Review Article

A LITERATURE REVIEW OF CYCLODEXTRINS INCLUSION COMPLEXES CHARACTERIZATION - PART I: PHASE SOLUBILITY DIAGRAM, DISSOLUTION AND SCANNING ELECTRON MICROSCOPY

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ABSTRACT

Cyclodextrins are cyclic oligosaccharides with a hydrophobic cavity and a hydrophilic surface. Such characteristics result in an improvement in the solubility of lipophilic molecules when inclusion complexes are formed. Characterization of the drug-cyclodextrin complex is not an easy task and a set of analytical techniques is necessary to explore the different characteristics of the isolated drug, cyclodextrin and resulting complex. As there are no studies that organize the most common techniques used to identify inclusion complexes, the aim of this review is detail the analytical tools phase solubility diagram, dissolution and electron scanning microscopy employed in this task.

Keywords: Cyclodextrin, Dissolution, Phase solubility diagram, Scanning Electron Microscopy.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides whose structures are formed by six (αCD), seven (βCD) or eight (γCD) glucose unites, arranged in an open-ended hollow cylinder. The CD cavity is hydrophobic and the surface is hydrophilic, which results in better solubility of hydrophobic molecules with the formation of inclusion complexes[1].

When a lipophilic guest molecule (drug) takes the place of the water inside the CD cavity, the system becomes more favorable and thermodynamically more stable. Noncovalent bonds are formed between the drug and CD. Size, geometry and polarity of the guest molecule are examples of limiting factors in obtaining an inclusion complex[2].

On the other hand, the type of CD, the solution pH, the temperature, the method employed to prepare complexes, as well as the addition of polymers, are also very important factors in drug complexation involving CDs[3].

CDs, besides improving the drug solubility of hydrophobic molecules, can also be used to mask unpleasant tastes or odors, stabilize volatile substances, protect molecules which are sensitive to light or oxygen, convert liquid substances in powder, reduce gastric or ocular irritation and prevent interaction between substances. Applications for CDs are being publicized throughout the pharmaceutical, cosmetic, agricultural and food industries[1,2].

αCD and γCD are absorbed in very small amounts when administered orally, the remainder being excreted in the urine without modifications. Studies have shown that up to 0.8 g/Kg/day and 2 g/Kg/day of βCD can be administered orally to rats and dogs, respectively. However, when administered parenterally, it has been shown to cause nephrotoxicity and hemolysis. In humans the acceptable daily intake is 1.4 g for αCD, 0.35 g for βCD and 10 g for γCD. Hydroxy-propyl-βCD (HPβCD) is considered non-toxic in low to moderate doses, and can be found on the market in orally- and intravenously-administered drugs, in doses higher than 8 mg/day and 16 mg/day, respectively[4].

To assess the formation of inclusion complexes involving CD, it is often necessary to use a set of techniques to ascertain the complexion. Currently, the most commonly employed techniques are the construction of the phase solubility diagram, thermal analysis, X-ray diffraction, infrared spectroscopy, nuclear magnetic resonance, dissolution and scanning electron microscopy.

As there are no studies classifying the techniques commonly employed in the evaluation of drug-CD complexes, the objective of this review is to detail the analytical tools phase solubility diagram, dissolution and scanning electron microscopy used to characterize such complexes.

METHODOLOGY

This research was undertaken using the Embase and Web of Science data bases. The name of the methods and the word cyclodextrin were used as key words in a cross-reference search, and the scope of the study was to give priority to the last 5 years. Preference was given to articles dealing with drugs.

Methods for identifying and characterizing inclusion complexes

Phase solubility diagram

The phase solubility diagram is one of the most common techniques employed in the characterization of CD inclusion complexes. It is obtained from the solubility

results of the guest molecule in increasing concentrations of CDs[1].

According to a model proposed by Higuchi and Connors[5], the diagrams can be of type A, where the solubility of the guest molecule increases as the CD concentration rises, indicating the formation of soluble complexes, or type B, when the complex is insoluble and the concentration of the guest molecule decreases as CD increases (Figure 1).

Furthermore, the diagrams can be classified as AL (linear) type, with a straight positive gradient; AN (negative), with an initial positive gradient, which, after a certain CD concentration, tends to negative; and AP (positive), with a positive gradient, which, after a certain CD concentration, becomes more pronounced.

In the AL-type diagram, the linear increase in solubility depends on the CD concentration, and if the slope is less than or equal to one, a stoichiometry of 1:1 is assumed. Furthermore, a slope of greater than one indicates a higher order of complex formation with regards to the guest molecule. When the diagram is of AP-type, the complexes formed are of greater order greater than one for the host molecule after a certain concentration of CD, and diagrams of the AN-type may be explained by changes in the solubilizing agent at high concentrations or aggregation of the complexes formed[4].

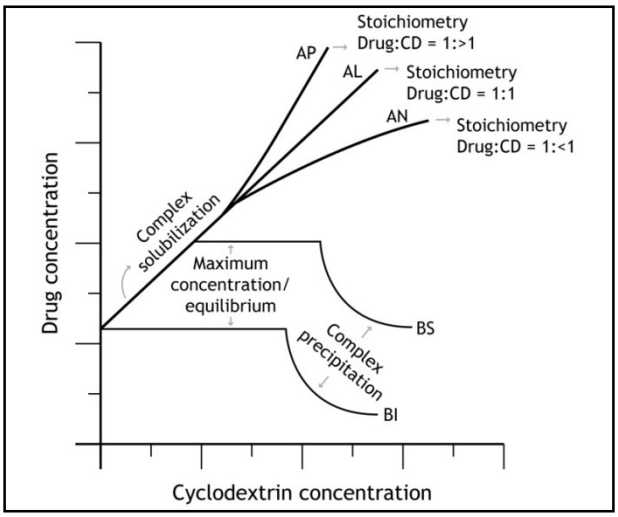

Figure 1: Types of phase solubility diagrams obtained from the complexation of drugs with cyclodextrins.

Type-B diagrams can take the BS (soluble) conformation where the complex has limited solubility. Initially, there is an increasing concentration of the guest molecule, and when it reaches the limit of solubility, precipitation occurs, thus lowering the concentration. Type-BI diagrams (insoluble) are obtained when the complex is insoluble and there is an initial balance, but after a certain concentration, complex precipitation occurs[1,4].

When the diagram shows the conformation of the AL-type, in other words, the rise in solubility is linear as CD concentration increases, the stability constant (Kc) can be calculated using the following equation:

Kc= slope/S0 (1-slope)

Where *S0* is the intrinsic solubility of the guest molecule.

AL-type diagrams are the most common when CD inclusion complexes are being evaluated. In such cases, the Kc value is calculated to determine the bond strength of the guest molecule to the host. In Table 1, the values for Kc and the bond strengths are defined[6].

Table 1: Bond strength between the guest molecule and CD, and the values for Kc

Kc value (M^{-1})	Bond strength
<500	Very weak
500-1000	Weak
1000-5000	Moderate
5000-20000	Strong
>20000	Very strong

For guest molecules with low solubility with AL-type diagrams, there may be differences between the solubility in an aqueous medium and the interception of the line in y, resulting in different Kc values. Alternatively, a value for complexation efficiency (CE) can be calculated. It considers only the slope value of the line equation of the diagram.

CE= Slope/(1-Slope)

The ratio of guest molecule to CD and the increase in formulation bulk with the addition of CD can also be determined from the CE value[7,8].

Guest Molecule:CD= 1/ (1+1/CE)

Increase in formulation bulk = (MWCD/MW Guest molecule) (1+1/CE)

Where MWCD is the molecular weight of cyclodextrin and MW guest molecule is the molecular weight of the guest molecule.

However, the use of CE is not the most usual method of assessing the complexation of drugs with CDs. There are a few studies in scientific literature that use this parameter[9-12].

Moreover, the Kc value is found in a much larger number of studies, some examples of which are shown in Table 2. This is an indication of the extent of researcher preference for this parameter.

Dissolution

The dissolution test is used to evaluate the occurrence of complexation, where the objective of complex formation is to increase the aqueous solubility of poorly soluble drugs. In some studies the dissolution profile is obtained using tablets of the drug, the physical mixture or the complex plus excipients[14], and in others the dissolution profile is obtained from powder, without compression[58].

An evaluation of the complexation is made by comparing the amount of drug dissolved and the dissolution

efficiency (Figure 2). When the formation of the complex occurs, higher dissolution efficiency is expected than that of either the drug or the physical mixture. This occurs because of the increased solubility provided by the complexation of the drug[59].

Table 2: Some examples of recent studies that use the phase solubility diagram in the characterization of inclusion complexes

Guest molecule	CD	Diagram type	Ref
5-nitroindazole	DMβCD[a]	AL	13
Aceclofenac	HPβCD	AL	14
AG11	HPβCD	AL	15
Benzophenone-3	HPβCD	AL	16
Bicalutamide	βCD	AL	17
Candesartan cilexetil	αCD, βCD, γCD and HPβCD	AL	18
Carvedilol	MβCD[b]	AL	19
Cefdinir	βCD and HPβCD	AL	20
Celecoxib	HPβCD	AL	21
Dipyridamole	βCD	AL	22
Efavirenz	βCD, HPβCD and RMβCD[c]	AL and AP	23
Etodolac	βCD, HPβCD and γCD	AL and BS	24
Etoricoxib	HPβCD	AL	25
Finasteride	HPβCD	AL	26
Flavonols	βCD	AL	27
Fluorofenidone	βCD and HPβCD	AL	28
Flurbiprofen	HPβCD	AL	29
Glyburide	βCD and HPβCD	AL	30
Granisetron	βCD and HPβCD	AL	31
Granisetron	αCD and γCD	BS	31
Hydrocortisone	βCD and γCD	BS	32
Hydroximethyl nitrofurazone	HPβCD	AL	33
Ibuprofen	βCD, MβCD and HPβCD	AL	34
Imatinib	βCD and RMβCD	AL	35
Iprodione	βCD	AL	36
Irbesartan	βCD	AL	37
Itraconazole	HPβCD and SBEβCD[d]	AP and AL	38
Lamotrigine	βCD	AL	39
Lidocain	βCD	AN	40
Loratadine	αCD, βCD, HPβCD and γCD	AP and AL	41
Loratadine	Heptakis -DMβCD[e]	AL	42
Losartan potassium	HPβCD	BS	43
Meloxicam	βCD	AL	44
Miconazole	βCD	AL	45
Nefopam	βCD and derivatives	AL and AN	46
Omeprazole	MβCD[f]	AL	47
Oxaprozin	βCD, DMβCD and RMβCD	AL	48
Prednisone	αCD, βCD, HPβCD and γCD	AL and BS	49
Pyrimethamine	αCD	AL	50
Simvastatin	αCD and βCD	AL and AP	51
Spironolactone	HPβCD	AL	52
Sulfadiazine	HPβCD	AL	53
TG44	βCD	AL	54
Triclosan	βCD	BS	55
Zaleplon	βCD	AL	56
Zerumbone	HPβCD	AP	57

[a]DMβCD: Dimethyl-βCD
[b]MβCD: Methyl-βCD
[c]RMβCD: Randomly-methylated-βCD
[d]SBEβCD: Sulfobutylether-βCD
[e]Heptakis -DMβCD: heptakis-(2.6-di-O-methyl)-βCD
[f]MβCD: Dimethyl-βCD

Table 3: Some examples of recent studies that use dissolution profiles for the characterization of inclusion complexes

Guest molecule	CD	Evidence of complexation	Ref
Aceclofenac	HPβCD	Dissolution efficiency in 10 minutes	14
Bicalutamide	βCD	Time required to release 90%	17
Budesonide	γCD	Percentage dissolved in 15 minutes	60
Bupivacaine hydrochloride	βCD and EPIβCD	Percentage dissolved in 90 minutes	61
Camptothecin	βCD	Percentage dissolved in 24 hours	62
Carvedilol	MβCD	Dissolution rate	19
Cefdinir	βCD and HPβCD	Percentage dissolved in 5, 10, 30 and minutes	20
Celecoxib	HPβCD	Percentage dissolved in 10 minutes	21
Celecoxib	βCD	Time required to release 50%	63
Clarithromycin	βCD	Dissolution rate	64
Danazol	HPβCD	Percentage dissolved	65
Efavirenz	βCD, HPβCD and RMβCD	Dissolution efficiency in 30 and 180 minutes	23
Etodolac	βCD, HPβCD and γCD	Percentage dissolved in 5 minutes	24
Etoricoxib	HPβCD	Percentage dissolved in 2, 15 and 30 minutes and dissolution efficiency in 45 minutes	25
Finasteride	HPβCD	Dissolution rate	26
Fluorofenidone	βCD e HPβCD	Percentage dissolved in 2 minutes	28
Glyburide	βCD and HPβCD	Percentage dissolved in 10 and 60 minutes	30
Granisetron	HPβCD	Percentage dissolved in 120 minutes	31
Halofantrina	HPβCD	Percentage dissolved in 60 and 180 minutes	66
Ibuprofen	βCD	Percentage dissolved in 15 and 75 minutes	58
Irbesartan	βCD	Dissolution rate	37
Itraconazole	HPβCD	Percentage dissolved	67
Ketoprofen	EPIβCD and EPICMβCD[a]	Percentage dissolved in 60 minutes	68
Loratadine	αCD, βCD, HPβCD and γCD	Percentage dissolved in 5 minutes	41
Loratadine	Heptakis -DMβCD	Percentage dissolved in 120 minutes	69
Loratadine	DIMEB[b]	Percentage dissolved in 120 minutes	70
Lovastatin	HPβCD	Percentage dissolved in 30 minutes and time required to release 50%	71
Losartan potassium	HPβCD	Percentage dissolved in 24 hours	43
Metformin	Triacetil-βCD	Time required to release 50%	72
Naproxen	HPβCD	Percentage dissolved in 10 and 30 minutes, dissolution efficiency in 60 minutes and dissolution rate in 5 minutes.	73
Omeprazole	βCD and MβCD	Percentage dissolved in 6 minutes, dissolution efficiency in 60 minutes	74
Oxaprozin	βCD, DMβCD and RMβCD	Dissolution rate	48
Piroxicam	HPβCD	Percentage dissolved in 10 and 60 minutes	75
Simvastatin	HPβCD	Percentage dissolved	76
Triclosan	βCD and EPIβCD	Percentage dissolved in 120 minutes	55
Zaleplon	βCD	Time required to release 90%	56

[a]EPICMβCD: Epichlorohydrincarboxymethylathed-β-CD
[b]DIMEB: Dimethyl-β-CD

Table 4: Some examples of recent studies that feature the use of scanning electron microscopy in the characterization of inclusion complexes

Guest molecule	CD	Evidence of complexation	Ref
Aceclofenac	HPβCD	Formation of a single phase	14
API[b]	γCD and RAMEB[c]	Loss of original shape and formation of a single phase	77
BMDBM[a]	HPβCD	Loss of original shape and formation of a single phase	78
Bupivacaine hydrochloride	βCD and EPIβCD	Loss of the crystallinity	61
Celecoxib	βCD	Formation of a single phase	63
Clarithromycin	βCD	Formation of a single phase	79
Coumestrol	βCD	Loss of original shape and formation of a single phase	80
Dipyridamole	βCD	Formation of a single phase	22
Efavirenz	βCD, HPβCD and RMβCD	Loss of original shape and formation of a single phase	23
Enalapril maleate	βCD	Loss of original shape and formation of a single phase	81
Ibuprofen	βCD	Loss of original shape	58
Irbesartan	βCD	Loss of original shape	37
Itraconazole	HPβCD	Loss of original shape	67
Metformin	Triacetil-βCD	Loss of original shape and formation of a single phase	72
Omeprazole	βCD and MβCD	Loss of original shape and formation of a single phase	74
Oxaprozin	βCD, DMβCD and RMβCD	Loss of original shape and formation of a single phase	48
Piroxicam	HPβCD	Loss of original shape	75
Prednisone	αCD, βCD, HPβCD and γCD	Loss of original shape and formation of a single phase	49
Ropivacaine	HPβCD	Formation of a single phase	9
Simvastatin	HPβCD	Loss of original shape	59
Vinpocetin	βCD and SBEβCD	Loss of original shape and formation of a single phase	82

[a]BMDBM: Butyl methoxydibenzoylmethane
[b]API: drug was referred by the authors as API due to reasons of Industrial Property Rights
[c]RAMEB: Randomly methylated beta cyclodextrin

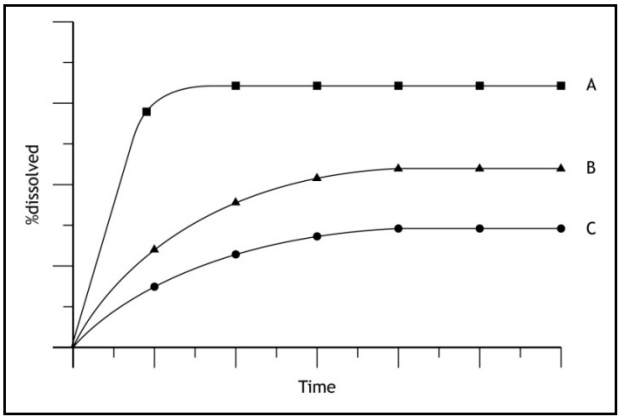

Figure 2: Hypothetical model of dissolution analysis for the inclusion complex (A), physical mixture (B) and complexed drug (C).

Table 3 presents recent studies that use dissolution profiles to assess the formation of inclusion complexes.

Scanning electron microscopy

Scanning electron microscopy is a technique used to qualitatively define the formation of inclusion complexes. Analysis is carried out by morphologically comparing the complex with the drug, CD and physical mixture. When inclusion complexes are formed, the image, contrary to the physical mixture, does not have two distinct components, but rather only one, which is different from the original form[74].

Recent works featuring the use of scanning electron microscopy to evaluate the formation of inclusion complexes are presented in Table 4.

CONCLUSION

Characterizing complex drug-CDs is not a simple task and requires the use of various analytical methods, which have been discussed in this study. Such analyses must be performed together, as each method explores a feature of the inclusion complex, before a decision is made about complexation.

REFERENCES

1. Veiga FJB,Pecorelli CCMF, Ribeiro LSS, As ciclodextrinasem tecnologia farmacêutica.1 ed., Minerva Coimbra Editora, Coimbra, 2006, 228p.
2. Valle EMMD. Cyclodextrins and their uses: a review, Process Biochem., 39, 2004, 1033-1046.
3. Challa R,AhujaA.,Ali J,Khar RK,Cyclodextrin in drug delivery: An update review,AAPS Pharm. Sci. Tech., 6, 2005, E329-E357.
4. Brewster ME, Loftsson, T,Cyclodextrins as pharmaceutical solubilizers, Adv. Drug Delivery Rev., 59, 2007, 645-666.
5. Higuchi T, Connors, AK,.Phase-solubility techniques, Adv. Anal. Chem. Instrum., 4, 1965, 117-212.
6. Carrier RL, Miller LA, Ahmed I, The utility of cyclodextrins for enhancing oral bioavailability, J. Controlled Release, 123, 2007, 78-99.
7. Loftsson T,Hreinsdóttir D,Másson M, Evaluation of cyclodextrinsolubilization of drugs, Int. J. Pharm., 302, 2005, 18-28.
8. Loftsson T,HreinsdóttirD,Másson M, The complexation efficiency, J.Incl.Phenom. Macrocycl.Chem., 57, 2007, 545-542.
9. Araujo DR,TsunedaSS,Cereda CMS,Carvalho FGF,Preté PSC,Fernandes SA,Yokaichiya F, Franco MKKD, Mazzarol,Fraceto LF, Braga AFA, Paula E,Development and pharmacological evaluation of ropivacaine-2-hydroxypropyl-β-cyclodextrin inclusion complex,Eur. J. Pharm. Sci., 33, 2008, 60-71.
10. Jug M,Becirevic-Lacan M,Bengez S, Novel cyclodextrin-based film formulation intended for buccal delivery of atenolol, Drug Dev. Ind. Pharm., 35, 2009, 796-807.
11. MeloNFS,Grillo R, Rosa AH,Fraceto LF,Interaction between nitroheterocyclic compounds with β-cyclodextrins: Phase solubility and HPLC studies,J. Pharm. Biomed. Anal., 47, 2008, 865-869.
12. Tewes F,Brillault J,Couet W, Olivier JC, Formulation of rifampicin - cyclodextrin complexes for lung nebulization, J. Controlled Release, 129, 2008, 93-99.
13. Jullian C, Morales-Montecinos J, Zapata-Torres G, Aguilera B, Rodriguez J,Arán V,Olea-Azar C, Characterization, phase-solubility, and molecular modeling of inclusion complex of 5-nitroindazole derivative with cyclodextrins, Bioorg. Med. Chem., 16, 2008, 5078-5084.
14. Dahiya S,PathakK, Influence of amorphous cyclodextrin derivatives on aceclofenac release from directly compressible tablets,Pharmazie, 62, 2007, 278-283.
15. Stancanelli R,Ficarra R,Cannavà C, Guardo M,Calabrò ML,Ficarra P,Ottanà R,Maccari R,Crupi V, Majolino D,Venuti V, UV-vis and FTIR-ATR characterization of 9-fluorenon-2-carboxyester/ (2-hydroxypropyl)-β-cyclodextrin inclusion complex,J. Pharm. Biomed. Anal., 47, 2008, 704-709.

16. Berbicz F,Nogueira AC,Neto AM,Natali MRM,Baesso ML,Matioli G, Use of photoacoustic spectroscopy in the characterization of inclusion complexes of benzophenone-3-hydroxypropyl-β-cyclodextrin and *ex vivo* evaluation of the percutaneous penetration of sunscreen, Eur. J. Pharm. Biopharm., 2011, doi: 10.1016/j.ejpb.2011.03.026.
17. Patil AL, Pore YV,Kuchekar BS, Late SG, Solid-state characterization and dissolution properties of bicalutamide-β-cyclodextrin inclusion complex,Pharmazie, 63, 2008, 282-285.
18. AlOmari AA, AlOmari MM,Badwan AA, AL-Sou'Od KA, Effect of cyclodextrins on the solubility and stability of candesartan cilexetil in solution and solid state, J. Pharm. Biom. Anal., 54, 2011, 503-509.
19. Hirlekar R, Kadam V,Preparation and characterization of inclusion complexes of carvedilol with methyl-β-cyclodextrin, J. Incl. Phenom. Macrocycl. Chem., 63, 2009, 219-224.
20. Aleem O, Kuchekar B, Pore Y, Late S, Effect of β-cyclodextrin and hydroxypropyl β-cyclodextrin complexation on physicochemical properties and antimicrobial activity of cefdinir, J. Pharm. Biomed. Anal., 47, 2008, 535-540.
21. Capello B, DiMaio C, Iervolino M,Miro A, Combined effect of hydroxypropyl methylcellulose and hydroxypropyl-β-cyclodextrin on physicochemical and dissolution properties of celecoxib,J. Incl. Phenom. Macrocycl. Chem., 59, 2007, 237-244.
22. AlOmari MM, El-Barghouthi MI,Zughul MB, Davies JED,Dipyridamole/β-cyclodextrincomplexation: Effect of buffer species, thermodynamics, and guest-host interactions probed by ^{1}H-NMR and molecular modeling studies,J. Incl. Phenom. Macrocycl. Chem., 64, 2009, 305-315.
23. Sathigari S,Chadha G, Lee YHP, Wright N, Parsons DL,Rangari VK,Fasina O,BabuRJ, Physicochemical characterization of efavirenz-cyclodextrin inclusion complexes,AAPS Pharm. Sci. Tech., 10, 2009, 81-87.
24. Cappello B, DiMaio C,Iervolino M,Miro A,Calignano A,Etodolac/cyclodextrin formulations: Physicochemical characterization and in vivo pharmacological studies,Drug Dev. Ind. Pharm., 35, 2009, 877-886.
25. Shah M,Karekar P,Sancheti P,Vyas V, Pore Y, Effect of PVP K30 and/or L-Arginine on stability constant of Etoricoxib–HPβCD inclusion complex: preparation and characterization of Etoricoxib–HPβCD binary system,Drug Dev. Ind. Pharm., 35, 2009, 118-129.
26. Asbahr ACC, Franco L,Barison A, Silva CWP,Ferraz HG, Rodrigues LNC,Binary and ternary inclusion complexes of finasteride in HPβCD and polymers: Preparation and characterization,Bioorg. Med. Chem., 17, 2009, 2718-2723.
27. Dias K,Nikolau S, DeGiovani WF,Synthesis and spectral investigation of Al(III) catechin/β-cyclodextrin and Al(III) quercetin/β-cyclodextrin inclusion compounds,Spectrochim. Acta, Part A, 70, 2008, 154-161.
28. Wang S, Ding Y, Yao Y, Inclusion complexes of fluorofenidone with β -cyclodextrin and hydroxypropyl-β-cyclodextrin,Drug Dev. Ind. Pharm., 35, 2009, 808-813.
29. Kim JK, Kim MS, Park JS, Kim CK, Thermo-reversible flurbiprofen liquid suppository with HP-β-CD as a solubility enhancer: improvement of rectal bioavailability,J. Incl. Phenom. Macrocycl. Chem., 64, 2009, 265-272.
30. Cirri M,Righi MF,Maestrelli F, Mura P,Valleri M, Development of glyburide fast-dissolving tablets based on the combined use of cyclodextrins and polymers,Drug Dev. Ind. Pharm., 35, 2009, 73-82.
31. ChoHJ,Balakrishnan P, Shim WS, Chung SJ, Shim CK, Kim DD, Characterization and *in vitro* evaluation of freeze-dried microparticles composed of granisetron-cyclodextrin complex and carboxymethylcellulose for intranasal delivery,Int. J. Pharm., 2010, 400, 59-65.
32. Messner M,Kurkov SV, Brewster ME, Jansook P,Loftsson T, Self-assembly of cyclodextrin complexes: Agregation of hydrocortisone/cyclodextrin complexes,Int. J. Pharm., 407, 2011, 174-183.
33. Grillo R,Melo NFS,Moraes CM, Lima R,Menezes CMS, Ferreira EI, Rosa AH,Fraceto LF,Study of the interaction between hydroxymethylnitrofurazone and 2-hydroxypropyl-β-cyclodextrin,J. Pharm. Biomed. Anal.,47, 2008, 295-302.
34. DiCagno M, Stein PC,Skalko-Basnet N,Brandl M, Bauer-Brandl A,Solubilization of ibuprofen with β-cyclodextrin derivatives: Energetic and structural studies,J. Pharm. Biomed. Anal., 55, 2011, 446-451.
35. Beni S,Szakács Z,Csernák O,Barcza L, Noszál B,Cyclodextrin/imatinibcomplexation: Binding mode and charge dependent stabilities,Eur. J. Pharm. Sci., 30, 2007, 167-174.
36. Zhu XL, Wang HB, Chen Q, Yang WC, Yang GF, Preparation and characterization of inclusion complex of iprodione and β-cyclodextrin to improve fungicidal activity,J. Agric. Food Chem., 55, 2007, 3535-3539.
37. Hirlekar R,Kadam V,Preformulation Study of the Inclusion Complex Irbesartan-β-Cyclodextrin,AAPS Pharm. Sci. Tech., 10, 2009, 276-281.
38. Brewster ME,Vandecruys R,Peeters J,Neeskens P,Verreck G,Loftsson T, Comparative interaction of 2-hydroxypropyl-β-cyclodextrin and sulfobutylether-β-cyclodextrin with itraconazole: Phase-solubility behavior and stabilization of supersaturated drug solutions,Eur. J. Pharm. Sci., 34, 2008, 94-103.
39. Shinde VR,Shelake MR,Shetty SS,Chavan-Patil AB, Pore YV, Late SG, Enhanced solubility and dissolution rate of lamotrigine by inclusion complexation and solid dispersion technique,J. Pharm. Pharmacol., 60, 2008, 1121-1129.
40. Tatai A,Aigner Z, Eros I, Kata M, Preparation and investigation of mixtures containing lidocaine base and β-cyclodextrin,J. Incl. Phenom. Macrocycl. Chem.,59, 2007, 105-113.
41. Omar L, El-Barghouthi MI,Masoud NA, Abdoh AA,Al-Omari MM,Zughul MB,Badwan AA, Inclusion complexation of loratadine with natural and modified cyclodextrins:phase solubility and thermodynamic studies,J. Solution Chem., 36, 2007, 605-616.
42. Nacsa A,Berkesi O,Szabó-Révész P,Aigner Z, Achievement of pH-independence of poorly-soluble, ionizable loratadine by inclusion complex formation with dimethyl-*b*-cyclodextrin,J. Incl. Phenom. Macrocycl. Chem.,64, 2009, 249-254.
43. De Paula W,Denadai AML, Santoro MM, Braga ANG, Santos RAS,Sinisterra RD,Supramolecular interactions beween losartan and hydroxypropyl-β-CD: ESI mass-spectrometry, NMR techniques, phase solubility, isothermal titration calorimetry and anti-hypertensive studies,Int. J. Pharm., 404, 2011, 116-123.
44. Obaidat AA,Khanfar RA,Khawam MN, The effect of β-cyclodextrin on the solubility and dissolution rate of meloxicam and investigation of the driving force for complexation using molecular modeling,J. Incl. Phenom. Macrocycl. Chem., 63, 2009, 273-279.
45. Wang J,Cai Z, Investigation of inclusion complex of miconazole nitrate with β- cyclodextrin,Carbohydr. Polym., 72, 2008, 255-260.
46. Brun H, Paul M,Razzouq N,Binhas M,Gibaud S,Astier A,Cyclodextrin inclusion complexes of the central analgesic drug nefopam,Drug Dev. Ind. Pharm., 32, 2006, 1123-1134.
47. Figueiras A,Sarraguça JMG,Carvalho RA,Pais AACC,Veiga FJB,Interaction of omeprazole with a methylated derivative of β-cyclodextrin: Phase solubility, NMR spectroscopy and molecular simulation,Pharm. Res., 24, 2007, 377-389.
48. Maestrelli F,Cecchi M, Cirri M,Capasso G,Mennini N, Mura P, Comparative study of oxaprozin complexation with natural and chemically-modified cyclodextrins in solution and in the solid state,J. Incl. Phenom. Macrocycl., 63, 2009, 17-25.
49. Ghuzlaan A, AlOmari MM,Al-Sou'Od KA, Prednisone/cyclodextrin inclusion complexation: phase solubility, thermodynamic, physicochemical and computational analysis,J. Solution Chem., 38, 2009, 83-94.
50. Araujo MVG, Macedo OFL, Nascimento CC,Conegero LS, Barreto LS, Almeida LE, Costa-Jr NB, Gimenez IF,Characterization, phasesolubilityand molecular modelingofα-cyclodextrin/pyrimethamineinclusioncomplex,Spectrochim. Acta, Part A, 72, 2009, 165-170.

51. Wen X, Liu Z, Zhu T, Mass spectrometry and molecular modeling studies on the inclusion complexes between α, β-cyclodextrins and simvastatin,Chem. Phys. Lett., 405, 2005, 114-117.
52. Rajabi O,Tayyari F,Salari R,Tayyari SF,Study of interaction of spironolactone with hydroxypropyl-β-cyclodextrin in aqueous solution and in solid state,J. Mol. Struct., 878, 2008, 78-83.
53. Araújo MVG, Vieira EKB, Lázaro GS,Conegero LS, Ferreira OP, Almeida LE,Barreto LS, Costa-Jr NB,Gimenez IF,Sulfadiazine/hydroxypropyl-β-cyclodextrin host-guest system: Characterization, phase-solubility and molecular modeling,Bioorg. Med. Chem., 16, 2008, 5788-5794.
54. Anzai K,Mizoguchi J,Yanagi T, Hirayama F, Arima H,Uekama K,Improvement of dissolution properties of a new Helicobacter pylori eradicating agent (TG44) by inclusion complexation with β-cyclodextrin,Chem. Pharm. Bull., 55, 2007, 1466-1470.
55. Jug M,Kosalec I,Maestrelli F, Mura P, Analysis of triclosan inclusion complexes with β-cyclodextrin and its water-soluble polymeric derivative,J. Pharm. Biom. Anal., 54, 2011, 1030-1039.
56. Doiphode D,Gaikwad S, Pore Y, Kuchekar B, Late S, Effect of β-cyclodextrin complexation on physicochemical properties of zaleplon,J. Incl. Phenom. Macrocycl. Chem., 62, 2008, 43-50.
57. Eid EEM, Abdul AB,Suliman FEO,Sukari MA,Rasedee A, Fatah SS, Characterization of the inclusion complex of zerumbone with hydroxypropyl-β-cyclodextrin,Carbohydrate Polymers, 83, 2011, 1707-1714.
58. Hussei K, Türk M, Wahl MA, Comparative evaluation of ibuprofen/β-cyclodextrin complexes obtained by supercritical carbon dioxide and other conventional methods,Pharm. Res., 24, 2007, 585-592.
59. Jun SW, Kim MS, Kim JS, Park HJ, Lee S, Woo JS, Hwang SJ, Preparation and characterization of simvastatin/hydroxypropyl-β-cyclodextrin inclusion complex using supercritical antisolvent (SAS) process,Eur. J. Pharm. Biopharm., 66, 2007, 413-421.
60. Toropainen T,Velaga S,Heikkilä T,Matilainen L,Jarho P,Carlfors J,Lehto VP,Järvinen T,Järvinem K, Preparation of budesonide/γ-cyclodextrin complexes in supercritical fluids with a novel SEDS method. emulsion based formulations,J. Pharm. Sci., 95, 2006, 2235-2245.
61. Jug M,Maestrelli F,BragagniM, Mura P, Preparation and solid-state characterization of bupivacaine hydrochloride cyclodextrin complexes aimed for bucal delivery,J. Pharm.Biom.Anal., 52, 2010, 9-18.
62. Swaminathan S,Pastero L,Serpe L, Trotta F,Vavia P,Aquilano D,Trotta M, Zara G,Cavalli R,Cyclodextrin-based nanosponges encapsulating camptothecin: Physicochemical characterization, stability and cytotoxity,Eur. J. Pharm. Biopharm., 74, 2010, 193-201.
63. Sinha VR, Anitha R,Ghosh S,Amita,Kumria R,Bhinge JR, Kumar M, Physicochemical characterization and in vitrodissolution behaviour of celecoxib-β-cyclodextrin inclusion complexes,Acta Pharm., 57, 2007, 47-60.
1. 64.Zhang X,Zou M, Li S, Chen X,Zhong D, Bioavailability of clarithromycin cyclodextrin ternary complexes upon oral administration to healthy beagle dogs,Drug Dev. Ind. Pharm., 34, 2008, 163-171.
64. Rogers TL, Nelsen AC, Hu J, Brown JN,Sarkari M, Young TJ, Johnston KP, Williams III RO, A novel particle engineering technology to enhance dissolution of poorly water soluble drugs: spray-freezing into liquid,Eur. J. Pharm. Biopharm., 54, 2002, 271-280.
65. Onyeji CO,Omoruyi SI,Oladimeji FA, Dissolution properties and characterization of halofantrine-2-hydroxypropyl-β-cyclodextrin binary systems, Pharmazie, 62, 2007, 858-863.
66. Lee SY, Jung II, Kim JK, Lim GB,Ryu JH, Preparation of itraconazole/HP-β-CD inclusion complexes using supercritical aerosol solvent extraction system and their dissolution characteristics,J. Supercrit. Fluids.,44, 2008, 400-408.
67. CirriM,Bragagni M,Mennini N, Mura P, Development of a new delivery system consisting in "drug – in cyclodextrin – in nanostructured lipid carriers" for ketoprofen topical delivery,Eur. J. Pharm. Biopharm., (2011), doi: 10.1016/j.ejpb.2011.07.015.
68. Nacsa A,Ambrus R,Berkesi O,Szabó-Révéz P,Aigner Z, Water-soluble loratadine inclusion complex: Analytical control of the preparation by microwave irradiation,J. Pharm. Biomed. Anal., 48, 2008, 1020-1023.
69. Szabados-Nacsa Á,Sipos P,Martinek T,Mándity I,Blazsó G,Balogh Á,Szabó-Révész P,Aigner Z,Physico-chemical characterization and *in vitro/in vivo* evaluation of loratadine:dimethyl-β-cyclodextrin inclusion complex,J. Pharm. Biom. Anal., 55, 2011, 294-300.
70. Patel RP, Patel MM, Solid-state characterization and dissolution properties of lovastatin hydroxypropyl-β-cyclodextrin inclusion complex,Pharm. Tech., 31, 2007, 72-82.
71. Corti G,Capasso G,Maestrelli F, Cirri M, Mura P, Physical-chemical characterization of binary systems of metformin hydrochloride with triacetyl-β-cyclodextrin,J. Pharm. Biomed. Anal., 45, 2007, 480-486.
72. Mura P,Bettinetti GP, Cirri M,Maestrelli F,Sorrenti M,Catenacci L, Solid-state characterization and dissolution properties of Naproxen–Arginine–Hydroxypropyl-β-cyclodextrin ternary system,Eur. J. Pharm. Biopharm., 59, 2005, 99-106.
73. Figueiras A,Carvalho RA, Ribeiro L, Torres-Labandeira JJ, Veiga FJB,Solid-state characterization and dissolution profiles of the inclusion complexes of omeprazole with native and chemically modified β-cyclodextrin,Eur. J. Pharm. Biopharm., 67, 2007, 531-539.
74. Zhang X, Wu D, Lai J, Lu Y, Yin Z, Wu W,Piroxicam/2-Hydroxypropyl-β-Cyclodextrin Inclusion Complex Prepared by a New Fluid-Bed Coating Technique,J. Pharm. Sci., 98, 2009, 665-675.
75. Ungaro F,Giovino C,Catanzano O,Miro A,Mele A,Quaglia F, LaRotonda MI,Use of cyclodextrins as solubilizing agents for simvastatin: Effect of hydroxypropyl-β-cyclodextrin on lactone/hydroxyacid aqueous equilibrium, Int. J. Pharm., 404, 2011, 49-56.
76. Vajna B,Farkas I,Farkas A, Pataki H, Nagy Z,Madarász J,Marosi G, Characterization of drug-cyclodextrin formulations using Raman mapping and multivariate curve resolution,J. Pharm. Biom. Anal., 56, 2011, 38-44.
77. Scalia S,Coppi G,Iannuccelli V,Microencapsulation of a cyclodextrin complex of the UV filter, butyl methoxydibenzoylmethane: In vivo skin penetration studies,J. Pharm. Biom. Anal., 54, 2011, 345-350.
78. Zhang X, Zhang Y,Zhong D, Chen Y, Li S, Investigation and Physicochemical characterization of clarithromycin-citric acid-cyclodextrins ternary complexes,Drug Dev. Ind. Pharm., 33, 2007, 163-171.
79. Franco C,Schwingel L, Lula I,Sinisterra RD, Koester LS,Bassani VL,Studies on coumestrol/β-cyclodextrin association: Inclusion complex characterization, Int. J. Pharm., 369, 2009, 5-11.
80. Zoppi A,Garnero C,Linck YG,Chattah AK,Monti GA,Longhi MR,Enalapril:β-CD complex: Stability enhancement in solid state,Carbohydrate Polymers, 86, 2011, 716-721.
81. Ribeiro LSS, Ferreira DC, Veiga FJB,Phisicochemical investigation of the effects of water-soluble polymers on vinpocetinecomplexation with β-cyclodextrin and its sulfobutyl ether derivate is solution and solid state,Eur. J. Pharm. Sci., 20, 2003, 253-266.

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