

Recent List of Cyclodextrin-Containing Drug Products

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Abstract

The number of the cyclodextrin-containing drug formulations on the market has been continuously growing since the first drug (prostaglandin E1 formulated with α -cyclodextrin) was launched in Japan in 1976. We have collected a list of drugs from various sources available on the internet to find 130 approved pharmaceutical ingredients formulated with either parent cyclodextrins or their hydroxypropyl, sulfobutyl, random methylated or sulfolipo derivatives. We have sorted the drug products according to the cavity size of the cyclodextrins, the administration route and dosage forms.

Keywords

approved pharmaceutical products, cyclodextrins, hydroxypropyl cyclodextrin, sulfobutyl cyclodextrin, random methylated cyclodextrin

1 Introduction

Cyclodextrins (CDs) are cyclic carbohydrates consisting of usually 6, 7 or 8 glucopyranose units (called α -, β - and γ -CDs, respectively) able to form non-covalent host-guest inclusion complexes with other molecules such as drugs. Their beneficial effects (enhancement of solubility and bioavailability, improvement of stability and taste, etc.) on various pharmaceuticals have been reviewed several times [1–4]. The very first drug marketed in the form of a CD complex was a prostaglandin produced by Ono Pharmaceutical Co. (Japan) as injection containing α -CD/prostaglandin E1 and later tablets of β -CD/prostaglandin E2 [5]. In Europe at first β -CD/piroxicam, the product of Chiesi Pharmaceutici (Italy), was introduced to the market in 1988 with a brand name Brexin [6]. The first drug in the US market appeared in 1997; it was the hydroxypropyl- β -CD/itraconazol solution (Sporanox) produced by Janssen Pharmaceutical Co. (Belgium) [7].

The list of the CD-containing pharmaceutical products approved and marketed has been continuously increasing since then. The first list collected by Davis and Brewster in 2004 contained 24 active pharmaceutical ingredients (APIs) [8]. This list was enlarged to 35 items in 2007 by Brewster and Loftsson [9]. A bit longer list was published in the Cyclodextrin News in 2013 with 48 APIs [10]. This list has been continuously enlarged by the data available from internet e.g. from drugs.com, a platform on marketed drugs informing also on the excipients [11]. More recently

a similar webpage on the drugs marketed in Japan has been also explored [12]. In September 2022 the total number of CD-formulated active ingredients in the marketed drugs – we found so far – is as much as 129. Further data are expected from China and India.

2 List of pharmaceutical actives marketed in CD-containing formulations

Table 1 gives a summary of the number of active ingredients in marketed drugs formulated with various CDs showing that most of them contain β -CD or its derivatives. Among the derivatives hydroxypropyl β - and γ -CDs (HP- β -CD and HP- γ -CD), sulfobutyl ether (SBECD), random methyl (RAMEB) and sulfolipo- β -CDs can be found in drug formulations. Their abundance follows this order.

From Table 2 one can get an overview on the administration routes, showing that the native CDs are utilized

Table 1 Number of active pharmaceutical ingredients formulated with various cyclodextrins

	α -CD	β -CD	γ -CD	n.s.
Parent	3	53	4	5
HP		36	4	2
SBE		14		
RM		3		
Sulfolipo		1		
Total	3	111	8	

n.s.: not specified

mostly in oral formulations, while the soluble sulfobutyl CD derivative is used only parenterally. The hydroxypropyl β -CD is applied both in oral and parenteral formulations as well as in ocular solutions.

In Table 3, the drugs are sorted according to the dosage forms. The complete list is given in Tables 4–7.

We have to note that these tables do not show the drugs where the active ingredient is a CD itself: Bridion (Sugammadex) and HP- β -CD, which are used for reversal of neuromuscular block in anesthesia and for the treatment of fatal genetic Niemann Pick Type C disease, a cholesterol metabolism disorder, respectively. There is available also a tablet for atherosclerosis regression to prevent stroke and heart disease, which contains α -CD as active (Belytrim, Maxcure Nutravedics Ltd.).

Vitamins, various herbal compositions, phytosterols, carotenoids, unsaturated fatty acids, fish oil, etc. usually marketed as nutraceuticals have not been taken into account although they are on the borderline between drugs and healthy foods. The nutrition supplements with steroids for body builders have not been included either.

3 Conclusions

We have collected via internet and several scientific reports the list of CD-formulated drugs available on the market. Although this list is not complete due to the difficulties in finding the relevant information, it shows that more than 120 active ingredients are already marketed in drug formulations containing also CDs as excipients. Some of them are already generic produced by several manufacturers under different trade names.

It can be concluded that β -CD and its hydroxypropylated and sulfobutylated derivatives (HP- β -CD and SBECD) are dominating the market. HP- β -CD was the first semi synthetic cyclodextrin derivative that was used in final dosage forms, however SBECD is also a powerful solubilizing and stabilizing agent, especially for weak bases and is used in more and more products.

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Table 2 Number of active pharmaceutical ingredients formulated with various cyclodextrins sorted according to the administration route

	α -CD	β -CD	γ -CD	HP- β -CD	HP- γ -CD	SBE- β -CD	RM- β -CD	Sulfolipo CD	n.s.
Oral	2	46	3	13					1
Nasal							1		
Rectal		3		1					
Vaginal		1							
Dermal/ungual		5	1	2					5
Ocular		1		8	2		2		1
Parenteral	1	1		17	2	14		1	
Total	3	57	4	41	4	14	3	1	7

Table 3 Number of active pharmaceutical ingredients formulated with various cyclodextrins sorted according to the dosage form

	α -CD	β -CD	γ -CD	HP- β -CD	HP- γ -CD	SBE- β -CD	RM- β -CD	Sulfolipo CD	n.s.
Tablet/Capsule	3	43	1	8					1
Oral solution		5	2	7					
Nasal spray							1		
Suppository		3		1					
Cream, ointment		4	1						4
Vaginal gel		1							
Lacquer				2					
Face mask									1
Deodorant stick		1							
Eye drops		1		8	2		2		1
Infusion/injection	1	1		17	2	14		1	
Total	3	58	4	43	4	14	3	1	7

Table 4 Approved pharmaceutical products with parent cyclodextrins

Drug	CD	Trade name	Dosage form	Company
Aceclofenac	β -CD	Aceclofenac-B-Cyclodextrin, Acerap	tablet	Taj Pharm.
Acetaminophen	β -CD	Acetaminophen Chewable Gels	tablet, chewable	7T Pharma, USA
Aluminum Zirconium Trichlorohydrate Gly	β -CD	Secret, Outlast, Olay, Old Spice, Gillette	deodorant stick	Procter & Gamble, Navajo
Amlodipine maleate	β -CD	Conjupri	tablet	CSPC Ouyi Pharm, Shijiazhuang
Anagliptin + metformin	α -CD	Metoana Combination Tablets	tablet	Sanwa Kagaku Kenkyusho
Benexate	β -CD	Ulgut, Lonmiel	capsule	Teikoku, Shionogi, Negase
Benzoyl peroxide	γ -CD	Nujevi Acne	cream	Nujevi
Betahistine	β -CD	Betahist	tablet	Geno Pharm.
Bilastin	β -CD	Ilaxten	oral solution (pediatric)	Menarini Farm. Int.
Brivaracetam	β -CD	Briviact	tablet	UCB Pharma
Bromhexin	β -CD	Bisolvon	tablet	Sanofi
Cefotiam	β -CD	Pansporin-T	tablet	Takeda
Cefditoren pivoxil	β -CD	Meiact	tablet	Meiji
Cetirizine	β -CD	Zyrtec, WalZyr, Revicet	chewing tablet, OD tablet, dry syrup	Losan Pharma, UCB Pharma, Sandoz, Walgreen, Sawai Pharm., Nichi-Iko, Takeda
Cisapride	β -CD	Propulsid, Coordinax	suppository	Janssen
Curcumin extract	γ -CD	Curcumin Extract 45	capsules	Dr. Wolz Zell GmbH (Germany)
	CD	Curuline	powder (veterinary)	KB'S Solution
Chlordiazepoxide	β -CD	Transilium	tablet	Gador
Chlorpheniramine maleate + acetaminophen	β -CD	Cold Remedy Soothing	tablet	Foshang Dezhong Pharm. (China)
Cholecalciferol	β -CD	Vitamin D3	tablet	Natures Aid (U.K.)
Dexamethasone	β -CD	Glymesason	tablet, ointment	Fujinaga
Dextromethorphan	β -CD	Rynathiol	tablet	Synthelabo
Desloratadine	β -CD	Desloratadine	tablet	Northstar Rx
Diphenhydramine	β -CD	Stada-Travel	chewing tablet	Stada
Ethinyl estradiol + drospirenone + levomefolate	β -CD	Safyral, Beyaz, Yaz	tablet	Bayer Healthcare
Ethinyl estradiol + drospirenone	β -CD	Yaz, Yasminiq, Gianvi, Rajani, Loryna	tablet	Bayer
Famotidine	β -CD	Famotidine OD Tablets	OD tablet	Takeda Teva, Taiko
Fenofibrate	β -CD	Fenofibrate, Fenacor, Fibrate, Lipicard, Fibrolip, Fenacor, Fibril, Thrombiflo, Lotgl	tablet, capsule, injection	Karalex Pharma, Avinash Health, Taj Pharm., US Vitamins, Emcure Pharm., Medindia, Torrent, Grandix
Fingolimod	β -CD	Fingolimod beta	capsule	Betapharm
Flunarizine	β -CD	Fluner	tablet	Geno Pharm.
Flupentixol dihydrochloride	β -CD	Fluanxol	tablet	Lundbeck (UK)
Garlic Extract	β -CD		various dragees	Various
Glucagon	β -CD	Baqsimi	tablet	Eli Lilly
Histamine dihydrochloride	β -CD	Australian dream	pain relieving antiarthritis cream	Nature's Health Connection
Iodine	β -CD	Mena-Gargle	solution	Kyushin
Meloxicam	β -CD	Mobitil	tablet, suppository	Med. Union Pharm.

Continuation of Table 4

Menthol/camphor	β -CD	Pain relief gel	ointment	MMA Elite, Doctor Hoy's
Mequitazine	β -CD	Zeslan, Nipolazine	pediatric syrup	Asahi Kasei, Alfresa
Metronidazole	β -CD	Metrogel, Flagyl, Vandazol, Nidagel	vaginal gel	Curatek, Fougera, Tolmar, Malderma Labs
Methyl salicylate	β -CD	Xceptor Pain	cream	Xceptor
Miconazole	β -CD	MiconHex-Triz	wipes (veterinary)	Dechra Veterinary
Midazolam	γ -CD	Ozalin	oral solution	Advicenne, Valdepharm
Minoxidil	γ -CD	Alopexy	solution	Pierre Fabre
Naphasoline hydrochloride	β -CD	Clear eyes	eye drop	Medtech
Nateglinide	β -CD	Nateglinide Tablets	tablet	Teva Takeda
Niacinamide + adenosine	CD	Botanic Heal boH Air Jet Daily Mask Panthenol	anti-wrinkle mask	Cj Olive networks
Nicotine	β -CD	Nicorex, Nicorette	tablet	Pierre Fabre
		Nicogum	chewing gum	Pfizer
Nimesulide	β -CD	Nimedex	tablet	Novartis, others
Nitroglycerin	β -CD	Nitropen	sublingual tablet	Nippon Kayaku
Norfloracin and Tinidazole	β -CD	Entronor –TZ, Noroxin	tablet	India
Olmesartan medoxomil	β -CD	Olmetec OD Tablets, Olmesartan OD tables	OD tablets	Daiichi Sankyo
		Omebeta, Losamel	enteric capsule	Betafarm, Stada
Omeprazol	β -CD	Prostavasin	intra-arterial inf.	Ono, Schwarz
		Viridal, Alprostadil, Edex, Caverject, Rigidur,	intra-cavernous inj.	Schwarz, Ferring, Pfizer
		Prostandin 500	infusion	Ono
PGE1	β -CD	Opalmon	tablet	Ono
	α -CD + β -CD	Limaprost, Prorenal	tablet	Sawai Pharm., Nichiiko, Sumitomo
PGE2	β -CD	Prostarmon E, Dinoprostion-betadex	sublingual tablets	Ono
		Cycladol, Brexin, Flamexin, Pyrodex, Medicam	tablet	Chiesi, Ranbaxy, Sun, MMC
Piroxicam	β -CD	Brexin	suppository	Chiesi
		Flogene	pediatric liquid	Ache
Pramipexole Dihydrochloride	β -CD	Pramipexole Dihydrochloride	tablet	Endo Pharmaceuticals
Rofecoxib	β -CD	Rofizgel	tablet	Wockhardt
Salicylic acid	CD	Prosoria, Clarity Clear Skin Essentials Acne Treatment Cream	psoriasis treatment gel, acne treatment cream	Nuvothera, Melaleuca
Solifenacin	β -CD	Solifenacin Succinate OD Tablets	OD tablet	Japan generic
Thiomersal	β -CD	Vitaseptol	eye drop	Novartis, Europhtha
Tiaprofenic acid	β -CD	Surgamyl	tablet	Roussel-Maestrelli
Valeriana extract + α -bromoisovaleric acid ethyl ester + phenobarbital + peppermint oil	β -CD	Corvalol	tablet	Farmak (Ukraine)

Table 5 Approved pharmaceutical formulations with hydroxypropyl cyclodextrin derivatives

Drug	CD	Trade Name	Dosage form	Company
Acetaminophen	HP- β -CD	Paracetamol	infusion, chewable tablet	Uni-Pharma, 7T Pharma
Ad26.COVS.2.S	HP- β -CD	Jcovden (previously COVID-19 Vaccine Janssen)	vaccine	J&J
Alfaxalone	HP- β -CD	Alfaxan	i.v. (veterinary)	Jurox, CTD
Azelastine	HP- β -CD	Antalerg	eye drop	Unimed Pharma
Biotin and surfactants	HP- β -CD	RegeNail	nail lacquer	Reig Jofre, S.A (Spain)
Ciclopirox	HP- β -CD	Dexulac	nail lacquer	Reig Jofre, S.A (Spain)
Ciprofloxacin + Deaxamethasone	HP- β -CD	Kombinil-Duo	eye and ear drops	Promed Exports (India)
Cisapride	HP- β -CD	Prepulsid	suppository	Janssen
Cladribine	HP- β -CD	Mavenclad	tablet	Merck
Diclofenac	HP- β -CD	Dyloject, Diclofenac-Solofarm, Ivinak-Solofarm,	i.v. and i.m. solution, eye drops	Javelin Pharm.,Vidal
	HP- γ -CD	Voltaren Ophta CD, Voltarol	eye drop	Novartis
Diphenhydramine HCl	HP- β -CD	FirstCare - Children's Allergy Relief	chewable bars	FirstCare
Docetaxel	HP- β -CD	Docetaxel Teva Generics	infusion	Teva
Fingolimod	HP- β -CD	Gilenya	capsule	Novartis
Florbetaben	HP- β -CD	Neuraceq	solution of contrasting agent	Piramal Imaging SA
Flurbiprofen	β -CD and HP- β -CD	Strephen, Strepfen, Strefzap, Strefen, Flurbiprofen Geiser, Dobendan, FrobenGolmed, Benactividol	oromucosal spray	Reckitt (U.K.), Mylan, Fear, Busetti
Hitchner B1 strain	HP- β -CD	Cevac	vaccine	Ceva-Phylaxia
Hyaluronic acid	HP- β -CD	DOLATROX®hcc	injection	Kolinpharma
		Vijointhcc	injection	Innventa
Hydrocortisone	HP- β -CD	Dexacort	mouth wash	Actavis
Indomethacin	HP- β -CD	Indocid, Indocyllir	eye drop	Chauvin, Baush & Lomb
Itraconazole	HP- β -CD	Sporanox, Scemblix, Itrafungol (vet)	oral solution, i.v. solution	Janssen, Eli Lilly, Elanco, Mylan EPD
	HP- γ -CD	Itraconazol Altan	i.v. solution	Altan
Lanosterol	HP- β -CD	Lanomax	eye drops (veterinary)	Ventura Labs (US CA)
Larotrectinib	HP- β -CD	Vitrakvi	capsules, oral solutions	Bayer
Letermovir	HP- β -CD	Prevymis	i.v.	Merck
Levocabastine	HP- β -CD	Allergiflash	eye drops	Bausch & Lomb
L-thyroxine sodium	HP- β -CD	Leventa	oral solution (veterinary)	Intervet, Merck, Shering Plough
Methylethylpyridinol	HP- β -CD	Vixipin	eye drops	Grotex (Russia)
Mitomycin	HP- β -CD	MitoExtra, Mitozytrex	i.v. infusion	Novartis, SuperGen
Noxamovir	HP- β -CD	Prevymis	i.v. injection	Merck
Olopatadine	HP- β -CD	PrPazeo, Pazeomelph, Opatanol, Olantin	eye drop	Novartis, Alcori
Oritavancin	HP- β -CD	Kimyrsa	i.v. injection	Melinta
Perindopril tert.butylamine	HP- β -CD	Perindopril Erbumine	tablets	Sandoz
Progesterone	HP- β -CD	Lubion	injection	Hikma (Portugal)
Quizartinib	HP- β -CD	Vanflyta	i.v.	Daiichi Sankyo
Televancin	HP- β -CD	Vibativ	i.v. solution	Astellas Pharma, Therevance

Continuation of Table 5

Thyme herb extract (Nerba Thymi vulgaris)	HP- β -CD	Bronchipret	oral solution	Bionorica (Germany)
Voriconazole	HP- β -CD	Vorzu, Voriconazole Synthron	tablet, powder for infusion	Rhambaxy, Synthron
Tc-99 Teboroxime	HP- γ -CD	CardioTec	i.v. solution	Bracco
Umbralisib tosylate	HP- β -CD	UKONIQ	tablet	TG Therapeutics, Inc.
Lanosterol (0.25%) + n-acetylcarnosine (1%)	HP- β -CD + RAMEB	LumenPro	pet cataracts eye drops	Heliostatics
Panthenol, Allantoin	HPCD	bdrRe-lax	elixir	Hanaim Intern.
Salicylic acid	HPCD	Age Defying Blemish Treatment, Lipo™ CD-SA	cream	Wasatch, Vantage

Table 6 Approved pharmaceutical formulations with sulfobutyl β -cyclodextrin

Drug	CD	Trade name	Dosage form	Company
Alfaxalone	SBECD	Phaxan	i.v.	Drawbridge Pharm., Chemic Labs
Amiodarone	SBECD	Nexterone	i.v. solution	Baxter
Aripiprazole	SBECD	Abilify	i.m. solution	BMS, Otsuka
Brexanolone (Allopregnalone)	SBECD	Zulresso	injection solution	SAGE Therap
Carbamazepine	SBECD	Carnexiv	i.v.	Lundbeck
Carfilzomib	SBECD	Kyprolis	i.v.	Amgen (Onyx), Ono
Delafloxacin	SBECD	Baxdela	i.v.	Melinta
Fosphenytoin	SBECD	Sesqient, Cerebyx	i.v. and i.m.	Sedor Pharmaceuticals
Maropitant	SBECD	Cerenia	parenteral solution	Pfizer Animal Health
Melphalan	SBECD	Evomela	i.v.	Spectrum
Posaconazole	SBECD	Noxafil	i.v. solution	Merck
Remdesivir	SBECD	Veklury	i.v.	Gilead Sciences
Voriconazole	SBECD	Vfend, Voriconazole (vet)	i.v. solution	Pfizer, Sandoz
Ziprasidone	SBECD	Geodon, Zeldox	i.m. solution	Pfizer

Table 7 Marketed pharmaceutical formulations with random methyl and sulfolipo β -cyclodextrin

Drug	CD	Trade name	Dosage form	Company
Chloramphenicol	RAMEB	Clorocil	eye drop	Oftalder
Estradiol	RAMEB	Aerodiol	nasal spray	Servier
Lanosterol (0.25%) + n-acetylcarnosine (1%)	HPBCD + RAMEB	LumenPro	pet cataracts eye drops	Heliostatics
Inactivated porcine circovirus	Sulfolipo-CD	Suvaxin-PCV	vaccine	Pfizer

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