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Review Article

CYCLODEXTRIN: AN OVERVIEW

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Abstract: Cyclodextrins are versatile pharmaceutical excipients used to enhance the solubility, stability, safety and bioavailability of drugs. Besides, being used to reduce gastrointestinal drug irritation, convert liquid drugs into microcrystalline or amorphous powder, and prevent drug–drug and drug–excipient interactions, they have shown to display adjuvant activity in vaccine therapy, prophylactic and therapeutic use in the treatment of several host-pathogen infections. Cyclodextrins (CDs) are chemically cyclic oligosaccharides which have been recognized as useful pharmaceutical excipients. The molecular structure of these glucose derivatives generates a hydrophilic exterior surface and a non-polar cavity interior. Such CDs can interact with appropriate size drug molecules which lead to the formation of inclusion complexes A number of CDs based products are available in the market based on their ability to camouflage undesirable physicochemical properties of drugs. Current review enlightens the various aspects of CD'S with regard to their chemical characteristics, properties, approaches used for complexation, characterization techniques, uses along with and future potential.

Keywords: Cyclodextrins, Bioavailability, Complexation, Drug Molecules

INTRODUCTION

Cyclodextrins have been known for over 100 years as excipients of considerable importance in the pharmaceutical field [1, 2, 3]. A French scientist Villiers, first described CDs as a crystalline substance isolated from bacteria *(Bacillus macerans*) by digestion of starch.[4,5] CDs are toroidal shape structures exhibiting high potential to entrap entirely or at least partially a wide variety of branched as well as unbranched drug molecules. The hydrophilic external surface and hydrophobic inner surface makes CD's important organic compounds, capable of forming more soluble and stable non covalent bonds with host-guest systems. [6-8] CDs also known as cycloamylosis or 'Schardinger dextrins' are water soluble, non-reducing, macrocyclic polymers containing glucose molecules joined by α 1, 4- linkages. The most common of these compounds are α, β and γ (fig.1) CD's formed by 6, 7 and 8 glucose units respectively. The ring shaped molecule encloses a cavity of about 6, 8 and 10 A^{o} in diameter for the β and γ CD's respectively [9-12]

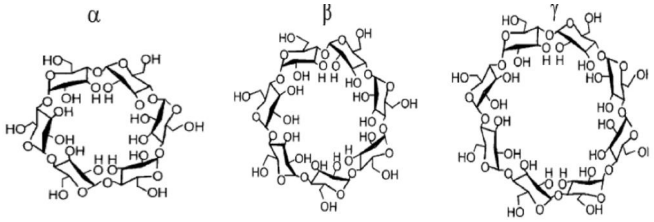

Fig. 1:

The CD's are produced by the degradation and cyclization of starch by an enzyme produced by *Bacillus macerans.* Molecules of a suitable size and shape are held within the cavity of particular CD's by Vander walls forces. [13] The ability to form inclusion compounds in aqueous solution is due to the typical arrangement of the glucose units. The CD structure forms a torus or doughnut ring and the molecule actually exists as a truncated cone. The interior of the cavity is relatively hydrophobic because of the CH_2 groups, whereas the cavity entrances are hydrophilic, owing to the presence of primary and secondary hydroxyl groups. Molecules of appropriate size and stereochemistry can be included in the CD cavity by hydrophobic interaction. CD's are studied as solubilising and stabilizing agents in pharmaceutical dosage forms.[14-19] Cyclodextrin derivatives of pharmaceutical interest include the hydroxy propyl derivatives of β- and γ cyclodextrin, the randomly methylated β Cyclodextrin, sulfo butyl ether β Cyclodextrin, and the so-called branched Cyclodextrins, such as glucosyl–β Cyclodextrin .

Cyclodextrins derivatives, their properties, characterization and route of administration:

The different type's cyclodextrins with their properties route of administration, characteristics are shown in Table 1 and 2 respectively.

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Table.1: Cyclodextrins derivatives, their properties and route of administration [20- 22]

Cyclodextrin derivatives	Property	Route of administration
1.Alpha methylated beta CDs	water soluble	Oral, Ocular, Nasal
a. Dimethyl β CDs	water soluble	Oral, Ocular, Nasal
b.Trimethyl β CDs	water soluble	Oral, Ocular, Nasal
c.Randomly methylated β CDs	water soluble	Oral, Ocular, Nasal
2.Hydroxyl alkylated β CDs amorphous mixture with different degree of substitution, less toxic	highly water soluble	Oral, Ocular, Rectal, Intravenous
a..2-hydroxy ethylβ CDs	highly water soluble	Oral, Ocular, Rectal, Intravenous
b.2-hydroxy propyl β CDs	highly water soluble	Oral, Ocular, Rectal, Intravenous
c.3-hydroxy propyl β CDs	highly water soluble	Oral, Ocular, Rectal, Intravenous
d.2,3 dihydroxy propyl β CDs	highly water soluble	Oral, Ocular, Rectal, Intravenous
3.Sulfobutyl ether β CDs	soluble in water	Oral, Ocular, Parenteral, Pulmonary

Table.2: Characteristics of cyclodextrins [1, 6, 11, 12]

CHARACTERISTICS	Types of cyclodextrins		
	α-CD	β-CD	γ-CD
Glucose unit numbers	6	7	8
Molecular weight	972	1135	1297
Cavity diameter (Ao)	4.7-5.3	6.0-6.5	7.5-8.3
Height of torus (Ao)	7.9±1	7.9±01	7.9±01
$T^{1/2}$ of ring opening (h)	33	29	15
Diameter of outer periphery (Ao)	14.6±0.4	15.4±0.4	17.5±0.4
Approximate volume of cavity Ao 3	174	262	427
Crystals forms from water	Hexagonal Plates	Monoclinic Parellograms	Quadratic Prisms
Crystal water % w/w	10. 2	13.2-14.5	8.13-17.7
Diffusion Constant at (40°C)	3.443	3.224	3.000
Hydrolysis by(Oryzae and alpha-Amylase)	Negligible	Slow	Rapid
Pka by Potentiometry at 25° C	12.332	12.202	12.081
Solubility in water at 25°C (g/100ml)	14.5	1.85	23.2
Melting Point (°C)	275	280	275

Approaches for CD complexation

Various approaches used for CD complexation depend upon the properties of drug molecules, processes involved, formulation ingredients, and the end object. Different methods used are discussed below.

Physical blending/Milling/Co-grinding/Solid phase complexation:

Drug and β-cyclodextrin or hydroxypropyl-β-cyclodextrin are taken in different molar ratios 1:1, 1:2, and are mixed in a mortar for about one hour with constant trituration and passed through sieve No.80 and stored in a dessicator. The physical mixtures are also made at large scale in rapid mass granulators for 30 minutes. The powdered mixtures are then stored at controlled temperatures, 25 ± 2°C and controlled humidity conditions. [21-23]

Kneading:

Drug and β-cyclodextrin or hydroxypropyl-β-cyclodextrin in different molar ratios are taken in a mortar and mixed thoroughly, small quantity of water is added while triturating to get slurry like consistency. The trituration is continued for one hour. Slurry is taken and air dried at room temperature, pulverized and passed through sieve No.80 and stored in a desiccator. For large scale production, granulators are used with trituration timings varying from 15minutes to one hour at controlled humidity of 40-50%. [24,25]

Co-precipitation:

The cyclodextrin and active drug are added to water or a short chain alcohol (eg. ethanol or isopropanol) at 40-60°C to form a saturated solution. Upon cooling, the complex precipitate is formed which is isolated by filtration or centrifugation. In this method, Complexation time may vary from 24 to 48 hours. [25,26]

Neutralization /Precipitation:

The active drug is dissolved in alkaline solution and mixed with aqueous solution of cyclodextrin. The resultant clear solution is then neutralized under stirring using hydrochloric acid solution till equivalence point. At equivalence point, a white precipitate is formed, confirming the formation of inclusion complex. [26]

Solvent Evaporation:

The cyclodextrin and active drug are dissolved separately in two different miscible solvents and mixing of both solutions gives molecular dispersion of drug and complexing agent. The solvent is evaporated finally under vacuum to obtain a solid powdered inclusion compound. [26,27]

Spray Drying /Atomisation:

The cyclodextrin is either dissolved or suspended in water (ratio usually 1:10) at room temperature and solution stirred vigorously. The active drug is slowly added to the water cyclodextrin solution or suspension. The active drug can either be added as is or dissolved in a solvent. [27]

Freeze Drying/lyophilisation:

The cyclodextrin and active drug are dissolved in water and a co-solvent mixture. The complex is isolated

by freeze drying the solution in a lyophiliser. The lyophilisation can be done at -20 to -60°C. [28,29]

Microwave irradiation:

The cyclodextrin and active drug are dissolved in a mixture of water and organic solvent. The mixture is allowed to react for short time of about one or two minutes at 60°C in the microwave oven. After completion of the reaction, adequate amount of solvent mixture is added to the above reaction mixture to remove the residual un-complexed free drug and cyclodextrin. The precipitate obtain is filtered and dried in vacuum oven for a sufficient time [1].

Supercritical Anti-solvent:

The Cyclodextrin and drug is dissolved in a solvent. The solution is then fed into a pressure vessel under supercritical conditions, through a nozzle (i.e. sprayed into supercritical fluid anti-solvent). When the solution is sprayed into supercritical fluid anti-solvent, the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent counter diffuses into the anti-solvent. The mixture becomes supersaturated and resulting precipitation of solute occurs. The remaining solvent is carried away with the supercritical fluid flow [1].

Types of CD's [30-33].

Approximately 1500 Cyclodextrins derivatives have been reported in literature and the most common parent CD'S are α, β and γ containing 6, 7, 8, glucopyranose units respectively. Cyclodextrins less than six glucopyronose cannot be formed due to steric hindrances. These parent CD's are natural, non-reducing, crystalline, homogenous, non-hygroscopic having limited aqueous solubility due to strong inter molecular hydrogen bonding in the crystal lattice. However these CD's also have limitations to extend their physicochemical properties and inclusion capacity. Chemically modified derivatives have been prepared which are amorphous, non crystallizable with enhanced aqueous solubility, physical and microbiological stability and reduced parenteral toxicity Various derivatives of CDs are

Natural CD's (α, β, γ CD)
Hydroxy alkylated CD's, HP β CD and HP γ CD
Methylated CD's (randomly methylated β CD)
Acetylated CD's acetyl γ CD
SBEβ CD (sulfo butyl ether β CD)
Branched CD's-maltosyl and glycosyl β CD
Reactive CD's –chlortrianzyl

Characterization Techniques of Drug- Cyclodextrin Complex:

In solid state[1]:

Thermo-analytical methods: Analyzes change in the active drug (melting, evaporation, decomposition, oxidation or polymorphic transition). Characterizes broadening, shifting and appearance of new peaks or disappearance of certain peaks in the thermogram obtained by Differential Scanning colorimetric (DSC) and Differential Thermal Analysis.

Scanning Electron Microscopy: Characterizes crystallization or amorphous state of the active drug and the complex.

X-ray diffractiometry (XRD): Characterizes differences in diffraction pattern of active drug and the complex.

Dissolution tests

Characterizes improved solubility of the complex as compared to active drug.

Infra-Red (I R) spectroscopy

Characterizes the shifts of absorbance bands to the lower frequency, increases the intensity and widens the band caused by stretching vibration of the group involved in the formation of the hydrogen bonds with cyclodextrin-active drug complex.

Thin Layer chromatography

Characterizes the RF values of an active drug diminishes to considerable extent and this helps in identifying the completion of complex formation.

In solution State[1]

Electrochemistry

a) Polarography: characterizes electron distribution of a complexed electro active guest molecule in aqueous solution which is different from that in the non-complexed state in aqueous solution.
b) Conductivity: conductivities are dramatically affected by inclusion complex formation with cyclodextrins.
c) Polarimetry: A polarimetric study as a supporting tool for the complex formation because beta CD is optically active in nature.

Solubility

Characterized by enhancement of solubility of active drug

Spectroscopy

a) Nuclear Magnetic Resonance (NMR) – provides direct evidence for the inclusion of a drug into a cyclodextrin cavity in solution.
b) Electron Spin Resonance (ESR) - useful technique to investigate inclusion complexation with radicals in aqueous solutions. The hyperfine coupling constant of radicals is known to be sensitiv to the polarity of the medium. If the hyperfine coupling constant alters, the movement of a radical to an

environment less polar than water is indicated and confirms the inclusion complex formation.

c) Ultraviolet/Visible (UV/VIS) – characterized by change in the absorption spectrum of a drug.
d) Fluorescence spectroscopy - characterized by change of excitation and emission wavelength of the drug.
e) Circular Dichroism (CD) - characterized by changes in circular Dichroism (CD) spectra of drug and complex.

pH-Potentiometric Titration:

Useful technique, when active drug has a prototropic function the pka value of an acidic drug molecule is usually increased, while those of basic ones are usually decreased by binding to Cyclodextrin [34]

Micro-Calorimetry:

Characterized by change in thermodynamic properties (enthalpy & entropy) of drug and inclusion complex. An increase in hydrophobic interaction as the active drug inserts itself into the polar cyclodextrin cavity. Initial equilibrium to form complex is very rapid (within minutes), while the final equilibrium can take longer to reach. Once, inside the cyclodextrin cavity, the active drug makes conformational adjustments to take maximum advantage of the weak Van-der -Waals forces that exist [35]. In vivo dissociation of the inclusion complex is a relatively rapid process, which is driven by dilution. The resulting concentration gradient shifts the equilibrium to the left .In highly dilute and dynamic system, like in body, the active drug is either absorbed or has difficulty in finding another cyclodextrin to reform the complex and is left free in solution [36].

Mechanism of complexation:

There are four favorable interactions between Cyclodextrin and active drug which shift the equilibrium towards complex formation (Fig 2) [15,32]

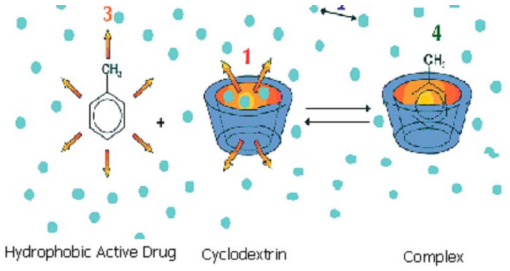

Fig.2: Entrapment of drug molecule into a sugar ring and thereby reducing its taste [33]

1. The displacement of polar water molecules from the polar cyclodextrin cavity.
2. The increased number of hydrogen bonds formed as the displaced water returns to the larger pool.
3. A reduction of repulsive interaction between the hydrophobic active drug and the aqueous environment.
4. An increase in hydrophobic interaction as the active drug inserts itself into the polar cyclodextrin cavity.

Initial equilibrium to form complex is very rapid (within minutes), while the final equilibrium can take longer to reach. Once inside the cyclodextrin cavity, the active drug makes conformational adjustments to take maximum advantage of the weak Vander Waals forces that exists [30].

In vivo dissociation of the inclusion complex is a relatively rapid process, which is driven by dilution. In highly dilute and dynamic system, like in body, the active drug is either absorbed or has difficulty in finding another cyclodextrin to reform the complex and is left free in solution. (Fig.2).

Pharmaceutical applications of cyclodextrins.

Characteristics of Cyclodextrins make them to be used in almost every drug delivery system. Large number of references & marketed products are available for application in drug delivery for example cyclodextrin in oral drug delivery, sublingual, ocular, nasal, rectal, pulmonary, dermal and others novel drug delivery systems.[1,6,13,37]

Oral drug delivery:

A large number of drugs are available which have poor aqueous solubility. The hydrophilic cyclodextrins are extensively applied for the enhancement of solubility and oral bioavailability of poorly soluble drugs while the hydrophobic cyclodextrins are widely used for prolong or modify the release of drug [14, 31]

Sublingual or Buccal drug delivery

Sublingual or buccal drug delivery is one of the ways to bypass hepatic first-pass metabolism. Aqueous solubility, dissolution and drug absorption are the rate limiting steps for lipophilic drugs. Cyclodextrin based complex not only improve the drug absorption, but also mask the bitter taste of drugs [38]

Ocular drug delivery

The outermost layer of the eye cornea is a lipophilic epithelium and thus, drugs must be somewhat lipophilic to able to permeate through the cornea into the eye. Cyclodextrin solubilization of drug will increase the amount of dissolved drug at the lipophilic membrane surface, but excess cyclodextrin will decreases the ability of the drug molecules to partition into the lipophilic barrier. Thus, excess cyclodextrin can result in decreased drug delivery through the cornea. Cyclodextrin have also been used

to reduce ocular drug irritation and to increase chemical stability of drug in aqueous ocular solutions [1].

Nasal drug delivery

The nasal route is another effective way to bypass the hepatic first pass metabolism, due to good permeability properties of nasal mucosa. In nasal formulations, cyclodextrin are normally used to increases the aqueous solubility of lipophilic drugs. However, lipophilic cyclodextrin can also interact with biological membranes and act as permeation enhancers, especially in nasal delivery of peptides. Most of the cyclodextrins are eliminated from the nasal cavity by nasal mucociliary system, which transports it to the oesophagus and ultimately into the gastrointestinal tract. Cyclodextrins have very low local toxicity after nasal administration [1].

Rectal drug delivery:

Rectal delivery is also effective delivery system for drugs having bitter or nauseous taste, have first pass metabolism and degrade in the stomach pH. It is an ideal route for unconscious patients, children and infants. Hydrophilic cyclodextrins enhance the release of poorly water soluble drugs from the oleaginous suppository bases because of the lesser interaction of the resultant complexes with the vehicles. The complexation of lipophilic drugs with hydrophilic cyclodextrins makes them insoluble in hydrophobic vehicles. The complexation not only enhances drug dissolution at the interface between the molten base and the surrounding fluid but also inhibits the reverse diffusion of drug into the vehicles[1].

Pulmonary drug delivery:

Pulmonary drug delivery is also an attractive route for systemic drug delivery and intended for local treatment of diseases like asthma, chronic obstructive pulmonary disease or other lungs disease. In the pulmonary delivery, cyclodextrins increases the solubility, stability and dissolution rate of water insoluble and chemically unstable drugs [1].

Dermal drug delivery:

The outer most layer of skin (Stratum Corneum) is the main barrier for drug absorption through skin. Hence, various permeation enhancers are used to decrease its property. Cyclodextrins have a significant safety margin in dermal application and can be used to optimize the transdermal delivery of drug intended for local or systemic effect. They enhance the drug delivery through aqueous diffusion layers, but not through lipophilic barrier stratum corneum. Thus a suitable vehicle must be selected so that cyclodextrin fully exert their functions.

Novel drug delivery:

Cyclodextrins have applications in the design of novel drug delivery Systems like Liposomes, Microspheres, Nanoparticles, Osmotic delivery, Peptide and Protein delivery [34].

Other applications in the field of chemistry:

By employing the host-guest property, CDs have been applied for various fields such as biochemistry, material chemistry, catalysis and electronics. Especially, recent developments in supra molecular chemistry using CDs as a building blocks are extremely remarkable. Various supra molecular structures such as catenanes, rotaxanes, polyrotaxane, and supra molecular polymers have been reported. The field of chemical sensors besides recent findings have shown them to display adjuvant activity in vaccine therapy and prophylactic and therapeutic activity in the treatment of several host-pathogen infections .has been a growing research area and a wide range of books and reviews has been published in this field over the last three decades. Among them, optical chemical sensors are quite interesting and useful because optical changes such as colour and fluorescence by recognition of guest molecules can be directly and immediately seen with the naked human eye [39].

Cyclodextrin in health care:

Besides recent findings have shown them to display adjuvant activity in vaccine therapy and prophylactic and therapeutic activity in the treatment of several host-pathogen infections. In vaccine therapy dimethyl-beta-cyclodextrin is used for vaccine production. For example diphtheria and tetanus toxoids and acellular pertussis vaccine as DAPTACEL^{R} Sanofi Aventis Pasteur [40].

Cyclodextrin and photostability:

The aqueous solubility and as photostability of acitretin which is used in the treatment of psoriasis was improved by using cyclodextrins. The adjustment of pH value further enhanced the aqueous solubility of acitretin. Investigation of physicochemical characterization confirmed the cyclodextrin inclusion complex of acitretin.[41]

Marketed preparations of CD's:

Marketed Pharmaceutical Products containing Cyclodextrin complexes were prepared by Japanese pharmaceutical companies and were the first to put Cyclodextrin containing pharmaceuticals on the market anywhere in the world. Ono, Teikoku, Shinogi, Fujinaga, Takeda, Nippon Kayaku, Kyushin, Meiji Seika have been selling pharmaceutical products using cyclodextrins. Some marketed preparations of cyclodextrins available in world are shown Table.3.

Table.3: Marketed preparation of CD'S available worldwide[1]

Trade name	Dosage form	CD	API	Company/country
ProstarmomE	Sublingual	β- cd	PgE2	Ono Japan
Prostavastin	Parenteral	α-cd	Pg E1	Ono Japan
Opalmon	Tablet	γ- cd	op-1206	Ono Japan
Brexin	Tablet	β-cd	Piroxicam	Chiesi, Europe
Cicladol	Suppository	β-cd	Piroxicam	Ranbaxy, India
Ulget	Capsule	β-cd	Benexate	Teikoku, Japan
Nitropen	Sublingual	β- cd	Nitroglycerin	Nippon Kayaku, Japan
Transulium	Tablet	β-cd	Chlordiazepoxide	Gador , Argentinia
Dexocort	Solution	Hp β- cd	Hydrocortisone	Actavis ,Europe
Mitoextra,mitozytrex	I.V infusion	Hp β-cd	Mitomycin	Novartis, Europe
Cetrizin	Chewable tablet	β -cd	Cetrizine	Losan Pharma Switzerland
Rofizgel	Tablet	β -cd	Rofecoxib	Wockhard, India
Fluner	Tablet	β- cd	Blunarizine	Genopharm, India
Betahist	Tablet	β- cd	Betahistidine	Genopharm India
Alopexy	Solution	γ- cd	Minoxidil	Pierre fabre, Europe
Vitaseptol	Eyedrop	β- cd	Thiomersol	Europhia, Monaco
Mobitil	Tablet,suppository	β- cd	Meloxicam	Medical union pharma, Egypt
Cerenia	Parenteral solution	β- cd	Ariprazole sulfobutyl	Pfizer, USA
Panosprin-t	Tablet	α-cd	Cefotiam hexetil hcl	Takeda, Japan
Caverject dual	I.V solution	α-cd	Alprostadial	Pfizer , Europe
Meiact	Tablet	β-cd	Cephalosporin	M Seiko, Japan
Ombeta	Tablet	β-cd	Omeperazole	Beta-form, Europe
Surgamyl	Tablet	β-cd	Tiaprofenic	Roussel Maestrolli, Europe
Stada travel	Chewable tablet	β-cd	Diphenhydramine and Chlortheophylline	Stada, Europe
Nicorette	Sublingual tablet	β-cd	Nicotine	Pfizer
Lonmiel	Capsule	β- cd	Benexate hcl	Shinogi, Japan
Glymesason	Ointment/tablet	β-cd	Dexamethasone	Fujinaga, Japan
Mena gargle	Solution	β-cd	Iodine	Kyashin, Japan
Flogene	Suppository	β-cd	Piroxicam	Ache, Brazil
Propulsid	Suppository	2-hβ-cd	Itraconazole	Janssen, Europe
Indocid	Eye drops	2-hβcd	Indomethacin	Chauvin, Europe
Aerodial	Nasal spray	β-cd	17-βestradiol	Servier, Europe
Clorocil	Eye drops	β-cd	Chloramphenicol	Ofatalder, Europe
Abilify	Intramuscular solution	Sulfobutyl ethyl ether β-cd	Arepiprazole	Bristol Meyers, USA
Geodem	Intramuscular solution	Sulfobutyl ether β-cd	Ziprasidone mesylate	Pfizer, USA

Advantages of CD complexation [1,2, 6,16]

- Enhancement of solubility of poorly water soluble drugs
- Stability augmentation towards various degradation reactions.
- Bioavailability enhancement of poorly absorbed drugs.
- Reduction or elimination of toxicity and ulcerogenic effects of drugs e:g Indomethacin and Piroxicam.
- Conversion of a liquid substance into a solid complex thereby improving its processing characteristics.
- Alteration of chemical reactivity of drug.
- Usage as antidote for metal poisoning.
- Taste masking of bitter taste drugs.
- Masking of unpleasant /obnoxious odour.
- Reduction in volatility of drugs.
- Co usage of incompatible drugs.
- Improvement in content uniformity.
- As chemical sensors in chemistry [30, 31]
- Some other advantages of cyclodextrins in novel drug delivery system are shown in table 4.

Table.4: Advantages of cyclodextrin in novel drug delivery [1]

Liposomes	Improve the stability of liposomes, Improve the drug loading efficiency
Microspheres	Improve the drug loading efficiency, As a stabilising agent for lysozyme and bovine serum albumin preparation, As a cross linking agent
Nanoparticles	Provide hydrolytic or protolytic stability of drug As a solubiliser
Osmotic delivery	As a solubilizer
Peptide and protein delivery	As a solubiliser and improve chemical and enzymatic absorption, improve stability

Future prospects of cyclodextrins [30, 34]

The future of Cyclodextrins in the pharmaceutical industry seems to be bright ranging from drug delivery to role in treatment of HIV infections, in health care and space science to cosmetics. New uses of cyclodextrins are likely to be explored as the properties of cyclodextrins are expanding with good number of commercialized and FDA-approved variants. Although presently only conventional formulations such as tablets, capsules, solutions, ointment and intravenous solutions have been commercialized using Cyclodextrins. Nowadays Cyclodextrins are extensively being studied for their application in Novel drug delivery such as Nanoparticles, Liposome, Microspheres and targeted drug delivery and they can become commercially available in future. Gene therapy is also continues to generate interest with cyclodextrins. With the difficulty in viral gene delivery, non-viral methods are being further explored. Polycation Cyclodextrins have unique properties that could be useful in the non-viral delivery of nucleic acids. These materials show promise for gene delivery in animals, although their utility in humans remains to be proven.

Number of cd-related publications in a 5-year sum [42, 43]

The best indicator of tremendous potential of CD's in the drug delivery is the constantly increasing graph of publications and patents having been filed since 1965. There is a very steep rise in CD related publications and shown in fig. 3.

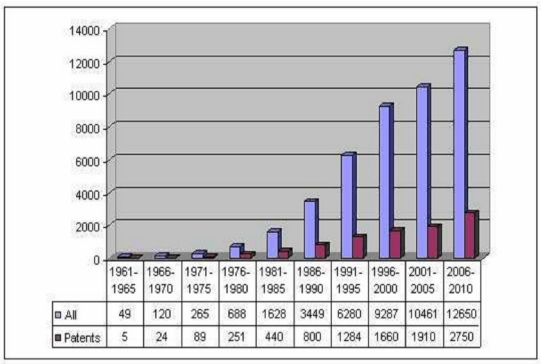

Fig. 3: Publication Frequency over last 40 Years

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