Supramolecular cyclodextrin complexes of biologically active nitrogen heterocycles

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The review is devoted to the rapidly developing field of modern supramolecular chemistry – cyclodextrin complexes of biologically active nitrogen heterocycles, such as piperidines, piperazines, morpholines and pyridines. Interest in cyclodextrin complexes is growing due to the search and construction of supramolecular assemblies for targeted drug delivery. The latter is achieved as a result of supramolecular self-assembly, based on the principles of molecular recognition, and is one of the areas of modern chemistry, leading to the creation of new materials with new properties.

This review fully demonstrates the ongoing scientific and practical interest in the problem of encapsulation with cyclodextrins, including nanoencapsulation. Encapsulation with cyclodextrins provides a wide range of advantages: obtaining solid dosage forms from liquid ones, stabilizing and protecting active substances from the adverse effects of external factors, increasing solubility, increasing bioavailability, reducing toxicity, prolonging action, etc.

The presented review includes recent advances in the field of supramolecular complexes of biologically active nitrogen heterocycles with cyclodextrins and concludes with a discussion and identification of future promising directions for research. The review presents the results of supramolecular self-assembly of biologically active azaheterocycles with cyclodextrins.

Keywords: supramolecular complexes; cyclodextrins; biological activity; nitrogen heterocycles; piperidines; piperazines; morpholines; pyridines.

Биологиялық белсенді азотты гетероциклдердің супрамолекулалық циклодекстриндік кешендері

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Шолу қазіргі заманғы супрамолекулалық химияның қарқынды дамып келе жатқан бағыттарының бірі – пиперидиндер, пиперазиндер, морфолиндер және пиридиндер сияқты биологиялық белсенді азотты гетероциклдердің циклодекстриндік кешендеріне арналған. Циклодекстрин кешеніне қызығушылық дәрі-дәрмектерді мақсатты жеткізу үшін супрамолекулалық ансамбльдерді іздеуге және жобалауға байланысты артып келеді. Соңғысына молекулалық тану принциптеріне негізделген супрамолекулалық өзін-өзі құрастыру негізінде қол жеткізіледі және жаңа қасиеттері бар жаңа материалдардың жаңадан құруына әкелетін заманауи химияның бағыттарының бірі болып табылады.

Бұл шолу циклодекстриндермен капсулдау мәселесіне, соның ішінде нанокапсуляцияға ғылыми және практикалық қызығушылықты толығымен көрсетеді. Циклодекстриндермен капсулдау көптеген артықшылықтар береді: сұйық заттардан қатты дәрілік формаларды алу, белсенді заттарды сыртқы факторлардың қолайсыз әсерінен тұрақтандыру және қорғау, ерігіштіктің жоғарылауы, биожетімділіктің жоғарылауы, уыттылықтың төмендеуі, әсердің ұзаруы және т. б.

Ұсынылған шолу циклодекстриндермен биологиялық белсенді азотты гетероциклдердің супрамолекулалық кешендері саласының соңғы жетістіктерін қамтиды және болашақ перспективалық зерттеу бағыттарын талқылау және анықтаумен аяқталады. Шолуда биологиялық белсенді азагетероциклдердің циклодекстриндермен супрамолекулалық өзін-өзі құрастыру нәтижелері ұсынылады.

Түйін сөздер: супрамолекулалық кешендер; циклодекстриндер; биологиялық белсенділік; азотты гетероциклдер; пиперидиндер; пиперазиндер; морфолиндер; пиридиндер.

Супрамолекулярные циклодекстриновые комплексы биологически активных азотистых гетероциклов

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Обзор посвящен одному из бурно развивающихся направлений современной супрамолекулярной химии – циклодекстриновым комплексам биологически активных азотистых гетероциклов, таких как пиперидины, пиперазины, морфолины и пиридины. Интерес к циклодекстриновым комплексам растет в связи с поиском и конструированием супрамолекулярных ансамблей для адресной доставки лекарств. Последнее достигается в результате супрамолекулярной самосборки, основанной на принципах молекулярного распознавания, и является одним из направлений современной химии, приводящим к созданию новых материалов с новыми свойствами.

Настоящий обзор в полной мере демонстрирует неугасающий научный и практический интерес к проблеме капсулирования циклодекстринами, в том числе нанокапсулированию. Капсулирование циклодекстринами дает широкий спектр преимуществ: получение твердых лекарственных форм из жидких, стабилизация и защита активных веществ от неблагоприятного воздействия внешних факторов, увеличение растворимости, повышение биодоступности, снижение токсичности, пролонгация действия и др.

Представленный обзор включает последние достижения в области супрамолекулярных комплексов биологически активных азотистых гетероциклов с циклодекстринами и завершается обсуждением и определением будущих перспективных направлений исследований. В обзоре представлены результаты супрамолекулярной самосборки биологически активных азагетероциклов с циклодекстринами.

Ключевые слова: супрамолекулярные комплексы; циклодекстрины; биологическая активность; азотистые гетероциклы; пиперидины; пиперазины; морфолины; пиридины.

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Review

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1. Introduction

The use of cyclodextrins (CDs) to create complexes including biologically active compounds, pharmaceuticals and drugs is one of the main directions in the development of supramolecular chemistry and the new forms of medicinal substances production [1-7]. Among the currently widely known encapsulating receptor compounds for pharmaceutically active compounds, such as c [8,9], crown ethers [10], calixarenes [11, 12] and others, CDs are distinguished by a number of remarkable properties due to their structure and serve reference host molecules for a wide range of natural and synthetic molecules. Cyclodextrins are among the available semi-natural compounds obtained from starch.

The CD molecule consists of several glucopyranose units and has the shape of a torus (a truncated hollow cone). The most common types of cyclodextrins are its α-, β- and γ-forms, containing 6, 7 and 8 glucopyranose units, respectively (Figure 1):

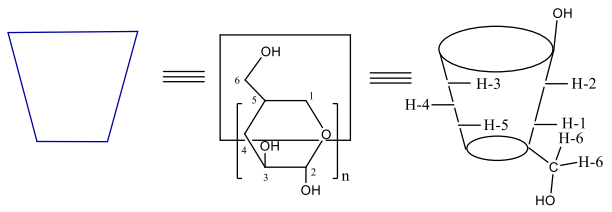

Figure 1 – Structure and arrangement of hydrogen atoms in CD (α-CD: n=6; β-CD: n=7; γ-CD: n=8) [1-7]

The most important distinguishing feature of CD is the ability to hydrophobically bind a guest molecule in its cavity (host) in an aqueous environment. This is due to the fact that all the primary hydroxyl groups of the CD molecule are directed outward, the secondary ones are directed into the cavity, where the H-3 and H-5 atoms and the glycosidic oxygen are also located. The result of this structure is the formation of the outer hydrophilic structure of the CD, while the inner cavity has hydrophobic properties. This CD configuration promotes the formation of inclusion complexes with guest molecules those are less polar than water and if their geometry and structure are complementary to the cavity of the cyclodextrin receptor.

To regulate the solubility of cyclodextrin complexes, in recent years, intensive work has been carried out in the field of preparation and use of various CD derivatives as drug receptors, which differ significantly from the original cyclic oligosaccharide in physicochemical properties and solubility [13-18].

Currently, alkyl, hydroxyalkyl, acyl, carboxyl, phosphono-diamidoester, amino, maltosyl, glucosyl derivatives of CD are known [19], which are characterized by good solubility in water. Hydrophobic derivatives of CD are represented by diethyl and triethyl analogues [20]. They are poorly soluble in water and can be used to prolong the action of a pharmaceutical drug as part of an inclusion complex. Zwitterionic derivatives of CD – carboxyl and amino derivatives – are characterized by a strong dependence of solubility in water on the acidity of the medium.

It should be noted that work towards the production of CD derivatives is being carried out on a large scale and with high returns.

Scientific and practical interest in the problem of encapsulation with cyclodextrins [21,22], including nanoencapsulation [23-28], remains high, as evidenced by the available literature on this topic, published in periodicals and materials of international conferences and symposia.

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Complexation with CD often makes it possible to solve such issues as instability of a substance during storage, insufficient solubility in water, and an inconvenient state of aggregation to use. It is noted that the latest achievements in chemistry of intermolecular interactions and the most promising areas of its use are associated with the processes of self-assembly and self-organization, which, in particular, can be implemented in the supramolecular creation of nanoencapsulated complexes of pharmaceuticals with CDs.

Particular interest in CDs as drug carriers compared to other complexing agents is due to three properties: high stability, a sufficiently large cavity diameter, and good body tolerance of cyclodextrin dosage forms.

As a result of complexation with CD, the following is achieved:

1) reduction of toxicity;

2) the possibility of converting liquid substrates into crystalline ones;

3) increased pharmacological activity;

4) increasing the stability of drugs to hydrolysis and oxidation.

Among those used to obtain inclusion complexes, the most affordable one is currently β-CD, while prices for α- and γ-CD are still quite high. However, it should be noted that β-CD is insufficiently soluble in water (18.5 mg/ml at 25°C [1]).

Supramolecular nanoencapsulation of pharmaceuticals with cyclodextrins makes it possible to obtain solid dosage forms from liquid ones, helps stabilize active substances to the external effects of light, heat, and atmospheric oxygen, and also increases solubility, improves bioavailability, and masks undesirable odors and taste of biologically active compounds. As a result of encapsulation of medicinal substances, it is possible to obtain drugs with prolonged, programmed and transdermal effects. In addition, the possibility of targeted transport of the drug in the body directly to the site of its action increases.

The reversibility of the process of supramolecular interaction of a biologically active compound with an encapsulating agent plays an important role in regulating the ability of a substance to pass through biomembranes or lipophilic barriers. The rate and extent of bioavailability of a pharmaceutically active substrate can be adjusted by changing various environmental factors that affect the solubility of the complex, its destruction in the biological environment and, consequently, the ability of the drug to penetrate obstacles to the intended target organ. In the equilibrium mechanism of dissolution and destruction of supramolecular complexes, competing processes of exchange of the “guest” molecule in the CD cavity can also occur [29].

The choice of pharmaceutical substrates for the preparation of supramolecular assemblies is determined by the pharmaceutical activity of the encapsulated molecules and the tasks assigned to researchers.

Currently, organic chemists are conducting a significant amount of work on the study of biologically active nitrogen heterocycles [30-32]. Heterocyclic aza compounds are widespread in nature and are essential for many biological functions. Nitrogen heterocycles are isolated in large quantities from natural compounds, and new synthetic biological active compounds with a predicted wide spectrum of pharmacological action are being created [33-36].

When studying CD inclusion complexes with guest molecules, high-resolution NMR spectroscopy is widely used to establish the structure and configuration of supramolecular assemblies [37]. The exclusive role of the NMR method in chemical research, especially complex formation, is determined by the fact that it turns out to be a very useful and often irreplaceable source of information at all stages of research - from studying the composition of complex reaction mixtures to establishing the structure and characteristics of complex compounds, the distribution of electron density in them and intermolecular interactions. Based on the change in the chemical shifts of cyclodextrin protons during complex formation with guest molecules, it is concluded that the substrate is included in the internal cavity of the CD receptor or the formation of external or mixed complexes [37,38].

In this review, biologically active nitrogen heterocycles such as piperidines, piperazines, morpholines, pyridines and their derivatives will be considered as substrates in supramolecular complex formation. An analysis of the literature on the preparation, structure and properties of supramolecular inclusion complexes of cyclodextrins with biologically active azaheterocycles will include data for the last decade. The collected material indicates an ever-increasing interest in ensembles consisting of nanosized supramolecular CD particles with biologically active azaheterocycles, and there is no doubt that the development of high-tech and less expensive technologies for creating supramolecular nanodispersed drugs is a very relevant and sought-after topic.

2. Main Part

2.1 Supramolecular cyclodextrin inclusion complexes with piperidines

The complexation of 4-(but-3-en-1-yn-1-yl)-1-(3-butoxypropyl)piperidin-4-yl benzoate **1** with *β*-CD (Figure 2) was studied using NMR spectroscopy [39]. The inclusion of **1** into the cavity of the *β*-CD molecule leads to significant changes in the chemical shifts of the H-3 and H-5 protons of *β*-CD located in the internal cavity. In the ROESY spectrum of the inclusion complex **1**/(*β*-CD)$_2$, cross-peaks are observed corresponding to intermolecular interactions of the H-3 and H-5 protons of *β*-CD with the protons of the aromatic and piperidine rings of **1**. The authors believe that the most probable is the formation of inclusion complexes composition **1**/(*β*-CD)$_2$ (Figure 2).

The works [40,41] present the results of the supramolecular self-assembly of the inclusion complex of 1-(2-ethoxyethyl)-4-phenylpiperidin-4-yl acetate **2** with β-CD (Figure 3). Data obtained by NMR spectroscopy, thermal analysis and molecular modeling suggest that the composition of the

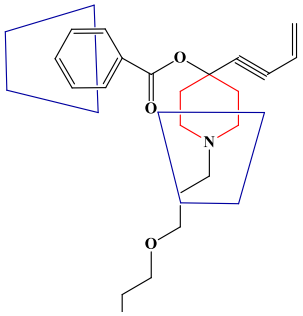

Figure 2 – Proposed structure of the inclusion complex **1**/(β-CD)$_2$

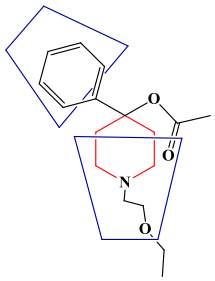

Figure 3 – Proposed structure of the inclusion complex **2**/(β-CD)$_2$

resulting inclusion complex corresponds to **2**/(β-CD)$_2$. The primary portion of the guest molecule resides within the cavity of one β-CD molecule, comprising part of the piperidine ring, ethoxyethyl, and acetoxy groups. Meanwhile, the phenyl group of the guest molecule is enclosed within the cavity of another β-CD molecule (Figure 3). Pharmacological investi-gations have indicated that the **2**/(β-CD)$_2$ supracomplex is promising for further extensive testing, notably for its enhanced and prolonged conduction anesthesia effects.

A comparative analysis of the ^{1}H and ^{13}C NMR spectra of 1-(2-ethoxyethyl)-4-[(3-propylacetylene)-1-yl]piperidin-4-ol **3** and its benzoate **4** was carried out and their inclusion complexes with β-CD [42]. The alterations in chemical shift values for the ^{1}H and ^{13}C nuclei of both substrates and the receptor in inclusion complexes were analyzed. It was shown that the supramolecular interaction of **3** and **4** with β-CD is accompanied by the entry of one N-ethoxyethyl moiety of the substrate molecule into the inner sphere of one receptor molecule (Figure 4).

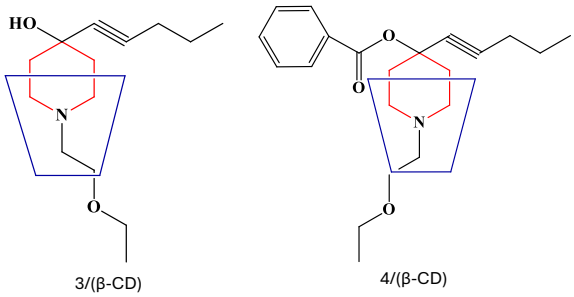

Figure 4 – Proposed structure of inclusion complexes **3**/(β-CD) и **4**/(β-CD)

The use of 1-methylpiperidin-4-ol **5** in supramolecular self-assembly with β-CD (Figure 5) [43] led to the formation of inclusion complexes with the composition **5**/β-CD. The inclusion complex crystallizes in the monoclinic space group.

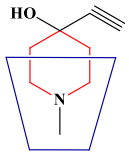

Figure 5 – Proposed structure of inclusion complexes **5**/(β-CD)

It was shown in [44] that (2E,4E)-5-(2H-1,3-benzodioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one (piperine) **6** forms inclusion complexes of the composition **6**/(α-CD)$_2$ and **6**/γ-CD (Figure 6). In dissolution tests, **6**/(α-CD)$_2$ and **6**/γ-CD showed higher solubility than free **6** and similar physical mixtures. NOESY spectroscopy measurements revealed that the structure of **6**/(α-CD)$_2$ is an inclusion complex in which interaction occurs through the aliphatic -HC=CH- and methylenedioxyphenyl groups of **6** with two α-CD molecules in a head-to-head manner. In γ-CD, the interaction occurs preferentially with the O–CH$_2$–O functional group of the methylenedioxyphenyl group in a 1:1 molar ratio (Figure 6) [44].

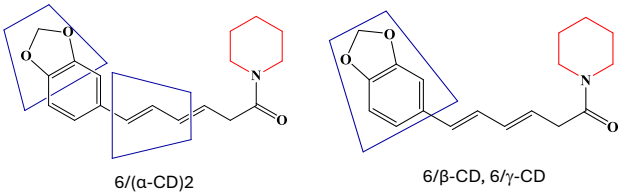

Figure 6 – Proposed structure of inclusion complexes **6**/(α-CD)$_2$, **6**/β-CD и **6**/γ-CD

Later [45], the inclusion complex **6**/Ethylenediamine (EDA)-β-CD was synthesized by coevaporation. The structure and properties of the inclusion complex were confirmed using IR, UV, XRD, TGA, ^{1}H and 2D ROESY NMR. ^{1}H and 2D ROESY NMR curves showed that **6** should penetrate into the EDA-β-CD cavity from the wide side of the conical rim by the methylenedioxyphenyl [45]. Molecular modeling confirmed that the complex has the composition **6**/EDA-β-CD (Figure 7). The authors [45] believe that the inclusion complex may contribute to the widespread clinical use of piperine in the future.

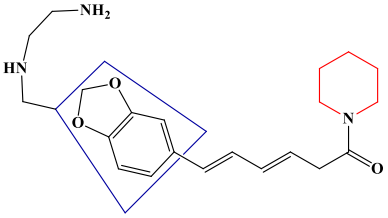

Figure 7 – Proposed structure of inclusion complexes **6**/EDA-β-CD

Complexation of β-CD with 2-methyl-3-(piperidin-1-yl)-1-(*p*-tolyl)propan-1-one (tolperisone) **7** (Figure 8), is accompanied by the introduction of a structural fragment of one guest molecule into the inner sphere of one host those [46]. The study's findings offer valuable insights into utilizing β-CD's complexation with tolperisone, suggesting it as a promising approach for formulating solid pharmaceuticals using β-CD as a drug carrier system.

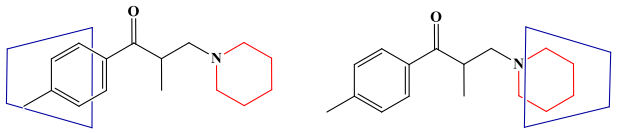

Figure 8 – Proposed structures of inclusion complexes **7**/β-CD

On the possibility of creating a supramolecular complex 1',4-didehydro-1-deoxy-1,4-dihydro-5'-(2-methylpropyl)-1-oxorifamycin XIV (rifabutin) **8** (Figure 9) with HP-β-CD (HP – 2-prop-2-ol-1-yl), formed as a result of the interaction of piperidine component **8** and the hydrophobic cavity of HP-β-CD, was reported in [47]. For the **8**/HP-β-CD complex, the stability constant was determined and the standard Gibbs energy of formation of the intermolecular complex was calculated [47]. Later, these authors [48] reported that molecules **8** do not form inclusion complexes with HP-β-CD molecules. Moreover, the increase in solubility of **8** is due to the formation of weak intermolecular associates. The limited bonding between the piperidine segment of molecule 8 and the HP-β-CD cavity results in the creation of soluble complexes of 8-HP-β-CD ranging in size from 100 to 600 nm. Consequently, this enhances the solubility of 8 by threefold in water and significantly boosts its efficacy against experimental tuberculosis infection [48].

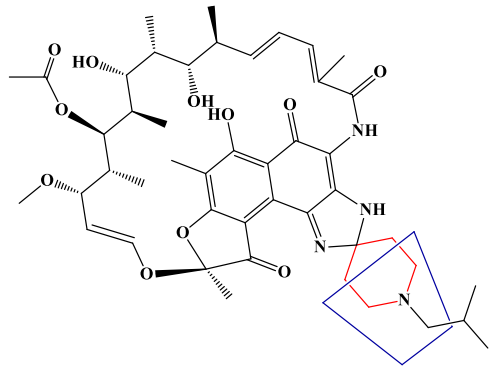

Figure 9 – Proposed associate structure **8**/HP-β-CD

The complexation of 2-(pyridinyl-3)piperidine (alkaloid anabasine) **9** with β-CD was studied using NMR spectroscopy (Figure 10) [49]. It was established that anabasine reacts with β-CD to form an inclusion complex of the composition **9**/β-CD, in which **9** enters the cyclodextrin cavity with a piperidine cycle.

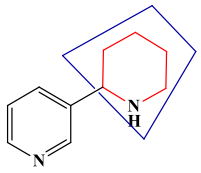

Figure 10 – Proposed structure of inclusion complexes **9**/β-CD

An inclusion complex of 6-amino-2-imino-4-(piperidin-1-yl)pyrimidin-1(2H)-ol (minoxidil) **10** with HP-β-CD of the composition **10**/ HP-β-CD (Figure 11) was obtained using the freeze-drying method [50]. The complex formation was validated by TLC, TGA and NMR results.

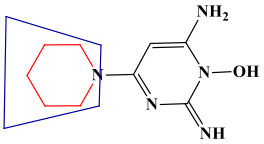

Figure 11 – Proposed structure of inclusion complexes **10**/HP-β-CD

Spectroscopic investigations, complemented by molecular modeling techniques, were employed to characterize the inclusion complex of 1-methyl-1-[2-(4-(trifluoromethyl)phenyl)thiazol-4-yl)methyl] piperidin-1-ium chloride **11** (Figure 12) with β-CD in both solution and the crystalline state [51]. The composition of the inclusion complex involving **11** and β-CD was identified through ^{1}H NMR spectroscopy as well as isothermal titration calorimetry. The likely structure of the inclusion complex (Figure 12), derived from molecular docking analysis, was strongly supported by the ROESY experiment [51].

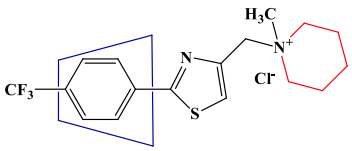

Figure 12 – Proposed structure of inclusion complexes **11**/β-CD

2.2 Supramolecular cyclodextrin inclusion complexes with piperazines

Inclusion complexes of 2-{2-[4-(4-chlorophenyl)(phenyl) methyl]piperazin-1-yl }ethoxyacetic acid (cetirizine) **12** and β-CD were obtained (Figure 13) [52].

The authors do not report the structure of the inclusion complex. Analysis of the solubility phase diagram of **12**-β-CD showed a linear increase in the solubility of **12** as the concentration of β-CD increased. The inclusion of **12** in the β-CD system significantly reduced the instability of **12** in the presence of oxidative factors. The ability to penetrate artificial biological membranes, exhibited by **12** after complexation, was also enhanced [52]. Further study of the inclusion complexes of **12**

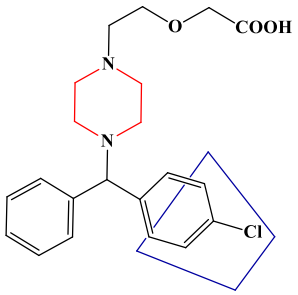

Figure 13 – Structure of the inclusion complex **12**/β-CD

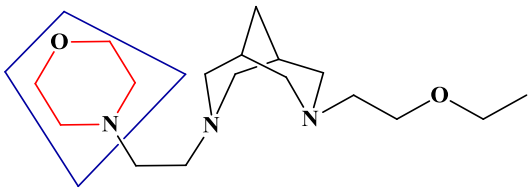

Figure 15 – Proposed scheme for the formation of inclusion complexes **14** with α-, β- и γ-CD

with α-CD and β-CD using molecular mechanical studies in the light mode and experimental ROESY studies allowed us to determine the exact structures of the complexes (Figure 13) [53]. The structures were tested using density functional theory, which is an accurate method for determining structure.

The inclusion complexes of 4-amino-5-fluoro-3-[5-(4-methylpiperazin-1-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-ylidene]quinolin-2(3*H*)-one (dovitinib) **13** were characterized using ^{1}H NMR (anticancer agent) with γ-CD, HP-γ-CD and SBE-γ-CD (SBE-sulfobutyl ether) (Figure 14), as well as the formation of nano- and microparticles using dynamic light scattering and *in vitro* permeability studies [54, 55]. Due to its ability to form ion pairs with **13**, SBE-β-CD was the best solubilizer among the CDs tested. However, the high molecular weight of SBE-β-CD compared to γ-CD leads to an increase in the volume of the drug and, accordingly, a decrease in penetration through membranes [54].

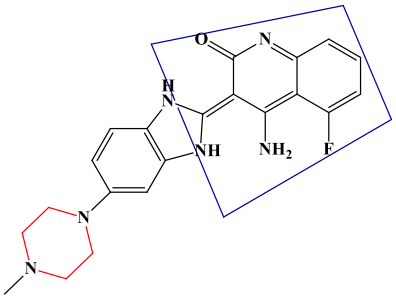

Figure 14 – Structure of the inclusion complex **13**/γ-CD, **13**/HP-γ-CD и **13**/SBE-γ-CD

2.3 Supramolecular cyclodextrin inclusion complexes with morpholines

The ^{1}H, ^{13}C, COSY and HMQC NMR spectra of 3-(2-ethoxyethyl)-7-[2-(N-morpholino)ethyl]-3,7-diazobicyclo[3.3.1]nonane **14** (Figure 15) and its inclusion complexes with α- , β- and γ-CD were interpreted [56]. It was demonstrated that the complexation of **14** with cyclodextrin involves the insertion of one morpholine fragment from the substrate molecule into the inner cavity of one receptor molecule (Figure 14).

The formation of supramolecular inclusion complexes is confirmed by changes in proton chemical shifts **14**. In all complexes, most of the proton signals of molecule **14** are shifted to the low-frequency region of the spectrum. A significant difference in chemical shifts is observed for H-14, H-15, H-17 and H-18, which are surrounded by more electronegative oxygen and nitrogen atoms. Such signal shifts indicate the entry of the morpholine moiety of molecule **14** into the internal spheres of cyclodextrins. It was noted that almost all hydrogen atoms **14** slightly change the position of the signals in the complexes, which indicates the presence of nonvalent interactions with outer-sphere CD protons and/or solvent molecules [56].

It was reported [57] that an inclusion complex of the local anesthetic – 4-[3-(4-butoxyphenoxy)propyl]morpholine (proxin) **15** (Figure 16) with HP-β-CD of a 1:1 composition was obtained. Complexation contributed to a 14-fold increase in the solubility of **15** in water. X-ray diffraction measurements revealed a loss of crystal structure of 15 in the presence of HP-β-CD, indicating the formation of an inclusion complex. Using ^{1}H NMR (DOSY) experiments, the association constant of **15** with HP-β-CD was determined (Ka = 923.1 mol/L), and Overhauser nuclear analysis (ROESY) confirmed the formation of the inclusion complex **15**/HP-β-CD, by detection of spatial proximity between the hydrogen atoms of the aromatic ring **15** and the HP-β-CD cavity [57].

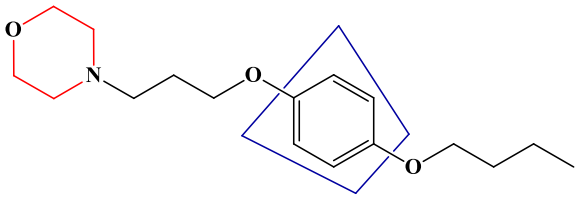

Figure 16 – Proposed scheme for the formation of inclusion complexes **15**/HP-β-CD

2.4 Supramolecular cyclodextrin inclusion complexes with pyridines

The complex formation of 3-(thiophen-2-yl)-[1,2,3]triazolo[1,5-a]pyridine **16** (Figure 17) with DM-β-CD (DM – dimaltosyl), HP-β-CD and β-CD showed that the inclusion complex is formed with a composition of 1:1 [58]. 2D NMR spectroscopy revealed that the thienyl group of compound **16** is encapsulated within the cyclodextrin (CD) cavity, whereas the triazolopyridine extends beyond the outer boundary of the DM-β-CD [58].

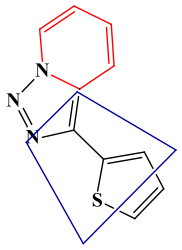

Figure 17 – Structure of inclusion complexes **16**/CD

The successful preparation of a stable inclusion complex between dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (nifendipine) **17** (Figure 18) EDA-β was reported [59]. - CD composition 1:1. Visible and FT-IR spectroscopy showed that the nitroaromatic moiety **17** was encapsulated inside the cavity of EDA-β-CD [59].

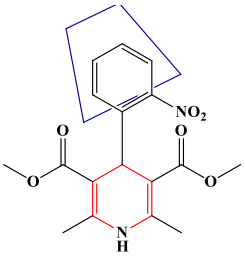

Figure 18 – Structure of **17**/EDA-β-CD inclusion complexes

An inclusion complex of [N1-methyl-N1-[(6-chloro-3-pyridyl)methyl]-N2-cyanoacetamidin]a (the insecticide acetamiprid) **18**, with β-CD (Figure 19) of a 1:1 composition was synthesized [60]. The inclusion of molecule **18** occurs by placing the chloropyridyl group on the wide side of the truncated rim, and the cyano group on the narrow side of the rim [60].

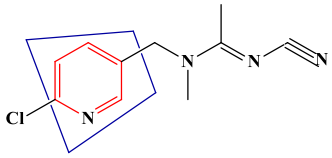

Figure 19 – Structure of **18**/β-CD inclusion complexes

It was established [61] that 2,2'-bipyridine **19** forms an inclusion complex with β-CD (Figure 20) in an aqueous solution.

Figure 20 – Chemical structure of **19**

The creation of inclusion complexes involving derivatives of thiourea — N-[(5-Cl **20** or 5-methyl **21)**pyridin-2-yl] carbamothioylthiophene-2-carboxamide, was studied (Figure 21) with both α- and β-CDs [62]. Thiourea derivatives can be accommodated within the cavity of a single cyclodextrin molecule or a cyclodextrin-dimer. The most stable inclusion complexes typically involve one thiourea molecule encapsulated by two CD molecules.

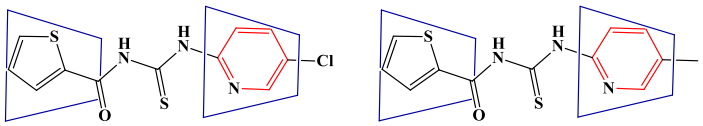

Figure 21 – Structure of inclusion complexes **20**/α-CD and **21**/(α-CD)2

3. Conclusion

Modern impressive successes in the preparation of cyclodextrin complexes of biologically active nitrogen heterocycles stimulate researchers to make wider use of the latest achievements of chemistry of intermolecular guest-host interactions in their research and inspire them to continue to pursue this promising and interesting problem. The literature data presented in this review over the past 10 years indicate the undoubted promise of this area, which is attracting increasingly close attention from researchers. The review highlights the importance of new supramolecular complexes of piperidine, piperazine, morpholine and pyridine. A special role is given to establishing the structure and characteristics of supramolecular complexes and the nature of intermolecular interactions during the formation of ensembles. Many beneficial properties of CDs and biologically active nitrogen heterocycles have been exploited in engineering to enhance and improve the quality of drug delivery. It is predicted that the solution to problems associated with targeted drug delivery will occur in the field of supramolecular design of nanoparticles and the use of nanotechnology. In this regard, the development of high-tech and less costly technologies for creating nanodispersed medicines remains very relevant and in demand. Advances in the field of supramolecular chemistry of complexes of biologically active azaheterocycles with CDs are due to the ability to ascertain the stoichiometry, association constants, and conformations of molecular complexes, as well as to offer insights into the symmetry of molecular assemblies using phase solubility diagrams, NMR, X-ray diffractometry, scanning

electron microscopy, differential scanning calorimetry and molecular mechanical modeling. Overall, this review can serve as a valuable resource for researchers, engineers, and parties interested in the development and application of supramolecular complexes, not only azaheterocycles with CDs, but also other classes of organic compounds with other intermolecular interaction receptors.

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Conflict of Interest

The authors of this article confirm that there is no conflict of interest.

Authors' Contributions

Seilkhanov T.M.: writing – original draft, conceptualization, investigation, methodology; Ten A.Yu.: writing – review & editing, investigation, validation; Tassibekov Kh.S.: project administration, supervision; Seilkhanov O.T.: writing – original draft, software, investigation; Zharkynbek T.Ye.: writing – review & editing, validation; Tursynova B.G.: writing – review & editing, validation; Yu V.K.: data curation, formal analysis, supervision, resources, funding acquisition.

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