD	Increased solubility, and permeability of the drug.	**(Giri, *et al.*, 2021)**
Genistein	SE	*β*CD	Inclusion complexes	**(Zafar, *et al.*, 2022)**
Tetracycline	SE	HP*β*CD	IC	**(Hsiung, *et al.*, 2022)**

****βCD: Beta Cyclodextrin; *HPβCD: Hydroxypropyl Beta Cyclodextrin; *KG: Kneding; *SE: Solvent Evaporation; *FD: Freeze Drying; *RC: Recrystallization.***

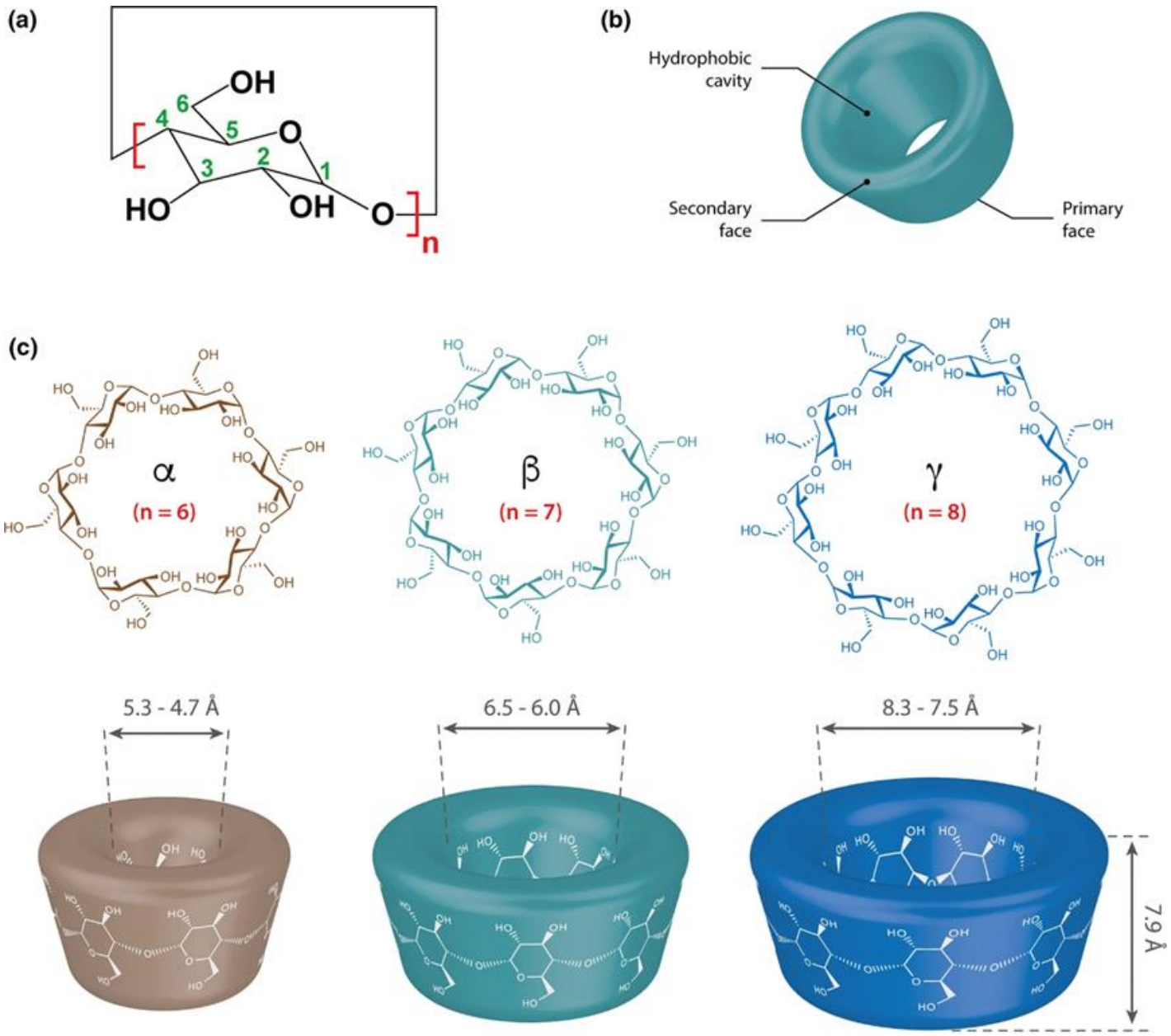

Figure 1: Cyclodextrin (a) chemical structure, (b)the 3 D structure of cyclodextrins, and (c) dimensions for *α*-, *β*- and *γ*-cyclodextrin (*n* = 6, 7 and 8, respectively) **(Crini *et al*., 2018)**

The polar CD cavity in aqueous solution is occupied by water molecules that are in an energetically unfavored state (Polar – a polar repulsion) and are thus easily replaced by an appropriate guest molecule that is less polar than water and forms an inclusion complex **(Shiralashetti *et al*.,2010).**

The lipophilicity and dimensions of the guest molecules determine the complexation degree. a part of guest molecule or whole of it must fit into the cavity of CD. γ-CD is preferred for many drugs because of large cavity size. Hiding the hydrophobic groups of poor solubility drugs in CDs will increase their aqueous solubility **(Challa *et al*., 2005).**

3.4.2 PREPARATION TECHNIQUES

3.4.2.1 Co-precipitation method

the co-precipitation method is used for water insoluble substances **(Cheirsilp and Rakmai, 2016)** .In this technique , CD is dissolved in water and the guest is dissolved in ethanol then adding the ethanol solution to CDs solution with agitation **(Jiang *et al*.,2019).** Organic solvents (such as benzene, diethyl ether or among others) can be used to dissolve The guest **(Cheirsilp & Rakmai, 2016).** Cooling and crystallization and precipitation of the solution occur **(Jiang *et al*., 2019)** .Washing the filtrate help to remove free guest molecules from the surface of CD **(Wadhwa *et al*., 2017).** In the same way, an antisolvent is used for precipitation of the complex **(Jacob & Nair, 2018)**. Co-precipitation is known to be the most used methods and characterized by its efficiency and simplicity **(Jiang *et al.*, 2019)** .

3.4.2.2 kneading method

Is a simple method and also called paste method **(da Silva Júnior *et al*., 2017)** .The CDs are mixed in a mortar with a small amount of water till obtaining a paste in which the guest is incorporated by mixing **(Wadhwa *et al*., 2017).** Then washing obtained solid with a few quantity of solvent **(Cheirsilp and Rakmai, 2016: Wadhwa *et al*., 2017)** . This method is simple, scalable, and high efficiency **(da Silva Júnior *et al*., 2017).**

3.4.2.3 Super critical carbon dioxide method

In this method, the CDs and the guest are put in a thermostatic autoclave and pressurized with carbon dioxide at a specified temperature and pressure **(Wadhwa *et al*., 2017).** Then rapid pressure drop by vaporizing the carbon dioxide leads to separation of the inclusion complex **(*Wadhwa et al*., 2017).** carbon dioxide is the most used solvent because of its low toxicity and low critical point **(Banchero, 2021)** . This method is better than other complexation techniques like coprecipitation or kneading because they have some limitations such as the encapsulation efficiency process time and the presence of residual organic solvent **(Banchero, 2021).**

3.4.3 APPLICATIONS OF CYCLODEXTRINS

the super critical carbon dioxide method can be applicable for commercial use because of its good yield. In addition, this method provides an ideal separation between the supercritical solvent and the processed products **(Banchero, 2021).**

3.4.2.4 Grinding method

Mixture of cyclodextrin and guest are grinded and trapped between the grinding media. the quasi-adiabatic energy is accumulated when the compounds receive intensity sufficient enough to allow a metastable structure formation **(Jug and Mura, 2018)**.

Reduction of particle size and increasing in the contact surface for the cyclodextrin and the guest interaction are obtained in this grinding process and resulted from the breakage of crystals **(Jug & Mura, 2018)**. this mechanical method is applied in the pharmaceutical industry and there is no need for several solvents. It is environmentally friendly , high efficiency, economic technology and clean method **(Borba et al., 2015)** .

3.4.2.5 Microwave irradiation method

CD and the guest are mixed and blended in an ethanol/water mixture and are put in a microwave oven to obtain a powder **(Khushbu, 2022)**. Then the powder was cleaned with ethanol To get rid of any guest residues **(Khushbu, 2022)**. This method have shorter reaction times , higher yields ,lack of residues and cost-effective **(Das and Subuddhi, 2015, Kaur et al., 2019)**.

3.4.2.6 spray drying method

This technique has three steps: the atomization of the liquid feed , the fine droplets drying by a stream of heated air and a final step where a separation of the dried particles from the air stream **(Watson *et al.*, 2017)**.this method is widely used because it has several advantages such as it is applicable on an industrial level, fast drying and of high yield.

From a microscopic perspective, the molecule is microencapsulated because each guest molecule is individually enclosed by a cyclodextrin (derivative). This improves the physical and chemical characteristics of the guest molecules. The following are some of the uses for cyclodextrin derivatives: stabilization of compounds that are susceptible to light or oxygen and enhancement of substance solubility **(Rajewski and stella, 1996).** Additionally, CDs can be utilized as stabilizers and enhancers of membrane permeability **(Loftsson and Brewster, 1996).**

Cyclodextrins improve the permeability through biological membranes, protect substances from microorganisms that can lead to their degradation **(Bogdan *et al*.,2005),** enhance stabilization and mask offensive tastes and odors. The use of cyclodextrins has increased recently in the domains of food, pharmaceuticals, chemicals, agriculture, and environmental engineering.

3.4.4 FUTURE ASPECTS

The majority of the newly discovered chemical substances have poor water solubility, which affects their bioavailability and therapeutic effect. The most attractive method to increase solubility is the inclusion complex with cyclodextrins. Because of their potential to form complexes with a wide range of therapeutic molecules, cyclodextrins and their derivatives have attracted a lot of attention in the pharmaceutical industry. Drugs' physicochemical characteristics, such as solubility, particle size, and crystal habit, can be changed by CDs, leading to the formation of a highly water-soluble amorphous form.

3.5 Absorption Enhancers

The drug permeability in the intestine can be increased by using many absorption enhancers.

Most common absorption enhancers used are chelating agents, salicylates, cholesterol, surfactants, bile salts and glycerides **(Aungst, 2012)**. Many absorption enhancers alter the paracellular permeability of hydrophilic drugs so increasing their transport **(LeCluyse and Sutton, 1997)**. However, a few absorption enhancers may cause systemic toxicity and mucosal damage.

The mechanism of P-gp inhibition by polymeric excipients includes competing with binding site of

An example of paracellular permeation enhancer is ethylene diamine tetraacetic acid (EDTA) which deplete magnesium and calcium in the tight junctions **(Lemmer and Hamman, 2013)**. When tight junctions open, drugs and other toxic molecules may be transported through the intestinal membrane, so these strategies have safety concerns. Transcellular promoters are known to disrupt the membrane integrity by solubilizing, fluidizing or reorganizing the intracellular phospholipids and therefore increase the absorption of oral drugs. Sodium salicylate and tartaric acid are examples of these enhancers**.**

3.6 Ion Pairing (Co-Crystals)

Co-crystals are defined as crystalline solids containing two or more ionic and molecular compounds where non-covalent forces have held them together **(Blagden *et al*., 2007)**. They are regarded as the crystalline form of solid dispersions. Ion pairs must have proper characteristics like biocompatibility, high lipophilicity, sufficient aqueous solubility and physiological stability. succinic acid, benzoic acid and phthalic acid are examples of counter ions most used in Ion pairing. However, counter ions which used may be in competition with endogenous compounds like phosphoglycerides, bile acids and sialic acids **(Varshosaz *et al*., 2018).** The delivery of highly polar antiviral drugs was achieved by naphthoic acid as a counter ion in Ion pairing **(Miller *et al*., 2010).**

3.7 Metabolism and Efflux Pump Inhibitors

Many excipients have the ability of modulating the efflux transporter's function, like polyethoxylated castor oil (Cremophor EL), polyethylene glycol (PEG), polysorbates (Tweens), tocopherol polyethylene glycol 1,000 succinate (TPGS 1000), and poloxamers (pluronic P85) **(Murakami and Takano, 2008)**. Some pharmaceutical polymers mentioned in recent studies have shown to inhibit the efflux pump activity **(Werle, 2008; Dahlgren and Lennernäs, 2019).**

substrate on the efflux transporter ,inhibiting the activity of the efflux pump ATPase, altering the fluidity of membrane lipid, acting directly on the mucosal surface P-gp protein or drug protection while avoiding the efflux **transporter (Takano *et al.*, 2006)**. Mucoadhesive polymers like chitosan, dextran, polyacrylic acid and polycarbophil affect the intestinal protease enzymes activity , mainly chymotrypsin, trypsin and carboxypeptidases, for the delivery of metabolically labile oral and increase their residence time. Reduction in the pre-systemic metabolism by CYP3A4 in intestinal enterocytes was shown when ketoconazole and grapefruit juice are administered together **(Dresser *et al*., 2000)**.

3.8 Lipid-Based Drug Delivery Systems (LBDDS)

LBDDS are one of the comprehensive solutions for the delivery of poorly water-soluble drugs (PWSDs), especially drugs with lipophilic nature **(Mehanna and Mneimneh 2021; Rawat *et al.* 2008)**. Such formulations account for 3% of all drug products available on the market **(Hauss, 2013).**

LBDDS can be classified into lipid suspensions, emulsions, self-micro-emulsifying systems, lipid solutions, solid lipid nanoparticles, solid lipid dispersions, liposomes, and niosomes. Several mechanisms make a lipid-based carrier efficient for the oral transport of small hydrophobic compounds. One of the primary strategies is to increase the rate of dissolution and solubility in the GI tract. bile salts that are excreted by the gallbladder, digest LBDDS into a colloidal form including mixed micelle, vesicles, and micellar carriers which increase the solubility of hydrophobic drugs in the intestine. Because of the composition and nature of these formulation (such as lipids, bile salt, phospholipid, complexation agents, surfactants, and co-solvents) the absorption is improved **(Hauss, 2007; Savla *et al*., 2017).**

3.9 Polymeric Micellar Carriers

By combining weakly soluble chemicals with surface-active substances known as copolymers, one can increase drug solubility and prevent drug precipitation following exposure to the GI environment.

Due to its impact on particle adherence, contact with the mucosal membrane, and drug-release Monomeric surfactant, and surfactants adsorbed as a film at the interface are the three systems in a surfactant solution where micellar systems occur in dynamic equilibrium. When the concentration of surfactant above the critical micellar concentration (CMC), micellar carriers arise **(Ribeiro *et al*., 2018).** By including lipophilic pharmaceuticals in the micellar core, micellar carriers can be used to improve the solubility of these drugs **(*Gaucher et al.*, 2005)**. Amphiphilic block copolymers have recently been created as solubility boosters **(Simões *et al.*, 2014).** One of the most utilized block copolymers for medication administration is the poloxamers surfactant group. These copolymers have CMCs that vary from 10–5 to 10–8 M. Micelles are more able to tolerate dilution than surfactants with low molecular weight because of their CMC of 10–6 M. Additionally, for increased target specificity, these micellar systems can be chemically altered through the attachment of antibodies on their side chains. It is important to keep in mind that antibody-conjugated micelles may be quickly cleared from the blood circulation as a result of their accumulation in the liver, particularly when there are insufficient target antigens **(Musacchio and Torchilin, 2019).**

3.10 Polymeric Nanocarriers

Oral drug delivery systems have been made using a variety of polymers with natural or synthetic bases. Dextran, chitosan, gelatin, and alginate are some examples of typical natural polymers, whereas polylactide-coglycolide (PLGA), polylactide (PLA), polycaprolactone (PCL), polyglycolide, polycyanoacrylate, and polyaziridine are examples of synthetic polymers used as oral drug delivery carriers (Ritika et al., 2012). The nanotechnology method entails the creation of medicines using nanoparticles with sizes between 10 and 1,000 nm.

The effective surface area increases as particle sizes are decreased to the nanoscale range, ultimately improving medication solubility and dissolving rates **(Mei *et al.*, 2013).**

Insoluble medications can be delivered using polymeric nanocarriers, which can also be used to target the pharmaceuticals to specific parts of the GI tract, reduce the impact of food on drug absorption, make it easier for drugs to pass the mucosal barrier, and enable receptor-mediated intracellular drug administration **(Mei *et al*., 2013; Ottenbrite and Kim, 2019).**

kinetics, particle size is crucial for oral drug administration **(Kulkarni and Feng, 2013; Alqahtani, 2017).** Through paracellular channels, enterocyte endocytosis, and cellular uptake by M cells in the Peyer's patch, particles with diameters of less than 50, 100–500 nm, and 5 m, respectively, pass through the GI barriers **(Desai *et al*., 1996)**. According to several studies, the rat GI mucosa prefers to ingest particles with sizes of 100 nm compared to bigger particles **(Desai *et al*., 1996; Janer *et al*., 2014).** There is often an upper limit on the concentration of polymers for oral delivery of drugs that is nontoxic **(Islam *et al*., 2019).** To get the necessary drug concentration for sustained release applications of strong medications, the formulation should be tuned for the desired polymeric ingredients or formulation technique. Drugs diffuse from nanoparticles in a controlled release profile as a result of bioerosion or swelling of polymers. Through cross-linking or chemical conjugation of the drug that is encapsulated, polymers can be altered to have the desired release profile **(Alqahtani *et al*., 2019).** To further customize the desired release profile, polymers can be mixed with hydrogels or scaffolds **(Liu, 2018).**

References:

Aithal, K. S., Nalini, K., Udupa, N., & Sreenivasan, K. K., 2005. Enhanced fluorescence emission of norfloxacin on complexation with cyclodextrin. *Indian drugs*, *42*(3), 162-166.

Banchero, M., 2021. Supercritical Carbon Dioxide as a Green Alternative to Achieve Drug Complexation with Cyclodextrins. *Pharmaceuticals*, *14*(6), 562.

Basit, A. W., Newton, J. M., Short, M. D., Waddington, W. A., Ell, P. J., and Lacey, L. F., 2001. The effect of polyethylene glycol 400 on gastrointestinal transit: implications for the formulation of poorly-water soluble drugs. *Pharm. Res*. 18 (8), 1146–1150.

Bettinetti, G., & Mura, P., 1994. Dissolution properties of naproxen in combinations with polyvinylpyrrolidone. *Drug development and industrial pharmacy*, *20*(8), 1353-1366.

Bogdan, M., Floare, C., Bogdan, D., & Farcas, S. I., 2005. Photo degradation of inclusion complexes of naproxen and niflumic acid with β-cyclodextrin. *National Institute for Research and Development of Isotopic and Molecular Technologies.*

Crini, G., Fourmentin, S., Fenyvesi, É., Torri, G., Fourmentin, M., & Morin-Crini, N., 2018. Cyclodextrins,

Borba, P. A. A., Pinotti, M., Andrade, G. R. S., da Costa Jr, N. B., Junior, L. R. O., Fernandes, D., ... & Stulzer, H. K., 2015. The effect of mechanical grinding on the formation, crystalline changes and dissolution behaviour of the inclusion complex of telmisartan and β-cyclodextrins. *Carbohydrate polymers*, *133*, 373-383.

Boyd, B. J., Mark, C. A. S., Vinarov, Z., Kuentz, M., Brouwers, J., Augustijns, P., et al., 2019. Successful oral delivery of poorly water-soluble drugs both depends on the intraluminal behavior of drugs and of appropriate advanced drug delivery systems. *Eur. J. Pharm. Sci*. 137, 104967.

Cao, F., Guo, J., & Ping, Q., 2005. The physicochemical characteristics of freeze-dried scutellarin-cyclodextrin tetracomponent complexes. *Drug development and industrial pharmacy*, *31*(8), 747-756.

Cavallari, C., Abertini, B., González-Rodríguez, M. L., & Rodriguez, L., 2002. Improved dissolution behaviour of steam-granulated piroxicam. *European journal of pharmaceutics and biopharmaceutics*, *54*(1), 65-73.

Celebioglu, A., & Uyar, T., 2020. Development of ferulic acid/cyclodextrin inclusion complex nanofibers for fast-dissolving drug delivery system. *International Journal of Pharmaceutics*, *584*, 119395.

Celebioglu, A., Yildiz, Z. I., & Uyar, T., 2018. Thymol/cyclodextrin inclusion complex nanofibrous webs: Enhanced water solubility, high thermal stability and antioxidant property of thymol. *Food research international*, *106*, 280-290.

Challa, R., Ahuja, A., Ali, J., & Khar, R. K., 2005. Cyclodextrins in drug delivery: an updated review. *Aaps Pharmscitech*, *6*(2), E329-E357.

Charman, W. N., and Porter, C. J. H., 1996. Lipophilic prodrugs designed for intestinal lymphatic transport. *Adv. Drug Del. Rev*. 19 (2), 149–169.

Cheirsilp, B., & Rakmai, J., 2016. Inclusion complex formation of cyclodextrin with its guest and their applications. *Biol Eng Med*, *2*(1), 1-6.

Choudhury, H., Gorain, B., Madheswaran, T., Pandey, M., Kesharwani, P., and Tekade, B. W., 2018. *Drug complexation implications in drug solubilization and oral bioavailability enhancement. Dosage form design considerations*. Amsterdam: Elsevier, 473–512.

Chowdary, K. P. R., & Srinivasan, S., 2011. Effects of cyclodextrins, Tween-80 and PVP on the solubility and dissolution rate of etoricoxib. *Journal of Pharmaceutical Sciences and Research*, *3*(7), 1344.

from molecules to applications. Environmental chemistry letters, 16(4), 1361-1375.

da Silva Júnior, W. F., de Oliveira Pinheiro, J. G., Moreira, C. D., de Souza, F. J., & de Lima, Á. A., 2017. Alternative technologies to improve solubility and stability of poorly water-soluble drugs. In *Multifunctional systems for combined delivery, biosensing and diagnostics* (pp. 281-305). Elsevier.

Das, S., & Subuddhi, U., 2015. Studies on the complexation of diclofenac sodium with β–cyclodextrin: Influence of method of preparation. *Journal of molecular structure*, *1099*, 482-489.

De Villiers, M. M., Melgardt, M., Pornanong, A., and Glen, S., 2008. *Nanotechnology in drug delivery*. Berlin: Springer Science and Business Media.

Devi, N. K. D., Rani, A. P., Javed, M., Kumar, K. S., Kaushik, J., & Sowjanya, V., 2010. Cyclodextrins in pharmacy-an overview. *Pharmacophore*, *1*(3), 155-165.

El-Zein, H., Riad, L., & Abd El-Bary, A., 1998. Enhancement of carbamazepine dissolution: in vitro and in vivo evaluation. *International journal of pharmaceutics*, *168*(2), 209-220.

Giri, B. R., Lee, J., Lim, D. Y., & Kim, D. W., 2021. Docetaxel/dimethyl-β-cyclodextrin inclusion complexes: preparation, in vitro evaluation and physicochemical characterization. *Drug Development and Industrial Pharmacy*, *47*(2), 319-328.

Greenwald, R. B., Conover, C. D., and Choe, Y. H., 2000. Poly (ethylene glycol) conjugated drugs and prodrugs: a comprehensive review. *Crit. Rev. Ther. Drug Carrier Syst*. 17 (2), 101–161.

Guyot, M., Fawaz, F., Bildet, J., Bonini, F., & Lagueny, A. M., 1995. Physicochemical characterization and dissolution of norfloxacin/cyclodextrin inclusion compounds and PEG solid dispersions. *International journal of pharmaceutics*, *123*(1), 53-63.

Hsiung, E., Celebioglu, A., Chowdhury, R., Kilic, M. E., Durgun, E., Altier, C., & Uyar, T., 2022. Antibacterial nanofibers of pullulan/tetracycline-cyclodextrin inclusion complexes for Fast-Disintegrating oral drug delivery. *Journal of Colloid and Interface Science*, *610*, 321-333.

Jacob, S., & Nair, A. B., 2018. Cyclodextrin complexes: Perspective from drug delivery and formulation. *Drug development research*, *79*(5), 201-217.

Loftsson, T., and Duchêne, D., 2007. Cyclodextrins and their pharmaceutical applications. *Int. J. Pharm*. 329 (1–

Jiang, L., Yang, J., Wang, Q., Ren, L., & Zhou, J., 2019. Physicochemical properties of catechin/β-cyclodextrin inclusion complex obtained via co-precipitation. *CyTA-Journal of Food*, *17*(1), 544-551.

Jindal, R., 2022. Cyclodextrin mediated controlled release of edaravone from pH-responsive sodium alginate and chitosan-based nanocomposites. *International Journal of Biological Macromolecules*, *202*, 11-25.

Jug, M., & Mura, P. A., 2018. Grinding as solvent-free green chemistry approach for cyclodextrin inclusion complex preparation in the solid state. *Pharmaceutics*, *10*(4), 189.

Jug, M., BECIREVIC-LACAN, M., Kwokal, A., & Cetina-Cizmek, B., 2005. Influence of cyclodextrin complexation on piroxicam gel formulations. *Acta Pharmaceutica*, *55*(3), 223-236.

Kaur, K., Jindal, R., & Jindal, D., 2019. Synthesis, characterization and studies on host-guest interactions of inclusion complexes of metformin hydrochloride with β–cyclodextrin. *Journal of Molecular Liquids*, *282*, 162-168.

Kumar, S. K., Sushma, M., & Raju, P. Y., 2013. Dissolution enhancement of poorly soluble drugs by using complexation technique-a review. *Journal of Pharmaceutical Sciences and Research*, *5*(5), 120

Lawrence, M. J., 1994. Surfactant systems: their use in drug delivery. *Chem. Soc. Rev*. 23 (6), 417–424.

Li, M., He, S., Fan, Y., Wang, Y., Ge, Z., Shan, L., Gao, C., et al., 2014. "Microenvironmental pH-modified solid dispersions to enhance the dissolution and bioavailability of poorly water-soluble weakly basic GT0918, a developing anti-prostate cancer drug: preparation, characterization and evaluation *in vivo*, *Int. J. Pharm*. 475, 97.

Liu, J., Alvarez, J., Ong, W., Román, E., & Kaifer, A. E., 2001. Tuning the catalytic activity of cyclodextrin-modified palladium nanoparticles through host− guest binding interactions. *Langmuir*, *17*(22), 6762-6764.

Liu, R. (2018). *Water-insoluble drug formulation*. Boca Raton: CRC Press.

Lo, Y., Hsu, C., Tsai, T., & Cham, T., 2006. Comparison of the solubility and dissolution rate of gliclazide-beta-cyclodextrin inclusion complexes prepared by liquid/liquid extraction and neutralization. *Journal of Food and Drug Analysis*, *14*(3), 230.

Loftsson, T., & Brewster, M. E., 1996. Pharmaceutical applications of cyclodextrins. 1. Drug solubilization and stabilization. *Journal of pharmaceutical sciences*, *85*(10), 1017-1025.

2), 1–11.

Mahapatra, A. P., Patil, V., & Patil, R., 2020. Solubility enhancement of poorly soluble drugs by using novel techniques: A comprehensive review. *Int. J. PharmTech Res*, *13*(2), 80-93.

Musuc, A. M., Anuta, V., Atkinson, I., Sarbu, I., Popa, V. T., Munteanu, C., ... & Mitu, M. A., 2021. Formulation of chewable tablets containing carbamazepine-β-cyclodextrin inclusion complex and f-melt disintegration excipient. The mathematical modeling of the release kinetics of carbamazepine. *Pharmaceutics*, *13*(6), 915.

Newman, A., (2015). *Pharmaceutical amorphous solid dispersions*. Hoboken: John Wiley & Sons.

Özkan, Y., Atay, T., Dikmen, N., Işimer, A., & Aboul-Enein, H. Y., 2000. Improvement of water solubility and in vitro dissolution rate of gliclazide by complexation with β-cyclodextrin. *Pharmaceutica Acta Helvetiae*, *74*(4), 365-370.

Patel, A. R., & Vavia, P. R., 2008. Preparation and evaluation of taste masked famotidine formulation using drug/β-cyclodextrin/polymer ternary complexation approach. *Aaps Pharmscitech*, *9*(2), 544-550.

Patel, R., & Purohit, N., 2009. Physico-Chemical Characterization and In Vitro Dissolution Assessment of Clonazepam—Cyclodextrins Inclusion Compounds. *Aaps Pharmscitech*, *10*(4), 1301-1312.

Prasad, V., De Jesús, K., and Mailankody, S., 2017. The high price of anticancer drugs: origins, implications, barriers, solutions. *Nat. Rev. Clin. Oncol*. 14 (6), 381.

Rajabi, O., Salari, R., & Tayyari, S. F., 2011. Study of structure and properties of Lidocaine: hydroxypropyl-ß-cyclodxtrin inclusion complex. *J Pharmacy Research*, *4*(5), 1562-3.

Rajewski, R. A., & Stella, V. J., 1996. Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery. *Journal of pharmaceutical sciences*, *85*(11), 1142-1169.

Rautio, J., Kumpulainen, H., Heimbach, T., Oliyai, R., Oh, D., Järvinen, T., et al., 2008. Prodrugs: design and clinical applications. *Nat Rev Drug Discov*. 7 (3), 255–270.

Rawat, S., Asgar, L. F., & Jain, S. K., 2005. A comparative dissolution study of commercial and prepared formulations of celecoxib. *Indian journal of pharmaceutical sciences*, *67*(5), 632.

Rogers, T. L., Nelsen, A. C.,... & Williams III, R. O., 2002. A novel particle engineering technology to enhance dissolution of poorly water-soluble drugs: spray-freezing into liquid. *European journal of pharmaceutics and biopharmaceutics*, *54*(3), 271-280.

Uekama, K., 2004. Design and evaluation of cyclodextrin-based drug formulation. *Chemical and*

Rubbens, J., Veiga, R., Brouwers, J., and Augustijns, P., 2018. Exploring gastric drug absorption in fasted and fed state rats. *Int. J. Pharmaceut*. 548 (1), 636–641.

Saharan, V., Kukkar, V., Kataria, M., Gera, M., & Choudhury, P. K., 2009. Dissolution enhancement of drugs. Part I: technologies and effect of carriers. *International Journal of Health Research*, *2*(2).

Schacht, E., Wang, A., Kenawy, E. R., Molly, K., Verstraete, W., Adriaensens, P., et al., 1996. Polymers for colon specific drug delivery. *J. Control. Release*. 39 (2), 327–338.

Serajuddin, A., 1999. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci*. 88 (10), 1058–1066.

Serajuddin, A. T., 2018. *Development of solid dispersion for poorly water-soluble drugs. Water-insoluble drug formulation*. Boca Raton: CRC Press, 541–573.

Shah, K., Fisher, D., Holgate, A. M., and Kime, N. D., 2020. Recent advancements in new drug design and development of prodrugs. *Rec. Adv. Prodrugs*. 12, 133.

Shiralashetti, S., Patil, A., & Patil, J., 2010. Influence of method of preparation on solubility, physicochemical properties and in-vitro release profile of Simvastatin-cyclodextrin inclusion complexes: A comparative study. *International Journal of ChemTech Research*, *2*(1), 562-571.

Singh, B. N., and Kim, K. H., 2002. Drug delivery-oral route. *Encycl. Pharmaceut. Technol*. 14, 886–909.

SN, H., GR, G., & VR, K. A. V., 2010. Studies on the Preparation, Characterization and Solubility of β-cyclodextrin-Nelfinavir Inclusion complexes. *Asian Journal of Pharmaceutical Research and Health Care*, *2*(3).

Sugimoto, M., Okagaki, T., Narisawa, S., Koida, Y., & Nakajima, K., 1998. Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel cogrinding method using water-soluble polymer. *International Journal of Pharmaceutics*, *160*(1), 11-19.

Suresh, S., Shivakumar, H. N., & Kumar, G. K., 2006. Effect of Î² Cyclodextrin complexation on the solubility and dissolution rate of carbamazepine from tablets. *Indian journal of pharmaceutical sciences*, *68*(3).

Trindade, G. G., Thrivikraman, G., Menezes, P. P., França, C. M., Lima, B. S., Carvalho, Y. M., ... & Araújo, A. A., 2019. Carvacrol/β-cyclodextrin inclusion complex inhibits cell proliferation and migration of prostate cancer cells. *Food and Chemical Toxicology*, *125*, 198-209.

pharmaceutical bulletin, *52*(8), 900-915.

Venuti, V., Crupi, V., Fazio, B., Majolino, D., Acri, G., Testagrossa, B., ... & Ventura, C. A., 2019. Physicochemical characterization and antioxidant activity evaluation of idebenone/hydroxypropyl-β-cyclodextrin inclusion complex. *Biomolecules*, *9*(10), 531.

Wadhwa, G., Kumar, S., Chhabra, L., Mahant, S., & Rao, R., 2017. Essential oil–cyclodextrin complexes: An updated review. *Journal of inclusion phenomena and macrocyclic chemistry*, *89*(1), 39-58.

Watson, M. A., Lea, J. M., & Bett-Garber, K. L., 2017. Spray drying of pomegranate juice using maltodextrin/cyclodextrin blends as the wall material. *Food science & nutrition*, *5*(3), 820-826.

Wong, S., Kellaway, I. W., and Murdan, S., 2006. Enhancement of the dissolution rate and oral absorption of a poorly water soluble drug by formation of surfactant-containing microparticles. *Int. J. Pharm*. 317 (1), 61–68.

Wu, C. Y., & Benet, L. Z., 2005. Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. *Pharmaceutical research*, *22*(1), 11-23.

Wu, H., Liang, H., Yuan, Q., Wang, T., & Yan, X., 2010. Preparation and stability investigation of the inclusion complex of sulforaphane with hydroxypropyl-β-cyclodextrin. *Carbohydrate Polymers*, *82*(3), 613-617.

Zafar, A., Alruwaili, N. K., Imam, S. S., Alsaidan, O. A., Alharbi, K. S., Mostafa, E. M., ... & Mohan, S., 2022. Formulation of ternary genistein β-cyclodextrin inclusion complex: In vitro characterization and cytotoxicity assessment using breast cancer cell line. *Journal of Drug Delivery Science and Technology*, *67*, 102932.

Zerrouk, N., Corti, G., Ancillotti, S., Maestrelli, F., Cirri, M., & Mura, P., 2006. Influence of cyclodextrins and chitosan, separately or in combination, on glyburide solubility and permeability. *European journal of pharmaceutics and biopharmaceutics*, *62*(3), 241-246.