International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 16, Issue 2, 2024

Review Article

CYCLODEXTRIN IN NOVEL FORMULATIONS AND SOLUBILITY ENHANCEMENT TECHNIQUES: A REVIEW

SHRADDHA TODKAR[1*], SHASHIKANT DHOLE[1], TANUJA UMATE[1], NILESH KULKARNI[1]

Department of Pharmaceutics, PES Modern College of Pharmacy (For Ladies), Moshi, Pune, Affiliated to Savitribai Phule Pune University, Pune-412105, Maharashtra, India

[*]Corresponding author: Shraddha Todkar; [*]Email: shraddhatodkar2506@gmail.com

Received: 21 Dec 2023, Revised and Accepted: 26 Jan 2024

ABSTRACT

Using cyclodextrin helps make different dosage forms more soluble. The oligosaccharide class known as cyclodextrins (CDs) is made up of glucose units bound together in a ring. CDs have the promising ability to assemble into complexes with drug molecules and improve their physicochemical properties without the need for molecular modifications. Generally, drug-CD complexes have a stoichiometry of 1:1. However, natural CDs have a tendency to self-assemble and form aggregates in aqueous media, which can reduce the solubility of the CDs by aggregating. One can increase their complexation capacity and solubility through derivative formation, but the final outcome depends on the kind and extent of substitution. Drug penetration through biological membranes can be improved by the formation of water-soluble drug-CD complexes. Solubility is the property of a solid dissolving into a liquid phase to form a homogenous system. Solubility is a crucial component in obtaining the right drug concentration in the systemic circulation for the optimal pharmacological response. Orally administered poorly soluble drugs often require high dosages to reach therapeutic plasma concentrations. Their low solubility in water is one of the primary problems with creating new chemical entities through formulation. The BCS classification system places these medications in class II, which is characterized by high permeability and poor solubility. To greatly improve these medications, it is possible to make them more bioavailable and soluble.

Keywords: Cyclodextrin, Complexation, Inclusion complex, Solubility, Solubility Enhancement

© 2024 The Authors. Published by Innovare Academic Sciences Pvt Ltd. This is an open access article under the CC BY license (https://creativecommons.org/licenses/by/4.0/)
DOI: https://dx.doi.org/10.22159/ijcpr.2024v16i2.4032 Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

Cyclodextrin [1]

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of α-1,4-linked glucose units with lipophilic central cavities and hydrophilic outer surfaces. Small amounts of natural products known as α-Cyclodextrin (αCD), β-Cyclodextrin (βCD), and γ-Cyclodextrin (γCD) can be found in a range of fermented consumer goods which include beer. Unsubstituted natural αCD, βCD, and γCD, as well as their complexes, are hydrophilic but only slightly soluble in aqueous solutions (particularly βCD). Thus, while low concentrations of both αCD and γCD are present in parenteral formulations, the more soluble derivatives of βCD, like 2-hydroxypropyl-βCD (HPβCD) and sulfobutylether βCD, are generally preferred. Moreover, CDs are present in pharmaceutical products that are sold all over the world. CDs are found in pharmaceutical products sold all over the world. Moreover, food, cosmetic, and toiletry products contain cyclodextrin. Because of their ability to change the physiochemical characteristics of drugs and other compounds, CDs are frequently referred to as enabling pharmaceutical excipients. By integrating a part of the drug molecule into the CD's central cavity, drugs, also known as guest molecules, can form inclusion complexes with CDs, also known as host molecules. This will change the physiochemical properties of the drug. Pharmaceutical scientists still view cyclodextrins as a relatively new class of pharmaceutical excipients despite their existence for more than a century.

Structure and properties [2, 3]

These structurally related natural products, cyclodextrin, are created when bacteria break down cellulose. These bucket-shaped cyclic oligosaccharides have a lipophilic core cavity and a hydrophilic exterior surface. They are composed of (α-1-4)-linked α-D glucopyranose units. The most prevalent naturally occurring cyclodextrins are α, β, and Υ. Six, seven, and eight glucopyranose units are included, respectively. The chair conformation of glucopyranose units, or cyclodextrins, has a truncated cone-like shape rather than a perfect cylinder.

The sugar residues' primary hydroxyl groups are located at the cone's narrow edge, while the secondary hydroxyl groups are located at its wider edge. The hydroxyl functions are oriented toward the cone's exterior. The skeletal carbons and ethereal oxygen of the glucose residues line the central cavity, giving it a lipophilic quality. According to estimates, the cavity's polarity is comparable to that of an aqueous ethanolic solution. Cyclodextrin has the unusual ability to hold a guest molecule inside its cavity and function as a molecular container because of the way its molecules are shaped and assembled.

While solutions of individual cyclodextrin molecules and cyclodextrin complexes are thought of as homogeneous molecular dispersions in an aqueous system, aqueous solutions of cyclodextrins have been recognized as true solutions. The ability of cyclodextrins and cyclodextrin complexes to self-associate to form an aggregate or micelle-like structure was demonstrated recently. Moreover, it has been demonstrated that polymers interact with such a system, and the aggregates that are created have the ability to solubilize medications by forming non-inclusion complexes.

Fig. 1 Structure (i) α-cyclodextrin, (ii) β-cyclodextrin, (iii) Υ-cyclodextrin

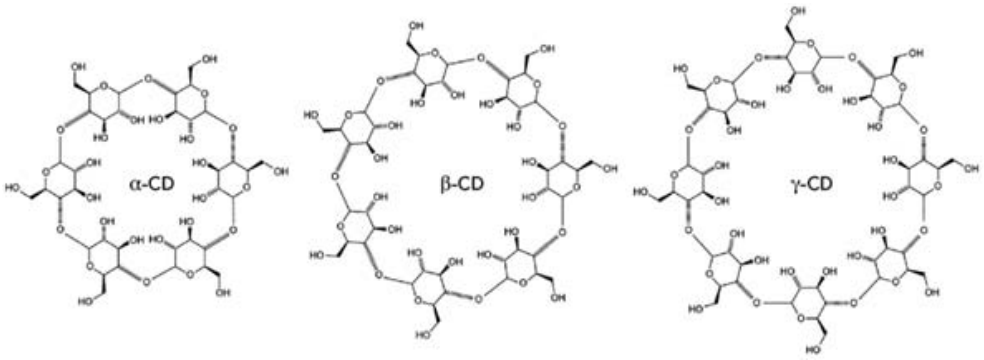
Properties of cyclodextrin [2, 3]

Described in table 1

Toxicological studies [4]

Only lipophilic biological membranes, like the cornea of the eye, can be permeated by natural cyclodextrins and their hydrophilic derivatives with great difficulty. Although it interacts with membranes more easily than the hydrophilic cyclodextrin derivatives, even the moderately lipophilic randomly methylated cyclodextrin does not readily permeate lipophilic membranes. Because they are not absorbed by the gastrointestinal system, cyclodextrins taken orally have been shown in all toxicity investigations to be essentially non-toxic. Additionally, a number of safety assessments have demonstrated that even when given parenterally, -cyclodextrin, 2-hydroxypropyl-b-cyclodextrin,

sulphobutylether-cyclodextrin, sulfated-cyclodextrin, and maltose-cyclodextrin seem to be safe. Nevertheless, toxicological research has also demonstrated that parent and methylated cyclodextrins, as well as cyclodextrin, are not appropriate for parenteral delivery.



α-cyclodextrin **β-cyclodextrin** **Y-cyclodextrin**

Fig. 1: Structure of cyclodextrin

Table 1: Properties of cyclodextrin

Properties	α-cyclodextrin	β-cyclodextrin	Y-cyclodextrin
Number of glucopyranose units	6	7	8
Molecular weight (Da)	972	1132	1297
Central cavity Diameter (A°)	4.7-5.3	6.0-6.5	7.5-8.3
Water solubility at 25 8C (g/100 ml)	14.5	1.85	23.2
Linkage	α (1-4)	α (1-4)	α (1-4)
Cavity diameter (nm)	0.47	0.60	0.75
Height of torus (nm)	0.79	0.79	0.79

α-Cyclodextrin

It binds specific lipids, causes some ocular irritation, absorbs between 2 and 3% when given orally to rats, has no metabolism in the upper gastrointestinal tract, and is only broken down by the intestinal flora of the colon and caecum. It also has an unpleasant after intraperitoneal injection. Rats: LD50 oral>10,000 mg/kg; LD50 intravenous: 500–750 mg/kg. After oral administration to germ-free rats, the following excretion occurred: 60% as CO2 (rats did not exhale CO2), 26–33% as metabolite incorporation, and 7–14% as metabolites in urine and faeces. After intravenous injections with t1/2 = 25 min in rats, these were mainly eliminated unaltered by the renal route.

β-cyclodextrin

It binds cholesterol, is less irritating than cyclodextrin after intraperitoneal injection, is absorbed in very small amounts (1-2%) after oral administration, has no metabolism in the upper intestinal tract, and undergoes metabolism by bacteria in the colon and caecum. It is currently the most commonly used cyclodextrin in pharmaceutical formulations and is, therefore, likely the most studied cyclodextrin in humans. Using large doses could be hazardous and is not advised; gas production and diarrhoea could result from bacterial degradation and fermentation in the colon. Rats: >5000 mg/kg for LD50 oral, 450–790 mg/kg for LD50 intravenous.

Y-cyclodextrin

This naturally occurring cyclodextrin has the following properties, which make it probably the least toxic: minimal irritation after intramuscular injection; almost no (0.1%) absorption (of intact-cyclodextrin) after oral administration; almost no metabolism after intravenous administration; intestinal enzymes quickly and completely break down to glucose in the upper gastrointestinal tract (even at high daily dosages, such as 10–20 g/kg). Marketed actively as a food additive by its primary manufacturers, it has a generally lower complexing capacity than cyclodextrin and its water-soluble derivatives. Rats' LD50 oral is 8000 mg/kg, and LD50 intraperitoneal is approximately 4000 mg/kg. Its complexes frequently have low solubility in aqueous solutions and tend to aggregate in aqueous solutions, resulting in an unclear solution (opalescence).

Formation inclusion complex [5]

The most remarkable property of cyclodextrins is their molecular complexation capacity to form solid inclusion complexes, also known as host–guest complexes, with a very broad spectrum of solid, liquid, and gaseous substances. A guest molecule is contained inside the cyclodextrin host molecule's cavity in these complexes. A dimensional fit between the guest molecule and the host cavity results in complex formation. Appropriately sized non-polar moieties can enter the lipophilic cavity of cyclodextrin molecules to create inclusion complexes. During the development of the inclusion complex, no covalent connections are broken or created. The release of enthalpy-rich water molecules from the cavity is the primary mechanism responsible for complex formation. To achieve this, more hydrophobic guest molecules in the solution displace the water molecules.

Any non-aqueous solvent can be used, and inclusion complexation can be carried out in a co-solvent solution. The physicochemical properties of guest molecules are significantly impacted by inclusion in cyclodextrins because the guest molecules are momentarily trapped or locked inside the host cavity, leading to advantageous alterations that would not be possible otherwise. These characteristics include improving the solubility of extremely insoluble guests, stabilizing labile guests against oxidation, heat, visible or UV light, and degradative effects, controlling volatility and sublimation, physically isolating incompatible compounds, masking off flavours, chromatographic separations, as well as unpleasant odours to modify taste, and releasing drugs and flavours under controlled conditions. Chemical modification significantly increases the functionality of cyclodextrins. The uses of cyclodextrins can be increased via alteration.

A cyclodextrin's ability to form an inclusion complex with a guest molecule is dependent on two key components. The first is steric and depends on the size of the cyclodextrin relative to the guest molecule or on certain significant functional groups in the guest molecule. If the guest is the wrong size, they won't fit into the cyclodextrin cavity sufficiently.

The second important factor is the thermodynamic interactions among the different components of the system: cyclodextrin, guest, and solvent. A complex can only form if there is a positive net energetic driving force that pulls the guest into the cyclodextrin fig. 2.

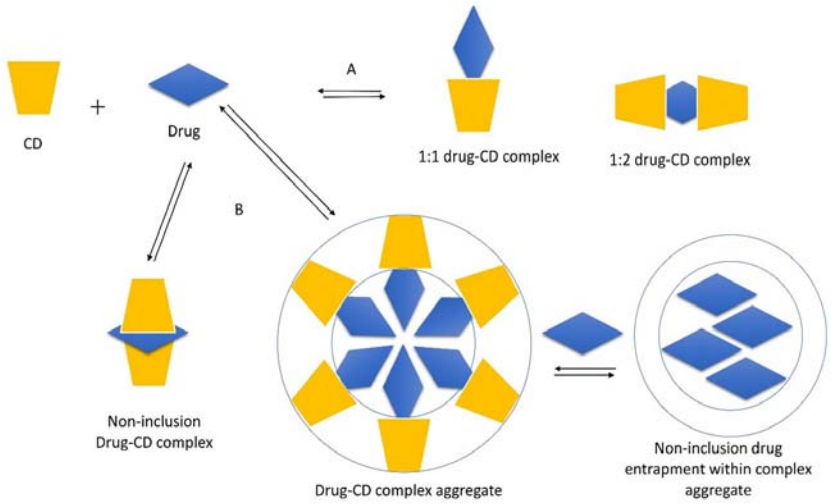


Fig. 2: Drug-cyclodextrin complex

Four interactions contribute to the formation of the inclusion complex by shifting the equilibrium in an energetically favourable way [5]:

The polar water molecules' displacement from the apolar cyclodextrin cavity.

The fact that as the displaced water moves back into the larger pool, more hydrogen bonds are formed.

A decrease in the hydrophobic guest's repellent interactions with the aqueous environment

As the visitor moves into the apolar cyclodextrin cavity, there is a rise in the hydrophobic interactions.

Method of preparation [6]

A stoichiometric molecular phenomenon known as "cyclodextrin inclusion" typically results in the entrapment of a single guest molecule through interaction with the cyclodextrin molecule's cavity. The formation of a stable complex is caused by a number of non-covalent forces, including hydrophobic interactions and van der Waals forces. Usually, one guest molecule is included in one cyclodextrin molecule, even though multiple guest molecules might fit into the spaces of some low molecular weight molecules and multiple cyclodextrin molecules may bind to the guest in some high molecular weight molecules. Essentially, for a molecule to form a complex, only a portion of it needs to fit into the cavity. One-to-one molar ratios are, therefore not always reached, particularly when dealing with guests that have high or low molecular weights.

Complexation techniques [3, 4]

Co-precipitation

Paste Complexation

Slurry Complexation

Damp Mixing and heating

Extrusion

Dry Mixing

Drying of complexes

Spray Drying

Low Temperature Drying

High Volatile Gustes

Characterization of CD-drug complexes [7]

Thermo-analytical methods

Characterizing inclusion complexes is a common application of thermo-analytical techniques. Drug thermal profiles can be compared before and after CD complexation using differential thermal analysis (DTA) or differential scanning calorimetry (DSC). Molecular transformations like melting, oxidation, or breakdown show up as distinctive peaks or troughs on the thermograms that are produced. Complex formation can be verified by peak shifts and/or the addition and subtraction of features on the thermogram. When complexed with CD molecules, several medications, such as salbutamol and famotidine, have been shown to lose their distinctive peaks on thermograms. The degree of drug complexation can also be quantitatively assessed using thermograms. Comparing the area under the DSC curve of a formed complex with that of a physical drug-CD mixture is necessary for this kind of characterization. It is possible to establish a correlation between the apparent degree of formation of complexes.

Chromatographic methods

Drugs, CDs, and complexes can be distinguished using thin TLC and HPLC because the three samples have different retention characteristics. One problem, particularly in TLC, is that complexation is a complex may separate during chromatographic analysis due to the reversible nature of the process. Nonetheless, the method can be applied to ascertain the drug-CD molecule affinities.

Wettability/Solubility studies

In wettability studies, the contact angle, sedimentation, and dissolution rates of powdered drug-CD complex in water are examined. Even though a powder's cumulative wettability can be increased by adding just CD, the conduction of dissolution. Research on the powder may provide a more accurate picture of whether drug-CD complexation has done in fact, happen. Tablets made of solid CD formulations can be put through to a test for dissolution. After media is collected at predetermined intervals and the drug content in the media is analysed, it is possible to ascertain whether the CD complexation has enhanced a drug's ability to dissolve. It is possible to compare the dissolution rates of complexes made using various techniques to ascertain which technique is best for improving medication breakdown.

Microscopic method

The crystalline states of the raw materials and the finished product after complexity can be imaged using TEM and SEM. The structural variations that have been noticed can be utilized to show the

creation of complexes that are inclusion or non-inclusion. Despite the fact that the techniques have been Frequently employed to describe CD complexes, they are deemed inconclusive in verifying complexation and ought to be utilized solely as supplementary methods to more resilient characterization approaches.

Spectroscopical method

H-NMR spectroscopic characterization is a reliable method for verifying inclusion complex formation. The method can also help identify the specific chemical groups in the drug and CD that are interacting when the complex forms.

By measuring how each molecule absorbs IR light according to its specific structure, infrared (IR) spectroscopy allows for the characterization of molecules. When a drug has functional groups like carbonyl or sulfonyl groups, which show up as distinctive bands on IR spectra, the technique is particularly helpful. If hydrogen bonds are created between these kinds of bands and CD during complexation, band widening or band intensity increases may appear on the spectrum. Previously, IR has been used to confirm CDs complexed with a variety of medications, such as clotrimazole, piroxicam, indomethacin, and naproxen.

Raman spectroscopy is a complementary technique to infrared spectroscopy that uses monochromatic light's inelastic scattering to identify a molecular fingerprint. Using this method, drug-CD complexation can be examined by evaluating the effects of intermolecular interactions on peak shifts and band intensities on the spectra. Different Raman spectroscopy has been used to confirm drug-CD complex systems, including for ibuprofen, and carotenoids.

X-ray techniques

The process of identifying complex formation through crystal structure analysis is known as X-ray diffraction (XRD). Diffraction peaks change as a result of complex formation depending on how the formation affects CD and drug crystallinity. A decline decrease in crystallinity is correlated with a peak sharpness decrease on the diffractogram. Molecular Structure Following complexation with different CDs, several medications, such as celecoxib, quercetin, and warfarin, all show losses in crystalline peaks, indicating the amorphous form of these various.

Release

A complex has a very long shelf life at room temperature in dry conditions once it has formed and dried. When one guest moves into a complex, another needs to be heated. Water can frequently take the place of the guest. There are two steps involved in the complexed guest's release when submerged in water. The complex is first dissolved. The complexed guest is released in the second stage when water molecules take its place. There will be a balance between the guest and the dissolved as well as undissolved complex and between the free and complexed cyclodextrin. Guest molecules are not always released in the same ratio as in the original guest mixture when complexes with different guest components or cyclodextrin types are involved. The solubility and rate at which each guest complex releases from the complex may vary. By modifying the guest formulation, an intended release pattern can be obtained if the rates of release for each component differ.

Advantages [8, 9]

Drug solubility and dissolution

Drug absorption

Control of drug release

Site-specific drug delivery

Drug safety

Drug stability

Inhibiting reverse diffusion

Effective with low dose of drug

Improve biomembrane permeability

Limitations

Not all drug classes make good substrates for CD complexation. A drug molecule that is to be complexed with CD needs to possess the properties listed below. While exceptions cannot be ignored, these qualities are typically preferred for pharmaceutical and medical benefits.

Atoms>5 (C, P, S, N) form the skeleton of the drug molecule.

Melting point of substance<250 °C.

Solubility in water<10 mg/ml.

Molecular weight between 100 and 400.

The guest molecule consists of less than five condensed rings.

In general, inorganic substances are not good candidates for complexation. The exceptions are halogens, non-dissociated acids (H3PO4, HI, etc.), and gases (Xe, CO2, etc.). Strongly hydrophilic compounds, such as proteins, peptides, enzymes, and the like, are typically excessively large to be complicated. However, it was discovered that large, soluble molecules in water that have side chains that can form complexes with cyclodextrins in aqueous solutions alter the solubility and stability of the mixture.

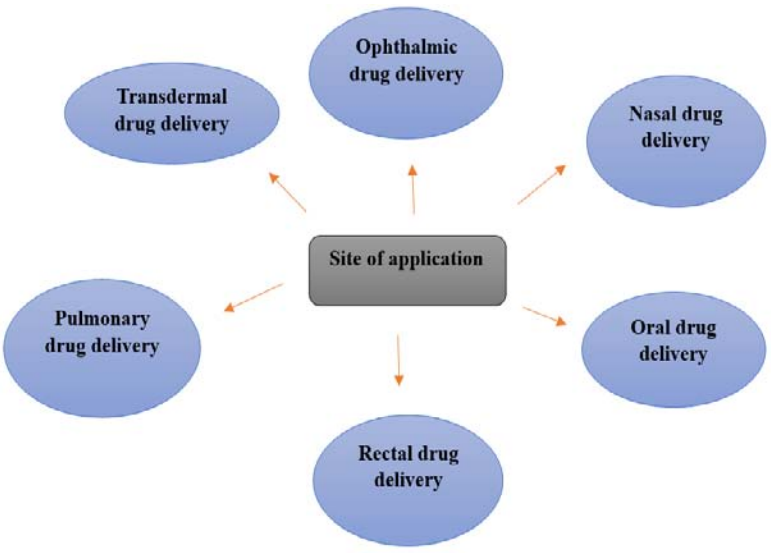


Fig. 3: Drug delivery approaches

Applications

Increased solubility of the substances

Stabilization of the substances that are sensitive to light and oxygen

Stabilization of highly volatile material

Converting liquid material to powder form

Alteration of guest molecules chemical reactivity

Masking unpleasant test and odour

Concealing colours

Defence against microbial deterioration of substances

Drug delivery approaches [3, 9]

Described in fig. 3.

Drug delivery systems with cyclodextrin [8]

Some of the drug delivery approaches are given in following chart

Described in fig. 4

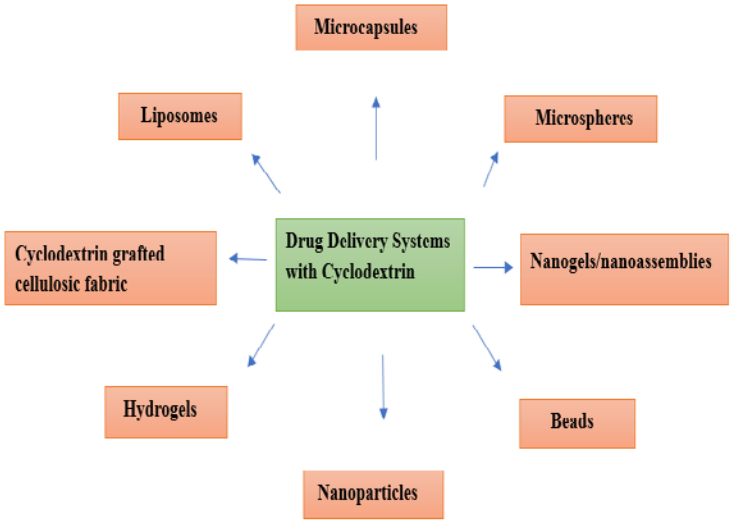


Fig. 4: Drug delivery systems with cyclodextrin

Table 2: Drug delivery with cyclodextrin examples

S. No.	Cyclodextrin type	Formulation	Drug	Method	References
1.	HP-Y-CD	Liposomes	Betamethasone	Film Evaporation Method	[10]
2.	β-CD	Liposomes	clonazepam	Thin Layer Evaporation Technique	[11]
3.	HP-Y-CD	Liposomes	Ketorolac	Kneading Method	[12]
4.	HP-Y-CD and β-CD	Liposomes	Ketoprofen	Coevaporation and Sealed-heating Methods	[13]
5.	β-CD	Liposomes	Meloxicam	Conventional Rotary Evaporator Method	[14]
6.	HP-Y-CD	Nanospheres	Flurbiprofen	Solvent Displacement Technique	[15]
7.	β-CD	Nanocapsules	Oxygen Delivery	Colloidal nanoprecipitation method	[16]
8.	HP-Y-CD	Nanoparticles	Docetaxel	Nanoprecipitation Method	[17]
9.	β-CD	Nanospheres	metronidazole	Nanocrystallization	[18]
10.	β-CD	Nanoparticles	Ketoprofen	ionotropic gelation method	[19]
11.	HP-Y-CD	Nanospheres	Flurbiprofen	Solvent Displacement Technique	[15]
12.	SBECD	Electrospun Nanofiber	Remdesivir	Electrospinning	[20]
13.	Y-CD, α-CD	Eye Drops	Cyclosporin		[21]
14.	β-CD	Nanosponges	Paclitaxel	Freeze Drying Method	[22]
15.	β-CD	Liposomes	Tretinoin	Kneading Method	[23]

Table 3: USP and BP solubility criteria

Class	Solubility	Permeability	Example
I	High	High	Propranolol
II	Low	High	Naproxen
III	High	Low	Metformin
IV	Low	Low	Taxol

Solubility [24]

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. Temperature, pressure as well as the solvent used affects the solubility of substance.

IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units. Table 3. Solubility criteria.

Pharmaceuticals are categorized using the BCS, a scientific paradigm, according to their intestinal permeability and water solubility. In addition to the drug product's *in vitro* dissolving characteristics, the BCS takes into account three crucial variables: intestinal permeability, solubility, and dissolution rate. These variables all affect the rate and

volume of oral drug absorption from sudden-release solid oral dosage forms. Based on their solubility and permeability, pharmaceuticals are divided into four basic classes by the US Food and Drug Administration (FDA) and the BCS Class II and class IV drugs have solubility issues. Thus, improving the solubility of BCS Class II and Class IV drugs increases their bioavailability table 4.

Table 4: BCS classification

Descriptive term	Parts of solvent required per part of solute
Very soluble	<1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10000
Practically insoluble	>10000

Solubilization [25]

Solubilization can be defined as "the preparation of a thermodynamically stable solution of a substance that is normally insoluble or very slightly soluble in a given solvent by the introduction of one or more amphiphilic component(s)".

Solubility enhancement

To improve dissolution and bioavailability by using novel techniques has great importance in pharmaceutical development to enhance clinical efficiency, particularly for poorly water-soluble drug as active ingredient. Also, the efforts and studies are going on. Absorption of drug is affected by the various factors of GI tract. Absorption of drug is dependent on the dissolution of the drug and the dissolution of drug is dependent on the solubility of the drugs in GI fluid. The most commonly used technique of enhancing oral absorption and bioavailability of poorly water-soluble drugs is to enhance their dissolution rates.

Techniques for solubility enhancement [26-30]

Physical modifications

Particle size

Micronization

Co-grinding

Coprecipitation

Nanosuspension

Crystal habit

Polymorph

Pseudo polymorph

Complexation/solubilization

Use of surfactants

Use of cyclodextrins

Drug dispersion in carriers

Solid dispersions (non-molecular)

Solid solutions

Fusion method

Method of solvent evaporation

Solubilization by surfactants

Microemulsion

SMEDDS

Chemical modifications

Co-solvency

Nanotechnology

Hydro trophy

Salt formation

Other methods

pH adjustment

Superficial fluid process

Liquisolid methods

Spray drying method

Inclusion complex

Cryogenic method

High-pressure homogenization

Neutralization

Eutectic mixtures

Precipitation

Solvent disposition

Sono crystallization

Spherical agglomeration

Physical modifications

Particle size

Particle size of drug affects the solubility of drug. Reduction in the particle size increases the surface area, which leads to an increase in the solubility. Drug particle size is often related to the bioavailability of poorly soluble drugs. This can be done by following techniques:

Micronization

In micronization technique, the dissolution rate of drugs increased through an increase surface area of particles. But, equilibrium solubility does not increase. Increasing the surface area of these drugs which cause decrease in particle size, enhance their rate of dissolution.

Nanosuspension

Drugs that are insoluble in water and oils can be made more soluble using a technique called nanosuspension. A biphasic system made up of nanoscale particles suspended in an aqueous medium is called nanosuspension. Surfactant stabilizes nanoscale drug particles for oral and tropical use, as well as parenteral and pulmonary administration. The solid particle size distribution in nanosuspension is typically less than one micron. Particle sizes range from 200 to 600 nm on average. This procedure was used for buparvaquone, amphotericin and paclitaxel, tarazepide, and atovaquone. There are several ways to prepare nanosuspensions, such as using Nanopore, Nanocrystals, and Nano edge.

Co-grinding

In order to enhance the rate of dissolution co-grinding is an effective method. Water soluble polymers act as co-ground carrier, from

which drugs are released. In this method there is no need of addition of organic solvent as well as increasing temperature.

Co-precipitation

Coprecipitate formation with pharmacologically inert polymeric material increases the rate of dissolution. This technique minimizes the use of organic solvent. Coprecipitation of water-insoluble drug with water-soluble polymer leads to increase in *in vitro* dissolution rate and/or *in vivo* absorption.

Crystal habit

Polymorphism: The capacity of a solid material to exist in two or more distinct crystalline forms with various arrangements within the crystal lattice is known as polymorphism. Different crystalline forms are called polymorphs. Drugs in crystalline form have the same chemical makeup, but they differ in their physiochemical characteristics, such as stability, solubility, texture, melting point, and density. In a comparable way, amorphous drugs are preferable to crystalline ones. because of its larger surface area and high energy content.

Polymorphs

Pseudo polymorph

Complexation

To increase a drug's water solubility and stability, cyclodextrins have been added to drug complexes. The most often used β-cyclodextrin derivatives with better water solubility are used in pharmaceutical formulations. Cyclodextrins are large molecules with molecular weights greater than 1000 Da, making it unlikely that they will readily penetrate skin. It has been observed that cyclodextrin complexity causes changes in skin penetration. In addition to their solubility enhancement application, CDs can also be used as stabilizing agents and enhancers of membrane permeability. Enhancement of permeability across biological membranes is achieved by the presence of cyclodextrins. The permeability of CDs can also be improved in pulmonary drug delivery systems.

Use of Surfactant

Use of Cyclodextrin

Drug dispersion in carriers [30]

Solid solution

Two crystalline solids are combined to form a new crystalline solid in this instance. Two components crystallize together to form a mixed crystal in a homogenous one-phase system. It provides a significantly higher rate of dissolution when compared to a basic enteric system.

Fusion process

In this method, the drug is mixed into the matrix while the carrier is heated above its melting point. The mixture is then cooled to distribute the drug evenly throughout the matrix.

Method of solvent evaporation

The carrier and active ingredient are dissolved in an appropriate organic solvent. To create a solid residue, a solvent is evaporated at a high temperature in a vacuum.

Solid dispersion

Sekiguchi and Obi introduced the idea of solid dispersion. A helpful pharmaceutical technique for increasing a drug's rate of absorption, dissolution, and therapeutic efficacy is solid dispersion. A group of solid products with a hydrophilic matrix and a hydrophobic drug are referred to as solid dispersions. Hydrophilic carriers such as polyethylene glycols, polyvinyl pyrrolidone, and plasdone-S630 are frequently utilized. In the process of solid dispersion formation, surfactants are frequently utilized. Table 5 carrier materials with example.

Table 5: Carrier materials with example

S. No.	Materials as a carrier	Examples
1.	Acids	Citric acid, succinic acid
2.	Polymeric Materials	Povidone (PVP), polyethylene glycol (PEG), hydroxypropyl methylcellulose, methylcellulose, hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose
3.	Surfactants	Poloxamer 188, text for AIP, deoxycholic acid, tweens, spans
4.	Sugars	Dextrose, sucrose, galactose, lactose
5.	Insoluble or enteric polymer	HPMC phthalate, eudragit L100, eudragit S100, Eudragit RL
6.	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea

Solubilization by surfactant [31, 32]

Microemulsion

A microemulsion is a system that is optically clear, transparent, thermodynamically stable, and isotropically translucent. It dissolves a drug that is poorly soluble in water by mixing an oil, surfactant, and hydrophilic solvent. The selection of a surfactant is based on two parameters: non-toxicity and HLB. The formulations self-emulsify when they come into contact with water, creating a small, homogeneous emulsion of tiny, transparent oil droplets that contain the weakly soluble medication that has been solubilized. Microemulsions have been used to incorporate proteins for oral, parenteral, and intravenous administration as well as to increase the solubility of many drugs that are almost insoluble in water. An oil-in-water (o/w) microemulsion is the best formulation because it is designed to improve solubility by dissolving molecules with low water solubility into an oil phase solubility.

SMEDDS

A transparent isotropic solution is produced by the combination of oil, surfactant, co-surfactant, and one or more hydrophilic solvents in the absence of an external phase (water) and the cosolvent. One kind of is the self-emulsifying solution. a solution with self-emulsifying properties. Additionally, some researchers have referred to it as "microemulsion pre-concentrate." When ingested, these novel colloidal formulations behave similar to microemulsions of oil in water.

Chemical modifications

Co-solvency

A combination of one or more miscible liquids called co-solvency is used to increase a drug's solubility. The solubility, miscibility, and dissolution of the solution can all be enhanced by the addition of a co-solvent solution. The co-solvent increased the low-solubility drug by nearly 1000 times compared to the simple drugs. For highly crystalline molecules that are highly soluble in the solvent mixture or poorly soluble lipophilic molecules, a co-solvent technique might be suitable.

Nanotechnology

Nanotechnology is the study and application of materials and structures at the nanoscale level, or less than 100 nanometres. For many new chemical entities with limited solubility, the oral bioavailability increase achieved through micronization is insufficient Because the effective surface area of micronized products is comparatively small for dissolving, the stage after that was nanonization.

Hydro trophy

A high concentration of a second solute is added to a third solute to increase its aqueous solubility through a process known as hydrotrophy. Its solubility-improving mechanism is more closely linked to complexation, which entails weak contact between hydrotropic substances like urea, sodium benzoate, sodium acetate, sodium alginate, and medications that are poorly soluble. "Salting in" non-electrolytes, sometimes referred to as "hydrotropic salts" brought on by numerous salts that have large cations or anions and are very soluble in water, a phenomenon referred to as "hydrotropism." Non-colloid hydrotropic solutions have a weak interaction between the solute and the hydrotropic agent.

Salt formation

By using salt generation techniques, drug solubility and dissolution can be improved. This technique is employed to watch how different medications or chemical reactions affect the body. Salt is created when a drug ionizes. It functions well in liquid and parenteral forms, in addition to solid ones.

Other techniques

pH adjustment

The solubility of a drug that is poorly soluble in water may be increased if the pH is adjusted; the buffer capacity and tolerability of the selected pH must be taken into account when obtaining solubility using this method. Excipients that raise the pH of the environment within the dosage form to a level higher than he pKa of weekly acidic pharmaceuticals increase the solubility of the drug; excipients that function as alkalizing agents may increase the solubility of weekly basic drugs. It can also be used on crystalline and lipophilic poorly soluble substances.

Superficial fluid process

Non-volatile solvents can be dissolved by supercritical fluids (SCFs) at the carbon dioxide critical point. A SCF is a single phase above its critical temperature and pressure. It is economical, safe, and environmentally beneficial. Pharmacological research is drawn to SCFs due to their low pressure and temperature operating parameters. SCFs possess attributes that are beneficial for product processing because they fall between pure liquid and pure gas. Additionally, small variations in the operating temperature, pressure, and pressure near the critical points density, transport characteristics (like viscosity and diffusivity), and other physical characteristics (like polarity and dielectric constant). Nitrous oxide, carbon dioxide, Common superficial solvents include ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water.

Numerous techniques have been developed to address different aspects of these shortcomings, including the following: precipitation with compressed antisolvents process (PCA), gas antisolvent recrystallization, rapid expansion of supercritical solutions, precipitation with impregnation or infusion of polymers with bioactive materials, gas antisolvent recrystallization, compressed fluid antisolvent, solution enhanced dispersion by supercritical fluid (SEDS), and aerosol based SCF processing.

Liquisolid method

A liquid medication can be made into a dry, non-adherent, free-flowing, compressible powder by blending it with specific powder excipients, such as the carrier and coating material. Coating materials include amorphous, microcrystalline cellulose, and silica powders. When a drug dissolved in a liquid vehicle is introduced into a carrier material with a porous surface and Fibers in its interior, such as cellulose, both adsorption as well as absorption occur; that is, the liquid is initially absorbed in the interior of the particles and is captured by its internal structure, and after this process has reached saturation, the liquid is adsorbed onto the internal-external surfaces of the porous carrier particles.

Cryogenic method

Cryogenic methods have been developed to produce nanostructured amorphous drugs, which increase the rate of drug dissolution particles at extremely low temperatures with a high degree of porosity. Innovations utilizing cryogenics can based on the kind of injection tool (capillary, ultrasonic, pneumatic, and rotating nozzle), placement nozzle (below or above the liquid level), as well as the cryogenic liquid's composition (hydrofluoroalkanes, Organic solvents, N2, Ar, and O2. Following cryogenic processing, there are several ways to obtain dry powder. Techniques for drying such as spray freeze drying, vacuum freeze drying, atmospheric freeze drying, as well as lyophilization.

Factors affecting solubility [29]

Temperature

A solid's solubility in a liquid is temperature-dependent. If heat is absorbed during the solution process, the solubility of the solute rises as the temperature rises. For the majority of the salts, this is the case. A solute's solubility will decrease with an increase in heat produced by the solute during the solution process.

Solute molecular structure

A compound's solubility in a particular liquid can be significantly impacted by even slight changes to its molecular structure. To show this, the addition of a hydrophilic hydroxyl group can result in a significant improvement. in solubility in water. Furthermore, the transformation of a weak acid yields a much higher sodium salt higher level of dissociation between the ions in the when it gets dissolved in water, a compound. In general, the way that a solute and solvent interact is significantly elevated and the solubility rises as a result. Furthermore, the esterification of medication will make it less soluble.

Nature of solvent

The significance of the solvent's nature has been examined in relation to the adage "like dissolves like" and in parameters of solubility. Furthermore, the point has been established that solvent mixtures could working. Such blends are frequently utilized in using pharmaceutical practice to produce water-based systems that have more solutes than they soluble in unadulterated water. To do this, one uses cosolvents like propylene glycol or ethanol, which act as and are miscible with water superior solute-solvent combinations.

Particle size of the solid

As different-sized particles dissolve, changes in the interfacial free energy that accompany those changes cause a substance's solubility to rise with decreasing the size of the particles. The rise in solubility stops when the particle size decreases the radius of a particle is incredibly small, so any Additional reduction in size results in a decline in solubility.

pH

When a weakly acidic drugs or its salt is dissolved in a solution, the percentage of unionized acid molecules in the solution rises. Therefore, precipitation may take place as a result of the unionized less than the ionized form's species. On the other hand, when it comes to weakly basic drugs or the precipitation of their salts is preferred by a rise in pH. Precipitation of this kind is one instance. A particular kind of chemical incompatibility that could occur during the creation of liquid medications.

Crystal properties

Various polymorphs, or crystalline forms, of the same substance, have varying lattice energies as a result, and this variation is represented by modifications to other attributes. The result of the solubility polymorphism is especially significant from a pharmaceutical perspective since it offers a method of raising a crystalline material's solubility and, consequently, its rate of breakdown when utilizing a metastable transmute. Lack of crystalline organization that is typically connected to a purported amorphous powder could potentially result in a rise in the drug's solubility in relation to its crystal structure.

Solubilizing agent

When these agents' concentrations rise above a certain point, they have the ability to form sizable aggregates or micelles in solution.

Within an aqueous solution, these aggregates centres likened to distinct organic phases and organic the aggregates have the potential to absorb solutes, so causing their apparent solubility to increase in the water. This occurrence is referred to as solubilization. A comparable occurrence takes place in solvents made of organic materials with dissolved solubilizing agents, given that the aggregates centre in these systems make up a region that is more polar. Greater than the majority of the organic solvent. In case polar these areas absorb solutes, and their evident solubility in the solvents that are organic are produced.

Complex formation

The addition of a third substance can either increase or decrease a solute's apparent solubility in a given liquid, which participates the to form an intermolecular complex solution. The complex's solubility will find the apparent shift in the solubility of the initial solute.

Polarity

The solubility will be impacted by the polarity of the solvent and solute molecules. "Like dissolves like". Which means polar molecule dissolve in polar solvent and vice versa. Polar molecules possess positive and negative ends. when they come in contact with the polar solvent, opposite attraction between solute and solvent molecule take place which means the negative end of the solute attracts towards the positive end of the solvent and vice versa. These intermolecular forces are known as dipole-dipole interaction. The London forces of attraction gives chance to the non-polar molecules for the interaction.

CONCLUSION

To sum up, cyclodextrins have shown to be adaptable and promising molecules with a broad range of uses in a variety of industries. Cyclodextrins are indispensable in pharmaceutical, food, cosmetic, and other industries because of their extraordinary capacity to encapsulate and solubilize hydrophobic substances due to their distinct structure. In the pharmaceutical industry, cyclodextrins are essential for increasing the stability, decreasing potential side effects, and increasing the bioavailability of poorly soluble drugs. Cyclodextrins show promise as adaptable and versatile tools for improving the solubility of medications that are poorly soluble in water, offering a workable answer to one of the main problems in drug development. Because of their distinct structural properties, cyclodextrins can combine with hydrophobic drug molecules to form inclusion complexes that improve their aqueous solubility and, in turn, their bioavailability. The results of a multitude of investigations and studies on cyclodextrin-based solubility enhancement have shown that these methods are effective across a broad spectrum of therapeutic classes. Cyclodextrins have demonstrated the capacity to handle solubility concerns with small molecules as well as complex biomolecules, providing opportunities for the creation of more potent and effective pharmaceutical formulations. the conclusion that cyclodextrins represent a useful and adaptable strategy to overcome solubility challenges in drug development is supported by a substantial body of evidence. Cyclodextrins have the potential to significantly improve the therapeutic efficacy of poorly water-soluble medications as long as research on the subject is conducted and the pharmaceutical industry is willing to adopt novel approaches.

The examination of methods for improving solubility highlights how crucial it is to overcome obstacles related to inadequate drug solubility. The wide range of approaches covered in this review demonstrates the ever-changing field of pharmaceutical research dedicated to enhancing the therapeutic efficacy and bioavailability of poorly soluble pharmaceuticals. A number of strategies have shown promise in improving drug solubility, including solid dispersion, cyclodextrin complexation, lipid-based formulations, and nanotechnology. Researchers and pharmaceutical scientists are able to customize their approach according to specific drug properties and desired outcomes because each technique has its own advantages and considerations. There is no one solubility enhancement method that is universal. The physicochemical characteristics of the drug, the needs for formulation, and the intended mode of administration all play a role in the choice of an appropriate method. For solubility enhancement techniques to be implemented successfully, a multidisciplinary approach combining knowledge from chemistry, pharmaceutics, and engineering is needed. Future advancements in drug delivery systems will be made possible by persistent research and innovation in solubility enhancement techniques, which will ultimately lead to the creation of pharmaceutical products that are both more patient-friendly and effective. The pharmaceutical industry is facing challenges related to the solubility of emerging drug candidates. Therefore, continuous investigation and improvement of these methodologies will be essential to guarantee the triumph of upcoming drug development initiatives.

ABBREVIATIONS

CD: Cyclodextrin, HP: Hydroxypropyl, UV: Ultraviolet, DSC: Differential Scanning Chromatography, DTA: Differential Thermal Analysis, TLC: Thin Layer Chromatography, HPLC: High-pressure Liquid Chromatography, TEM: Transmission Electron Microscopy, SEM: Scanning Electron Microscopy, H-NMR: Proton Nuclear Magnetic Resonance, IR: Infrared, XRD: X-ray Diffraction, BCS: Biopharmaceutical Classification System, GI: Gastro-intestinal, SMEDDS: Self-emulsifying Drug Delivery System, HLB: Hydrophilic-lipophilic Balance, SCFs: Super-critical Fluids, PCA: Precipitation with Compressed Antisolvents

ACKNOWLEDGEMENT

A special thanks to Dr. S. N. Dhole sir and Dr. N. S. Kulkarni sir for the endless support and guidance provided during the completion of this review article.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

No conflicts of interest to be declared

REFERENCES

1. Ain S, Kumar B, Pathak K. Cyclodextrins: versatile carrier in drug formulations and delivery systems. Int J Pharm Chem Biol Sci. 2015 Jul 1;5(3):583-98.
2. Saokham P, Muankaew C, Jansook P, Loftsson T. Solubility of cyclodextrins and drug/cyclodextrin complexes. Molecules. 2018 May 11;23(5):1161. doi: 10.3390/molecules23051161, PMID 29751694.
3. Shimpi S, Chauhan B, Shimpi P. Cyclodextrins: application in different routes of drug administration. Acta Pharm. 2005 Jun 1;55(2):139-56. PMID 16179128.
4. Del Valle EMM. Cyclodextrins and their uses: a review. Process Biochem. 2004 May 31;39(9):1033-46. doi: 10.1016/S0032-9592(03)00258-9.
5. Muankaew C, Loftsson T. Cyclodextrin-based formulations: a non-invasive platform for targeted drug delivery. Basic Clin Pharmacol Toxicol. 2018 Jan;122(1):46-55. doi: 10.1111/bcpt.12917, PMID 29024354.
6. Jacob S, Nair AB. Cyclodextrin complexes: perspective from drug delivery and formulation. Drug Dev Res. 2018 Aug;79(5):201-17. doi: 10.1002/ddr.21452, PMID 30188584.
7. Thakur SS, Parekh HS, Schwable CH, Gan Y, Ouyang D. Solubilization of poorly soluble drugs: cyclodextrin-based formulations. Comp Pharm. 2015 Jun 29:31-51.
8. Vyas A, Saraf S, Saraf S. Cyclodextrin based novel drug delivery systems. J Incl Phenom Macrocycl Chem. 2008 Oct;62(1-2):23-42. doi: 10.1007/s10847-008-9456-y.
9. Kim DH, Lee SE, Pyo YC, Tran P, Park JS. Solubility enhancement and application of cyclodextrins in local drug delivery. J Pharm Investig. 2020 Jan;50(1):17-27. doi: 10.1007/s40005-019-00434-2.
10. Gillet A, Grammenos A, Compère P, Evrard B, Piel G. Development of a new topical system: drug-in-cyclodextrin-in-deformable liposome. Int J Pharm. 2009 Oct 1;380(1-2):174-80. doi: 10.1016/j.ijpharm.2009.06.027, PMID 19576972.

11. Mura P, Bragagni M, Mennini N, Cirri M, Maestrelli F. Development of liposomal and microemulsion formulations for transdermal delivery of clonazepam: effect of randomly methylated β-cyclodextrin. Int J Pharm. 2014 Nov 20;475(1-2):306-14. doi: 10.1016/j.ijpharm.2014.08.066, PMID 25194352.
12. Nagarsenker MS, Amin L, Date AA. Potential of cyclodextrin complexation and liposomes in topical delivery of ketorolac: *in vitro* and *in vivo* evaluation. AAPS PharmSciTech. 2008 Dec;9(4):1165-70. doi: 10.1208/s12249-008-9157-2, PMID 19016331.
13. Maestrelli F, Gonzalez Rodriguez ML, Rabasco AM, Mura P. Preparation and characterisation of liposomes encapsulating ketoprofen–cyclodextrin complexes for transdermal drug delivery. Int J Pharm. 2005 Jul 14;298(1):55-67. doi: 10.1016/j.ijpharm.2005.03.033, PMID 15941634.
14. Jain SK, Gupta Y, Jain A, Amin S. Elastic liposomes bearing meloxicam-β-cyclodextrin for transdermal delivery. Curr Drug Deliv. 2008 Jul 1;5(3):207-14. doi: 10.2174/156720108784911677, PMID 18673264.
15. Vega E, Egea MA, Garduno Ramirez ML, Garcia ML, Sanchez E, Espina M. Flurbiprofen PLGA-PEG nanospheres: role of hydroxy-β-cyclodextrin on ex vivo human skin permeation and *in vivo* topical anti-inflammatory efficacy. Colloids Surf B Biointerfaces. 2013 Oct 1;110:339-46. doi: 10.1016/j.colsurfb.2013.04.045, PMID 23743255.
16. Skiba M, Skiba Lahiani M, Arnaud P. Design of nanocapsules based on novel fluorophilic cyclodextrin derivatives and their potential role in oxygen delivery. J Inclus Phenom Macrocyclic Chem. 2002 Dec;44(1/4):151-4. doi: 10.1023/A:1023090528809.
17. Varan C, Bilensoy E. Development of implantable hydroxypropyl-β-cyclodextrin coated polycaprolactone nanoparticles for the controlled delivery of docetaxel to solid tumors. J Incl Phenom Macrocycl Chem. 2014 Oct;80(1-2):9-15. doi: 10.1007/s10847-014-0422-6.
18. Lahiani Skiba M, Bounoure F, Shawky Tous S, Arnaud P, Skiba M. Optimization of entrapment of metronidazole in amphiphilic β-cyclodextrin nanospheres. J Pharm Biomed Anal. 2006 Jun 7;41(3):1017-21. doi: 10.1016/j.jpba.2006.01.021, PMID 16497467.
19. Nguyen TD. Synthesis and characterization of β-cyclodextrin/alginate nanoparticle as a novel drug delivery system. Chem Biochem Eng Q. 2015 Oct 14;29(3):429-35. doi: 10.15255/CABEQ.2014.2092.
20. Szente L, Puskas I, Sohajda T, Varga E, Vass P, Nagy ZK. Sulfobutylether-beta-cyclodextrin-enabled antiviral remdesivir: characterization of electrospun- and lyophilized formulations. Carbohydr Polym. 2021 Jul 15;264:118011. doi: 10.1016/j.carbpol.2021.118011, PMID 33910715.
21. Johannsdottir S, Jansook P, Stefansson E, Loftsson T. Development of a cyclodextrin-based aqueous cyclosporin a eye drop formulations. Int J Pharm. 2015 Sep 30;493(1-2):86-95. doi: 10.1016/j.ijpharm.2015.07.040, PMID 26220650.
22. Mognetti B, Barberis A, Marino S, Berta G, De Francia S, Trotta F. *In vitro* enhancement of the anticancer activity of paclitaxel by a cremophor-free cyclodextrin-based nanosponge formulation. J Incl Phenom Macrocycl Chem. 2012 Dec;74(1-4):201-10. doi: 10.1007/s10847-011-0101-9.
23. Ascenso A, Cruz M, Euleterio C, Carvalho FA, Santos NC, Marques HC. Novel tretinoin formulations: a drug-in-cyclodextrin-in-liposome approach. J Liposome Res. 2013 Sep 1;23(3):211-9. doi: 10.3109/08982104.2013.788026, PMID 23631723.
24. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:195727. doi: 10.5402/2012/195727, PMID 22830056.
25. Jambhekar SS, Breen PJ. Drug dissolution: significance of physicochemical properties and physiological conditions. Drug Discov Today. 2013 Dec 1;18(23-24):1173-84. doi: 10.1016/j.drudis.2013.08.013, PMID 24042023.
26. Khatri H, Hussain MS, Tyagi S. Solubility enhancement techniques: an overview. World Journal of Pharmaceutical Research. 2022;11(05):468-82. doi: 10.20959/wjpr20225-23812.
27. Kim CK, Park JS. Solubility enhancers for oral drug delivery: can chemical structure manipulation be avoided? Am J Drug Deliv. 2004 Jun;2(2):113-30. doi: 10.2165/00137696-200402020-00004.
28. Patel BB, Patel JK, Chakraborty S, Shukla D. Revealing facts behind spray dried solid dispersion technology used for solubility enhancement. Saudi Pharm J. 2015 Sep 1;23(4):352-65. doi: 10.1016/j.jsps.2013.12.013, PMID 27134535.
29. Deshmukh AS, Tiwari KJ, Mahajan VR. Solubility enhancement techniques for poorly water-soluble drugs. PCI-Approved-IJPSN. 2017 May 31;10(3):3701-8. doi: 10.37285/ijpsn.2017.10.3.1.
30. Patel JN, Rathod DM, Patel NA, Modasiya MK. Techniques to improve the solubility of poorly soluble drugs. Int J Pharm Life Sci. 2012 Feb 1;3(2).
31. Singh J, Walia M, Harikumar SL. Solubility enhancement by solid dispersion method: a review. J Drug Delivery Ther. 2013 Sep 14;3(5):148-55. doi: 10.22270/jddt.v3i5.632.
32. Dhirendra K, Lewis S, Udupa N, Atin K. Solid dispersions: a review. Pak J Pharm Sci. 2009 Apr;22(2):234-46. PMID 19339238.