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На правах рукописи

БУРХАНБАЕВА ТОЛКЫНАЙ ТАЖИБЕКОВНА

**Синтез и исследование новых комплексных соединений на основе
кукурбитурилов**

8D05301 – Химия

Диссертация в виде серии статей на соискание ученой степени доктора
философии (PhD)

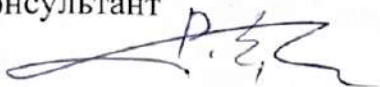
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Диссертационная работа выполнена на базе лаборатории кафедры химии, факультета естественных наук НАО «Евразийский национальный университет им. Л.Н. Гумилева» и лаборатории органического синтеза Томского государственного университета, г. Томск, РФ.

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АННОТАЦИЯ

диссертационной работы **Бурханбаевой Толкынай Тажибековны**
на тему **«Синтез и исследование новых комплексных соединений
на основе кукурбитурилов»**,

представленной на соискание степени доктора философии (PhD)
по образовательной программе «8D05301 – Химия»

Общая характеристика работы.

Диссертационная работа посвящена изучению комплексообразующих свойств семейства макроциклов (кукурбит[6,7,8]урилов), отдельных физико-химических свойств полученных комплексов, а также условий получения комплексных и биокomпозитных материалов с использованием гидроксипатита.

Диссертационная работа представлена в форме серии статей, опубликованных докторантом согласно требованиям пункта 5–1 Правил присуждения степеней, утвержденных приказом Министра образования и науки Республики Казахстан от 31 марта 2011 года № 127 (зарегистрирован в Реестре государственной регистрации нормативных правовых актов под № 6951) с изменением, внесенным приказом Министра образования и науки РК от 30.04.2020 № 170 и в соответствии с приказом Министра образования и науки РК от 09.03.2021 №98, изменениями, внесенными и.о. Министра науки и высшего образования РК от 09.01.2023 года № 7.

Актуальность работы.

В современную эпоху персонализированной медицины существует острая необходимость в создании новых материалов для имплантатов, которые должны соответствовать определенным требованиям. Основными характеристиками таких материалов являются их состав, структура и механические свойства, где особое внимание уделяется биосовместимости материала.

Ранее макроциклические соединения гликолурильного типа не использовались в качестве биоактивных молекул для насыщения пористых материалов с целью синтеза композиционных материалов, обладающих повышенной биосовместимостью. Одним из перспективных веществ для покрытия поверхности являются кукурбитурилы, которые обладают способностью инкапсулировать терапевтические агенты и постепенно их высвобождать под воздействием различных факторов.

Химия кукурбитурила продолжает активно развиваться, прежде всего, благодаря их супрамолекулярному приложению, которое относится к фронтальному областью знаний. Такого рода исследования носят, как правило, междисциплинарный характер, что требует применения методологии из различных областей науки для изучения супрамолекулярных свойств целевых веществ. Известно, что кукурбитурилы обладают склонностью к формированию системы «хозяин-гость», при которой инкапсуляция «гостя» в полость макроциклического «хозяина» обычно приводит к изменению его

физико-химических свойств, что позволяет модулировать целевые задачи исследования.

В связи с вышесказанным, актуальной задачей является синтез и исследование новых супрамолекулярных комплексов и композиционных материалов на основе кукурбитурилов, а также изучение влияния кукурбитурила на поверхность пористых материалов и определение их биомедицинских свойств. Такие исследования открывают перспективный путь для разработки и создания новых биокomпозитных материалов с заранее заданными характеристиками.

Цель диссертационного исследования.

Цель работы – исследование условий синтеза и изучение характеристик новой супрамолекулярной системы на основе дигидрохлорида 1,4-бис(2-гидроксиэтил)пиперазина и кукурбит[6,7,8]урила и разработка физико-химических основ получения новых биомедицинских материалов с использованием кукурбитурилов и гидроксиапатита для определения их биологических свойств.

Задачи:

1. Исследовать комплексообразование по типу «хозяин-гость» кукурбит[6]урила с дигидрохлоридом 1,4-бис(2-гидроксиэтил)пиперазина, определить структуру и свойства полученного супрамолекулярного соединения.

2. Исследовать гемолитический эффект и цитотоксичность полученных биокomпозиционных материалов на основе гидроксиапатита и семейства кукурбитурилов СВ[6] + НА, СВ[7] + НА, СВ[8] + НА.

3. Экспериментально установить наиболее эффективный метод модификации пористых неорганических скаффолдов на примере гидроксиапатита с использованием кукурбит[n]урила.

Объекты исследования – кукурбит[n]урилы, супрамолекулярный комплекс на основе кукурбит[6]урила с дигидрохлоридом 1,4-бис(2-гидроксиэтил)пиперазина, гидроксиапатит, пористые скаффолды на основе гидроксиапатита, модифицированные кукурбитурилом.

Научная новизна работы.

1. Впервые синтезирован новый супрамолекулярный комплекс типа «хозяин-гость» на основе кукурбит[6]урила с дигидрохлоридом 1,4-бис(2-гидроксиэтил)пиперазина. В результате проведенных анализов (РФА, ИК, XDR, TGA/DSC) установлено, что молекулы «гости» располагаются между карбонильными порталами «хозяина» и повышенная термостабильность (55°C) комплекса кукурбит[6]урила с дигидрохлоридом 1,4-бис(2-гидроксиэтил)пиперазина относительно исходного 1,4-бис(2-гидроксиэтил)пиперазина.

2. Впервые разработаны новые биокomпозиционные материалы (СВ[6] + НА, СВ[7] + НА и СВ[8] + НА) на основе пористого скаффолда – гидроксиапатита(НА) путем модификации его поверхности макроциклическими соединениями – кукурбитурилами(СВ), которые были

охарактеризованы с помощью ИК-спектроскопии, СЭМ и ЭДС, для них определен гемолитический эффект и цитотоксичность для клеток иммунной системы.

3. Предложен наиболее эффективный метод модификации поверхности гидроксиапатита кукурбитурилами. Установлено, что в зависимости от метода нанесения СВ[6] на поверхность и внутрь скаффолда из НА можно регулировать состав и структуру целевых биокomпозиционных материалов.

Основные положения диссертации, выносимые на защиту.

1. Условия и характеристики синтезированного нового супрамолекулярного комплекса по типу «хозяин-гость» на основе кукурбит[6]урилы и дигидрохлорида 1,4-бис(2-гидроксиэтил)пиперазина, который был охарактеризован с помощью ЯМР, ИК-спектроскопии, РФА, TGA/DSC. Установлено, что соотношение исходных веществ в комплексе составляет 1:1, со смещением полосы поглощения валентных колебаний карбонильных фрагментов кукурбит[6]урилы на 36 см^{-1} в длинноволновую область, свидетельствующий о комплексообразовании через карбонильные атомы кислорода кукурбит[6]урилы, с повышением термостабильности инкапсулированного дигидрохлорида 1,4-бис(2-гидроксиэтил)пиперазина на 55°C .

2. Результаты оценки влияния осаждения азотсодержащих макроциклических кавитандов кукурбитурилов на поверхность пористого скаффолда - гидроксиапатита. Полученные новые биокomпозиционные материалы на основе гидроксиапатита и кукурбитурилов (СВ[6] + НА, СВ[7] + НА и СВ[8] + НА) были охарактеризованы с помощью РФА, ИК-спектроскопии, СЭМ и ЭДС. Вариация покрытия поверхности гидроксиапатита кукурбитурилами позволяет создать перспективные материалы с подходящей микросредой для остеогенеза и контролируемого высвобождения биологически активных веществ, таких как антибактериальные препараты и др. Исследования биокomпозиционных материалов *in vitro* показали высокую биосовместимость (гемолитический эффект и цитотоксичность) для клеток иммунной системы.

3. Различные методы нанесения увеличивают вариативность потенциального применения биокomпозитов в зависимости от практического приложения. Так, осаждение кукурбит[6]урилы с использованием погружного метода на поверхность гидроксиапатита в найденных условиях (концентрация 1 мг/мл , температура – 50°C , время экспозиции – 45 минут, ультразвуковая ванна с частотой 37 kHz) увеличивает площадь покрытия поверхности НА и уменьшение количества конгломератов молекул СВ[6].

Практическая значимость работы.

Практическая значимость состоит в том, что в данном диссертационном исследовании синтезирован новый супрамолекулярный комплекс открывающий путь синтезу новых биокomпозиционных материалов. Разработаны эффективные методы получения биокomпозитов на основе кукурбитурилов и гидроксиапатита, имеющих высокую биосовместимость

(низкий гемолитический эффект и цитотоксичность), которые могут быть использованы для различных биомедицинских целей.

Получены новые результаты в области синтеза супрамолекулярных соединений, имеющих фундаментальное значение в области химии и материаловедения. Получены новые данные о влиянии кукурбит[6,7,8]урилы на биомедицинские свойства пористых неорганических материалов (скаффолдов).

Предложены методы нанесения СВ[6] на поверхность НА, которые открывают путь к функциональным композиционным материалам на основе СВ[6] и продуктов инкапсуляции (комплексов по типу «хозяин-гость»).

Тесты *in vitro* подтвердили высокую биосовместимость и низкую токсичность полученных биокomпозиционных материалов. Эти инновационные биокomпозиты обладают многообещающим потенциалом для тонкой модуляции биологических реакций, облегчаемой иммобилизацией НА+СВ[6], НА+СВ[7] и НА+СВ[8] на специальных носителях.

Предложенные методы нанесения СВ[6] на поверхность НА придают последним биоразнообразие и обеспечивают сродство к среде организма при создании новых функциональных композиционных материалов, в том числе с использованием супрамолекулярных систем на основе семейства СВ[n].

Выводы

В результате проведенных исследований был получен и охарактеризован с помощью ЯМР, ИК-спектроскопии и РСА новый комплекс типа «хозяин-гость» на основе кукурбит[6]урилы и дигидрохлорид 1,4-бис(2-гидроксиэтил)пиперазина. Установлено, что соотношение исходных веществ в комплексе составляет 1:1. Сравнительный анализ ИК-спектров исходных веществ и полученного комплекса, показал смещение полосы поглощения валентных колебаний карбонильных фрагментов кукурбит[6]урилы на 36 см⁻¹ в длинноволновую область, что говорит о комплексообразовании через карбонильные атомы кислорода кукурбит[6]урилы. Данные TGA/DSC позволяют утверждать о повышении термостабильности инкапсулированного дигидрохлорида 1,4-бис(2-гидроксиэтил)пиперазина на 55°C. В результате монокристаллической рентгеновской дифрактометрии установлена структура полученного комплекса, гостевая молекула – дигидрохлорида 1,4-бис(2-гидроксиэтил)пиперазина подвержена комплексообразованию через кватеренизированные атомы азота пиперазинового кольца и локализована на карбонильных порталах кукурбит[6]урилы.

Был успешно разработан новый метод функционализации поверхности гидроксиапатита с использованием макромолекулярных азотсодержащих гетероциклов, в частности СВ[6], СВ[7] и СВ[8]. Исследования *in vitro* продемонстрировали высокую биосовместимость и низкую токсичность полученных биокomпозитных материалов. Эти инновационные биокomпозиты обладают многообещающим потенциалом для тонкой модуляции биологических реакций, чему способствует включение НА + СВ[6], НА + СВ[7] и НА + СВ[8] в специализированные среды.

В зависимости от метода нанесения СВ[6] на поверхность и внутрь скаффолда из НА позволяет регулировать состав и структуру целевых композиционных материалов. Различные методы нанесения в свою очередь увеличивают вариативность потенциального применения композитов в зависимости от практического приложения. Применение ультразвукового воздействия увеличивает площадь покрытия поверхности НА и уменьшает количество конгломератов молекул СВ[6], что, по-видимому, обусловлено лучшей смачиваемостью поверхности НА и дезинтеграцией конгломератов СВ[6] в найденных условиях. Предложены методы нанесения СВ[6] на поверхность НА, которые открывают путь к функциональным композиционным материалам на основе СВ[6] и продуктов инкапсуляции (комплексов по типу «хозяин-гость»).

Личный вклад автора составил 75% и заключался в поиске литературы, анализе имеющихся сведений, а также в организации работ, разработке плана экспериментов. Автором осуществлялось выполнение химических реакции, выделение и очистка продуктов, оптимизация условий проводимых процессов, аналитика и обработка полученных результатов. Каждый раздел исследовательской работы выполнялся автором самостоятельно, равно как анализ литературы и обработка результатов, и оформление их в виде научных публикаций. Часть экспериментов в рамках исследовательской работы выполнены и опубликованы в виде совместных результатов, о чем соавторы не возражают.

Апробация работы.

Основные положения, выводы и научные результаты диссертации докладывались и обсуждались на международных конференциях: 8th International Scientific Conference «Research Reviews» (Чехия, 2025). The theoretical hypotheses and empirical results (Норвегия 2025), Modern scientific technology (Швеция, 2025).

Публикации. Основные результаты диссертационного исследования отражены в 6 опубликованных работах, из них 3 статьи в научных изданиях, входящих в первый и/или второй квартиль по импакт-фактору по данным Journal Citation Reports (Журнал Цитэйшэн Репортс) компании Clarivate Analytics (Кларивэйт Аналитикс); 3 работы в материалах международных конференций:

1. В статье **Burkhanbayeva, T.**; Guslyakov, A.; Tarikhov, F.; Pavlov, D.; Erkasov, R.; Bakibaev, A.; et al.; Synthesis and study of a novel supramolecular 'host-guest' complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. Int. J. of Saudi Chemical Society 2024, 28/2, 101819. соискатель является первым и корреспондирующим автором. Импакт-фактор журнала – за 2023 год равный 5,9 и квартиль по химии, междисциплинарным трудам – Q1. Имеет CiteScore за 2023 год равный 8,9 и процентиль по общей химии – 83. Докторант участвовала в проведении экспериментов и интерпретации результатов, занималась подготовлением и оформлением оригинального

проекта статьи. Кроме того, Бурханбаева Т.Т. занималась оформлением статьи в соответствии с требованиями журнала.

2. Докторант является первым и корреспондирующим автором в статье **Burkhanbayeva, T.; Ukhov, A.; Fedorishin, D.; Gubankov, A.; Kurzina, I.; Bakibaev, A.; Yerkassov, R.; et al. Development of New Composite Materials by Modifying the Surface of Porous Hydroxyapatite Using Cucurbit[n]urils. Materials** 2024, 17, 2041. Импакт-фактор журнала – за 2023 год равный 3,1 и квартиль по химии, физической – Q3; квартиль по материаловедению, междисциплинарным трудам – Q2; квартиль по физике, конденсированных сред – Q2. Имел CiteScore за 2023 год равный 5,8 и процентиль по физике конденсированных сред – 73; процентиль по общему материаловедению – 67. Бурханбаева Т.Т. принимала активное участие в проведении исследований, в сборе литературы и обработке данных и оформлении статьи.

3. В статье **Burkhanbayeva, T.; Ukhov, A.; Bakibaev, A.; Issabayeva, M.; Yerkassov, R.; et al. The Role of Methods for Applying Cucurbit[6]uril to Hydroxyapatite for the Morphological Tuning of Its Surface in the Process of Obtaining Composite Materials. Materials** 2024, 11, 4995, докторант является первым автором и автором-корреспондентом. Импакт-фактор журнала – за 2023 год равный 3,1 и квартиль по химии, физической – Q3; квартиль по материаловедению, междисциплинарным трудам – Q2; квартиль по физике, конденсированных сред – Q2. Имел CiteScore за 2023 год равный 5,8 и процентиль по физике конденсированных сред – 73; процентиль по общему материаловедению – 67. Бурханбаева Т.Т. принимала активное участие в проведении исследований, в сборе литературы и обработке данных и оформлении статьи.

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жаңа комплексті қосылыстарды синтездеу және зерттеу»**
тақырыбындағы диссертациялық жұмысына

АНДАТПА

Диссертациялық зерттеудің жалпы сипаттамасы.

Диссертациялық жұмыс макроциклдер (кукурбит[6,7,8]урилдер) комплекс түзу қасиеттерін, алынған кешендердің жеке физика-химиялық қасиеттерін, сонымен қатар гидроксипатит көмегімен күрделі және биокөмбіріттік материалдарды алу шарттарын зерттеуге арналған.

Диссертациялық жұмыс докторанттың ҚР Білім және ғылым министрінің 30.04.2020 жылғы №170 Бұйрығымен өзгерістер енгізілген Қазақстан Республикасы Білім және ғылым министрінің 2011 жылғы 31 наурыздағы №127 (нормативтік құқықтық актілерді мемлекеттік тіркеу тізілімінде № 6951 болып тіркелген) бұйрығымен бекітілген дәрежелерді беру қағидаларының 5-1 тармақтарына және ҚР Ғылым және жоғары білім министрінің м.а. 09.01.2023 жылғы № 7 өзгертулері енгізілген ҚР Білім және ғылым министрінің 09.03.2021 жылғы №98 бұйрығының талаптарына сәйкес жариялаған ғылыми мақалалар сериясы түрінде ұсынылады.

Зерттеудің өзектілігі.

Жекелендірілген медицинаның заманауи дәуірінде нақты талаптарға жауап беретін жаңа имплантациялық материалдарды әзірлеудің өзекті қажеттілігі туындайды. Мұндай материалдардың негізгі сипаттамалары олардың құрамы, құрылымы және механикалық қасиеттері болып табылады, әсіресе биокөмірісімділікке ерекше назар аударылады.

Бұрын гликолурил типті макроциклді қосылыстар биокөмірісімділігі жоғары композициялық материалдарды синтездеу үшін кеуекті материалдарды қанықтыру үшін биоактивті молекулалар ретінде пайдаланылмаған. Терапевтік агенттерді инкапсуляциялау және әртүрлі факторлардың әсерінен оларды біртіндеп босату мүмкіндігі бар, беткі қабатқа арналған перспективалы заттардың бірі – кукурбитурилдер болып табылады.

Кукурбитурил химиясы, ең алдымен, білімнің шекаралық саласы болып табылатын олардың супрамолекулалық қолданбаларына байланысты қарқынды дамуын жалғастыруда. Зерттеудің бұл түрі әдетте пәнаралық сипатта болады, мақсатты заттардың супрамолекулалық қасиеттерін зерттеу үшін әртүрлі ғылым салаларындағы әдістемелерді қолдануды талап етеді. Кукурбитурилдердің макроциклді қожайынның қуысына қонақтың инкапсуляциясы әдетте оның физикалық-химиялық қасиеттерінің өзгеруіне әкеледі, сәйкесінше зерттеу мақсаттарын модуляциялауға мүмкіндік беретін қожайын-қонақ жүйесін құруға бейімділігі белгілі.

Жоғарыда айтылғандарға байланысты, кукурбитурил негізіндегі жаңа супрамолекулалық кешендерді және композициялық материалдарды синтездеу және зерттеу, сонымен қатар кукурбитурилдің кеуекті материалдардың бетіне

әсерін зерттеу және олардың биомедициналық қасиеттерін анықтау өзекті міндет болып табылады. Мұндай зерттеулер алдын ала анықталған сипаттамалары бар жаңа биокомпозиттік материалдарды әзірлеу және жасау үшін перспективалы жол ашады.

Зерттеудің мақсаты.

Жұмыстың мақсаты 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлориді және кукурбит[6,7,8]урил негізіндегі жаңа супрамолекулалық жүйенің синтез шарттарын зерттеу және сипаттамаларын анықтау және кукурбитурил мен гидроксиапатиттің биологиялық қасиеттерін анықтау үшін жаңа биомедициналық материалдарды алудың физика-химиялық принциптерін әзірлеу.

Бұл мақсатқа жету келесі **міндеттерді** шешуді қамтиды:

1. Кукурбит[6]урилдің 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлоридімен қожайын-қонақ кешенін зерттеу және алынған супрамолекулалық қосылыстың құрылымы мен қасиеттерін анықтау.

2. Гидроксиапатит және кукурбитурил негізінде алынған биокомпозиттік материалдардың гемолитикалық әсері мен цитотоксикалық қасиетін зерттеу.

3. Гидроксиапатит мысалында кеуекті бейорганикалық скаффолдтарды кукурбит [6,7,8] урил (CB[6], CB[7] және CB[8]) модификациялаудың ең тиімді әдісін эксперименталды түрде анықтау.

Зерттеу нысаны – кукурбит[n]урил, кукурбит[6]урил мен 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлориді негізіндегі супрамолекулалық кешен, гидроксиапатит, кукурбит[n]урил кукурбитурилмен модификацияланған кеуекті гидроксиапатит негізіндегі тіректер.

Жұмыстың ғылыми жаңалығы.

1. Кукурбит[6]урил және 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлоридіне негізделген жаңа қожайын-қонақ супрамолекулалық кешен алғаш рет синтезделді. Талдау (рентген сәулелерінің дифракциясы, ИҚ-спектр, XDR, TGA/DSC) қонақ молекулаларының қожайынның карбонил порталдары арасында орналасқанын және бастапқы 1,4-бис(2-гидроксиэтил)пиперазинге қатысты 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлориді бар кукурбит[6]урил кешенінің термиялық тұрақтылығының (55°C-ге) жоғарылауы.

2. Алғаш рет кеуекті тірек – гидроксиапатит (НА) негізіндегі жаңа биокомпозиттік материалдар (CB[6] + НА, CB[7] + НА және CB[8] + НА) оның беткі қабатын макроциклді қосылыстармен – кукурбитурилдермен (CB) модификациялау арқылы әзірленді, олар ИҚ-спектр көмегімен сипатталды, олардың иммундық жүйе жасушалары үшін гемолитикалық әсері және цитотоксикалық әсерінің төмен, жоғары биоүйлесімділікке ие екені дәлелденді.

3. CB[6]-ны НА скаффолдтарының беткі қабатына және ішкі құрамына енгізуге негізделген қолдану әдісіне байланысты мақсатты биокомпозиттік материалдардың құрамы мен құрылымын реттеуге болатыны анықталды.

Қорғауға ұсынылған диссертацияның негізгі ережелері:

1. Кукурбит[6]урил және 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлориді негізінде синтезделген жаңа супрамолекулалық қожайын-қонақ

кешенінің шарттары мен сипаттамалары ЯМР, ИҚ спектр, XRD және TGA/DSC арқылы анықталды. Курбит[6]урилдің карбонил фрагменттерінің созылу тербелістерінің сіңіру жолағы 36 см^{-1} ұзын толқынды аймаққа ығысуы кукурбит[6]урилдің карбонил оттегі атомдары арқылы күрделі түзілуді көрсетеді, кешендегі бастапқы заттардың қатынасы 1:1 болатыны анықталды және инкапсуляцияланған 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлоридінің термиялық тұрақтылығының 55°C -ге жоғарылауы анықталды.

2. Құрамында азот бар макроциклді кукурбитурил кавитанттарының кеуекті тірек – гидроксипатит беткі қабатына отырғызу әсерін бағалау нәтижелері. Гидроксипатит пен кукурбитурил (CB[6] + HA, CB[7] + HA және CB[8] + HA) негізінде алынған жаңа биокөмпозиттік материалдар рентгендік дифракция, ИҚ спектроскопия, SEM және EDS көмегімен сипатталды. Гидроксипатит беткі қабатын кукурбитурилмен жабудағы вариациялар остеогенезге және биологиялық белсенді заттардың, мысалы, бактерияға қарсы препараттардың және т.б. бақыланатын шығарылуы үшін қолайлы микроортасы бар перспективалы материалдарды жасауға мүмкіндік береді. Биокөмпозиттік материалдардың *in vitro* зерттеулері (гемолитикалық әсер мен цитотоксикалық көрсеткіш) иммундық жүйе жасушалары үшін жоғары биоүйлесімділікті көрсетті.

3. Беткі қабатқа отырғызудың әртүрлі әдістері биокөмпозиттердің практикалық қолдануға байланысты әлеуетті өзгергіштігін арттырады. Мысалы, табылған жағдайларда гидроксипатит беткі қабатына батыру әдісін қолданып кукурбит[6]урилді тұндыру (концентрациясы 1 мг/1 мл , температура – 50°C , экспозиция уақыты – 45 минут, жиілігі 37 кГц ультрадыбыстық ванна) ГА беткі қабатының жабуын арттырады және CB[6] молекулаларының конгломераттарының мөлшерін азайтады.

Жұмыстың практикалық маңыздылығы.

Тәжірибелік маңыздылығы осы диссертациялық зерттеуде жаңа биокөмпозиттік материалдардың синтезіне жол ашатын жаңа супрамолекулалық кешен синтездеуінде. Кукурбитурил және гидроксипатит негізінде биокөмпозиттер алудың тиімді әдістері әзірленді, олар биоүйлесімділігі жоғары (төмен гемолитикалық және цитотоксикалық әсері, әртүрлі биомедициналық мақсаттарда қолдануға болады).

Химия мен материалтануда іргелі маңызы бар супрамолекулалық қосылыстарды синтездеуде жаңа нәтижелер алынды. Кеуекті бейорганикалық материалдардың биомедициналық қасиеттеріне кукурбит[6,7,8]урилдің әсері туралы жаңа деректер алынды (скаффолдар).

CB[6]-ны HA беткі қабатына отырғызу әдістері ұсынылған, олар CB[6] негізіндегі функционалды көмпозиттік материалдарға және инкапсуляциялық өнімдерге (қожайын-қонақ кешендері) жол ашады.

In vitro сынақтары алынған биокөмпозиттік материалдардың жоғары биоүйлесімділігін және төмен уыттылығын растады. Бұл инновациялық биокөмпозиттер мамандандырылған тасымалдаушыларда HA+CB[6],

НА+СВ[7] мен НА+СВ[8] иммобилизациясы арқылы биологиялық реакцияларды жақсы модуляциялауды дәл реттеуге мүмкіндік береді.

НА беткі қабатына СВ[6] отырғызудың ұсынылған әдістері соңғысына биоәртүрлілікті береді және жаңа функционалды композициялық материалдарды жасау кезінде, оның ішінде СВ[n] негізделген супрамолекулалық жүйелерді пайдалану кезінде ағза ортасына жақындығын қамтамасыз етеді.

Қорытынды

Жүргізілген зерттеулер нәтижесінде кукурбит[6]урил және 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлоридіне негізделген жаңа қожайын-қонақ кешені алынды және ЯМР, ИҚ-спектроскопия және рентген сәулелерінің дифракциясы арқылы сипатталды. Кешендегі бастапқы заттардың қатынасы 1:1 екені анықталды. Бастапқы материалдар мен алынған кешеннің ИҚ-спектрлерінің салыстырмалы талдауы кукурбит[6]урилдің карбонил фрагменттерінің созылу тербелістерінің сіңіру жолағында ұзын толқынды аймаққа 36 см⁻¹ ығысуын көрсетті, бұл курбиттің карбонил оттегі атомдары арқылы күрделі түзілуін көрсетеді. TGA/DSC деректері инкапсулирленген 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлоридінің термиялық тұрақтылығының 55°C жоғарылауын көрсетеді. Алынған кешеннің құрылымы монокристалды рентгендік дифрактометрия арқылы анықталды; қонақ молекуласы, 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлориді пиперазин сақинасының төрттенген азот атомдары арқылы комплекстенеді және кукурбит[6]урилдің карбонил порталдарында локализацияланады.

Құрамында макромолекулалық азот бар гетероциклдерді, атап айтқанда СВ[6], СВ[7] және СВ[8] пайдалана отырып, гидроксипатиттің беттік функционализациясының жаңа әдісі сәтті жасалды. In vitro зерттеулер нәтижесінде алынған биокомпозиттік материалдардың жоғары биоүйлесімділігін және төмен уыттылығын көрсетті. Бұл инновациялық биокомпозиттер мамандандырылған орталарға НА + СВ[6], НА + СВ[7] және НА + СВ[8] қосу арқылы биологиялық жауаптардың нақты модуляциясының перспективалық әлеуетін көрсетеді.

Қолдану әдісіне байланысты НА скаффолдының бетіндегі және ішіндегі СВ[6] мақсатты композиттік материалдардың құрамы мен құрылымын бақылауға мүмкіндік береді. Әртүрлі қолдану әдістері, өз кезегінде, композиттердің практикалық қолданылуына байланысты әлеуетті қолданудың әмбебаптығын арттырады. Ультрадыбыстық өңдеуді қолдану НА бетінің қамту аймағын арттырады және СВ[6] молекуласының конгломераттарының мөлшерін азайтады, бұл НА бетінің жақсы ылғалдануымен және табылған жағдайларда СВ[6] конгломераттарының ыдырауымен байланысты. СВ[6]-ны НА бетіне қолдану әдістері ұсынылған, олар СВ[6] негізіндегі функционалды композиттік материалдарға және инкапсуляциялық өнімдерге (қожайын-қонақ кешендері) жол ашады.

Автордың жеке үлесі 75% құрап, әдебиеттерді іздеуден, қолда бар ақпаратты талдаудан, сонымен қатар жұмысты ұйымдастырудан,

эксперименттік жоспарды құрудан тұрды. Автор химиялық реакцияларды, өнімдерді оқшаулау мен тазартуды, процестердің шарттарын оңтайландыруды, алынған нәтижелерді талдауды және өңдеуді жүзеге асырды. Зерттеу жұмысының әрбір бөлімін автор өз бетінше орындады, сонымен қатар әдебиеттерді талдау және нәтижелерді өңдеу және оларды ғылыми басылымдар түрінде ресімдеу. Зерттеу жұмысы аясында кейбір эксперименттер бірлескен түрде жүргізіліп, нәтижелер жарияланды, бұған бірлескен авторлар қарсы емес.

Жұмысты апробациялау.

Диссертацияның негізгі ережелері, қорытындылары және ғылыми нәтижелері халықаралық конференцияларда баяндалып, талқыланды: «Зерттеу шолулары» 8-ші халықаралық ғылыми конференциясы (Чехия, 2025 ж.). Теориялық гипотезалар мен эмпирикалық нәтижелер (Норвегия 2025), Заманауи ғылыми технологиялар (Швеция, 2025).

Жарияланымдар. Диссертациялық зерттеудің негізгі нәтижелері жарияланған 6 жұмыста көрсетілген, оның ішінде 3 мақала Clarivate Analytics (Clarivate Analytics) Journal Citation Reports (Journal Citation Reports) бойынша импакт-фактор бойынша бірінші және/немесе екінші квартильге енгізілген ғылыми жарияланымдарда және халықаралық конференциялар материалдарындағы 3 жұмыс:

Burkhanbayeva, T.; Guslyakov, A.; Tarikhov, F.; Pavlov, D.; Erkasov, R.; Bakibaev, A.; et al. Synthesis and study of a novel supramolecular 'host-guest' complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. Int. J. of Saudi Chemical Society 2024, 28/2, 101819. мақаласында докторант бірінші және корреспондент автор болып табылады. 2023 жылға арналған журналдың импакт-факторы – 5,9, ал химия және пәнаралық жұмыстар үшін квартиль – 1-тоқсан. 2023 жылға арналған CiteScore 8,9 және жалпы химия бойынша пайыздық көрсеткіші 83. Докторант эксперименттер жүргізуге және нәтижелерді интерпретациялауға қатысты, мақаланың түпнұсқа жобасын дайындауға және ресімдеуге қатысты. Сонымен қатар журнал талаптарына сәйкес мақаланы дайындауға Бурханбаева Т.Т.

Burkhanbayeva, T.; Ukhov, A.; Fedorishin, D.; Gubankov, A.; Kurzina, I.; Bakibaev, A.; Yerkassov, R.; et al. Development of New Composite Materials by Modifying the Surface of Porous Hydroxyapatite Using Cucurbit[n]urils. Materials 2024, 17, 2041. мақаласында үміткер бірінші және корреспондент автор болып табылады, зерттеу жүргізді, жарияланымдар үшін материал дайындады және редакциялады. Журналдың импакт-факторы 2023 жылға 3,1, ал химия және физика бойынша квартиль 3-тоқсан; материалтану, пәнаралық жұмыстар бойынша квартиль – Q2; физикадағы квартиль, конденсацияланған зат – Q2. 2023 жылғы CiteScore 5,8 және конденсацияланған заттар физикасында 73 пайыздық көрсеткішке ие болды; жалпы материалтану бойынша пайыздық көрсеткіш – 67.

Burkhanbayeva, T.; Ukhov, A.; Bakibaev, A.; Issabayeva, M.; Yerkassov, R.; et al. The Role of Methods for Applying Cucurbit[6]uril to Hydroxyapatite for the Morphological Tuning of Its Surface in the Process of Obtaining Composite

ANNOTATION

on the dissertation of **Burkhanbayeva Tolkynay Tazhibekovna** on the topic
“**Synthesis and study of new complex compounds based on cucurbiturils**”,
submitted for the degree of Doctor of Philosophy (PhD)
in the educational program “8D05301 – Chemistry”

General description of the work.

The dissertation is devoted to the study of the complexing properties of a family of macrocycles (cucurbit[6,7,8]urils), individual physicochemical properties of the obtained complexes, as well as the conditions for obtaining complex and biocomposite materials using hydroxyapatite.

The dissertation work is presented in the form of a series of two articles and one review published by a doctoral student in accordance with the requirements of paragraph 5-1 of the Rules for Awarding Degrees approved by Order No. 127 of the Minister of Education and Science of the Republic of Kazakhstan dated March 31, 2011 (registered in the Register of State Registration of Normative Legal Acts under No. 6951) as amended by Order No. 170 of the Minister of Education and Science of the Republic of Kazakhstan dated 30.04.2020 and in accordance with the Order of the Minister of Education and Science of the Republic of Kazakhstan dated 09.03.2021 No. 98, as amended by the Acting Minister of Science and Higher Education of the Republic of Kazakhstan dated 09.01.2023 No. 7.

The relevance of the work.

In the modern era of personalized medicine, there is a pressing need to develop new implant materials that meet specific requirements. The key characteristics of such materials are their composition, structure, and mechanical properties, with particular attention paid to their biocompatibility.

Previously, macrocyclic compounds of the glycoluril type have not been used as bioactive molecules for saturating porous materials for the synthesis of composite materials with increased biocompatibility. One of the promising substances for surface coating is cucurbiturils, which have the ability to encapsulate therapeutic agents and gradually release them under the influence of various factors.

Cucurbituril chemistry continues to develop rapidly, primarily due to its supramolecular applications, which are a frontier area of knowledge. Such research is typically interdisciplinary, requiring the application of methodologies from various fields of science to study the supramolecular properties of target compounds. Cucurbiturils are known to have a tendency to form a host-guest system, in which encapsulation of the guest into the cavity of the macrocyclic host usually leads to a change in its physicochemical properties, which allows modulation of the target research objectives.

In connection with the above, an urgent task is the synthesis and study of new supramolecular complexes and composite materials based on cucurbiturils, as well as the study of the effect of cucurbituril on the surface of porous materials and the determination of their biomedical properties. Such studies open up a promising avenue for the development and creation of new biocomposite materials with predetermined characteristics.

The purpose of the dissertation research.

The aim of the work is to study the synthesis conditions and study the characteristics of a new supramolecular system based on 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride and cucurbit[6,7,8]uril and to develop the physicochemical principles for obtaining new biomedical materials using cucurbiturils and hydroxyapatite to determine their biological properties.

Tasks:

1. To study the host-guest complexation of cucurbit[6]uril with 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride and to determine the structure and properties of the resulting supramolecular compound.
2. To study the hemolytic effect and cytotoxicity of the obtained biocomposite materials based on hydroxyapatite and the cucurbiturils family CB[6] + HA, CB[7] + HA, CB[8] + HA.
3. To experimentally establish the most effective method for modifying porous inorganic scaffolds using hydroxyapatite as an example using cucurbit[6]uril.

The objects of research cucurbit[n]urils, supramolecular complex based on cucurbit[6]uril with 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride, hydroxyapatite, porous scaffolds based on hydroxyapatite modified with cucurbituril.

The scientific novelty of the work.

1. A new host-guest supramolecular complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride was synthesized for the first time. Analysis (XRD, IR, XDR, TGA/DSC) revealed that the guest molecules are located between the carbonyl portals of the host and increased thermal stability (55°C) of the cucurbit[6]uril complex with 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride relative to the original 1,4-bis(2-hydroxyethyl)piperazine.
2. For the first time, new biocomposite materials (CB[6] + HA, CB[7] + HA and CB[8] + HA) based on a porous scaffold – hydroxyapatite (HA) – have been developed by modifying its surface with macrocyclic compounds – cucurbiturils (CB), which were characterized using IR spectroscopy, SEM and EDS, for them the hemolytic effect and cytotoxicity for immune system cells have been determined.
3. The most effective method for modifying the surface of hydroxyapatite with cucurbiturils has been proposed. It has been established that, depending on the method of applying CB[6] to the surface and into the HA scaffold, the composition and structure of the target biocomposite materials can be controlled.

The main provisions of the dissertation submitted for defense.

1. The conditions and characteristics of the synthesized novel supramolecular host-guest complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride were characterized by NMR, IR spectroscopy, XRD, and TGA/DSC. It was established that the ratio of the starting materials in the complex is 1:1, with a shift of the absorption band of the stretching vibrations of the carbonyl fragments of cucurbit[6]uril by 36 cm⁻¹ to the long-wave region, indicating complex formation through the carbonyl oxygen atoms of cucurbit[6]uril, with an increase in thermal stability encapsulated 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride at 55°C.

2. Results of assessing the effect of precipitation of nitrogen-containing macrocyclic cucurbiturils cavitands on the surface of a porous scaffold—hydroxyapatite. The resulting new biocomposite materials based on hydroxyapatite and cucurbiturils (CB[6] + HA, CB[7] + HA, and CB[8] + HA) were characterized using X-ray diffraction, IR spectroscopy, SEM, and EDS. Variations in the surface coating of hydroxyapatite with cucurbiturils make it possible to create promising materials with a suitable microenvironment for osteogenesis and controlled release of biologically active substances, such as antibacterial drugs, etc. In vitro studies of biocomposite materials have shown high biocompatibility (hemolytic effect and cytotoxicity) for immune system cells.

3. Various application methods increase the variability of the potential applications of biocomposites, depending on the practical application. For example, the deposition of cucurbit[6]uril using the immersion method on the hydroxyapatite surface under the conditions found (concentration 1 mg/1 ml, temperature – 50 ° C, exposure time – 45 minutes, ultrasonic bath with a frequency of 37 kHz) increases the surface coverage of HA and reduces the amount of CB[6] molecule conglomerates.

The practical significance of the work.

The practical significance lies in the fact that this dissertation study synthesized a new supramolecular complex, opening the way to the synthesis of new biocomposite materials. Effective methods for producing biocomposites based on cucurbiturils and hydroxyapatite, which have high biocompatibility (low hemolytic effect and cytotoxicity), which can be used for various biomedical purposes.

New results have been obtained in the synthesis of supramolecular compounds of fundamental importance in chemistry and materials science. New data have been obtained on the influence of cucurbit[6,7,8]uril on the biomedical properties of porous inorganic materials (scaffolds).

Methods for applying CB[6] onto the HA surface are proposed, which open the way to functional composite materials based on CB[6] and encapsulation products (host-guest complexes).

In vitro tests confirmed the high biocompatibility and low toxicity of the resulting biocomposite materials. These innovative biocomposites hold promise for fine-tuning biological responses, facilitated by the immobilization of HA+CB[6], HA+CB[7], and HA+CB[8] on specialized carriers.

The proposed methods for applying CB[6] to the surface of HA impart biodiversity to the latter and ensure affinity to the body environment when creating new functional composite materials, including using supramolecular systems based on the CB[n] family.

Conclusion

In this study successfully synthesized and characterized a novel “host-guest” complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride using various analytical techniques, including NMR, IR spectroscopy, and TGA/DSC analysis. The comparative analysis of the IR spectra of the starting materials and the synthesized complex revealed a shift and splitting of the absorption band of carbonyl vibrations of cucurbit[6]uril by 36 cm⁻¹ and 12 cm⁻¹

towards smaller wave numbers, which indicates the formation of a complex due to carbonyl oxygen atoms of cucurbit[6]uril. TGA/DSC data suggested an increase in the thermal stability of the encapsulated 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride by 55°C. Additionally, single-crystal XRD confirmed the structure of the obtained complex, showing that the guest molecule, 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride, formed complexes through the quaternized nitrogen atoms of the piperazine ring and was localized at the carbonyl portals of cucurbit[6]uril.

The study's findings highlight the potential of using conglomerate ensembles of CB[n] molecules to enhance the biocompatibility of materials, particularly when deposited on porous substrates, like HA. HA, known for its biocompatibility and porosity, serves as an excellent matrix for such modifications. By depositing nitrogen-containing macrocyclic cavitands, such as CB[6], CB[7], and CB[8], onto the surface of porous materials, like HA, it becomes feasible to create promising biomaterials conducive to osteogenesis while enabling controlled release of biologically active substances, including antibacterial drugs and other therapeutic agents.

The study has successfully developed a novel method for functionalizing the surface of hydroxyapatite using macromolecular nitrogen-containing heterocycles, specifically CB[6], CB[7], and CB[8]. In vitro assessments have demonstrated the high biocompatibility and low toxicity of the resulting biocomposite materials. These innovative biocomposites hold promising potential for finely modulating biological responses, facilitated by the incorporation of HA + CB[6], HA + CB[7], and HA + CB[8] on specialized media. Further research will delve into exploring and harnessing the full capabilities of these materials in various biomedical applications.

The comprehensive studies conducted on materials based on macrocyclic compounds, including CB[n] and Bu[6], have revealed a plethora of potential applications for these materials. Their unique ability to serve as containers for medicinal or biologically active substances presents an urgent and promising avenue for further exploration.

Summarizing the above, it should be noted that, depending on the method of applying CB[6] to the surface and inside the HA scaffold, it is possible to adjust the composition and structure of the target composite materials. Different application methods in turn increase the variability of the potential applications of composites depending on the practical application. The use of ultrasonic influence increases the surface coverage of HA and reduces the number of conglomerates of CB[6] molecules, which is apparently due to better wettability of the HA surface and disintegration of CB[6] conglomerates under the determined conditions. Methods for applying CB[6] to the surface of HA have been proposed, which opens the way to functional composite materials based on CB[6] and encapsulation products (host–guest complexes).

The author's personal contribution was 75% and consisted of searching the literature, analyzing the available information, as well as organizing the work, developing the experimental plan. The author carried out chemical reactions,

isolation and purification of products, optimization of the conditions of the processes, analysis and processing of the obtained results. Each section of the research work was carried out by the author independently, as well as the analysis of literature and processing of results, and their design in the form of scientific publications. Some experiments within the framework of the research work were carried out and published as joint results, which the co-authors do not object to.

Approbation of the work.

The main provisions, conclusions, and scientific results of the dissertation were presented and discussed at international conferences: the 8th International Scientific Conference "Research Reviews" (Czech Republic, 2025), ****The Theoretical Hypotheses and Empirical Results**** (Norway, 2025), and ****Modern Scientific Technology**** (Sweden, 2025).

Publications.

The main results of the dissertation research are reflected in six published works, including three articles in scientific journals ranked in the first and/or second quartile by impact factor according to ****Journal Citation Reports**** by ****Clarivate Analytics****, and three works published in the proceedings of national and international conferences:

1. The doctoral student conducted research, prepared and presented material for publication in the article **Burkhanbayeva, T.**; Guslyakov, A.; Tarikhov, F.; Pavlov, D.; Erkasov, R.; Bakibaev, A.; et al. Synthesis and study of a novel supramolecular 'host-guest' complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. Int. J. of Saudi Chemical Society 2024, 28/2, 101819. The doctoral candidate is the first and corresponding author. The journal's impact factor for 2023 is 5.9, with a Q1 quartile ranking in chemistry and interdisciplinary studies. It has a CiteScore of 8.9 for 2023, with a percentile of 83 in general chemistry. The doctoral candidate participated in conducting experiments and interpreting the results, as well as in preparing and structuring the original manuscript. Additionally, Burkhanbayeva T.T. was responsible for formatting the article in accordance with the journal's requirements.

The doctoral candidate is the first and corresponding author of the article:

2. In the article **Burkhanbayeva, T.**; Ukhov, A.; Fedorishin, D.; Gubankov, A.; Kurzina, I.; Bakibaev, A.; Yerkassov, R.; et al. Development of New Composite Materials by Modifying the Surface of Porous Hydroxyapatite Using Cucurbit[n]urils. Materials 2024, 17, 2041 the applicant conducted research, prepared and presented material for publication. The impact factor for 2024 of the journal is 3.1, and has a quartile in Polymer Science – Q3. It has a CiteScore of 5.8 for 2023, the percentile in General Chemistry - 81; the percentile in Polymers and Plastics - 80. Quartile rankings: Q3 in Physical Chemistry, Q2 in Materials Science (Interdisciplinary), Q2 in Condensed Matter Physics 73.

3. In the article **Burkhanbayeva, T.**; Ukhov, A.; Bakibaev, A.; Issabayeva, M.; Yerkassov, R.; et al. The Role of Methods for Applying Cucurbit[6]uril to Hydroxyapatite for the Morphological Tuning of Its Surface in the Process of Obtaining Composite Materials. Materials 2024, 11, 4995. The impact factor for 2023

of the journal is 3.1, and has a quartile in Polymer Science – Q3. It has a CiteScore of 5.8 for 2023, the percentile in General Chemistry - 81; the percentile in Polymers and Plastics - 80. Quartile rankings: Q3 in Physical Chemistry, Q2 in Materials Science (Interdisciplinary), Q2 in Condensed Matter Physics 73. Burkhanbayeva T.T. played a direct role in obtaining experimental data, processing and interpreting the results, and writing conclusions for the manuscript.

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Synthesis and study of a novel supramolecular 'host-guest' complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride

Аңдатпа

Макроцикл порталдарында локализацияланған кукурбит[6]урил (CB[6]) негізінде хост-қонақ типіндегі жаңа супрамолекулалық $C_{44}H_{71}C_{12}N_{26}O_{22}$ (CB[6]@Pipa*2HCl) кешені синтезделді. ¹H ЯМР және рентгендік дифракция деректеріне сәйкес, табылған шарттарда кешенде қожайын:қонақ қатынасы 1:1 болды. Сонымен қатар, ИҚ-спектроскопиялық деректер кешендердің түзілуін қолдайды, мұнда CB[6]@Pipa*2HCl-де кукурбит[6]урил карбонил фрагментінің созылу тербелістерінің сіңіру жолағының бастапқы CB[6]-ға қатысты 36 см^{-1} ұзын толқынды аймаққа ығысуы байқалды. TGA/DSC талдауының нәтижелері алынған CB[6]@Pipa*2HCl кешенінің термиялық тұрақтылығының бастапқы 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлоридіне қатысты 55°C жоғарылағанын көрсетті. Алынған CB[6]@Pipa*2HCl кешенінің құрылымы монокристалды дифрактометрия көмегімен анықталды.

Түйінді сөздер: кукурбит[6]урил, супрамолекула, қожайын-қонақ кешені, құрылым, 1,4-бис(2-гидроксиэтил)пиперазин дигидрохлориді, рентгендік дифракция, ИҚ-спектроскопия.



Synthesis and study of a novel supramolecular 'host-guest' complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride

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ABSTRACT

A novel supramolecular complex $C_{44}H_{71}Cl_2N_{26}O_{22}$ (CB[6]@Pipa-2HCl) of the "host-guest" type has been synthesized. It is based on cucurbit[6]uril (CB[6]) with dihydrochloride 1,4-bis(2-hydroxyethyl)piperazine (Pipa-2HCl) localized within the portals of the macrocycle. Based on ¹H NMR and X-ray crystallography, the host-guest ratio in the complex under the specified conditions was determined to be 1:1. Further evidence of complex formation was observed through IR spectroscopy, where a shift in the absorption band of carbonyl vibrational frequencies of cucurbit[6]uril by 36 cm^{-1} towards the longer wavelength region was detected in CB[6]@Pipa-2HCl compared to the original CB[6]. TGA/DSC analysis results indicated an increase in thermal stability by $55\text{ }^{\circ}\text{C}$ for the obtained CB[6]@Pipa-2HCl complex compared to the initial 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. The structure of the synthesized CB[6]@Pipa-2HCl complex was confirmed using single-crystal XRD.

1. Introduction

Supramolecular chemistry represents a recognized research field with the potential to make significant contributions to several key applications, including drug delivery, sensing, and catalysis [1–6]. Within the area of supramolecular chemistry, the "host-guest" chemistry focuses on investigating molecular interactions between macrocyclic receptors, known as "hosts," and low-molecular-weight ligands, referred to as "guests," primarily through non-covalent interactions [7,8]. Well-known complexation agents, such as cyclodextrins [9,10], calixarenes [11,12], cucurbiturils [13,14], and pillararenes [15,16] constitute established supramolecular macrocycles capable of encapsulating both organic and inorganic guest molecules within their cavities. Typically, encapsulation of a "guest" within the cavity of a macrocyclic "host" leads to changes in its physicochemical properties [17]. Among the promising "hosts" in this context are cucurbit[n]urils, a class of macrocyclic hosts that exhibit a pumpkin-like shape and consist of five or more glycoluril units connected by pairs of methylene bridges

[18–20].

The cavity of CB[6], as depicted in Fig. 1, is classified as a hydrophobic nanospace capable of binding hydrophobic compounds and neutral guest molecules in aqueous environments [21–23]. Furthermore, the negatively charged carbonyl portals promote the binding affinity towards metal ions and cationic compounds [24–27]. Following the interpretation of the structure of the original hexameric homologue of CB[6], Mock and colleagues discovered the strong binding of alkylammonium and alkyl-diammonium ions to CB[6] [28,29], opening ways for the synthesis of analogous supramolecular systems.

On the other hand, 1,4-bis(2-hydroxyethyl)piperazine (Pipa) (Fig. 2) is a non-planar saturated heterocyclic diol, containing two tertiary amine groups within a six-membered ring and two primary hydroxyethyl groups bound to nitrogen atoms. Consequently, this compound exhibits bifunctionality, both in terms of hydroxyl and amine groups. Owing to these structural attributes, the Pipa molecule can act as a ligand and form stable complexes with transition metals [30,31]. The complexation properties of Pipa have been used in the synthesis of novel

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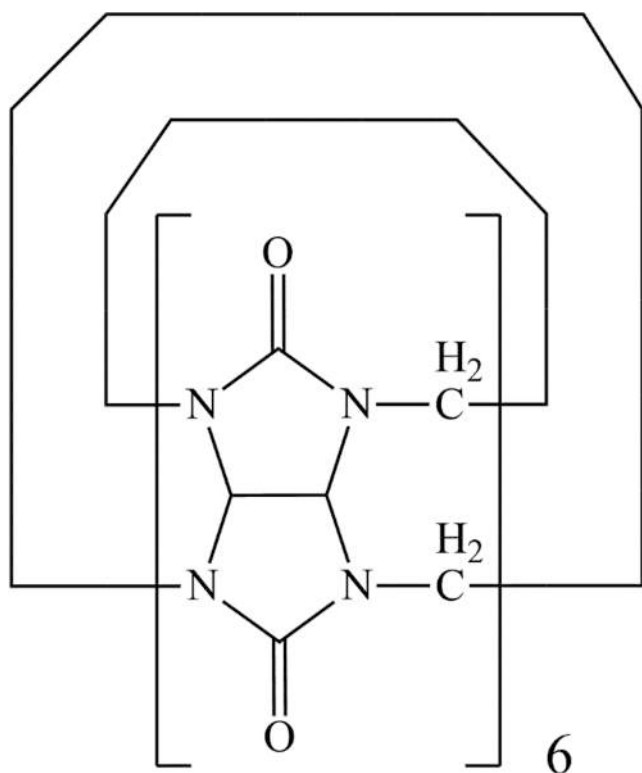


Fig. 1. Molecular Structure of CB.

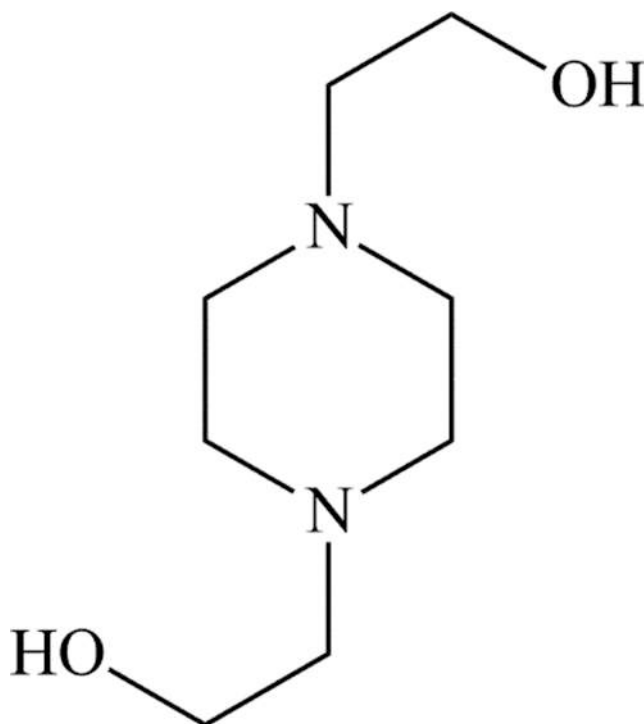


Fig. 2. Molecular Structure of 1,4-bis(2-hydroxyethyl)piperazine.

metal–organic framework structures (MOFs) [32,33] and polyoxometalates (POMs) [34–37]. The piperazine ring serves as a pharmacophore group, a vital structural element in many biologically active compounds. For instance, the antispasmodic drug Nafiverine is a direct diacylated derivative of **Pipa** [38]. In light of this, **Pipa** holds particular interest as a substrate for the synthesis of novel bioactive compounds

[39].

It is noteworthy that 1,4-bis(2-hydroxyethyl)piperazine readily undergoes mono- and diprotonation upon exposure to acids, yielding the corresponding salts [40].

Considering the aforementioned, the objective of this study is the synthesis and investigation of a novel supramolecular system based on 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride and cucurbit[6]uril.

The exploration of the obtained complex holds promising potential for its future utilization as a precursor in the synthesis of new metal–organic framework structures and novel bioactive compounds.

2. Materials and methods

Cucurbit[6]uril (CB[6]) was synthesized according to literature [41]. Briefly, glycoluril (21.4 g, 0.15 mol), oxyethylenediphosphonic acid (61.8 g, 0.30 mol), and 120 mL of water were combined in a 250 mL round-bottom flask equipped with a magnetic stirrer. The mixture was heated to 50 °C, and paraformaldehyde (9 g, 0.30 mol) was slowly added, allowing the solution to mix thoroughly. The resulting solution was stirred for an additional 30 min until it solidified into a gel, which was then heated to 100 °C, causing the gel to dissolve rapidly. The reaction mixture was boiled for 20 h at 100 °C. Subsequently, the solution was cooled to room temperature. The obtained precipitate was filtered and washed with hot water, and dissolved in boiling 37 % HCl solution. The resulting solution was cooled and left at 0 °C for a week for crystallization. Colorless hexagonal **CB[6]** crystals of high purity were formed on the vessel walls. **CB[6]** was obtained as a white powder with a yield of 6.3 g (25 %). IR spectrum, ν , cm^{-1} : 3328 (H_2O), 2448 (CH_2), 1684 ($\text{C}=\text{O}$). ^1H NMR (400 MHz, $\text{F}_3\text{CSO}_3\text{H}/\text{D}_2\text{O}$, TMS) δ , ppm: 5.82 (s, 12H, CH); 5.58 (d, 12H, CH_2); 4.63 (d, 12H, CH_2). ^{13}C NMR (101 MHz, $\text{F}_3\text{CSO}_3\text{H}/\text{D}_2\text{O}$, TMS) δ , ppm: 160.21 ($\text{C}=\text{O}$); 72.71 (CH); 52.04 (CH_2). The structure of the obtained **CB[6]** was confirmed by powder X-ray diffraction (Fig. S1, supplementary material).

1,4-bis(2-hydroxyethyl) dihydrochloride Piperazine (Pipa-2HCl) was obtained by dissolving 1,4-bis(2-hydroxyethyl)piperazine (17.4 g, 0.1 mol) in 20 % HCl. The resulting solution was evaporated to half of its volume and left to crystallize. The obtained crystals were filtered and recrystallized twice from a mixture of methanol/water = 50/50. The yield was 18 g (73 %).

^1H NMR (400 MHz, D_2O , TMS) δ , ppm: 3.32 (q, 4H, $-\text{CH}_2-\text{N} <$); 3.63 (s, 8H, $-\text{CH}_2-\text{N}(\text{cycle})$); 3.82 (q, 4H, $-\text{CH}_2-\text{OH}$).

^{13}C NMR (101 MHz, D_2O , TMS) δ , ppm: 48.48 (CH_2 (cycle)); 54.74 ($-\text{CH}_2-\text{N} <$); 58.00 ($-\text{CH}_2-\text{OH}$).

2.1. Encapsulation of 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride in the cavity of cucurbit[6]uril in an aqueous environment

Cucurbit[6]uril (1 g, 0.001 mol) was dissolved in 100 mL of water under constant stirring until complete dissolution. Subsequently, 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride (0.248 g, 0.001 mol) was added, and the mixture was stirred until complete dissolution. The resulting solution was filtered and left in the open air for 14 days for slow solvent evaporation. After 5 days the precipitation of the first **CB[6]**@**Pipa-2HCl** crystals was observed. After 14 days, the precipitated crystals were filtered and air-dried. The mass of the obtained **CB[6]**@**Pipa-2HCl** was 0.63 g (50.5 %).

NMR spectra were recorded on a Bruker AVANCE III HD spectrometer (Bruker Corporation, Germany) with an operating frequency of 400 and 100 MHz for ^1H and ^{13}C nuclei respectively, in solutions of $\text{DMSO}-d_6$, $\text{F}_3\text{CSO}_3\text{H}$ and D_2O . The internal standard was tetramethylsilane (TMS).

IR spectra of the starting materials and the obtained complex were recorded on a Nicolet 6700 Fourier-transform infrared spectrometer with a diamond crystal attachment at a resolution of 4 cm^{-1} , 64 scans, in the range of $500\text{--}3700\text{ cm}^{-1}$.

2.2. Single crystal X-ray diffraction

Single crystal XRD data were collected on a Bruker D8 Venture diffractometer with a CMOS PHOTON III detector and I μ S 3.0 source (mirror optics, $\lambda(\text{MoK}\alpha) = 0.71073 \text{ \AA}$). The φ - and ω -scan techniques were employed to measure intensities. The crystal structure was solved using the SHELXT [42] and was refined using SHELXL [43], programs with OLEX2 GUI [44]. Atomic displacement parameters for non-hydrogen atoms were refined anisotropically, hydrogen atoms were placed geometrically and refined in the riding model.

Crystal data for **CB[6]@Pipa-2HCl** ($\text{C}_{44}\text{H}_{71}\text{Cl}_2\text{N}_{26}\text{O}_{22}$) ($M = 1387.17 \text{ g/mol}$): monoclinic, space group $P2_1/c$, $a = 12.1074(6) \text{ \AA}$, $b = 20.3920(9) \text{ \AA}$, $c = 12.6061(5) \text{ \AA}$, $\beta = 112.368(2)^\circ$, $V = 2878.2(2) \text{ \AA}^3$, $Z = 2$, $T = 150(2) \text{ K}$, $\mu(\text{CuK}\alpha) = 0.22 \text{ mm}^{-1}$, $D_{\text{calc}} = 1.601 \text{ g/cm}^3$, 20,000 reflections measured ($3.6^\circ \leq 2\theta \leq 52.8^\circ$), 5894 unique ($R_{\text{int}} = 0.0494$, $R_{\text{sigma}} = 0.0602$) which were used in all calculations. The final R_1 was 0.093 ($I > 2\sigma(I)$) and wR_2 was 0.295 (all data); $\Delta\rho_{\text{max}} = 1.24 \text{ e \AA}^{-3}$, $\Delta\rho_{\text{min}} = -0.78 \text{ e \AA}^{-3}$.

Cambridge Crystallographic DataCentre (CCDC) deposition Number 2295984 contains the supplementary crystallographic data for this paper. These data are provided free of charge from CCDC at <https://www.ccdc.cam.ac.uk/structures>.

TGA/DSC- were conducted using a Simultaneous Thermal Analyzer (STA) 6000 instrument in a temperature range of 30–800 °C under a nitrogen atmosphere, with a heating rate of 10 °C/min.

Elemental analysis CHNS was carried out on an instrument HCNS-O UNICUBE -ORGANIC ELEMENTAL ANALYZER. Standard: sulfanilamide. Detector: Thermal Conductivity Detector (TCD) and Infrared (IR) for sulfur Maximum furnace temperature: 1,200° C.

Elemental analysis CHNS (%) calculated for **CB[6]@Pipa-2HCl**: N – 26.24, C – 38.06, H – 5.12. Found: N – 25.24, C – 38.00, H – 5.15.

3. Results and discussion

3.1. Single crystal X-ray diffraction

The inclusion compound **CB[6]@Pipa-2HCl** crystallizes in a monoclinic crystal system, symmetry space group $P2_1/c$. The asymmetric unit contains half of **CB[6]** host, half of **Pipa-2HCl** guest molecule, one chloride anion and four solvate water molecules. The

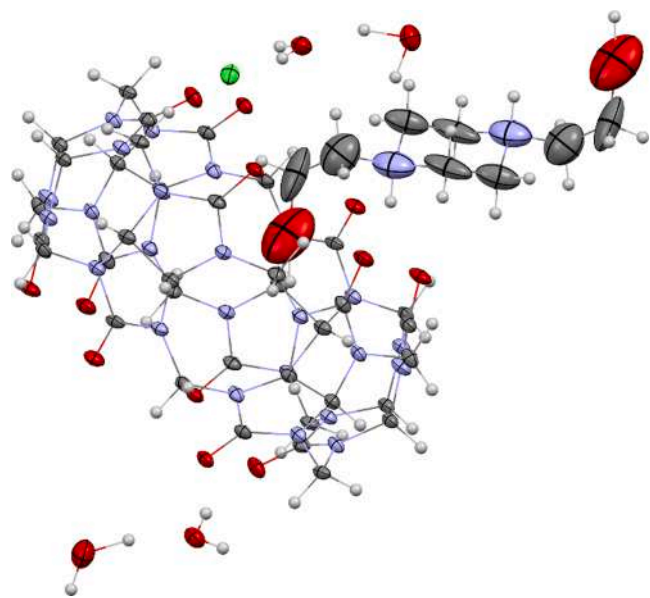


Fig. 3. Molecular structure of **CB[6]@Pipa-2HCl** according to SCXRD analysis. Thermal ellipsoids are shown at 30 % probability for the guest molecule and at 50 % for the rest of the atoms.

molecular structure is shown in Fig. 3.

The guest molecules, **Pipa-2HCl**, are located between the portals of the neighboring **CB[6]** molecules. The methylene and NH groups of the guest molecules are involved in multiple C–H...O and N–H...O interactions with five out of six carbonyl groups of **CB[6]** hosts (Fig. 4a). Two distinct types of N–H...O interactions are observed, with H...O internuclear distances of 1.919 Å and 2.524 Å, while the C–H...O interactions are mostly uniform with the average H...O distance of 2.45 Å. Both of the indicated interactions join the **CB[6]** molecules into supramolecular chains oriented along the crystallographic axis c (Fig. 4b, Fig. S2). The chains are linked by C–H...O interactions ($d(\text{H}\cdots\text{O}) = 2.646 \text{ \AA}$) involving the methylene and carbonyl groups of **CB[6]** molecules from different chains (Fig. 4b).

3.2. NMR analysis of **CB[6]@Pipa-2HCl**

The results obtained from single-crystal X-ray diffraction are corroborated by nuclear magnetic resonance (NMR) spectroscopy. NMR spectra of the synthesized material were recorded in D_2O . In the ^1H NMR spectra (Fig. 5), two doublets corresponding to the methylene protons of cucurbit[6]uril were observed at 5.59 and 4.17 ppm, indicative of signals originating from the obtained complex. Additionally, a signal at 5.43 ppm corresponding to the methine protons in cucurbit[6]uril was identified. The signal for the methylene protons in the piperazine ring of 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride appeared as a singlet at 3.73 ppm, with a weak field shift of 0.1 ppm into the weak field area compared to free 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. A substantial field shift of the $-\text{CH}_2\text{-OH}$ group of the encapsulated 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride, by 0.47 ppm into the weak field area relative to 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride, resulted in the methylene protons ($-\text{CH}_2\text{-OH}$) forming a complex multiplet signal within the 2-hydroxyethyl group. A figure comparing the NMR spectra of ^1H of the initial compounds and the resulting compound is given in the supplementary material (Fig. S3).

In the ^{13}C NMR spectrum of **CB[6]@Pipa-2HCl** (Fig. 6), two distinctive signals at 156.21 and 156.66 ppm correspond to the carbonyl carbon atoms. This signal splitting suggests that one of the portals of cucurbit[6]uril experiences stronger interactions with the guest molecule. Additional signals at 70.23 and 51.29 ppm are attributed to the methine and methylene carbon atoms of cucurbit[6]uril, respectively.

In the case of the encapsulated 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride molecule, signals were observed at 54.74 ppm for $-\text{CH}_2\text{-N} <$ and at 48.82 ppm for methylene carbon atoms within the ring. Notably, these signals exhibited chemical shifts of 0.34 ppm and 0.23 ppm, respectively, in a weaker field compared to the free 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. A figure comparing the NMR spectra of ^{13}C of the initial compounds and the resulting compound is given in the supplementary material (Fig. S4).

These NMR spectroscopic findings provide compelling evidence of complex formation and the localization of the guest molecule, 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride, at the portals of cucurbit[6]uril.

3.3. IR spectroscopy

The IR spectrum of **CB[6]@Pipa-2HCl** (Fig. 7) exhibits a complex profile, making it challenging to provide a definitive interpretation of the signals. However, a comparative analysis of the IR spectra of the starting materials and the resulting complex shows a splitting of the absorption band corresponding to the valence vibrations of the carbonyl groups of cucurbit[6]uril, as well as their noticeable shift by 36 cm^{-1} and 12 cm^{-1} towards short-wave numbers. Splitting of the absorption band of valence vibrations of carbonyl groups indicates the presence of two groups of nonequivalent carbonyl groups in the supramolecular complex, which is confirmed by the data of single crystal X-ray diffraction. The absorption band at 1684 cm^{-1} corresponds to five of the

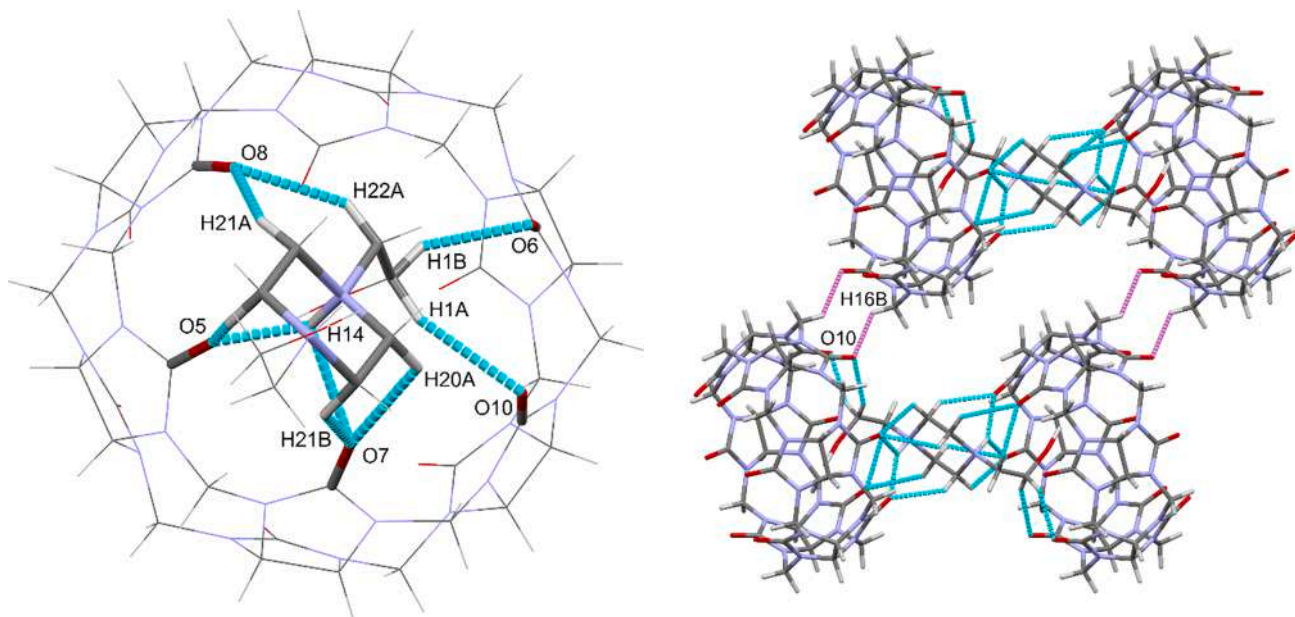


Fig. 4. Supramolecular interactions in the crystal structure of CB[6]@Pipa·2HCl: (a) host-guest C-H...O and N-H...O contacts (shown in blue), view along the crystallographic axis c; (b) C-H...O contacts between the supramolecular chains (shown in purple), view along the crystallographic axis b. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

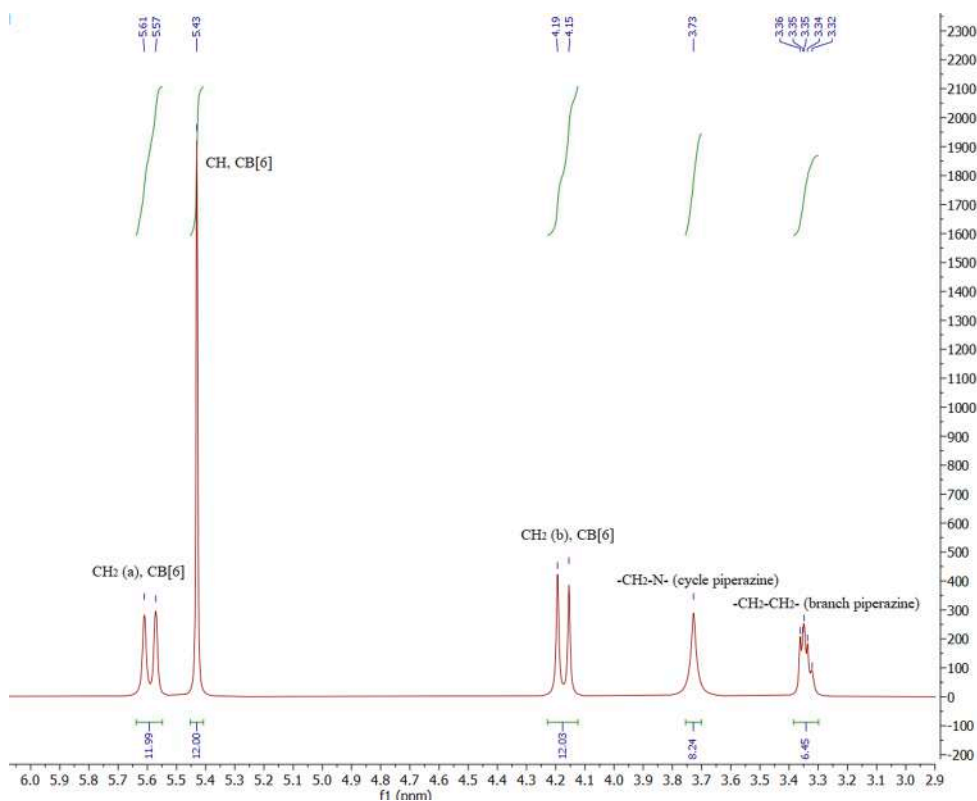


Fig. 5. ¹H NMR spectrum of CB[6]@Pipa·2HCl.

six carbonyl groups that are susceptible to interaction with 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. This experimental fact unequivocally confirms the occurrence.

3.4. TGA/DSC

TGA/DSC analyses were performed for the pristine CB[6],

Pipa·2HCl, and the synthesized CB[6]@Pipa·2HCl complex, covering the temperature range of 30–800 °C under an inert nitrogen atmosphere (Figs. 8 and 9). The results revealed that the thermal stability of the encapsulated 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride was enhanced by 55 °C compared to the free 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. However, it is noteworthy that the overall TG curve profile of the obtained complex coincides with that of pure

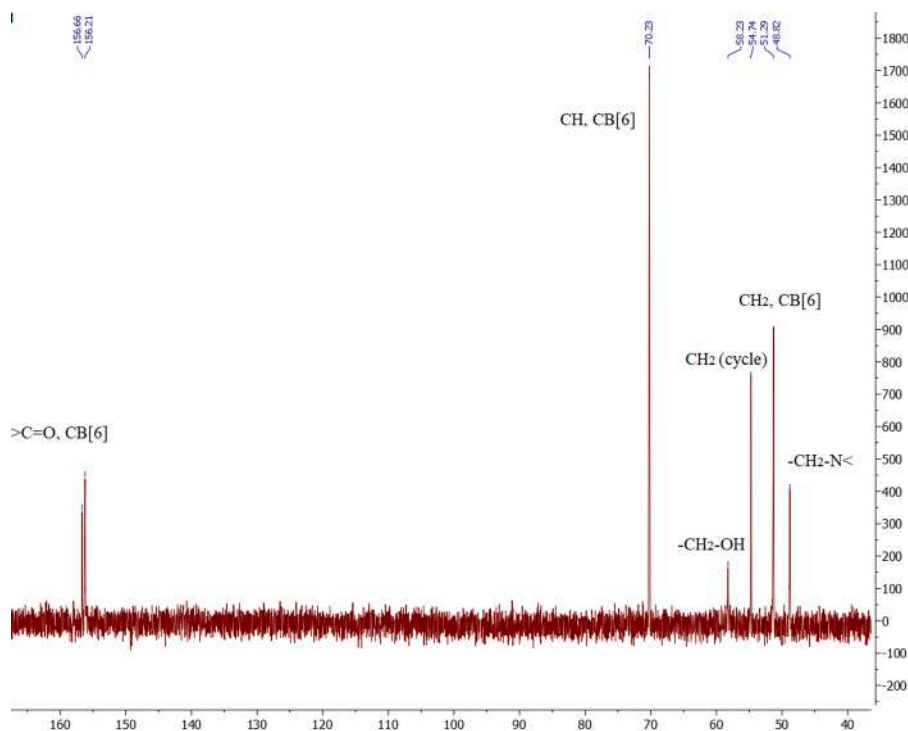


Fig. 6. ^{13}C NMR spectrum of $\text{CB}[6]@\text{Pipa}\cdot 2\text{HCl}$.

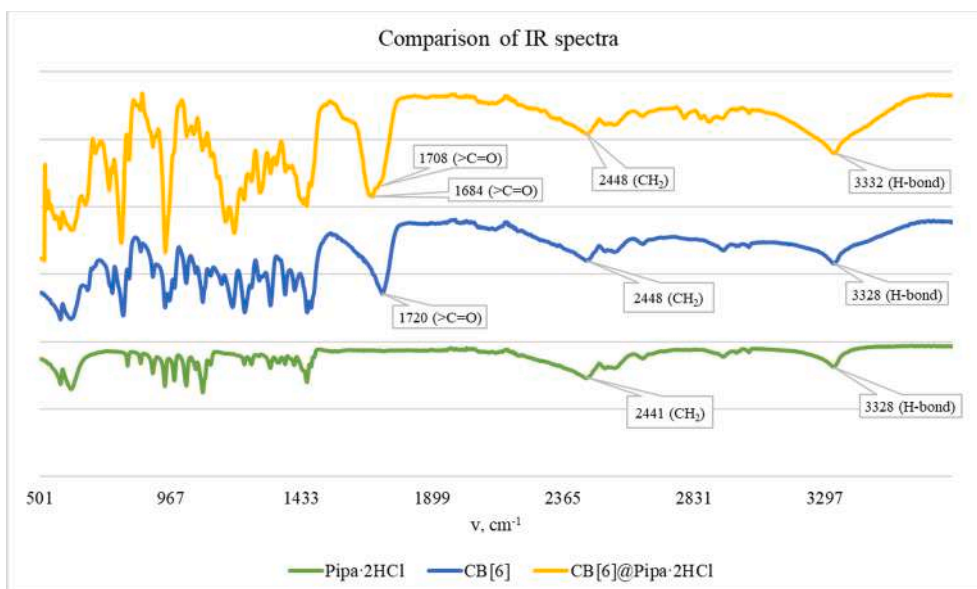


Fig. 7. Comparative analysis of IR spectra of the obtained complex $\text{CB}[6]@\text{Pipa}\cdot 2\text{HCl}$ and the starting materials $\text{CB}[6]$ and $\text{Pipa}\cdot 2\text{HCl}$.

cucurbit[6]uril. Although the decomposition of this complex occurs at 473°C , which is 44°C lower than the decomposition of free cucurbit[6]uril. A significant increase in the stability of 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride in the complex is due to the fact that it is located in the cavity of cucurbit[6]uril and is retained due to intermolecular non-covalent bonds.

4. Conclusion

In this study successfully synthesized and characterized a novel “host-guest” complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride using various analytical techniques,

including NMR, IR spectroscopy, and TGA/DSC analysis. The comparative analysis of the IR spectra of the starting materials and the synthesized complex revealed a shift and splitting of the absorption band of carbonyl vibrations of cucurbit[6]uril by 36 cm^{-1} and 12 cm^{-1} towards smaller wave numbers, which indicates the formation of a complex due to carbonyl oxygen atoms of cucurbit[6]uril. TGA/DSC data suggested an increase in the thermal stability of the encapsulated 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride by 55°C . Additionally, single-crystal XRD confirmed the structure of the obtained complex, showing that the guest molecule, 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride, formed complexes through the quaternized nitrogen atoms of the piperazine ring and was localized at the carbonyl portals of cucurbit[6]

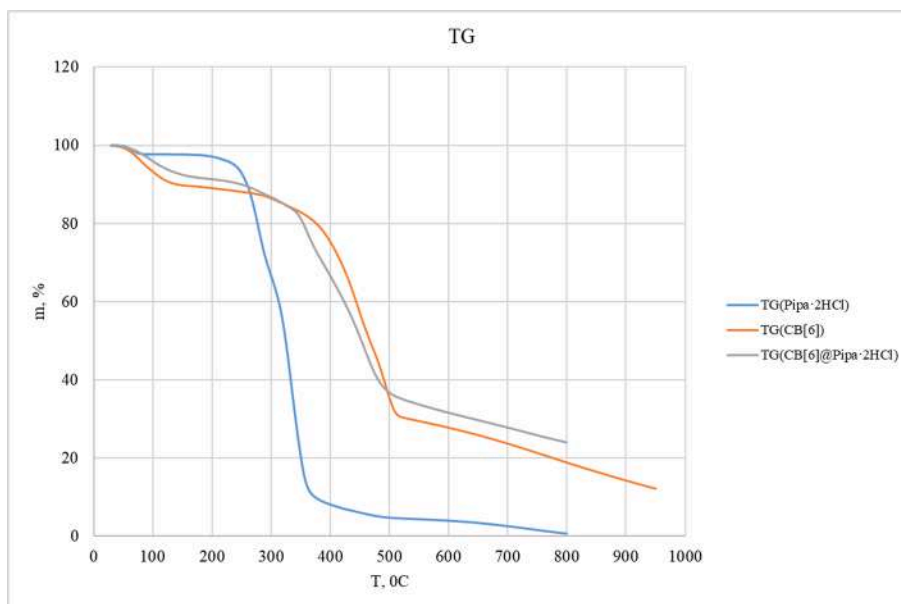


Fig. 8. TGA of Pristine CB[6], Pipa-2HCl, and the synthesized CB[6]@Pipa-2HCl complex.

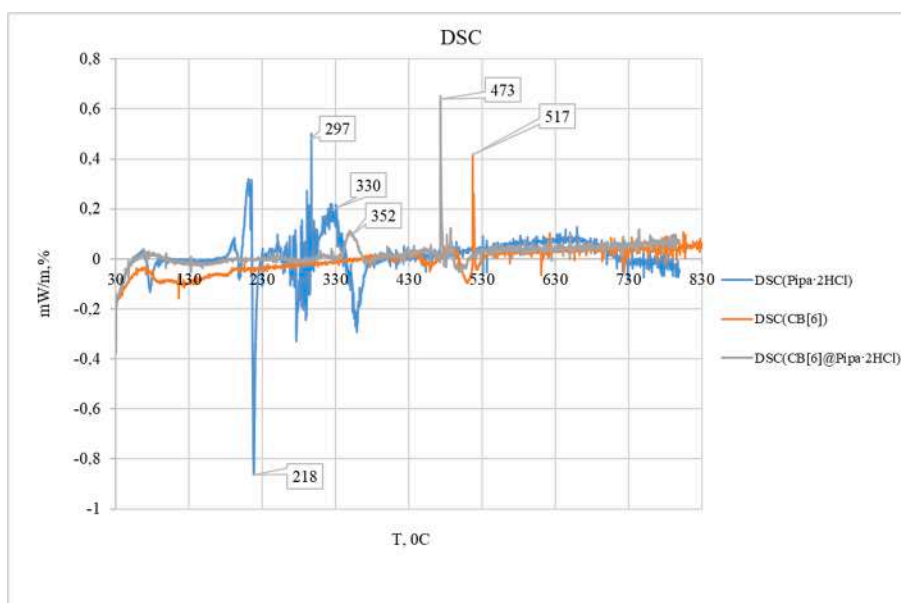


Fig. 9. DSC analysis of pristine CB[6], Pipa-2HCl, and the synthesized CB[6]@Pipa-2HCl complex.

uril.

CRediT authorship contribution statement

Tolkynay Burkhanbayeva: Investigation, Writing – original draft, Validation. **Alexey N. Guslyakov:** Investigation, Writing – original draft. **Farkhad F. Tarikhov:** Validation, Visualization. **Dmitry I. Pavlov:** Conceptualization, Methodology. **Rakhmetulla S. Erkasov:** Project administration, Data curation. **Abdigali A. Bakibaev:** Writing – review & editing. **Andrei S. Potapov:** Software. **Vyacheslav A. Yanovsky:** Formal analysis. **Victor S. Malkov:** Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jscs.2024.101819>.

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Development of new composite biocompatible materials by modifying the surface of porous hydroxyapatite using cucur-bit[n]urils

Аңдатпа

Бұл жұмыста кеуекті бейорганикалық қосылыс – гидроксипатит негізінде оның бетін перспективті макроциклді қосылыстар – кукурбит[n]urils көмегімен модификациялау арқылы алғаш рет жаңа композициялық материалдар әзірленді. Модификация процесі гидроксипатит бетіне судағы кукурбит[n]урилді қолдануды қамтыды. Кешенді сипаттама ИҚ-спектроскопия және SEM көмегімен орындалды. Материалдар гемолитикалық әсерге, қабынуға қарсы әрекетке және цитотоксикалық әсерге бағаланды. Нәтижелер бетімен байланысқан кукурбит[n]урил бар материалдардың тән гемолитикалық әсерлерін көрсетпейтінін көрсетті, бұл оларды биоүйлесімді материалдар ретінде пайдалану үшін негіз береді. Бұл нәтижелер ұқсас процестерде инкапсуляцияланған кукурбит[n]урил көмегімен супрамолекулалық стратегияларды ашатын сенімді және тиімді биокөмпазиттерді құрудың балама тәсілі ретінде маңызды уәде береді.

Түйін сөздер: кукурбит[n]урил; гидроксипатит; биоүйлесімді материалдар; гемолитикалық белсенділік; цитотоксикалық; қабынуға қарсы әрекет.

Article

Development of New Composite Materials by Modifying the Surface of Porous Hydroxyapatite Using Cucurbit[n]urils

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Abstract: This study represents an advancement in the field of composite material engineering, focusing on the synthesis of composite materials derived from porous hydroxyapatite via surface modification employing cucurbit[n]urils, which are highly promising macrocyclic compounds. The surface modification procedure entailed the application of cucurbit[n]urils in an aqueous medium onto the hydroxyapatite surface. A comprehensive characterization of the resulting materials was undertaken, employing analytical techniques including infrared (IR) spectroscopy and scanning electron microscopy (SEM). Subsequently, the materials were subjected to rigorous evaluation for their hemolytic effect, anti-inflammatory properties, and cytotoxicity. Remarkably, the findings revealed a notable absence of typical hemolytic effects in materials incorporating surface-bound cucurbit[n]urils. This observation underscores the potential of these modified materials as biocompatible alternatives. Notably, this discovery presents a promising avenue for the fabrication of resilient and efficient biocomposites, offering a viable alternative to conventional approaches. Furthermore, these findings hint at the prospect of employing supramolecular strategies involving encapsulated cucurbit[n]urils in analogous processes. This suggests a novel direction for further research, potentially unlocking new frontiers in material engineering through the exploitation of supramolecular interactions.

Keywords: biocompatible materials; hydroxyapatite; cucurbit[n]urils; cytotoxicity; hemolytic activity; anti-inflammatory effect



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1. Introduction

In the contemporary era of personalized medicine, there exists a pressing demand for the development of novel materials tailored for implants, each mandated to possess specific characteristics. To ensure their efficacy in medical applications, such materials necessitate an optimal blend of diverse properties [1]. As the demand for precise and tailored treatments increases, ongoing research focuses on enhancing traditional biomaterials for established applications while also seeking new bioactive materials suitable for diverse advanced applications, such as regenerative medicine and addressing various health issues, including theranostic biomaterials (offering diagnostic, monitoring, and combined therapeutic capabilities). In contemporary medical practice, biomaterials play a significant role, serving to stimulate healing and facilitate the restoration of initial biological or functional activity. These biomaterials may be derived from natural sources or synthetically produced [2].

The fundamental attributes of these materials encompass their composition, shape, structure, and mechanical properties. Biocompatibility emerges as a critical facet, denoting the capacity to interface with surrounding tissues without provoking adverse reactions or inflammation. Moreover, it is advantageous for such materials to promote the proliferation of blood vessels or bones in their vicinity, thereby facilitating the healing and regeneration of impaired tissues. Whether employed in implants or wound treatment, these properties delineate the material's capability to interface with adjacent tissues. Bioactive materials hold the potential to serve as a scaffold for tissue regeneration, hastening the repair of damage [1].

Conversely, materials in direct contact with the body's internal environment ought to exhibit minimal toxicity towards cells and tissues. Nevertheless, numerous substances boasting potent antibacterial attributes often carry significant toxicity, thereby compromising their biocompatibility. This underscores the intricate nature of the interaction between biomaterials and host tissues, representing a paramount challenge in biomaterials research [3]. Biocompatibility refers to the immune rejection or inflammatory response of the surrounding tissue systems triggered by the presence of a foreign body within the body [3].

In adherence to the rigorous clinical standards governing medical device deployment, a meticulous surface modification protocol stands as an imperative prerequisite prior to implantation within the human body, aiming to bolster biocompatibility. Consequently, the quest for materials exhibiting dual characteristics of biocompatibility and specific biological functionality presents a formidable scientific endeavor [4].

Moreover, modern clinical therapeutic strategies hinge upon the administration of drugs via oral ingestion or intravenous infusion, facilitating rapid elevation of drug concentration in the bloodstream following dosage administration. However, this concentration swiftly diminishes below the therapeutic threshold. Consequently, there is a risk of the drug level spiking to toxic levels post-administration, followed by a drop below the therapeutic range, rendering the therapy ineffective [4].

The advent of drug-releasing implants presents a compelling departure from traditional routes of drug delivery, such as oral ingestion and intravenous infusion, offering an array of promising applications across diverse clinical treatments. Key materials currently under exploration for the fabrication of such implants include titanium nanotubes, porous silicon, polymers, hydrogels, and microtechnologies [5].

Drug-releasing implants hold immense potential for enabling sustained, remotely controlled, programmable, and localized drug release at specific sites within the body. This capability not only enhances therapeutic effectiveness but also minimizes adverse effects experienced by patients. These attributes significantly surpass the capabilities of conventional systemic drug administration methods, marking a significant stride in the field of therapeutic interventions [5].

Bioactive materials hold a unique position among implants due to their capacity to promote the growth of new tissue in their vicinity. This capability facilitates enhanced healing and recovery processes, making them particularly crucial for medical applications pertaining to wound and injury treatment [6].

All these attributes of implant materials play a vital role in their application in medical practice. Ongoing research and development in this domain is continually advancing, aiming to identify the most suitable materials that fulfill all prerequisites and deliver optimal outcomes for patients [6].

There exists a necessity to devise materials that engage with the body's internal environment while imposing minimal toxicity on cells and tissues. Nonetheless, numerous substances endowed with antibacterial properties can exert significant toxicity on living tissues. Consequently, a dilemma frequently arises: heightened antibacterial efficacy coincides with diminished biocompatibility. This complicates the challenge of crafting materials possessing both antibacterial attributes and robust biocompatibility [6].

One potentially promising material is modified hydroxyapatite (**HA**) augmented with biologically active compounds. Hydroxyapatite constitutes a pivotal component of bones (comprising roughly 50% of total weight) and teeth (constituting 96% of enamel) and can exist in both synthetic and natural forms.

In the medical realm, synthetic hydroxyapatite (**HA**) serves multifaceted roles, including as a filler for the restoration of bone defects and as a coating on implants to facilitate the regeneration of new bone tissue [7]. Additionally, **HA** finds application as a constituent in biocomposites and as coatings for surgical implants. Notably, these materials exhibit inertness towards living tissues and demonstrate low toxicity levels [7].

Furthermore, the utilization of synthetic hydroxyapatites is associated with a minimal risk of eliciting allergic reactions, inflammation, or mutagenic effects. Modified forms of hydroxyapatites have been demonstrated to expedite the process of reparative osteogenesis at the implantation site while concurrently augmenting osteoblast proliferation. These attributes collectively underscore the pivotal role of synthetic hydroxyapatites in advancing regenerative medicine and orthopedic surgery [8].

To date, techniques for the surface modification of porous materials through saturation with biologically active compounds, such as macrocyclic compounds, are gaining prominence. These methods afford the ability to regulate the release of antibiotics, drugs, biologically active substances, and cells [9].

Macrocyclic compounds are frequently favored over alternative drug delivery systems, like dendrimers, liposomes, micelles, carbon nanotubes, hydrogels, and polymers. This preference stems from several advantages that they offer [10–12]. Macrocyclic compounds typically exhibit enhanced stability and enable a controlled rate of drug release [10–12]. The development of efficient drug and biologically active substance delivery systems represents a significant stride in advancing novel approaches in medicine and various other domains of science and technology [10–12].

Macrocyclic systems derived from glycoluril and its derivatives, such as cucurbit[n]urils and bambusurils, serve as ideal starting reagents for surface modification of porous materials. In contrast to cucurbit[n]urils (**CB[n]**), bambus[6]uril (**BU[6]**) exhibits a relatively weaker affinity for hydrogen bonding with anions situated within its hydrophobic cavity [13]. The positively charged electrostatic domain of **BU[6]** facilitates the attraction of anions, while the portal carbonyl oxygen atoms generate a negative region capable of interacting with positively charged particles. Our investigations focused on evaluating the hemocompatibility and the capacity for human plasma protein adsorption of materials incorporating **BU[6]** and hydroxyapatite [14].

Modification of **BU[6]** samples resulted in a reduction in protein adsorption, thereby enhancing their hemocompatibility. This phenomenon is likely attributed to alterations in the surface properties of the material induced during **BU[6]** modification, including changes in surface tension, free surface energy, roughness, and hydrophilicity. Deposition of **BU[6]** onto the surface of porous materials is speculated to induce modifications in surface charge, mimicking characteristics akin to blood [14]. Consequently, the diminished plasma protein adsorption mitigates thrombogenicity, thereby augmenting hemocompatibility [14].

In contrast to **BU[6]**, **CB[n]** showcases a distinct capacity for forming host–guest complexes with cationic molecules and boasts a broader spectrum of molecular cavity sizes [15]. **CB[n]** displays an inherent ability to selectively accommodate diverse organic guest molecules through a repertoire of interaction mechanisms including hydrophobic interactions, hydrogen bonding, Van der Waals forces, π - π stacking, and ion–dipole effects, culminating in the formation of inclusion complexes [16,17].

The utilization of **CB[n]**'s hydrophobic cavity in assembling biologically active functional molecules has garnered considerable attention among researchers. This interest extends beyond its role as a targeted drug delivery system to encompass applications in disease diagnosis and various other domains [18,19]. Unlike many other macrocyclic hosts, **CB[n]** exhibits an exceptionally rigid structure, rendering the determination of cavity parameters particularly elucidative. For instance, all **CB[n]** variants ($n = 5$ –8

and 10) share a uniform height ($d = 9.1 \text{ \AA}$) while manifesting significant discrepancies in cavity width. **CB[5]** has an inner diameter of $4.4 \text{ \AA}$, while **CB[8]** has twice that size at $8.8 \text{ \AA}$ [20,21]. This characteristic enables the accommodation of drug molecules of varying sizes within the **CB[n]** cavity, thereby expanding its potential applications across various fields. Presently, antitumor, antibacterial, anticholinergic drugs, antioxidants, neurotransmitters, cholinesterase reactivators, and other compounds are being encapsulated within the **CB[n]** cavity [22]. Leveraging these properties enables researchers to impart various necessary characteristics into materials. Currently, techniques for surface modification of porous materials through impregnation with biologically active compounds, including macromolecular entities, are experiencing widespread adoption for various applications [22]. These methodologies offer meticulous control over the release kinetics of antibiotics, pharmaceutical agents, biologically active substances, and cells, thus presenting versatile avenues for tailored therapeutic interventions and biomedical applications [9].

In summary, the utilization of nitrogen-containing macrocyclic compounds for the surface modification of porous materials serves two primary objectives: enhancing biocompatibility and enabling the development of medical biomaterials with controlled drug release capabilities. Consequently, **CB[n]** emerges as unique and intriguing molecules for the fabrication of biocompatible materials with multifaceted applications across various fields. Continued research in this domain holds the potential to further broaden the horizons of their utilization and uncover new breakthroughs.

This study marks the inaugural deposition of a series of cucurbit[n]urils (**CB[6]**, **CB[7]**, and **CB[8]**) onto the surface of hydroxyapatite (**HA**). This innovative approach serves as a foundation for saturating the cavities of cucurbit[n]urils with therapeutic agents, thereby imparting therapeutic functionality to hydroxyapatite and facilitating osteogenesis. Accordingly, the primary aim of this investigation is to assess the influence of cucurbit[n]uril precipitation on the structural integrity of hydroxyapatite (**HA**) and to evaluate the in vitro biocompatibility of the resultant biocomposite materials.

2. Materials and Methods

All chemicals were from Merck/Sigma-Aldrich (Darmstadt, Germany).

2.1. Instruments for Interpreting the Results

2.1.1. Fourier Transform Infrared (FTIR) Spectroscopy

The identification and structural investigation of the obtained samples were conducted using Fourier transform infrared (FTIR) spectroscopy on a Nicolet 6700 IR spectrometer manufactured by Thermo Fisher Scientific (Waltham, MA, USA). The samples underwent examination utilizing the attenuated total internal reflection (ATR) method within the spectral range of 400 to 4000 cm^{-1} , with a resolution of 4 cm^{-1} . The reflection spectra obtained were converted into absorption spectra utilizing the Kubelka–Munk transform.

2.1.2. Nuclear Magnetic Resonance (NMR) Spectroscopy

The NMR spectra of the obtained **CB[6]**, **CB[7]**, and **CB[8]** were acquired using a Bruker Avance 400 III HD NMR spectrometer (Billerica, MA, USA). The measurements were performed in DMSO- d_6 solution at a temperature of 25°C . The operating frequency for hydrogen nuclei was 400 MHz , while for carbon nuclei, it was 100 MHz . These NMR spectra provide valuable information about the molecular structure and chemical environment of the cucurbit[n]uril compounds, aiding in their characterization and analysis.

2.1.3. Scanning Electron Microscopy (SEM) Samples **CB[n]** + **HA**

The QUANTA 200 3D (Hillsboro, OR, USA) electronic and focused beam system is equipped with versatile capabilities for electron microscopy and imaging. It features a wide range of accelerating voltages from 200 to $30,000 \text{ V}$ continuously, allowing for flexible adjustments to suit various imaging requirements. In ESEM mode, it achieves a resolution of 3.5 nm at 30 kV , enabling high-quality imaging even under environmental conditions.

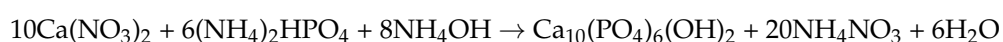
Additionally, in low vacuum mode, it can achieve a resolution of less than 15 nm at 3 kV, facilitating detailed imaging with enhanced contrast and reduced beam damage. This system is well-suited for a range of applications in materials science, nanotechnology, and biological research.

2.1.4. X-ray Diffraction (XRD)

The crystalline powders (**CB[6]**, **CB[7]**, and **CB[8]**) were analyzed using X-ray phase analysis. The examination was conducted utilizing an XRD-7000 X-ray diffractometer manufactured by Shimadzu, Kyoto, Japan. The instrument utilizes a copper (Cu) anode and a radiation wavelength of $\lambda(\text{Cu}) = 1.5406 \text{ \AA}$. The measuring range extended from 5° to 50° in 2θ , with a measuring speed of $30^\circ/\text{min}$. Identification of the analyzed samples was accomplished by comparing the spectrum with the diffractogram of reference substances using diffraction data from the Cambridge Crystallographic Data Centre database. This technique allows for the determination of the crystalline structure and phase composition of the samples.

2.2. Getting Scaffolds from HA

Hydroxyapatite (**HA**) synthesis was carried out by the liquid-phase method using microwave radiation at $\text{pH} \sim 11$ according to the following scheme [23]:



To prepare the initial solutions for hydroxyapatite synthesis, the following chemicals were used:

1. Calcium nitrate tetrahydrate ($\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$): This compound serves as the calcium precursor in the synthesis process. It is typically dissolved in distilled water to obtain a calcium-containing solution.
2. Ammonium phosphate ($(\text{NH}_4)_2\text{HPO}_4$): Ammonium phosphate acts as the phosphate precursor in the synthesis reaction. It is dissolved in distilled water to prepare a phosphate-containing solution.
3. Twenty-five percent aqueous ammonia solution: This solution is used to adjust the pH of the reaction mixture to around 11, creating suitable conditions for hydroxyapatite formation.
4. Distilled water: Distilled water is used as a solvent to dissolve the calcium nitrate tetrahydrate and ammonium phosphate precursors, as well as for dilution purposes and to ensure the purity of the reaction components.

By accurately preparing and combining these chemical solutions in the appropriate proportions, researchers can initiate the hydroxyapatite synthesis reaction under microwave irradiation to obtain the desired **HA** product (Figure 1).

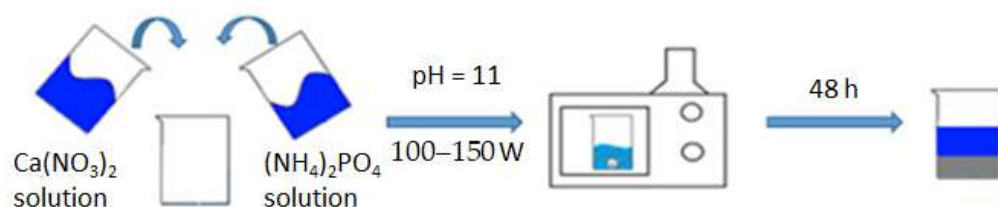


Figure 1. Synthesis scheme of HA.

A suspension of $m = 47.20 \text{ g}$ of $\text{Ca}(\text{NO}_3)_2$ was dissolved in a beaker $(300 \text{ mL})^2 \times 4\text{H}_2\text{O}$ with distilled water ($V = 200 \text{ mL}$), obtaining a solution with a concentration of 0.5 mol/L ; we similarly dissolved $m = 15.84 \text{ g}$ $(\text{NH}_4)_2\text{HPO}_4$ in 200 mL of distilled water, obtaining a solution with a concentration of 0.3 mol/L . The prepared solutions were mixed in one 500 mL glass and brought to $\text{pH} = 11$, adding 25% aqueous ammonia solution with constant stirring. The glass with the reaction mixture was covered with a film and placed in a

microwave oven; an operating power of 100–150 watts was set, and heating was turned on. The microwave exposure was carried out until the reaction mixture boiled. The contents of the reaction vessel were periodically stirred every 15 min of microwave synthesis in order to avoid local overheating. The total heating time in the microwave was 45 min. After that, the glass with its contents was removed and left at room temperature to form the hydroxyapatite phase for 48 h. The precipitated **HA** was filtered and dried in a drying cabinet at 110 °C to a constant weight (20 h), after which it was milled to a homogeneous state. From the resulting **HA** powder, carriers were formed in tablet form with a width of 2 cm and a thickness of about 1 mm, and then calcined at 600 °C to a constant mass and sintering of the material. For this standard technique, the physico-chemical parameters of the resulting compound do not practically differ from the literature data, namely in terms of particle sizes 0.5–1 nm, specific area, $\text{m}^2/\text{g}^{-1} = 106.0$, total pore volume, $\text{cm}^3/\text{g}^{-1} = 0.50$, and their average size, which is 20 nm [6].

The results of the XRD indicate the formation of a hexagonal syngony, gr. P63/m, during the synthesis of stoichiometric **HA**, the gross formula of which can be described by the formula $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ (Table 1). The parameters of the synthesized **HA** cell are close in values to the tabular data (JCPDS data, No. 9-432 [6]) (Figure 2).

Table 1. Phase composition of **HA** synthesis products.

Sample	The Inorganic Phase	Parameters of the Electronic Cell, Å	
		a	c
Synthesis product (HA)	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$	9411	6863
JCPDS data, No. 9-432	$\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$	9418	6884

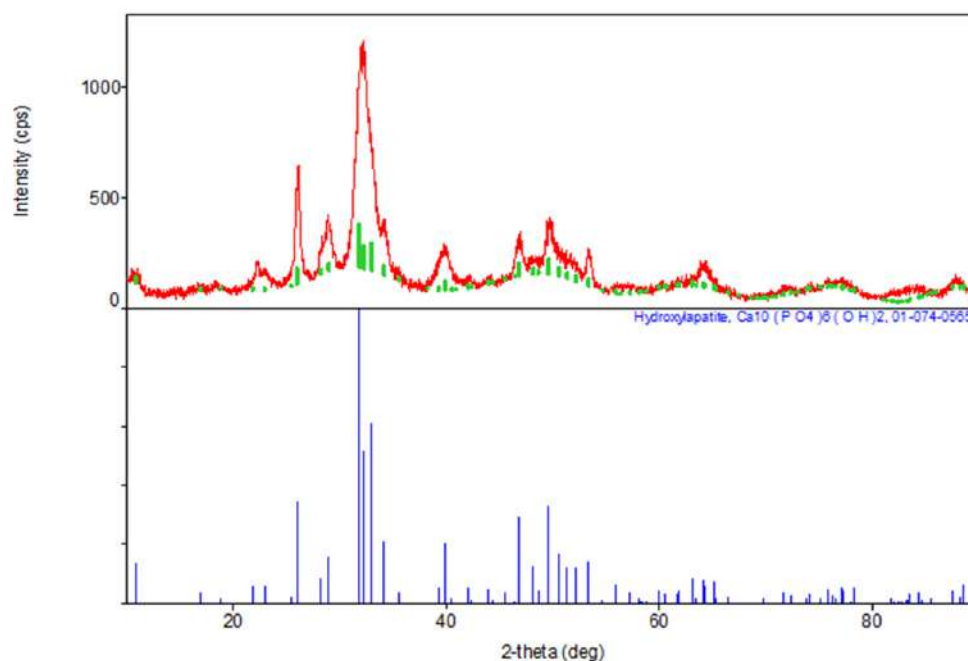


Figure 2. Diffractogram of synthesized stoichiometric **HA**, red color—obtained substance, green—standard.

2.3. Synthesis and Separation of **CB**[6], **CB**[7], and **CB**[8]

The synthesis was carried out according to the displayed method (Figure 3) [24,25]. A total of 4.22 g (0.14 mol) of paraformaldehyde and 14 mL of 10 M sulfuric acid were placed in a three-neck flask equipped with a magnetic stirrer and a reverse refrigerator, and mixed until the paraform was completely dissolved. Then, 10 g (0.07 mol) of glycoluril was

gradually added to the flask in small portions in order to avoid premature oligomerization. The reaction mass was thermostated and kept for 24 h at a temperature of 95 °C.

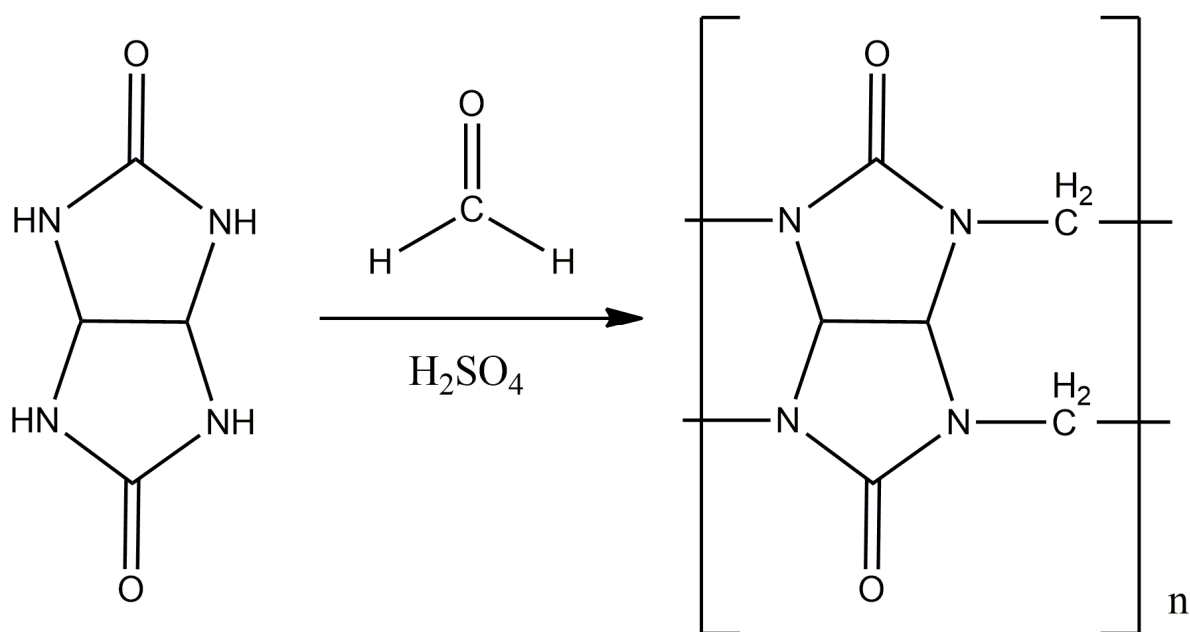


Figure 3. The synthesis scheme of **CB[n]**, where $n = 6, 7, 8$.

The reaction mass was evaporated to dry, and the resulting dry substance was ground to a powder, which was then dissolved in 150–200 mL of water and kept for a day with constant stirring. The solution was filtered to obtain masterbatch solution No. 1, and the precipitate was again placed in 150–200 mL of water and kept for a day at a temperature of 40 °C with constant stirring, after which it was filtered again to obtain masterbatch solution No. 2 and precipitate No. 1.

Masterbatch solutions No. 1 and No. 2 were combined and evaporated to 10–15 mL, obtaining solution No. 3.

Separation of CB[7]. A total of 80 mL of methanol was added to solution No. 3 and the mixture was mixed for 24 h, observing precipitation; it was then filtered and placed in a vacuum cabinet for 12 h at a temperature of 60 °C. The resulting powder was studied using NMR and XRD. Next, precipitate No. 1 was dissolved in 15 mL of a 40% formic acid solution, and the undissolved part was filtered out—this is precipitate No. 2, and the masterbatch solution was solution No. 4.

Separation of CB[8]. Precipitate No. 2 was recrystallized from concentrated HCl, and crystalline **CB[8]** was obtained. The structure was confirmed by NMR and XRD methods.

Separation of CB[6]. Solution No. 4 was evaporated to dry, and the precipitate was washed with 20 mL of water and then recrystallized from 8 M HCl to obtain crystalline **CB[6]**.

The structures of the obtained cucurbit[n]urils were proved using rentgenophase analysis by comparing the diffractograms obtained by us with the diffractograms available in the Cambridge Crystallographic Data Center database: **CB[6]** No. 7209204, **CB[7]** No. 1428201, and **CB[8]** No. 883371. The crystalline powders of cucurbituriles were kept in a vacuum drying cabinet at a temperature of 70 °C for 24 h to remove crystallization water and hydrochloric acid. Diffractograms of cucurbit[n]urils are shown in Figures 4–6. The coincidence of the diffractograms obtained by us when compared with known data not only confirms the structures of the obtained cucurbit[n]urils, but also indicates their sufficient division into individual macrocycles for further work with them.

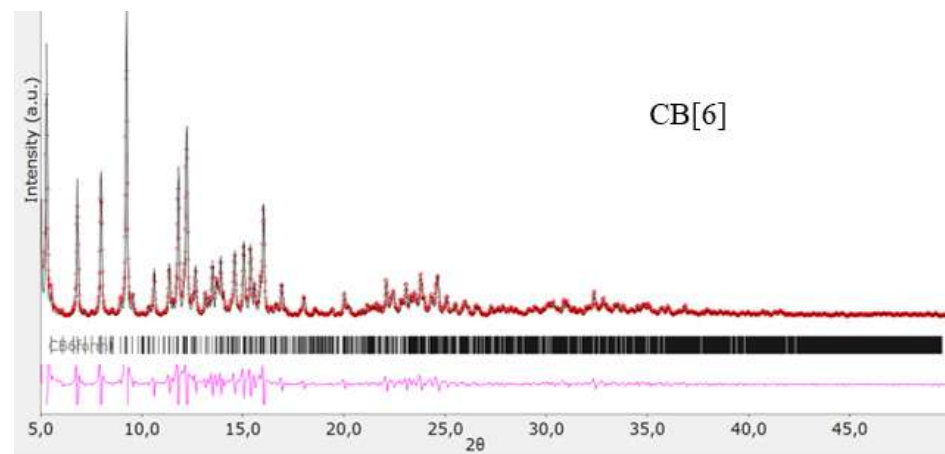


Figure 4. Diffractogram of CB[6], red color—obtained substance, black—standard.

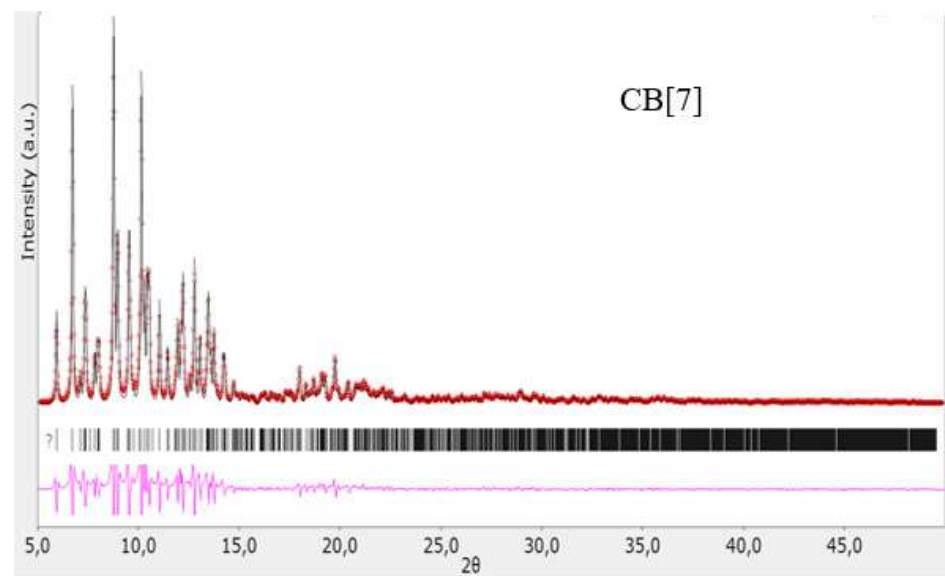


Figure 5. Diffractogram of CB[7], red color—obtained substance, black—standard.

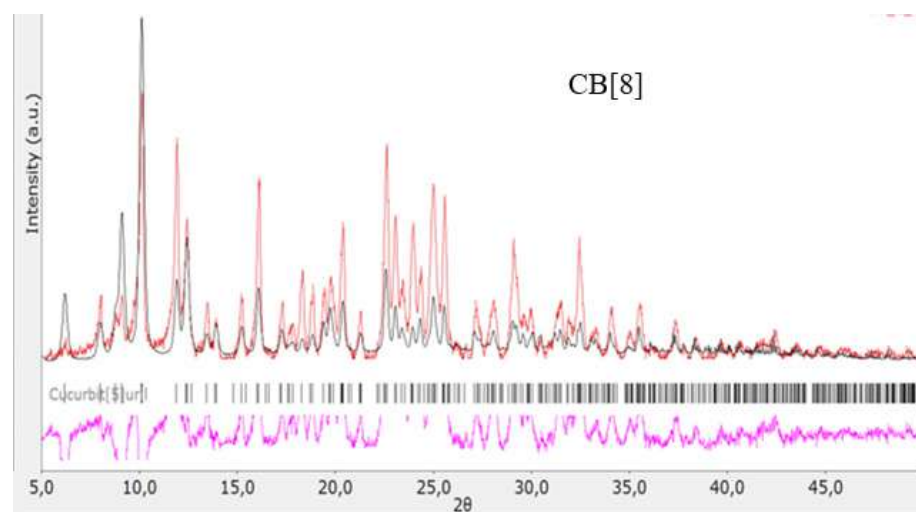


Figure 6. Diffractogram of CB[8], red color—obtained substance, black—standard.

2.4. Applying CB[n] to HA

The method of immersion in solution was used for the application (Figure 7). To implement it, the tablet from HA was immersed in solutions in CB[n] water for 45 min with a concentration of 1 mg/mL. Solutions of CB[6] and CB[8] were dispersed when CB[7] was completely dissolved in water. In parallel, a blank experiment was conducted—with distilled water instead of a solution with a bioactive substance to obtain comparison samples. The obtained samples were dried at room temperature to a constant weight for 24 h.

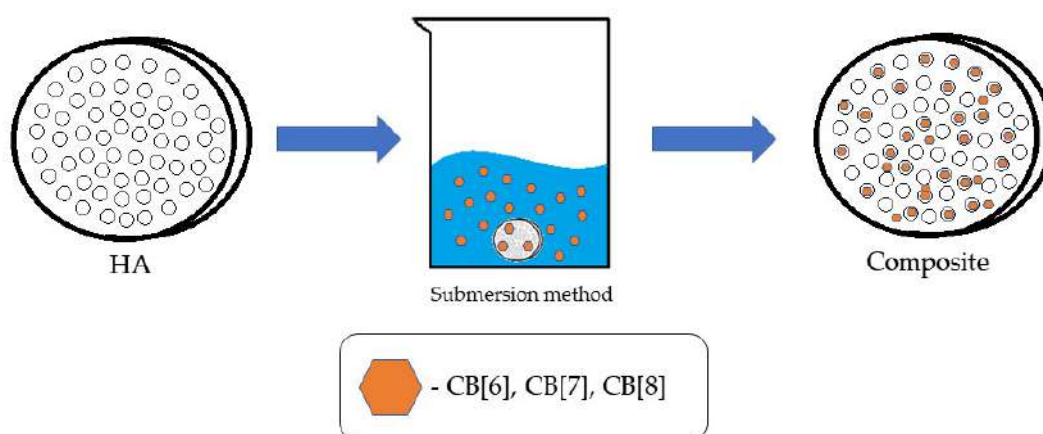


Figure 7. Illustration of the methods of applying CB[n] to HA.

The quantitative deposition of CB[n] was also investigated. To do this, the matrix solution was drained and evaporated. The resulting precipitate was calcined to a constant mass and weighed. The mass of the applied CB[n] ranged from 8 to 10 mg.

2.5. Assessment of Hemocompatibility of Biocomposites

One of the ways to assess overall cytotoxicity is to study hemolytic activity [26].

In this study, samples were used, which are pressed scaffolds made of hydroxyapatite (HA), shaped like a cylinder with a diameter of 20 mm and a height of 2 mm. The samples were pressed hydroxyapatite tablets with cucurbit[n]urils applied (CB[6], CB[7], and CB[8]).

Modification of the surface of the samples submitted for study was the application of CB[n] on them, and this was carried out by immersion in solution. In this case, a 1% solution of CB[n] in distilled water was used. The exposure time in all cases was 40 min. The samples were immersed in a solution in CB[n] followed by air drying at room temperature for 24 h. This method was chosen because of its high efficiency and low labor costs compared to instrumental application methods (using ultrasonic sound, vacuum blowing, or a microwave reactor).

The standard procedure prescribed by ISO 10993-4:2017 was used to assess the hemocompatibility of the samples [27]. To assess the hemocompatibility of the samples, whole hemostated blood from a healthy donor was used. The blood was centrifuged and the erythromass was separated. The resulting erythromass was diluted with a sterile solution of 1×PBS with a temperature of 37 °C in a ratio of 1:9. The samples were placed in a standard 12-well cell culture plate and filled with the resulting blood solution in PBS in a ratio of 1 mL of solution per 1 cm² of the sample surface area. Deionized water was used as a positive control (100% hemolysis), and a solution of 1×PBS (0% hemolysis) was used as a negative control. An unmodified hydroxyapatite was used as a control material. The tablet was then incubated in a thermostat at 37 °C for 60 min. After that, the blood from the wells of the tablet was transferred to centrifuge tubes and centrifuged for 5 min at 3000 rpm to precipitate the remaining red blood cells. Then, the supernatant was carefully removed and transferred to a standard 96-well plate for spectroscopic analysis, and the optical density

was read using a Tecan Infinite F50 IFA reader (Grödig, Austria) at 492 nm. The percentage of hemolysis was the average of three repetitions and was calculated using the following formula [27]:

$$\text{Hemolysis, \%} = \frac{\text{OD}_{\text{test}} - \text{OD}_{\text{control}}^{\text{negative}}}{\text{OD}_{\text{control}}^{\text{positive}} - \text{OD}_{\text{control}}^{\text{negative}}} \times 100\%$$

2.6. Assessment of Cytotoxicity of Biocomposites

To assess the cytotoxicity of the samples *in vitro*, cells of the immune system were used, namely monocytes isolated from the peripheral blood of healthy donors who gave informed consent. Blood sampling was performed by phlebotomy of the cubital vein. Monocytes were isolated from human peripheral blood according to the method proposed by J. Kzhyshkowska and colleagues [28]. The sterilization of biocomposite samples was carried out by ultraviolet irradiation in lime chloride vapor. After that, the samples were placed in the wells of a 12-well tablet and filled with 1 mL of a nutrient cell medium with monocytes with a cell concentration of 1×10^6 in 1 mL. Incubation was carried out at a temperature of 37 °C and 7.5% CO₂ for 144 h.

To study the effect of materials on the viability of mononuclear cells, an Alamar Blue test was used [29]. Assessment of the viability of cells of the immune system was carried out after incubation on the surface of the studied materials. After that, a supernatant was taken from each well, leaving 500 µL of medium with cells in the well. Additionally, 50 µL of Alamar Blue reagent was added to the wells (the volume ratio of Alamar Blue–cell medium was 1/10). Cells with Alamar Blue were incubated for 3 h at a temperature of 37 °C in a dark place. After incubation, a cellular medium with Alamar Blue was introduced into the 96-well plate (3 wells for each sample). The intensity of the fluorescence signal was measured using a Tecan Infinite 200 microrider at a wavelength of 540 nm [29]. Upon entering a living cell, the active component of the rezazurin indicator is converted into resorufin, a substance that has pronounced fluorescence in the red region. Thus, the method allows for a comparative analysis of cell viability and quantification [30].

Cells cultured on a substrate without samples were used as a positive control (CTRL 100%). Samples of unmodified hydroxyapatite (HA) exposed to the same effect as the experimental ones were used as a reference. The percentage of surviving cells was calculated using the following formula:

$$\text{Living cells, \%} = \frac{\text{IF}_{\text{test}} - \text{IF}_{\text{control}}^{\text{negative}}}{\text{IF}_{\text{control}}^{\text{positive}} - \text{IF}_{\text{control}}^{\text{negative}}} \times 100\%$$

where IF is the fluorescence intensity.

2.7. Evaluation of the Proinflammatory Properties of Biocomposites and Their Effect on Monocyte Activation

The effect of the samples on the activation of human peripheral blood monocytes was assessed by enzyme immunoassay (ELISA). Enzyme immunoassay was performed in accordance with the manufacturer's recommendations (Vector-BEST, Novosibirsk, Russia). To do this, a supernatant was selected from each well, leaving 500 µL of medium with cells in the well to assess viability according to the procedure described above. To study the immunomodulatory properties, the supernatants were stored at minus 80 °C.

2.8. Statistical Analysis

Statistical analysis was performed using STATISTICA 8.0 for Windows (STATISTICA, RRID: SCR_014213, Tibco, Palo Alto, CA, USA). The Mann–Whitney test and *t*-test for independent groups were implemented. The data were checked for normality of distribution using the Shapiro–Wilk statistical criterion. Results were considered to be significant with *** $p < 0.001$, ** $p < 0.01$, and * $p < 0.05$.

3. Results and Discussion

In this study, we explored the impact of macrocyclic compounds, specifically **CB[n]**, on the biocompatibility of hydroxyapatite (**HA**), with the aim of developing a matrix for promising biocomposite materials suitable for medical applications. The materials obtained were subjected to thorough characterization using infrared (IR) spectroscopy, scanning electron microscopy (SEM), and energy-dispersive X-ray fluorescence spectroscopy (EDS).

When analyzing the IR spectrum of the **CB[6] + HA** composite obtained through immersion (as shown in Figure 8), characteristic absorption bands of **CB[6]** are observed. Specifically, peaks at 1731 cm^{-1} are evident, corresponding to the valence vibration of carbonyl groups ($\text{C}=\text{O}$) present in the glycoluril linkage of **CB[6]**. In the IR spectrum, deformation vibrations of the CH_2 groups are detected in the range of $1200\text{--}1500\text{ cm}^{-1}$, along with vibrations of the OH groups at $3400\text{--}3500\text{ cm}^{-1}$. These OH vibrations correspond to both water molecules and hydroxyl groups of **HA**. The concurrent presence of these characteristic vibrations confirms the incorporation of **CB[6]** into the composition of the **HA + CB[6]** composite.

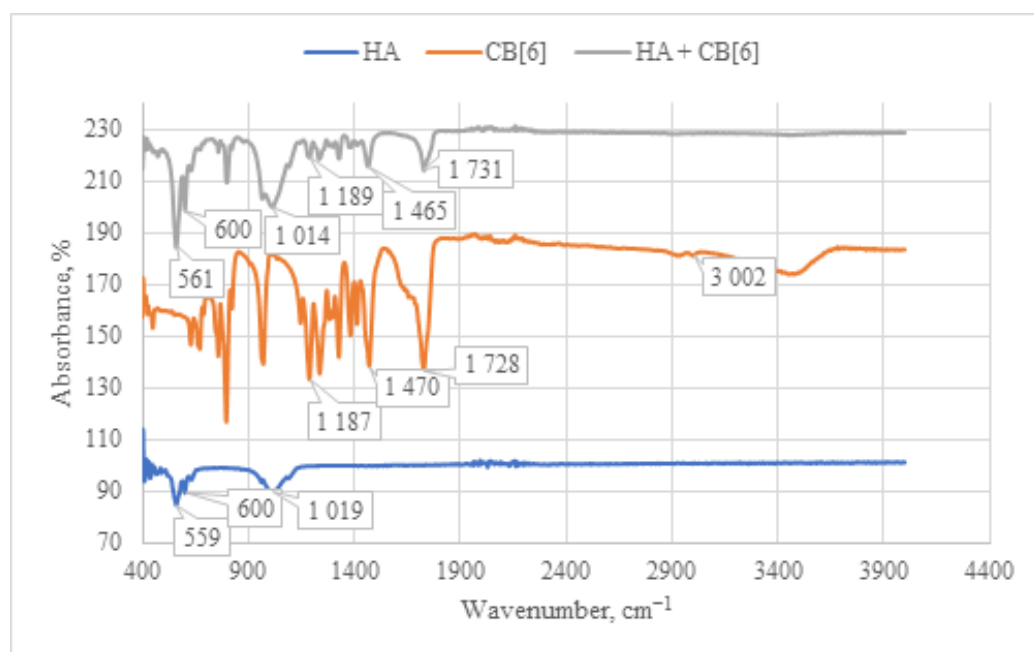


Figure 8. Comparative IR spectrum of the sample **HA + CB[6]** (gray line), **HA** (blue line), and **CB[6]** (orange line).

The IR spectrum of the **HA + CB[7]** sample exhibits a similar pattern to that of **HA + CB[6]** (as depicted in Figure 9), albeit with significantly lower signal intensity. This reduced intensity can be attributed to the high solubility of **CB[7]** in water. Consequently, the lower quantity of **CB[7]** on the surface leads to diminished signal intensity in the IR spectrum. This observation is further supported by SEM and EDS analyses, as depicted in Figures 12 and 13, which confirm the lower presence of **CB[7]** on the surface compared to **CB[6]**. Moreover, a notable shift of the carbonyl group $\text{C}=\text{O}$ signal is observed in the **HA + CB[7]** sample, amounting to 7 cm^{-1} towards the long-wavelength region. In contrast, the shift observed in **HA + CB[6]** (as depicted in Figure 8) is only 3 cm^{-1} . This discrepancy suggests a subtle interaction between **CB[7]** and the **HA** surface.

Upon examination of the IR spectrum of the **HA + CB[8]** sample (Figure 10), a pattern analogous to **HA + CB[6]** is observed. All characteristic absorption bands for **CB[8]** are present, including the $\text{C}=\text{O}$ signal at 1720 cm^{-1} , along with deformation vibrations of CH_2 groups within the $1200\text{--}1500\text{ cm}^{-1}$ range. Taken together, these observations affirm the presence of **CB[8]** in each of the samples.

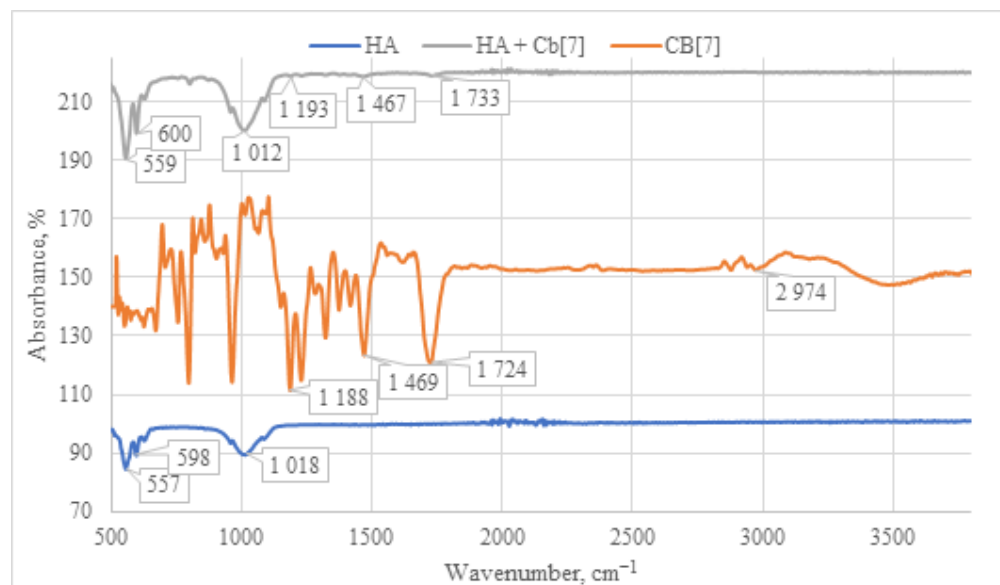


Figure 9. Comparative IR spectrum of the sample **HA + CB[7]** (gray line), **HA** (blue line), and **CB[7]** (orange line).

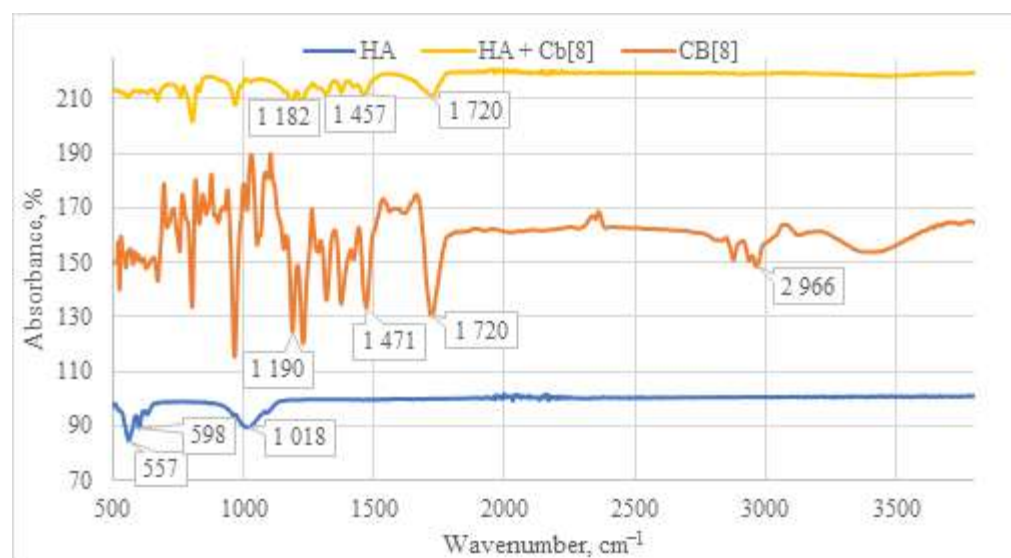


Figure 10. Comparative IR spectrum of the sample **HA + CB[8]** (yellow line), **HA** (blue line), and **CB[8]** (orange line).

Furthermore, SEM analysis was conducted to characterize the obtained composites. On the surface of the **HA** in the **CB[6] + HA** sample, distinct **CB[6]** particles are prominently observed (Figure 11A), ranging in size from 10 microns to 700 nm. These **CB[6]** particles are highlighted within the red square in the image.

Upon closer scrutiny, ensembles of **CB[6]** molecules are distinctly observed (Figure 11B), aligning with the dimensions of the pores. These ensembles exhibit diameters reaching up to 700 nm, as indicated by the red square in the image. The formation of such ensembles can be attributed to the propensity of **CB[6]** to form dispersed solutions in water. The diameter of certain **CB[6]** particles (highlighted by the red square) exceeds the pore size of the hydroxyapatite (**HA**) carrier, leading to overlapping pores where the **CB[6]** macrocycles remain on the surface. This uneven distribution across the surface arises from the partial solubility of **CB[6]**, causing some particles to penetrate into the surface. This penetration is confirmed by infrared spectroscopy of the scaffold chip.

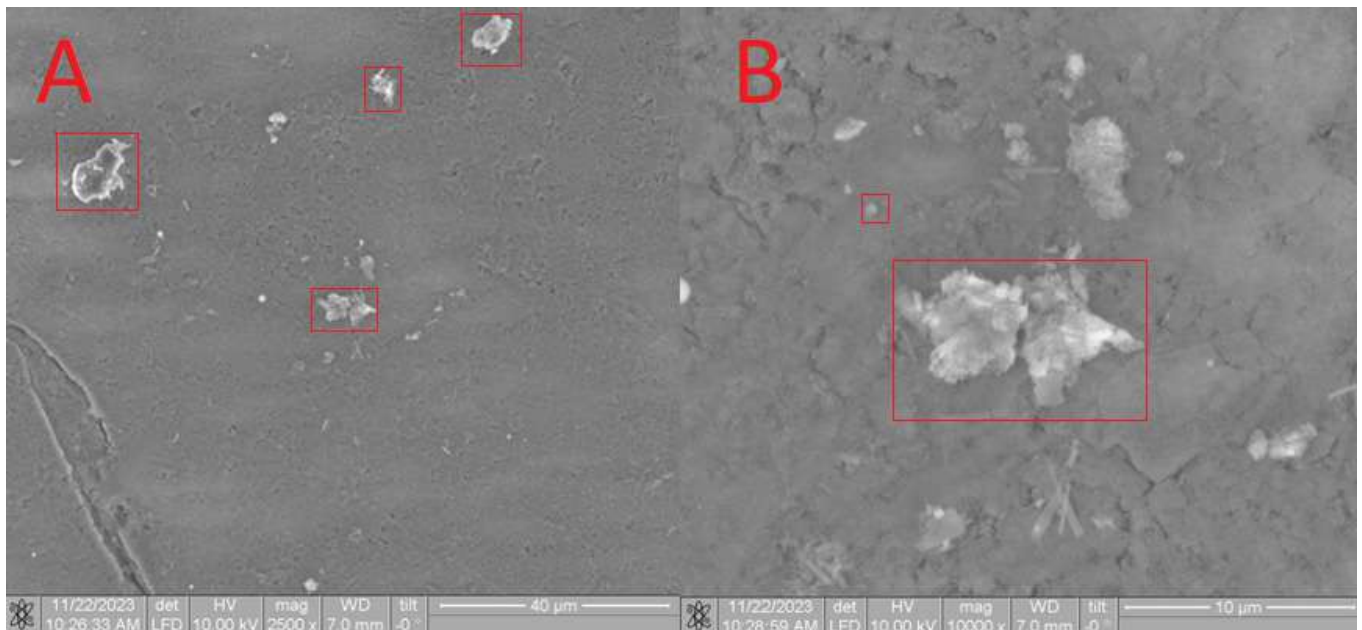


Figure 11. SEM image of the CB[6] + HA sample, approximating 40 microns (A) and 5 microns (B).

The composition was further validated using energy-dispersive X-ray fluorescence spectroscopy (EDS). As illustrated in Figure 12, aside from the predominant elements of hydroxyapatite (P and O), the presence of N and C atoms is evident. This observation confirms that the substance on the surface possesses an organic nature and is distinct from the carrier material.

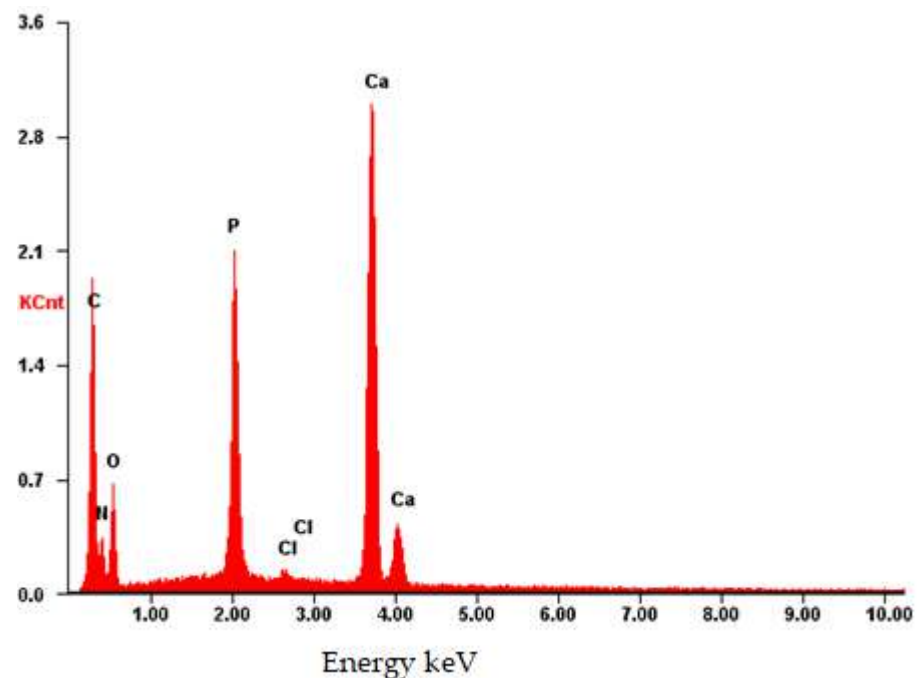


Figure 12. EDS of the CB[6] + HA sample.

Upon analysis of the CB[7] + HA sample (Figure 13), a distinct pattern is observed, which correlates with the complete dissolution of CB[7] in water. Consequently, during drying, only small particles ranging from 100 to 500 microns were formed on the surface. The presence of CB[7] is further evidenced by the observed increase in biocompatibility (as depicted in Figures 17–20). In its dissolved state, CB[7] can penetrate more effectively into

the material, facilitating slower release from the material's pores and, therefore, prolonging its action.



Figure 13. SEM image of the **CB[7] + HA** sample, approximating 200 microns (**A**) and 5 microns (**B**).

The EDS spectrum exhibits robust signals corresponding to Ca, P, and O, consistent with the predominant elements of hydroxyapatite. Despite the dominance of these elements, the spectrum also detects the presence of N and C atoms, although their signals may be less prominent due to overlapping with the signals from Ca, P, and O. Nonetheless, the detection of N and C atoms confirms their presence on the surface, as depicted in Figure 14.

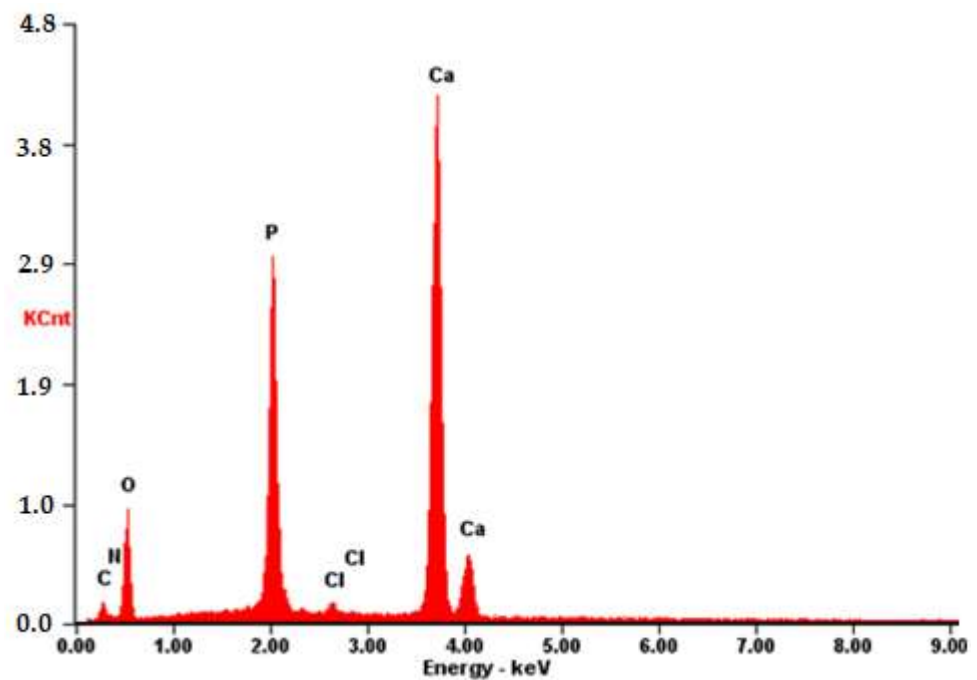


Figure 14. EDS of the **CB[7] + HA** sample.

Upon examination of the **CB[8] + HA** sample, a distinct observation is made. **CB[8]** disperses easily in an aqueous solution and is applied to the surface more uniformly

(as shown in Figure 15), forming larger conglomerates of molecules ranging from 7 to 20 microns in size. This characteristic enables an increase in the effective surface area of the material, thereby enhancing the overall efficiency of the material.

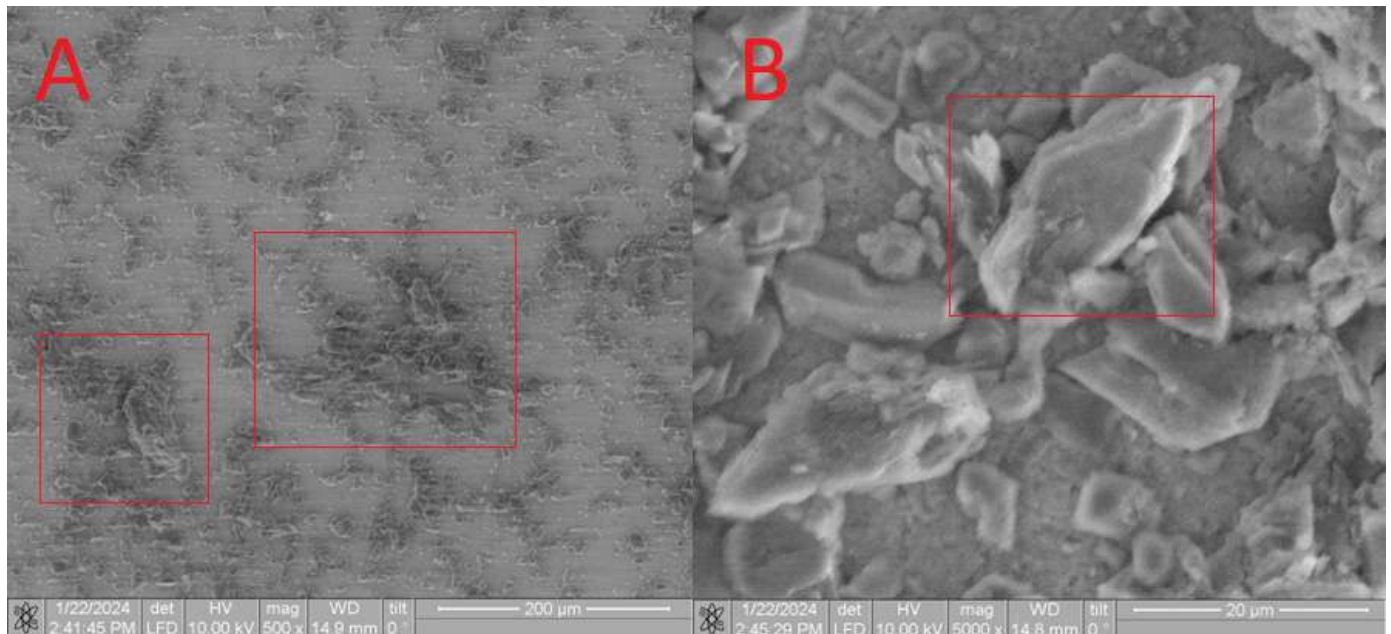


Figure 15. SEM image of the **CB[8] + HA** sample, approximating 200 microns (A) and 20 microns (B).

The EDS spectrum of the **CB[8] + HA** sample (Figure 16) exhibits prominent signals associated with the surface composition of HA, including Ca, P, and O. Furthermore, the presence of large conglomerates of **CB[8]** molecules is evident from clear signals of N and C atoms. These findings corroborate the earlier results obtained from Figures 8–10, confirming the successful incorporation of **CB[8]** into the composite material.

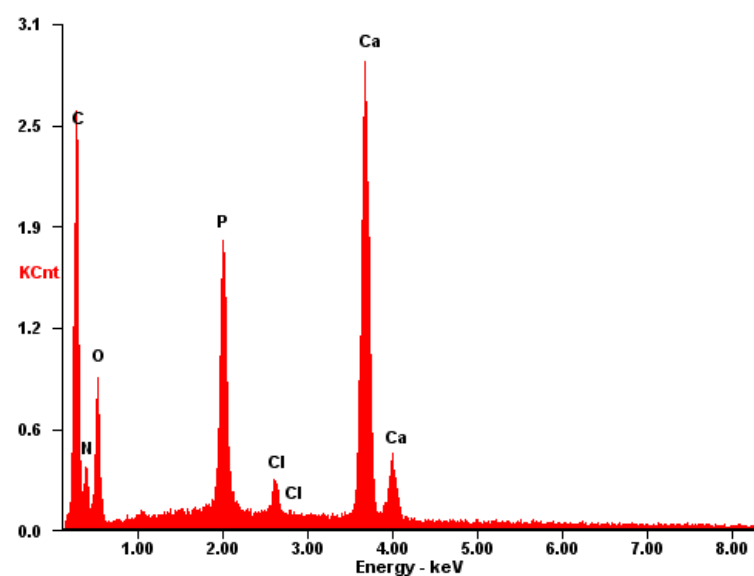


Figure 16. EDS of the **CB[8] + HA** sample.

In the subsequent phase of our investigation, we delved into the biological properties of the synthesized composites. The data presented in Table 2 indicate that all the tested samples of biocomposite materials exhibited hemolytic activity, a finding supported by statistical analysis ($p < 0.01$). Notably, both the modified **CB[n]** samples and their unmodified

counterparts displayed hemolytic activity. The investigation revealed that the hemolytic activity of the **HA + CB[6]**, **HA + CB[7]**, and **HA + CB[8]** samples falls below 5%, aligning with the requirements for medical materials [27]. Furthermore, statistical analysis indicated that the hemolytic activity of these samples did not significantly differ from that of unmodified hydroxyapatite (**HA**) ($p > 0.05$). Notably, the **HA + CB[8]** (HCl) samples displayed the highest level of hemolytic activity among the groups tested in Table 2, likely due to their lack of specific purification from HCl. This discrepancy can be attributed to the presence of hydrochloric acid, an impurity in the synthesis medium for the entire **CB[n]** series, when the feedstock is inadequately purified. Hydrochloric acid can significantly increase the hemolytic effect and pose considerable harm to the body. Therefore, in material preparation, it is crucial to minimize harmful impurities. A comparison between the purified sample (**HA + CB[8]**) and the untreated sample reveals a notable difference in hemolytic effect, aligning with the broader trends observed across the **CB[n]** series.

Table 2. The level of hemocompatibility of biocomposite samples.

No.	Sample	% of Hemolysis
1	HA + CB[6]	1.8665 ± 0.0008 *
2	HA + CB[7]	2.0138 ± 0.0019 *
3	HA + CB[8]	1.7611 ± 0.0050 *
4	HA	1.6004 ± 0.0018 *
5	HA + CB[8] (HCl)	44.1611 ± 0.0050 **
6	CTRL (Blood + PBS)	00
7	CTRL (Blood + H ₂ O)	100

Note: **HA**—hydroxyapatite; **CB[6]**—cucurbit[6]uril; **CB[7]**—cucurbit[7]uril; **CB[8]**—cucurbit[8]uril. *—the level of hemolysis is statistically significantly different from the negative control ($p < 0.01$). **—the level of hemolysis is statistically significantly different from the negative control ($p < 0.001$).

As per literature data, plasma proteins exhibit a propensity to adsorb onto any abiotic surface, with the composition of the adsorbed protein layer being notably influenced by surface charge and potential disparities. Specifically, if there is a positive potential difference between the medical material and the blood, the risk of thrombosis may increase [6]. It is hypothesized that the treatment methods employed for hydroxyapatite in this study may lead to a reduction in the positive potential difference between the sample surface and blood, consequently resulting in a decrease in hemolysis. Conversely, immersion-based treatment may not significantly mitigate the positive potential difference, potentially contributing to hemolysis.

The hemolytic activity of unmodified hydroxyapatite (**HA**) in relation to cucurbit[n]urils may also be influenced by its porosity. Functionalization of hydroxyapatite with various substances can lead to a reduction in porosity. According to the contemporary literature, the manifestation of hemolysis on inert material surfaces is intricately associated with the adsorption of plasma proteins, particularly fibrinogen, onto the material's surface in direct interaction with blood. Heightened levels of plasma protein adsorption are commonly correlated with increased hemolytic activity [31,32]. Hydroxyapatite is characterized by its porous nature with relatively small pore sizes, typically smaller than the size of protein molecules. Consequently, the adsorption of plasma proteins onto hydroxyapatite is considered to be insignificant [31]. It is reasonable to assume that this factor contributes to the low level of hemolysis observed in samples of unmodified hydroxyapatite (**HA**).

According to the literature findings, **CB[n]** without a carrier exhibits low toxicity towards various cell types [33]. Research has shown that **CB[n]** does not induce hemolysis, even at high concentrations (1 mM), under PBS conditions. Nevertheless, investigations have unveiled that **CB[n]** exhibits the capacity to elevate the level of early apoptosis, which is associated with the presence of phosphatidylserine on the cell surface. Remarkably, even under these conditions, the integrity of the cell membrane remained unaffected. Addition-

ally, **CB[7]** has been observed to induce hemolysis in the presence of albumin, albeit not under PBS conditions, except for **CB[7]** at a concentration of 2 mM. It is worth noting that **CB[7]**, along with other homologs (excluding **CB[5]** and **CB[6]**), have the capability to bind cholesterol molecules. Thus, the hemolytic impact induced by cucurbiturils may mirror the effects observed with cyclodextrins [34].

Hemolysis in the presence of albumin medium is primarily attributed to the indirect interaction of **CB[n]** with the components of the medium rather than the direct toxic effect of cucurbiturils themselves. It is established that **CB[7]** has the capability to form complexes with amino acids, peptides, and proteins [35]. However, due to its lower solubility, **CB[8]** was employed in lower concentrations compared to **CB[7]**. Hence, **CB[7]** at the employed concentration may interact with amino acid residues within albumin. Presumably, this interaction facilitates the delivery of **CB[7]** to red blood cells, resulting in cellular demise. The heightened hemolytic activity observed in the presence of **CB[7]** necessitates further exploration. Notably, this effect was not apparent in serum containing equivalent albumin concentrations, suggesting that a similar outcome may only manifest in experimental *in vitro* setups.

It is noteworthy that previous research [36] utilized **CB[n]** concentrations ranging from 2 to 0.01 mM, revealing **CB[n]** to be well-tolerated by cells at concentrations up to 0.3 mM. Concentrations exceeding 0.3 mM may not be required for drug delivery systems. The absence of such an effect in **CB[6]** is likely attributable to its smaller cavity size and distinctive chemical and biological properties, enabling effective binding to biologically active molecules within the experimental milieu. Therefore, the cucurbiturils examined in our study do not directly harm cells but have the potential to influence components of the cellular microenvironment [36].

It is imperative to emphasize the persistent challenge of undesired blood clot formation upon contact with implantable materials and devices, which remains unresolved. This issue arises due to the presence of protective mechanisms within a healthy vascular endothelium that resist thrombosis, mechanisms which are lacking in foreign materials introduced into the body. Instead, biomaterials often promote blood coagulation through the activation of a series of interconnected processes, including protein adsorption, platelet and leukocyte adhesion, thrombin production, and complement activation [36]. Therefore, the quest for methods that do not elevate the percentage of hemolysis in the functionalization of biocompatible materials is particularly pertinent.

3.1. Assessment of Cytotoxicity of Biocomposites

Based on the results of the hemocompatibility study, the cytotoxicity of several biocomposite materials (**HA + CB[6]**; **HA + CB[7]**; and **HA + CB[8]**) for immune system cells was investigated (Figure 17).

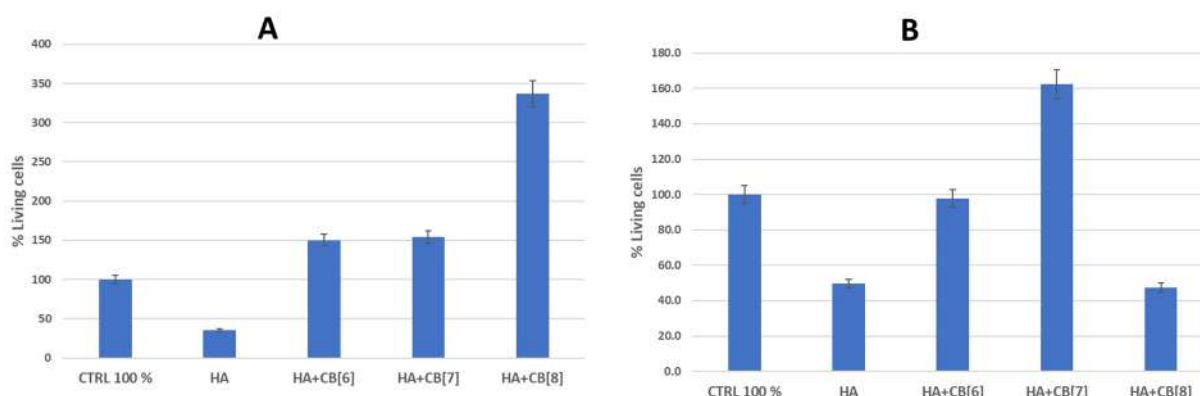


Figure 17. The effect of biocomposites on the viability of cells of the immune system. (A) is donor 1; (B) is donor 2. **HA**—hydroxyapatite; **CB[6]**—cucurbit[6]uril; **CB[7]**—cucurbit[7]uril; **CB[8]**—cucurbit[8]uril.

As follows from the data in Figure 16, the sample of unmodified hydroxyapatite (HA) had a toxic effect on the cells of the immune system of both donors. Perhaps this is a consequence of the insignificant background cytotoxicity of hydroxyapatite, which was confirmed as a result of experiments on the study of hemocompatibility of samples [31,37]. This observation could be attributed to the high surface energy of HA. Although pure HA exhibits notable cytotoxic properties, the inclusion of cucurbit[n]urils can notably decrease surface energy, enhancing cell viability, and consequently improving biocompatibility.

The HA + CB[6] sample, on the contrary, augmented the survival of immune system cells by 50.4% in donor 1 and showed a marginal decrease of 2.2% in donor 2 compared to the positive control. HA + CB[7] enhanced the survival rate of immune system cells by 54.0% in donor 1 and by 62.3% in donor 2. Meanwhile, HA + CB[8] elevated the number of cells surviving after incubation by 236.8% in donor 1, yet conversely decreased the number of cells by 52.5% in donor 2 compared to the positive control.

Based on the data obtained, all the examined samples of biocompositional materials (HA + CB[6], HA + CB[7], and HA + CB[8]) demonstrated high biocompatibility with both erythrocytes and mononuclear cells.

It is evident that the functionalization of hydroxyapatite with macrocyclic nitrogen-containing substances of the CB[n] family decreases its sorption capacity and the affinity of plasma proteins to the material's surface. Consequently, this leads to an enhancement in biocompatibility [31]. Discrepancies in the survival rates of cells obtained from various donors after incubation with the tested materials could stem from differing levels of immune reactivity.

3.2. Evaluation of the Proinflammatory Properties of Biocomposites and Their Effect on Monocyte Activation

The selection of key macrophage cytokines TNF- α , IL-1 β , IL-6, and IL-10 as the main parameters for studying immunomodulatory properties aligns with the model system employed in the study. Since the biological activity of cytokines primarily depends on their concentration in the extracellular medium rather than the level of gene expression, enzyme immunoassay was employed as the primary method to determine the effect of scaffolds on cytokine production.

Tumor necrosis factor (TNF, TNF- α) (Figure 18) is an extracellular protein, serving as a multifunctional proinflammatory cytokine primarily synthesized by monocytes and macrophages. TNF plays a crucial role as the main mediator of inflammation and serves as an important regulator of the immune response in reaction to infection and tumor development. Beyond its inflammatory functions, TNF- α also impacts lipid metabolism, coagulation, insulin resistance, and endothelial function. Furthermore, TNF- α stimulates the production of other cytokines, such as IL-1, IL-6, IL-8, and interferon-gamma, and activates leukocytes, contributing significantly to defense against intracellular parasites and viruses.

Interleukin 1 beta (IL-1 β) (Figure 19) is a cytokine known for regulating the progression of inflammatory reactions. Its biological role encompasses various effects, including immunomodulatory, hematopoietic, inflammatory, and intersystem functions. IL-1 β plays a critical role in initiating the early stages of the immune response, involving specific T-lymphocytes, particularly T-helper cells, in the process. Indeed, interleukin 1 beta (IL-1 β) plays a pivotal role in various immune processes. It promotes the differentiation of B lymphocytes into plasma cells, expediting antibody production. IL-1 β is among the earliest responders in the body's defense against pathogens, activating and regulating inflammatory and immune responses. It activates neutrophils and T and B lymphocytes, and also enhances the synthesis of acute phase proteins. Additionally, IL-1 β boosts phagocytosis, hematopoiesis, and vascular permeability, and exhibits cytotoxic and bactericidal activities. The inflammatory function of IL-1 β is absolutely significant. It amplifies the motility of neutrophils, augments cellular activity within inflammatory sites, and enhances the activity of other cytokines [38,39], contributing to the overall inflammatory response.

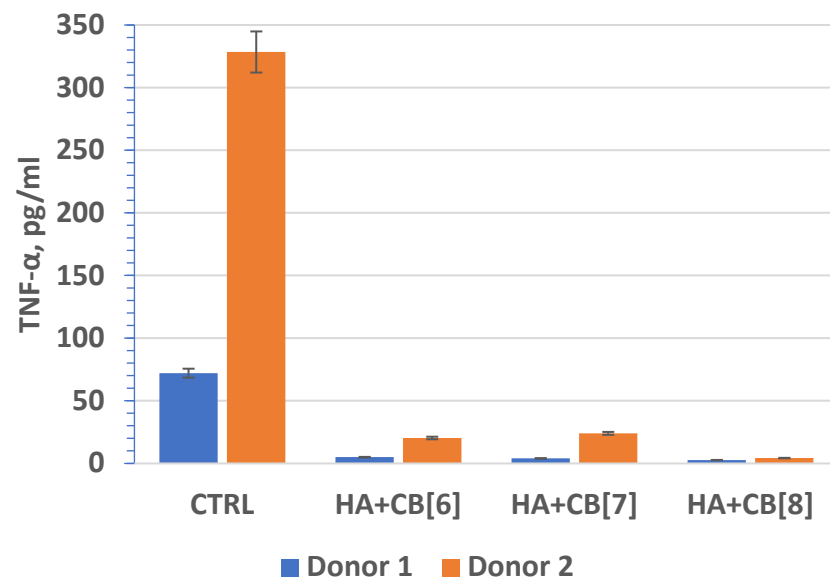


Figure 18. The effect of biocomposite samples on TNF- α production by primary human monocytic macrophages.

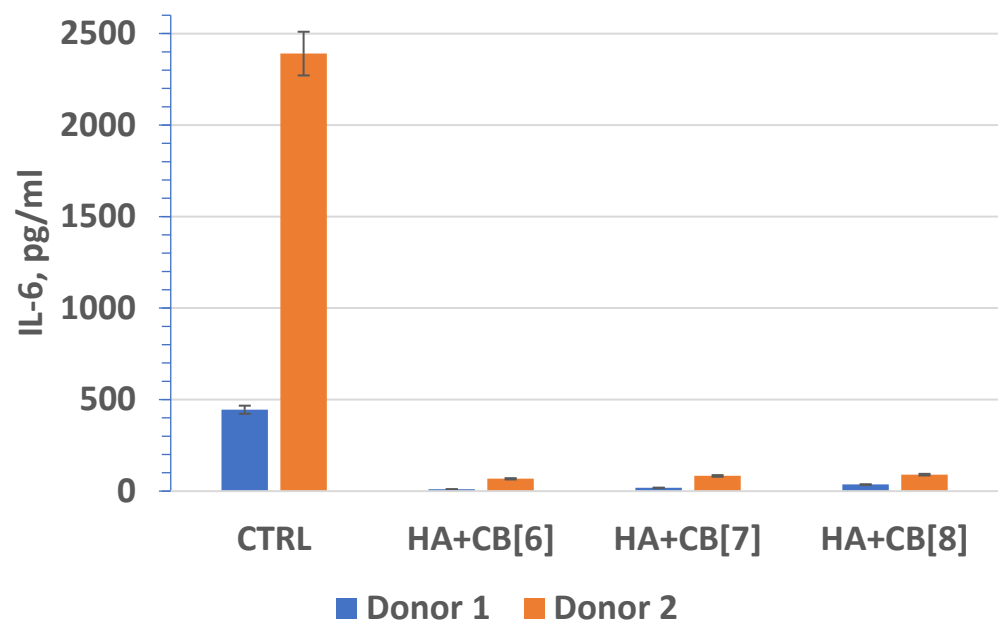


Figure 19. The effect of biocomposite samples on the production of IL-1 β by primary human monocytic macrophages.

In fact, interleukin-6 (IL-6) (Figure 20) plays a crucial role as a multifunctional cytokine. It participates in the differentiation of activated B lymphocytes into plasma cells that secrete immunoglobulins, and it regulates the acute phase response. Elevated levels of IL-6 have been observed in numerous inflammatory conditions, often correlating with laboratory markers of inflammatory activity [40].

Interleukin-10 (IL-10) is a vital cytokine with unique properties. It belongs to Class 2 cytokines and exhibits powerful anti-inflammatory effects by suppressing the production of proinflammatory cytokines, such as IFN γ , tumor necrosis factor α (TNF α), IL-1 β , and IL-6, in various cell types. Additionally, IL-10 hinders the maturation of dendritic cells, partly by suppressing IL-12 expression [41]. Absolutely, interleukin-10 (IL-10) demonstrates a multifaceted role in immune regulation. In addition to its anti-inflammatory properties, IL-10 also exhibits immunostimulatory effects. It can stimulate the production of IFN γ

in CD8⁺ T cells that are activated by anti-CD3/anti-CD28 or other cytokine cocktails. Moreover, IL-10 serves as a potent growth and differentiation factor for various immune cells, including B cells, mast cells, and thymocytes [42].

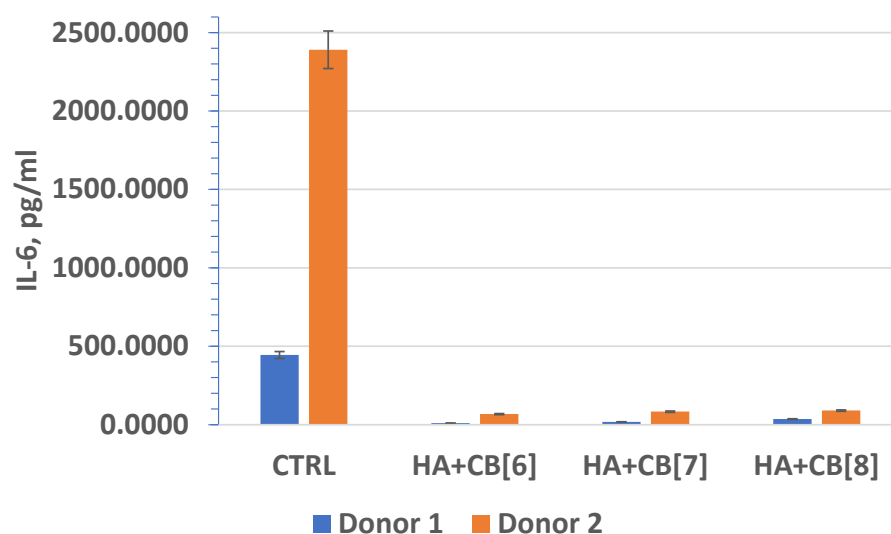


Figure 20. The effect of biocomposite samples on the production of IL-6 by primary human monocytic macrophages.

In fact, these findings are significant as they suggest that the biocomposites (**HA + CB[6]**, **HA + CB[7]**, and **HA + CB[8]**) have the potential to be used in biomedical applications without inducing or exacerbating inflammatory responses. This is essential for ensuring the safety and efficacy of such materials in various medical contexts, ranging from tissue engineering to drug delivery systems. The lack of stimulation of proinflammatory cytokine expression indicates the promising biocompatibility properties of these materials, which is crucial for their successful translation into clinical use. The finding that the concentration of IL-10 exceeded the lower limit of sensitivity of the analysis suggests that the materials studied may have induced an anti-inflammatory response. This is promising, as it indicates that the biocomposites (**HA + CB[6]**, **HA + CB[7]**, and **HA + CB[8]**) could potentially modulate the immune response towards an anti-inflammatory phenotype.

The absence of significant differences in the level of cytokine expression among the different materials suggests that they do not induce inflammation or provoke an immune response, at least under the experimental conditions tested. However, individual differences in immune reactivity may influence cytokine expression levels, highlighting the importance of considering patient-specific factors in the evaluation of biocompatibility and immunomodulatory effects of biomaterials.

4. Conclusions

The study's findings highlight the potential of using conglomerate ensembles of **CB[n]** molecules to enhance the biocompatibility of materials, particularly when deposited on porous substrates, like **HA**. **HA**, known for its biocompatibility and porosity, serves as an excellent matrix for such modifications. By depositing nitrogen-containing macrocyclic cavitands, such as **CB[6]**, **CB[7]**, and **CB[8]**, onto the surface of porous materials, like **HA**, it becomes feasible to create promising biomaterials conducive to osteogenesis while enabling controlled release of biologically active substances, including antibacterial drugs and other therapeutic agents.

The study has successfully developed a novel method for functionalizing the surface of hydroxyapatite using macromolecular nitrogen-containing heterocycles, specifically **CB[6]**, **CB[7]**, and **CB[8]**. In vitro assessments have demonstrated the high biocompatibility and low toxicity of the resulting biocomposite materials. These innovative biocomposites

hold promising potential for finely modulating biological responses, facilitated by the incorporation of HA + CB[6], HA + CB[7], and HA + CB[8] on specialized media. Further research will delve into exploring and harnessing the full capabilities of these materials in various biomedical applications.

The comprehensive studies conducted on materials based on macrocyclic compounds, including CB[n] and Bu[6], have revealed a plethora of potential applications for these materials. Their unique ability to serve as containers for medicinal or biologically active substances presents an urgent and promising avenue for further exploration. Leveraging the properties of CB[n] and Bu[6] to encapsulate therapeutic agents opens up exciting possibilities in drug delivery systems and other biomedical applications. This research paves the way for advancements that could significantly impact various fields, including medicine and biotechnology.

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The role of methods for applying cucurbit[6]uril to hy-droxy-apatite for the morphological tuning of its surface in the process of obtaining composite materials

Аңдатпа

Бұл зерттеу өте перспективалы макроциклді қосылыстар болып табылатын кукурбит[n]урил көмегімен беттік модификациялау арқылы кеуекті гидроксиапатиттен алынған композициялық материалдарды синтездеуге бағытталған композиттік материалдар инженериясы саласындағы жетістіктерді білдіреді. Беттік модификациялау процедурасы әртүрлі бетті модификациялау әдістерін қолдана отырып, су ортасындағы бетке кукурбит[6]урил гидроксиапатитін қолдануды қамтиды. Алынған материалдар инфрақызыл (ИК) спектроскопия және сканерлеуші электронды микроскопия (SEM) сияқты аналитикалық әдістерді қолдану арқылы зерттелді және сипатталды. Гидроксиапатит бетіне СВ[6] қолданудың ұсынылған әдістері соңғысына биологиялық әртүрлілікті береді және жаңа функционалды композициялық материалдарды құру кезінде, оның ішінде СВ[n] отбасына негізделген супрамолекулалық жүйелерді қолдану кезінде дене ортасына жақындығын қамтамасыз етеді.

Түйін сөздер: кукурбит[n]урил, гидроксиапатит, функционалдық материалдар, композиттік материалдар.

Article

The Role of Methods for Applying Cucurbit[6]uril to Hydroxyapatite for the Morphological Tuning of Its Surface in the Process of Obtaining Composite Materials

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Abstract: In this work, composite materials were obtained for the first time using various methods and the dependences of the resulting surface morphologies were investigated. This involves modifying the surface with cucurbit[n]urils, which are highly promising macrocyclic compounds. The process includes applying cucurbit[6]uril to the hydroxyapatite surface in water using different modification techniques. The first method involved precipitating a dispersion of **CB[6]** in undissolved form in water. The second method involved using fully dissolved **CB[6]** in deionized water, after which the composite materials were dried to constant weight. The third method involved several steps: first, **CB[6]** was dissolved in deionized water, then, upon heating, a dispersion of **CB[6]** was formed on the surface of **HA**. The fourth method involved using ultrasonic treatment. All four methods yielded materials with different surface morphologies, which were studied and characterized using techniques such as infrared (IR) spectroscopy and scanning electron microscopy (SEM). Based on these results, it is possible to vary the properties and surface morphology of the obtained materials. Depending on the method of applying **CB[6]** to the surface and inside the **HA** scaffold, it is possible to adjust the composition and structure of the target composite materials. The methods for applying **CB[6]** to the hydroxyapatite surface enhance its versatility and compatibility with the body's environment, which is crucial for developing new functional composite materials. This includes leveraging supramolecular systems based on the **CB[n]** family. The obtained results can be used to model the processes of obtaining biocomposite materials, as well as to predict the properties of future materials with biological activity.

Keywords: cucurbit[n]urils; hydroxyapatite; functional materials; composite materials

1. Introduction

In today's era of personalized medicine, there is a pressing demand to develop new implant materials that possess specific attributes. For these materials to be effectively used in medical applications, they must exhibit an ideal blend of various properties.

Any bone grafts must have the following properties: be completely biocompatible, porous, serve as a matrix on the surface of which the recipient's cells are fixed (osteocon-

ductivity), gradually resorb and be replaced by newly formed bone (creeping substitution). For successful bone formation, it is also necessary to comply with two important requirements—good vascularization and mechanical stability of the implantation area. Bone grafts are divided into auto-, allo-, xenografts, synthetic and composite materials. In addition, their main characteristics of composite biomaterials include their composition, shape, structure, surface texture and mechanical properties. The decisive factor is their biocompatibility, i.e., they must interact with surrounding tissues without causing adverse reactions or inflammation. Additionally, it is advantageous if these materials encourage the growth of blood vessels or bone around them, aiding in the healing and repair of damaged tissue.

For implants or wound healing materials, these properties collectively influence how well the material interacts with surrounding tissues. Bioactive materials, in particular, can promote the growth of new tissues and expedite the healing process. Therefore, advancing these materials is crucial for enhancing the quality of medical care and improving treatment outcomes [1]. The effectiveness of personalized medicine heavily relies on advancements in developing new implant materials that possess all the essential characteristics for safe and efficient interaction with biological tissues. Innovations in this field are paving the way for better treatments for a range of diseases and injuries, offering patients quicker recovery and an enhanced quality of life.

Materials interacting with the internal environment of the body should be as non-toxic as possible for cells and tissues. However, many substances with pronounced antibacterial properties often turn out to be quite toxic, which leads to low biocompatibility. Biocompatibility, which is determined by the nature and degree of interaction of biomaterials with body tissues, is one of the key problems in biomaterial research [2–4]. This covers such processes as immune rejection or inflammatory tissue response to the presence of a foreign body. In this context, all biomedical devices must meet extremely stringent clinical requirements. Before being implanted into the human body, materials undergo meticulous surface modification to enhance their biocompatibility. Developing materials that are both biocompatible and possess specific biological activities is a challenging endeavor.

Furthermore, current clinical treatments often depend on oral or intravenous drug administration. This method results in high drug levels in the blood immediately after dosing, but the concentration rapidly drops below the therapeutic window. This fluctuation can lead to drug concentrations initially reaching toxic levels and then falling below therapeutic levels, reducing the effectiveness of the therapy.

Furthermore, current clinical treatments often depend on oral or intravenous drug administration. This method results in high drug levels in the blood immediately after dosing, but the concentration rapidly drops below the therapeutic window. This fluctuation can lead to drug concentrations initially reaching toxic levels and then falling below therapeutic levels, reducing the effectiveness of the therapy [5].

Drug-releasing implants have emerged as a promising alternative to traditional oral and intravenous drug administration for various clinical applications. Materials currently used for developing implants with controlled drug release include titanium nanotubes, porous silicon, polymers, and various microtechnologies [6].

Drug-releasing implants offer several unique advantages. They can deliver sustained, remotely controlled, programmable, and localized drug release directly to the target site, enhancing therapy effectiveness and minimizing side effects for patients. These capabilities are challenging to achieve with conventional systemic drug administration [6].

Bioactive materials occupy a special place among implants, as they are able to stimulate the growth of new tissue around them. This ability can significantly improve the healing and recovery processes, which is especially important in medical applications related to the treatment of wounds and injuries. Bioactive materials accelerate tissue regeneration, which makes them indispensable in medical practice.

All characteristics of implant materials that make them biosimilar are crucial for their medical applications. Research and development in this field are continuously advancing,

aiming to discover the best materials that meet all requirements and deliver optimal results for patients. Innovations in the development of these materials could lead to significant improvements in treating various diseases and injuries, offering patients faster and more effective recovery.

Thus, the creation and use of drug-releasing implants open new horizons in medical science and practice. These implants not only enhance the effectiveness of therapy but also significantly improve patients' quality of life by minimizing side effects and providing more precise and targeted treatment [7].

One of the potentially promising materials, in this context, is modified hydroxyapatite (HA) enriched with biologically active compounds. Hydroxyapatite is a key component of bones, comprising approximately 50% of their total mass, and teeth, where its content reaches 96% in enamel. Additionally, HA is the most suitable ceramic material for artificial teeth or bones due to its excellent biocompatibility and bioactivity [8]. This can be either synthetic or natural. In medicine, synthetic HA is used as a filler to repair lost bone tissue and as a coating on implants to promote new bone growth [9]. Pure HA is not found in biological systems, but due to its chemical similarity to bone and tooth minerals, it is commonly used as a coating on orthopedic implants (e.g., hip replacements) and dental implants [8,10–14]. HA bioceramics are also highly popular [15,16]. Due to its close similarity to biological apatite, HA has long been utilized in liquid chromatography for nucleic acids, proteins, and other biological compounds [17,18], as well as for drug delivery purposes [19]. Additionally, HA is included in some toothpaste brands as a mild polishing agent, replacing calcium carbonate [20]. These materials are inert to living tissues and exhibit low toxicity, resulting in a minimal risk of allergic reactions, inflammation, and mutagenic effects. Moreover, modified hydroxyapatites can speed up reparative osteogenesis at the implantation site and enhance the proliferation of osteoblasts [21].

Methods for modifying the surface of porous materials by saturating them with biologically active compounds, including macrocyclic compounds, are becoming increasingly relevant. These methods provide the opportunity to control the release of antibiotics, drugs, biologically active substances and cells. Modified hydroxyapatites have the potential to significantly improve the processes of healing and tissue regeneration, which makes them valuable in medicine [22].

Thus, advancing materials with enhanced biocompatibility and bioactive properties is a crucial challenge in biomaterials science. Ongoing research and development in this area, including innovative approaches to modifying hydroxyapatite and other materials, offer new opportunities to enhance treatment effectiveness and improve patient quality of life [22].

Macrocyclic compounds are often preferred over other drug delivery systems such as dendrimers, liposomes, micelles, carbon nanotubes, hydrogels, and polymers due to their advantages, including increased stability and more controlled drug release rates. [23–25].

Additionally, macrocyclic compounds exhibit high resistance to external factors, enabling them to retain their properties over extended periods. They offer a more predictable and sustained release of active substances, which reduces dosing frequency and enhances therapy effectiveness. The controlled release rate helps maintain optimal drug concentrations in the body, minimizing the risk of side effects and improving treatment outcomes [23–25].

These effective delivery systems for drugs and biologically active substances represent a significant advancement in the development of new approaches in medicine and other scientific and technological fields. They have the potential to greatly enhance patients' quality of life by ensuring more accurate and safe medication administration. Innovations in this area are also paving the way for new treatment possibilities for various diseases, including chronic and hard-to-treat conditions.

Research and development in macrocyclic delivery systems are advancing rapidly, promising even more sophisticated and effective solutions in the future. These advance-

ments have the potential to drive significant breakthroughs in medicine, pharmaceuticals, and related fields, resulting in safer, more effective, and personalized treatments.

For effective modification of the surface of porous materials, suitable starting reagents include nitrogen-containing macrocyclic systems based on glycoluril and its derivatives, such as cucurbit[n]urils and bamboo[n]urils.

Previously, we developed and studied new materials based on the cucurbit[6,7,8]uril family (**CB[6,7,8]**) and hydroxyapatite (**HA**) as a carrier [26]. Our research revealed that these biocomposite materials demonstrated high biocompatibility and low toxicity in vitro [26]. We observed a similar effect when applying bambus[6]uril to the surface of titanium nickelide [27] and **HA** [28].

Thus, the aim of this work is to study various methods for obtaining composite materials based on **CB[6]** and **HA** in order to study and optimize the surface of the composites, as well as to select the optimal conditions for obtaining and potential application of these composites.

2. Materials and Methods

2.1. Instruments for Interpreting Results

2.1.1. Infrared Spectroscopy

The identification and structure study of the obtained samples were carried out by FTIR spectroscopy on a Nicolet 6700 IR spectrometer from Thermo Fisher Scientific (Waltham, MA, USA). The samples were studied by the attenuated total internal reflection method in the spectral range from 400 to 4000 cm^{-1} with a resolution of 4 cm^{-1} . The obtained reflection spectra were converted to absorption spectra using the Kubelka-Munk transformation.

2.1.2. Scanning Electron Microscope (SEM) of **CB[6]** + **HA** Samples

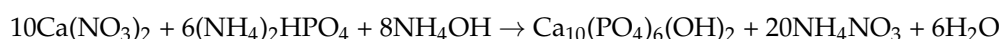
System with electron and focused beams QUANTA 200 3D (FEI, Hillsboro, OR, USA), accelerating voltage: 200–30,000 V continuous, resolution: 3.5 nm at 30 kV in the ESEM mode, <15 nm at 3 kV in the low vacuum mode.

2.1.3. X-ray Diffraction Analysis

The study of **CB[6]** crystalline powders was carried out using X-ray phase analysis. The samples were studied using a device—X-ray diffractometer XRD-7000 (Shimadzu, Kyoto, Japan), anode: Cu, radiation wavelength $\lambda(\text{Cu}) = 1.5406 \text{ \AA}$, measurement range $5\text{--}50^\circ$ in 2θ , measurement speed $30^\circ/\text{min}$. Identification of the analyzed sample was carried out when the spectrum coincided with the diffraction pattern of the reference substances using diffraction data from The Cambridge Crystallographic Data Center.

2.2. Preparation of Scaffolds from **HA**

The synthesis of hydroxyapatite (**HA**) was carried out by the liquid-phase method using microwave radiation at pH ~ 11 according to the scheme [29]:



To prepare the initial solutions, we used: calcium nitrate tetrahydrate $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, ammonium phosphate $(\text{NH}_4)_2\text{HPO}_4$, 25% aqueous ammonia solution and distilled water.

A suspension of 47.20 g $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ in 200 mL distilled water was dissolved in a 300 mL beaker to obtain a solution with a concentration of 0.5 mol/L. Similarly, 15.84 g $(\text{NH}_4)_2\text{HPO}_4$ were dissolved in 200 mL distilled water to obtain a solution with a concentration of 0.3 mol/L. These solutions were mixed in a 500 mL beaker and the pH was adjusted to 11 by adding 25% aqueous ammonia with constant stirring. The beaker with the reaction mixture was covered with film and placed in a microwave oven, where the power was set to 100–150 W, after which the heating was turned on. Irradiation in the microwave was carried out until the mixture boiled. The contents of the reaction vessel were stirred every 15 min to avoid local overheating. The total heating time was 45 min.

After that, the beaker with the contents was removed and left at room temperature for 48 h to form the hydroxyapatite phase. The precipitate was filtered, dried in an oven at 110 °C to constant weight (20 h), and then ground in a mill to a homogeneous state. From the obtained hydroxyapatite powder, carriers were formed in the form of tablets with a diameter of 2 cm and a thickness of about 1 mm, which were calcined at a temperature of 600 °C to constant weight and sintering of the material. According to the standard technique, the physicochemical parameters of the obtained compound are practically the same as in the literature: particle size 0.5–1 nm, specific surface area 106.0 m²/g, total pore volume 0.50 cm³/g, average pore size 20 nm [29].

The XRD results indicate the formation of a hexagonal system during the synthesis of stoichiometric HA, sp. gr. P63/m, the gross formula of which can be described by the formula Ca₁₀(PO₄)₆(OH)₂ (Table 1, Figure 1). The unit cell parameters of the synthesized HA are close in values to the tabulated data (JCPDS data, No. 9-432 [29]).

Table 1. Phase composition of HA synthesis products.

Sample	The Inorganic Phase	Parameters of the Electronic Cell, Å	
		a	c
Synthesis Product (HA)	Ca ₁₀ (PO ₄) ₆ (OH) ₂	9411	6863
JCPDS data, No.9-432	Ca ₁₀ (PO ₄) ₆ (OH) ₂	9418	6884

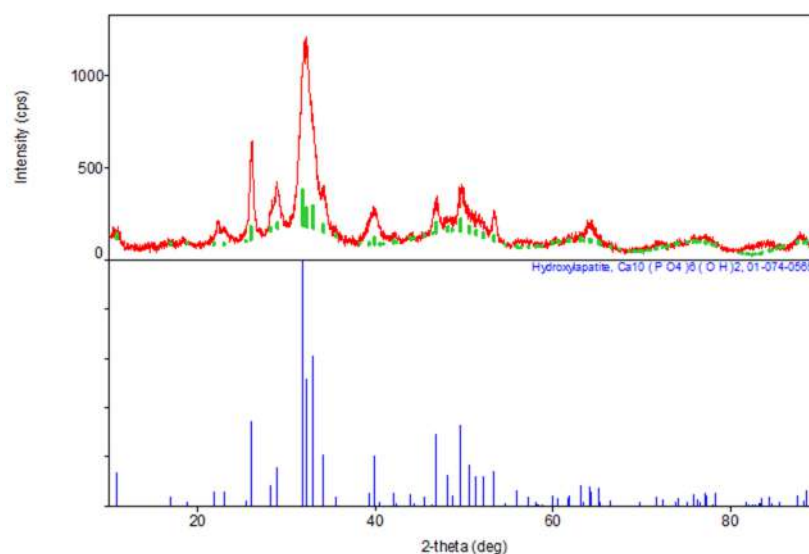


Figure 1. Diffractogram of synthesized stoichiometric HA (red line—synthesized HA, green line—standard).

2.3. Synthesis and Purification of CB[6]

Synthesis of **CB[6]** was carried out according to the procedure (Figure 2) [30]. 4.22 g (0.14 mol) of paraformaldehyde and 14 mL of 10 M sulfuric acid were placed in a three-necked flask with a magnetic stirrer and reflux condenser, after which the mixture was stirred until the paraformaldehyde was completely dissolved. Then, 10 g (0.07 mol) of glycoluril were gradually added to the flask in small portions to avoid premature oligomerization. The reaction mixture was maintained for 24 h at 95 °C.

After the reaction, the resulting precipitate was filtered off and recrystallized from an HCl solution (37%) to remove homologues and by-products of the reaction. Next, the crystalline **CB[6]** powder was kept in a vacuum oven at a temperature of 70 °C for 48 h to remove water of crystallization and hydrochloric acid. The structure of the resulting **CB[6]** was proven using X-ray phase analysis by comparing the diffraction patterns we obtained with the diffraction patterns available in the database of The Cambridge Crystallographic Data Center: **CB[6]** No. 7209204 (Figure 3).

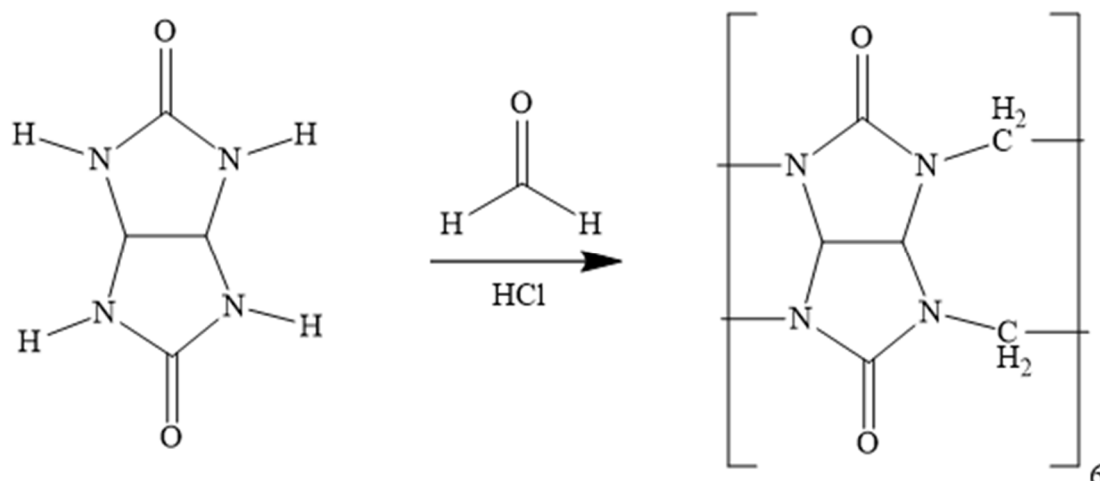


Figure 2. Synthesis scheme CB[6].

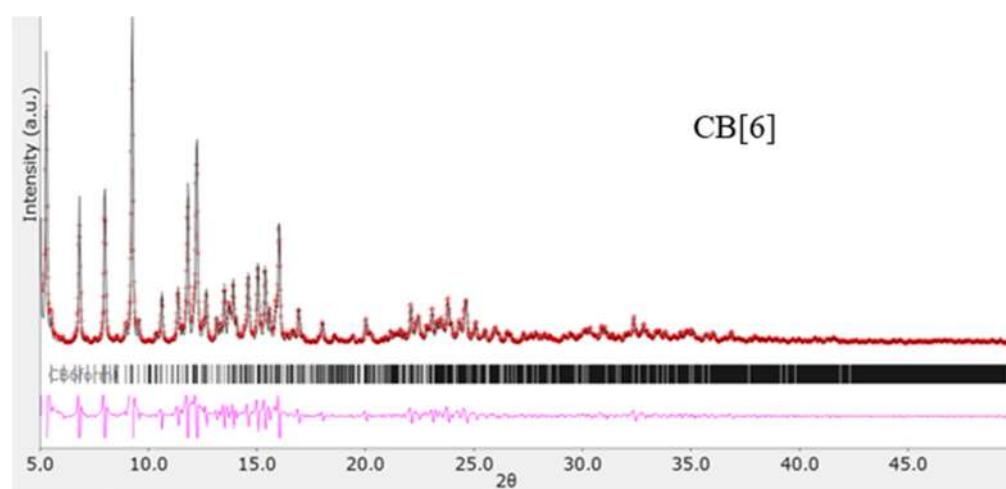


Figure 3. X-ray diffraction pattern CB[6].

3. Results and Discussion

As part of this study, we have developed three methodological approaches to the features of obtaining materials based on **CB[6]** and **HA**, which differ in the method of applying the macrocycle to the scaffold surface (Figure 4).

In the first case (**Method 1**), **CB[6]** was applied from a dispersed solution. In this case, uncalcined **CB[6]**, which usually contains water inside the cavity [31,32]. Traditionally, recrystallization of **CB[6]** is carried out from an aqueous solution of hydrochloric acid [33], due to which its solubility in water is greatly reduced and a dispersion of the original macrocycle is formed. To implement **Method 1**, 15 mg of uncalcined **CB[6]** was placed in deionized water and stirred for 10 min until a dispersion was obtained. Next, an **HA** scaffold in the form of a **HA** tablet with a diameter of 2 cm and a thickness of 2 mm was placed into the resulting dispersed solution and kept for 45 min. Finally, the resulting composite was dried to constant weight (Figure 4).

Another method (**Method 2**) was that **CB[6]** was applied after calcining it at 60 °C for two days (48 h), which in our opinion increases the solubility of **CB[6]** in water. To implement **Method 2**, 15 mg of calcined **CB[6]** was dissolved in 15 mL of deionized water, after which the **HA** scaffold was immersed in the resulting solution for 45 min. Then, the resulting composite was dried at room temperature to constant weight (Figure 4).

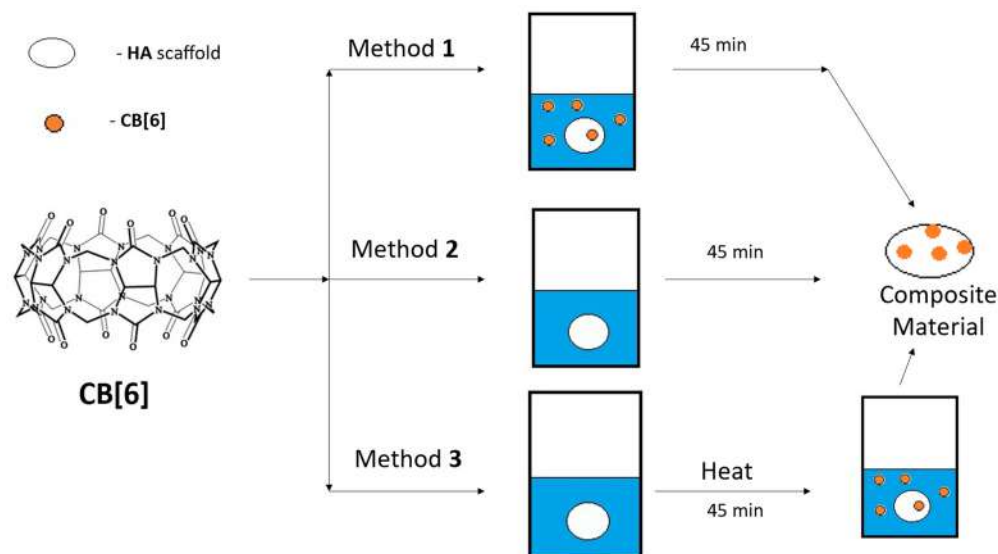


Figure 4. Scheme for applying **CB[6]** to the **HA** surface.

The next method (**Method 3**) is that **CB[6]** was precipitated from solution—15 mg of calcined **CB[6]** was dissolved in 15 mL of deionized water. Next, the **HA** scaffolds were immersed in a **CB[6]** solution and heated at a temperature of 50–60 °C. Within 12 min, the solution became cloudy, which is obviously due to the fact that **CB[6]** molecules adsorbed water when heated and, as a result, the formation of a dispersion was observed. After 45 min, the composite was removed and dried at room temperature to constant weight (Figure 4).

The composites obtained by **Methods 1–3** were studied using IR and SEM spectroscopy. Analysis of the IR spectra of samples obtained by **Methods 1–3** showed the following results. When the **HA** scaffold is immersed in a **CB[6]** dispersion (**Method 1**), the IR spectrum of the composite cleavage shows low intensity absorption bands associated with **CB[6]** (Figure 5). This fact suggests that most of the **CB[6]** is located on the surface of the scaffold, as convincingly evidenced by the SEM results (Figure 6).

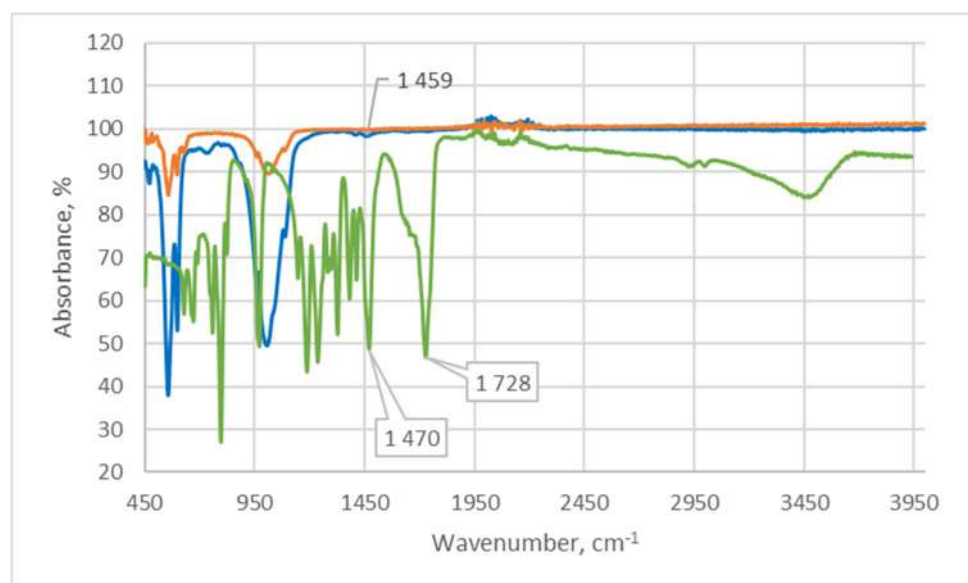


Figure 5. IR spectrum of the cleavage composite obtained by **Method 1**, **CB[6]** (green line), **HA** (orange line) and composite (blue line).

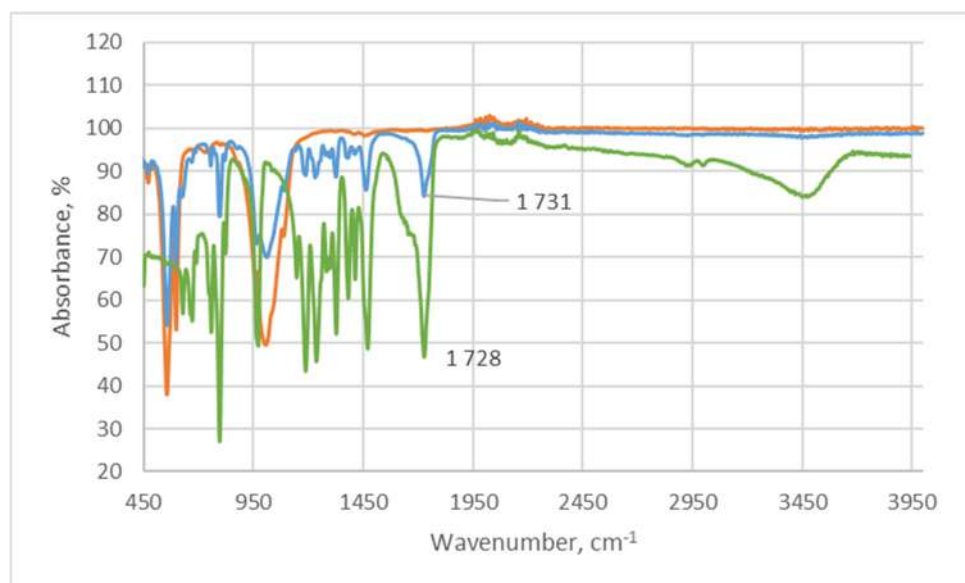


Figure 6. IR spectrum of the cleavage composite obtained by **Method 2**, **CB[6]** (green line), **HA** (orange line) and composite (blue line).

When producing composites using **Method 2** (immersion in a **CB[6]** solution), the spectral picture is noticeably different. Thus, in the IR spectrum of the cleavage sample **CB[6] + HA**, clear absorption bands are observed, which belong to **CB[6]**. Thus, at 1731 cm^{-1} an absorption band is observed, which corresponds to the stretching vibration of the carbonyl groups ($\text{C}=\text{O}$) of the glycoluril unit **CB[6]**. When compared with the IR spectrum of **CB[6]**, it is clear that there is a shift of 3 cm^{-1} to the long wavelength region, which indicates an insignificant interaction of the **HA** surface with **CB[6]**. At $1200\text{--}1500\text{ cm}^{-1}$, bending vibrations of CH_2 groups are identified. When comparing the IR spectra of the **CB[6] + HA** composite with the IR spectrum of **CB[6]**, it is clear that the main absorption bands related to **CB[6]** are present in the spectrum, but there are no absorption bands at 3400 cm^{-1} (stretching vibrations $-\text{OH}$ water groups) and $2900\text{--}3000\text{ cm}^{-1}$ (stretching vibrations of $-\text{CH}-\text{CH}-$ groups), which is obviously due to the fact that **CB[6]** is in a lower concentration compared to **HA** and the signals have low intensity.

The sample obtained by **Method 3** shows a similar picture—absorption bands related to **CB[6]** are also identified inside the sample cleavage.

Next, we analyzed SEM images of samples obtained using **Methods 1–3**. In the SEM images of composites prepared by **Method 1**, an uneven distribution of **CB[6]** is observed, appearing as conglomerates of molecules on the surface (Figure 7A). This conglomerate formation is likely due to the tendency of **CB[6]** molecules to self-assemble on the **HA** surface under these conditions. When examining the composite in a closer approximation (Figure 7B), one can notice that **CB[6]** on the **HA** surface consists of both conglomerates of **CB[6]** molecules and independent needle-shaped crystals. The formation of conglomerates of **CB[6]** molecules can be stimulated by the process of interaction of **CB[6]** with water, with the formation of aqua complexes of various compositions, which promotes the interaction of crystals with each other, thereby forming such an architecture of **CB[6]** conglomerates. Based on the above, we can conclude that application **Method 1** does not allow uniform coverage of the **HA** scaffold.

The SEM picture of the samples obtained by **Method 2** on the **HA** surface indicates a comparatively smaller number of **CB[6]** molecules (Figure 8). This statement is confirmed by examining SEM images at different zooms and comparing them with the images of composites obtained using **Method 1** (Figures 7A and 8A). Isolated needle-shaped crystals of **CB[6]** are also observed on the **HA** surface. When zooming in 10,000 times, it is clear that the **CB[6]** molecules that are on the surface are formed mainly by conglomerates

(Figure 8B). This observed fact is due to the fact that **CB[6]** was applied in dissolved form, and the residual aqueous layer of the solution, which was not removed from the surface due to the wettability effect (Figure 9), contributed to the formation of conglomerates. The **HA** scaffold was saturated with the solution, and most of the **CB[6]** is located inside the composite structure (as evidenced by the IR spectroscopy results shown in Figure 3). In the IR spectra of cleavage samples obtained by **Method 1**, the absorption bands have extremely low intensity, which indicates an insignificant concentration of **CB[6]** on the cleavages of the obtained composites, compared to **Method 2**.

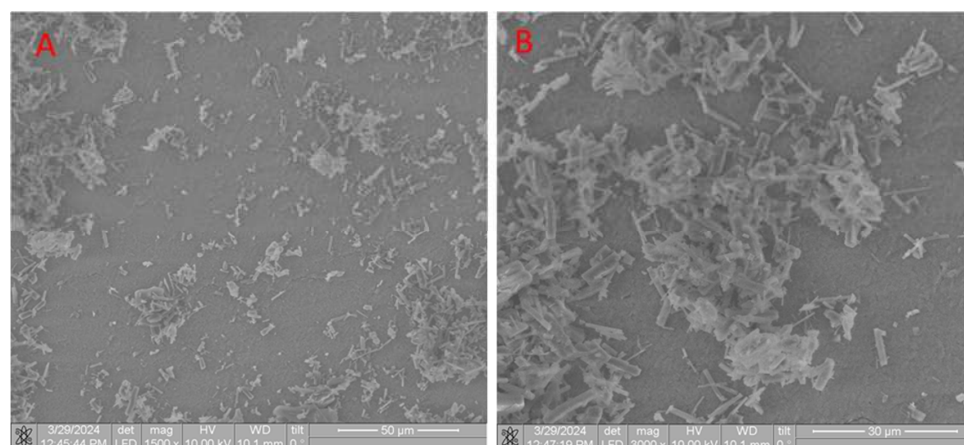


Figure 7. SEM images of samples obtained by **Method 1** ((A) 1500× magnification, (B) 3000× magnification).

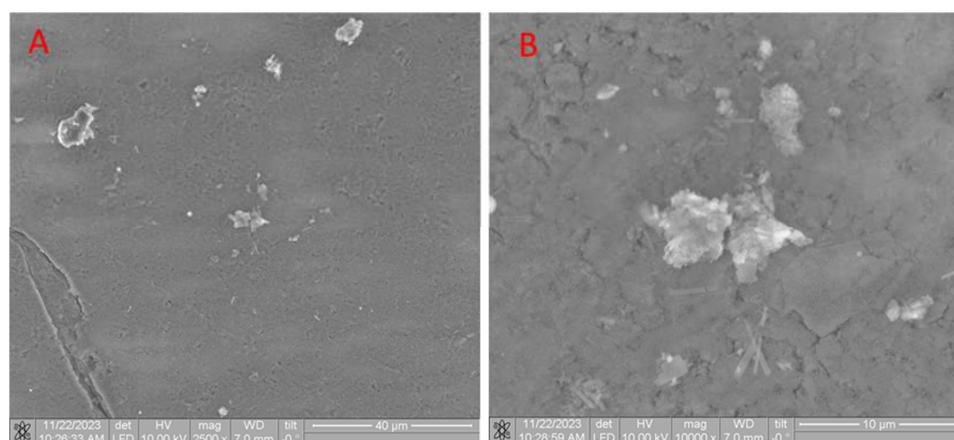


Figure 8. SEM images of samples obtained by **Method 2** ((A) 1500× magnification, (B) 10,000× magnification).

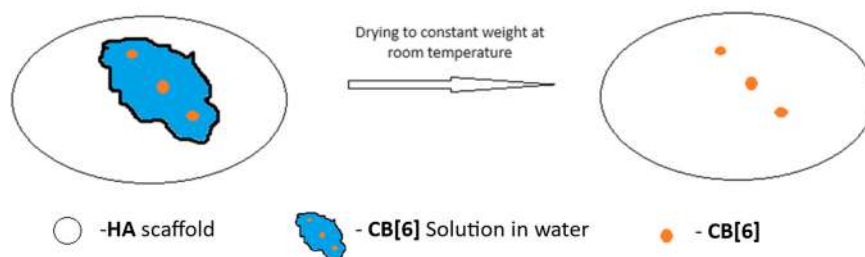


Figure 9. Schematic representation of the formation of conglomerates of **CB[6]** molecules on the surface of **HA** using **Method 2**.

When examining SEM images of samples obtained by **Method 3**, a uniform distribution of the **CB[6]** macrocycle on the **HA** surface is observed (Figure 10A). In this case,

the formation of needle-shaped crystals is observed over the entire surface of **HA**—the formation of **CB[6]** crystals occurs evenly and simultaneously over the entire surface of the composite. At 4000× zoom (Figure 10B), needle-shaped crystals are seen to cover almost the entire **HA** surface uniformly.

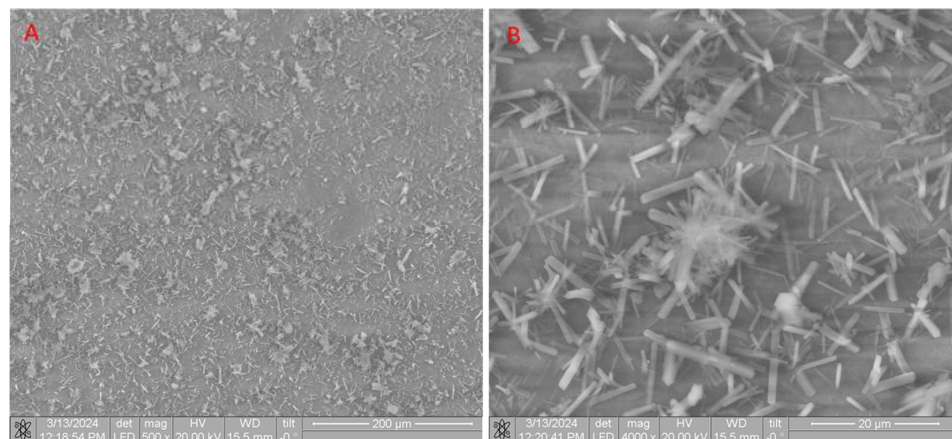


Figure 10. SEM images of samples obtained by **Method 3** ((A) 500× magnification, (B) 4000× magnification).

Based on the above, we have proposed a diversification of the scheme for obtaining materials based on **CB[6]** and **HA**. Thus, to uniformly apply **CB[6]** to the surface of materials, various methods can be used, depending on the potential purpose of the resulting materials. In the case of **Method 1**, the surface is covered unevenly; penetration of **CB[6]** into the scaffold does not occur due to low solubility with included water molecules in the cavities of **CB[6]** [33]. In addition, the authors of [34] showed by calculation methods that water molecules in the cucurbit[6]uril cavity are subject to structuring, which is due to their weak interaction with this macromolecule, and the cluster contained in the **CB[6]** cavity has the composition $(\text{H}_2\text{O})_6$. This method of modifying the **HA** surface can be used in cases where a low concentration of **CB[6]** is required on composite surfaces. Using **Method 2**, most of the **CB[6]** is located inside the scaffold, as confirmed by IR spectroscopy and gravimetry. To confirm this, the solution after application (residual solution) was drained and dried to a constant weight and weighed. When studying the residual mass of solutions after completing **Methods 1–3**, it was found that when using **Method 1**, the residual mass was 6 mg, when using **Method 2** it was 5 mg, and when using **Method 3**, it was 3 mg. The advantage of **Method 2** is that when interacting with the internal environment of the body, **CB[6]** will not be washed out from the surface of **HA**. The peculiarity of **Method 3** is explained by the ability of **CB[6]** to adsorb water, which leads to the penetration of water into the cavity of **CB[6]** and the formation of corresponding aqua complexes [34]. In addition, this method allows for more complete application of **CB[6]** both on the surface and inside the scaffold. When using **Method 3**, the surface is uniformly coated and **CB[6]** also penetrates into the **HA** scaffold, which in turn is the most effective combined option for modifying **HA** scaffolds in the framework of the studies.

In development of **Method 3**, the influence of ultrasonic influence on the process of applying **CB[6]** to the **HA** surface was studied. To implement this approach (**Method 4**), the **HA** scaffold was immersed in a solution of 15 mg of **CB[6]** in 15 mL of deionized water located in a Petri dish, then the dish was immersed in an ultrasonic bath with a frequency of 37 kHz. During the experiment, an increase in the temperature of the solution was observed (up to 50 °C for 15 min), and, as a result, cloudiness of the solution occurred (Figure 11). After 20 min, the resulting composite was removed and dried at room temperature to constant weight. In parallel, a similar experiment was carried out, but without external interaction (**Method 3**). The resulting composites were examined using SEM, comparative images of which are shown in Figure 12.

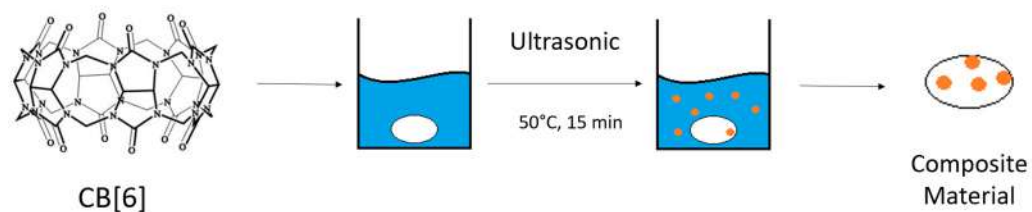


Figure 11. Scheme for producing composites using ultrasonic interaction.

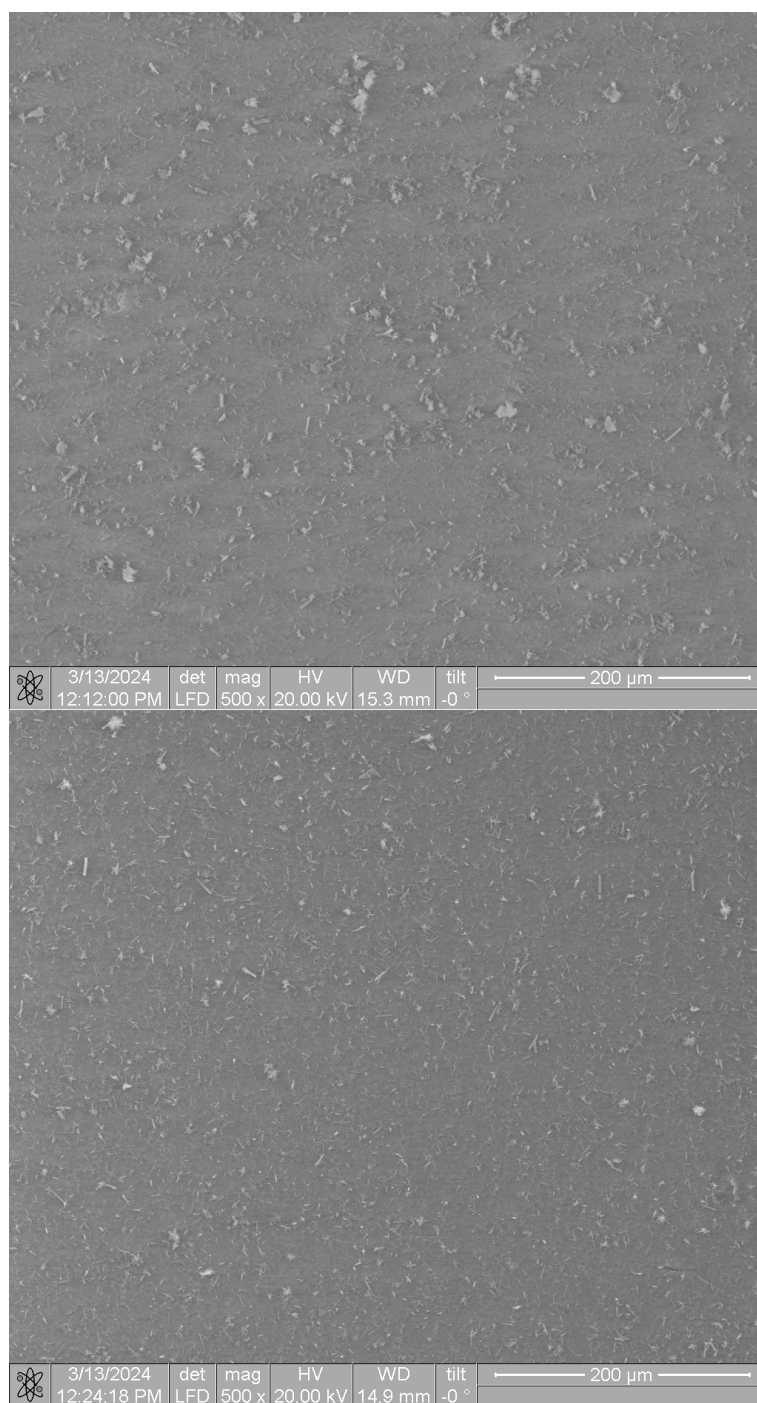


Figure 12. SEM images of composites obtained by **Method 3** (upper image) and when composites were obtained by ultrasound interaction (lower image).

When comparing SEM images of the obtained composites with and without ultrasonic interaction (Figure 12) at the same approximation of 500 times, it is clear that when HA is applied using ultrasonic influence on the surface, a more uniform distribution of CB[6] over the surface is observed. The number of molecular conglomerates decreases compared to Method 3, and at the same time the amount of HA surface area free from the macrocycle decreases. This fact indicates that external ultrasonic influence increases the distribution density of CB[6] on the HA surface.

Moving on to potential applications in the field of personalized medicine, there is the problem of fixation of CB[n] with incorporated biological substrates on composite materials, which will be subsequently used in medicine and medical practice. The fundamental issue that needs to be addressed is to ensure that the components are held together by non-covalent interactions. Since the preparation of CB[n]-based host–guest complexes as solid products involves mixing hosts and guests in the appropriate stoichiometry, isolation of the complexes in solid form using either lyophilization [35], co-solvent treatment [36], or ball milling [37] is needed. However, the resulting complexes may be inert and not fixed on the surface of the material. Studies of the processes of obtaining biocomposite materials help to choose the necessary and optimal method for obtaining these biomaterials.

4. Conclusions

Summarizing the above, it should be noted that, depending on the method of applying CB[6] to the surface and inside the HA scaffold, it is possible to adjust the composition and structure of the target composite materials. Different application methods in turn increase the variability of the potential applications of composites depending on the practical application. The use of ultrasonic influence increases the surface coverage of HA and reduces the number of conglomerates of CB[6] molecules, which is apparently due to better wettability of the HA surface and disintegration of CB[6] conglomerates under the determined conditions. Methods for applying CB[6] to the surface of HA have been proposed, which opens the way to functional composite materials based on CB[6] and encapsulation products (host–guest complexes).

The proposed methods for applying CB[6] to the surface of HA impart biodiversity to the latter and provide affinity for the body's environment when creating new functional composite materials, including the use of supramolecular systems based on the CB[n] family.

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Synthesis and Study of a novel supramolecular 'host-guest' complex based on cucurbit[6]uril and 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride

Tolkynay Burkhanbayeva

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A novel supramolecular complex $C_{44}H_{71}Cl_2N_{26}O_{22}$ (**CB[6]@Pipa·2HCl**) of the "host-guest" type has been synthesized. It is based on cucurbit[6]uril (**CB[6]**) with dihydrochloride 1,4-bis(2-hydroxyethyl)piperazine (**Pipa·2HCl**) localized within the portals of the macrocycle. Based on ^1H NMR and X-ray crystallography, the host-guest ratio in the complex under the specified conditions was determined to be 1:1. Further evidence of complex formation was observed through IR spectroscopy, where a splitting and shift in the absorption band of carbonyl vibrational frequencies of cucurbit[6]uril by 36 cm^{-1} and 12 cm^{-1} towards the side of smaller wave numbers was detected in **CB[6]@Pipa·2HCl** compared to the original **CB[6]**. TGA/DSC analysis results indicated an increase in thermal stability by 55°C for the obtained **CB[6]@Pipa·2HCl** complex compared to the initial 1,4-bis(2-hydroxyethyl)piperazine dihydrochloride. The structure of the synthesized **CB[6]@Pipa·2HCl** complex was confirmed using single-crystal XRD

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Роль методов нанесения кукурбит[6]урила на гидрокси-апатит для морфологической настройки его поверхности в процессе получения КОМПОЗИЦИОННЫХ материалов

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В современную эпоху персонализированной медицины существует значительная потребность в создании новых материалов для имплантатов, которые должны обладать определенными характеристиками. Для успешного применения в медицинских целях такие материалы должны иметь оптимальное сочетание различных свойств.

Ключевыми характеристиками композиционных биоматериалов являются их состав, форма, структура, морфология поверхности и механические свойства. Важным аспектом таких материалов является их биосовместимость, то есть способность взаимодействовать с окружающими тканями без вызывания нежелательных реакций или воспалений. Кроме того, желательно, чтобы такие материалы стимулировали рост сосудов или костей вокруг них, способствуя заживлению и восстановлению поврежденных тканей.

В случае с имплантатами или материалами для лечения ран все эти свойства определяют способность материала взаимодействовать с окружающими тканями. Биоактивные материалы могут служить основой для роста новых тканей, например, для ускорения регенерации повреждений. Таким образом, разработка таких материалов является ключевым аспектом в улучшении качества медицинской помощи и повышении эффективности лечения. Успех персонализированной медицины в значительной степени зависит от прогресса в области разработки новых материалов для имплантатов, обладающих всеми необходимыми характеристиками для безопасного и эффективного взаимодействия с биологическими тканями. Инновации в этой области открывают новые горизонты для лечения различных заболеваний и повреждений, обеспечивая пациентам более быстрое восстановление и улучшение качества жизни.

С другой стороны, материалы, контактирующие с внутренней средой организма, должны быть максимально нетоксичными для клеток и тканей. Однако многие вещества, обладающие высокими антибактериальными свойствами, часто оказываются достаточно токсичными, что приводит к низкой биосовместимости. Биосовместимость определяется характером и степенью взаимодействия между биоматериалами и тканями организма и является одной из важнейших проблем в исследованиях биоматериалов. Она включает

иммунное отторжение или воспалительную реакцию окружающих тканей на присутствие инородного тела в организме.

В связи с этим, ко всем биомедицинским устройствам предъявляются чрезвычайно высокие клинические требования. Перед имплантацией в организм человека требуется тщательный процесс модификации поверхности материалов для повышения их биосовместимости. Создание материалов, которые одновременно являются биосовместимыми и обладают специфической биологической активностью, представляет собой нетривиальную задачу.

Помимо этого, современные клинические методы лечения часто основаны на пероральном или внутривенном введении лекарственных средств. Такой подход обеспечивает высокий уровень препарата в крови сразу после введения дозы, но затем его концентрация быстро снижается ниже терапевтического окна. Это может привести к тому, что концентрация препарата сначала достигает токсического уровня, а затем падает ниже терапевтического, делая терапию менее эффективной.

Следовательно, разработка новых биоматериалов и методов доставки лекарственных средств требует решения множества сложных задач. Необходимо создавать материалы, которые не только минимально токсичны и биосовместимы, но и обладают необходимой биологической активностью для обеспечения эффективного лечения. Инновационные подходы в этой области могут значительно улучшить качество медицинской помощи, предоставляемой пациентам, и повысить эффективность лечения различных заболеваний и повреждений.

Имплантаты, высвобождающие лекарственные средства, стали перспективной альтернативой традиционным методам перорального и внутривенного введения лекарств для широкого спектра клинических применений. В настоящее время известны такие материалы, используемые для разработки имплантатов с контролируемым высвобождением лекарств, как титановые нанотрубки, пористый кремний, полимеры и различные микротехнологии.

Импланты высвобождающие лекарственные средства, обладают рядом уникальных преимуществ. Они могут обеспечивать устойчивое, дистанционно контролируемое, программируемое и локализованное высвобождение лекарств непосредственно в нужном месте. Это делает терапию более эффективной, снижая риск побочных эффектов для пациентов. Такие возможности трудно достичь при обычном системном введении лекарств.

Особое место среди имплантатов занимают биоактивные материалы, способные стимулировать рост новой ткани вокруг себя. Это позволяет значительно улучшить процессы заживления и восстановления, что особенно важно в медицинских применениях, связанных с лечением ран и повреждений. Биоактивные материалы могут ускорять регенерацию тканей, что делает их незаменимыми в медицинской практике.

Все характеристики материалов для имплантатов, позволяющие придать биоподобность играют важную роль в их применении в медицине. Исследования и разработки в этой области постоянно продвигаются вперед, стремясь найти лучшие материалы, которые удовлетворяют всем требованиям и обеспечивают оптимальные результаты для пациентов. Инновации в разработке таких материалов могут привести к значительным улучшениям в лечении различных заболеваний и повреждений, обеспечивая более быстрое и эффективное восстановление пациентов.

Таким образом, создание и применение имплантатов, высвобождающих лекарственные средства, открывают новые горизонты в медицинской науке и практике. Они не только повышают эффективность терапии, но и значительно улучшают качество жизни пациентов, минимизируя побочные эффекты и обеспечивая более точное и целенаправленное лечение.

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Следовательно, разработка новых биоматериалов и методов доставки лекарственных средств требует решения множества сложных задач. Необходимо создавать материалы, которые не только минимально токсичны и биосовместимы, но и обладают необходимой биологической активностью для обеспечения эффективного лечения. Инновационные подходы в этой области могут значительно улучшить качество медицинской помощи, предоставляемой пациентам, и повысить эффективность лечения различных заболеваний и повреждений.

Имплантаты, высвобождающие лекарственные средства, стали перспективной альтернативой традиционным методам перорального и внутривенного введения лекарств для широкого спектра клинических применений. В настоящее время известны такие материалы, используемые для разработки имплантатов с контролируемым высвобождением лекарств, как титановые нанотрубки, пористый кремний, полимеры и различные микротехнологии.

Импланты высвобождающие лекарственные средства, обладают рядом уникальных преимуществ. Они могут обеспечивать устойчивое, дистанционно контролируемое, программируемое и локализованное высвобождение лекарств непосредственно в нужном месте. Это делает терапию более эффективной, снижая риск побочных эффектов для пациентов. Такие возможности трудно достичь при обычном системном введении лекарств.

Особое место среди имплантатов занимают биоактивные материалы, способные стимулировать рост новой ткани вокруг себя. Это позволяет значительно улучшить процессы заживления и восстановления, что особенно важно в медицинских применениях, связанных с лечением ран и повреждений. Биоактивные материалы могут ускорять регенерацию тканей, что делает их незаменимыми в медицинской практике.

Все характеристики материалов для имплантатов, позволяющие придать биоподобность играют важную роль в их применении в медицине. Исследования и разработки в этой области постоянно продвигаются вперед, стремясь найти лучшие материалы, которые удовлетворяют всем требованиям и обеспечивают оптимальные результаты для пациентов. Инновации в разработке таких материалов могут привести к значительным улучшениям в лечении различных заболеваний и повреждений, обеспечивая более быстрое и эффективное восстановление пациентов.

Таким образом, создание и применение имплантатов, высвобождающих лекарственные средства, открывают новые горизонты в медицинской науке и практике. Они не только повышают эффективность терапии, но и значительно улучшают качество жизни пациентов, минимизируя побочные эффекты и обеспечивая более точное и целенаправленное лечение.