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Polymer Microencapsulation and Insilico Study Approach of Celecoxib for the Management of Alzheimer's Disease.

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KEYWORDS

Celecoxib, Polymer microencapsulation, Solubility, Molecular Docking, Neurodegeneration.

ABSTRACT:

Introduction: The study investigates the impact of microencapsulation on the physicochemical properties of Celecoxib (CXB) when combined with polymers. This process aimed to enhance the dissolution rate and solubility of CXB, which is particularly evident in the ME-2 formulation.

Objective: The primary goal was to determine whether microencapsulation could improve CXB's solubility and dissolution rate, potentially offering benefits for the management of neurodegenerative disorders. Further computational studies like Molecular Docking and Binding affinity study of celecoxib with AD related proteins to assess whether CXB is a potent drug for the management of AD.

Method: The solvent evaporation technique was employed to microencapsulate CXB with various polymers. The resulting formulations were then analyzed for changes in solubility and dissolution rates. The molecular docking study was done using AutoDock vina to identify the interaction of celecoxib with selected AD protein targets in selected active sites.

Results: Microencapsulation produced micronized particles, leading to a higher dissolution rate than pure CXB. The ME-2 formulation showed the most significant improvement. SEM analysis confirmed changes in particle shape and size post-microencapsulation, while DSC tests indicated that CXB was in an amorphous state. FTIR spectra suggested the formation of hydrogen bonds between CXB and the polymers, which could account for the increased solubility. Additionally, molecular docking studies suggested that CXB has the potential to combat neurodegeneration due to its binding energy with related proteins.

Conclusion: Microencapsulation of CXB significantly enhances its solubility and permeability, which may be beneficial in treating neurodegenerative diseases. The findings support the potential of microencapsulated CXB as a therapeutic agent, with further animal studies recommended to evaluate its efficacy in managing Alzheimer's Disease (AD).

1. Introduction

Alzheimer's disease has a global prevalence of 50 million people, and it is projected that the number of people living with dementia will rise to 82 million by 2030 and 152 million by 2050. This places a significant burden on caregivers, with 82% of people with dementia being cared for by family members, resulting in various emotional, physical, and financial challenges.[1,2,3]

The significance of curing Alzheimer's disease cannot be overstated, as it would alleviate immense suffering for affected individuals. With Alzheimer's being a global health challenge, finding a cure would have far-reaching benefits, positively impacting millions worldwide across diverse cultures. Scientific breakthroughs in the pursuit of a cure would not only advance our understanding of the brain and neurobiology but also propel the field of neuroscience forward. Such a breakthrough would inspire hope within the scientific and medical communities, showcasing the potential of research and innovation in combating complex diseases.[4]

There are several treatments available for the management of AD. However, due to inadequate Absorption, distribution, metabolism, and excretion

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(ADME) profile, blood-brain barrier (BBB) penetration, and dissolution properties, many traditional treatments fall short of producing appropriate therapeutic effects [5, 6]. As a result, there are FDA marketed drugs are being developed using methods like microencapsulation, for the management of NDs for example Risperdal Consta (Risperidone), Rytary (Carbidopa and Levodopa), Invega Sustenna (Paliperidone palmitate) which offers several substantial advantages in reducing the severity of neurological disorders by improving drug delivery, enhancing drug stability, and increasing patient compliance.

Celecoxib (CXB) is a selective inhibitor of COX-2, used to treat a variety of diseases such as osteoarthritis, rheumatoid arthritis familial adenomatous polyposis, etc. [7]. In recent times, multiple studies have also /highlighted the roles of celecoxib in neurodegenerative diseases.[8] Studies also revealed that CXB plays a vital role in maintaining neuronal survival [9]. Although CXB possesses wide therapeutic efficacy in numerous chronic diseases, its utility can be confined, owing to its minimal drug solubility, slower drug absorption rate, and bioavailability. Thus, conventional drugs, like CXB often fail to interact with cellular targets, which renders them ineffective. Despite its high therapeutic efficacy, CXB's low solubility limits its wide applications, such as treating neurodegenerative diseases. There are numerous biochemical explanations for neurodegenerative disease that have been suggested in the literature, including cholinergic deficiency and the buildup of amyloid beta plaque in the brain.

Polymer-based nanoparticles are shown as innovative treatments given their potential for enhancing medication bioavailability, cellular tolerance, and reduce side effects. In addition to improving their therapeutic effect in a synergistic or additive manner, these compounds may retain multiple therapeutic agents, which can be used to both counteract acquired resistance and strengthen therapeutic effect [10,11]. They possess unique characteristics including their nanometric size, high surface area to volume ratio, favorable drug release profiles, and targeting features that enhance their ability to bind to preferred targets. Hence, optimizing the physicochemical aspects of CXB by such nanotechnological approaches provides a possible non-invasive solution, as a potential targeted therapeutic strategy for several neurological conditions. One such technique for developing polymer-based carriers involves microencapsulation [12,13,14]. Several studies have implied the aspects of the microencapsulation technique as a promising tool in enhancing drug solubility for a wide range of medications, including, Aceclofenac, Ibuprofen, Ketoprofen, and Celecoxib [15,16,17]. Therefore, this study aims to improve the solubility and permeability of microencapsulated CXB using various polymers.

Further the in-silico approach holds significant potential for enhancing the development and application of celecoxib, particularly for treating Alzheimer's Disease (AD). And hence the Molecular Docking studies provides detailed insights into how celecoxib interacts with specific molecular targets, helping to elucidate its mechanism of action at the molecular level. Similarly Binding Affinities calculations predicts the strength and nature of the interactions between celecoxib and its targets, guiding modifications to improve efficacy.

By leveraging polymer microencapsulation and in-silico studies, researchers can develop a more effective and targeted delivery system for celecoxib in treating Alzheimer's Disease. This approach combines the physical benefits of controlled release and enhanced stability with the predictive power of computational modelling to accelerate and refine the development process.

2. Objectives

This study aims to improve the solubility and permeability of microencapsulated CXB using various polymers and further computational studies like Molecular Docking and Binding affinity study of celecoxib with AD related proteins to assess whether CXB is a potent drug for the management of AD.

3. Methods

Materials: Soluplus, Kollidon VA 64, Kollicoat IR, and Kollicoat Protect were gift samples from BASF India. The CXB drug was a gift sample from Apotex Research Pvt. Ltd. India. Ethanol, methanol, and sodium lauryl sulphate (SLS) were purchased from Merck, Lab Supplies India. Distilled water was used for preparing the microencapsulation of CXB.

Preparation of microencapsulation of Celecoxib by various polymers. The microencapsulation of Celecoxib

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was prepared by a common solvent evaporation method employing Ethanol as solvent. The specific ratio of polymer and drug as mentioned in Table-1 was weighed separately. The polymer was dissolved, and the drug was dissolved separately to get a clear solution, and both were mixed later, to get a clear mixture. The corresponding mixture was kept on a magnetic stirrer to evaporate and get nearly dry mass was obtained. The collected mass was dried in a hot air oven at 40°C for 4 hours. The dried sample was then crushed and sieved using a 250 µm mesh for Microencapsulated formulation.[18,19,20].

Table 1. Formulation of Celecoxib Microencapsulation

S No	Formulation code	Drug: Polymer		Polymer
1	ME-1	1	5	Soluplus
2	ME-2	1	5	Kollidon VA 64
3	ME-3	1	3	Kollicoat IR
4	ME-4	1	3	Kollicoat Protect

Determination of solvent evaporation yield and Drug loading: The yield of solvent-evaporated microencapsulated celecoxib was calculated by dividing the weight of the recovered particles by the total solid content of celecoxib and polymer used in the ethanolic suspension. The percentage yield was determined using the following formula:

%Yield = (Weight recovered / Weight added) * 100

To quantify drug loading, an accurately weighed amount of each microencapsulated formulation was dissolved in a methanol and water mixture (75:25). The concentration of celecoxib was then measured using a chromatographic method based on a calibration curve for celecoxib at a wavelength of 250 nm. The polymers did not interfere with the detection of celecoxib at this wavelength. [21].

Scanning Electron Microscope study (SEM): Scanning Electron Microscopy (SEM) was conducted to study the surface morphologies of pure Celecoxib, pure polymers, and microencapsulated CXB samples. For SEM analysis, tests were conducted using JSM-6510LV, JEOL make Scanning Electron Microscope with Secondary Electron Image. The samples were loaded on an SEM sample stab and sputtered with a platinum fine coat and then the sample was analysed using SEM [22].

Differential Scanning Calorimetry (DSC): The melting temperature (Tm) of Pure Celecoxib and after microencapsulation samples was determined using TA Instrument DSC instrument DSCQ2000 in a nitrogen atmosphere and the samples of 4-8 mg were taken for DSC analysis [23].

Dissolution studies: Dissolution is the process in which a substance forms a solution. In this regard, the dissolution profile of microencapsulated CXB and pure CXB was performed using the DS 8000 (Labindia, India). A 1% sodium lauryl sulfate and 900 mL of water were used for the determination of the dissolution rate. Then to maintain sink conditions sodium lauryl sulfate was added to the dissolution fluid. During each test 37 ± 1 °C temperature and speed up to 50 rpm was maintained. Further, at different time intervals, the sample of dissolution medium (5 mL) was centrifuged at 12000 rpm for 5 minutes. Finally, sample absorbance was noted at 254 nm using UV [21,24,25,26].

Detection of drug-polymer interaction using Fourier Transform Infrared spectroscopy: For FTIR (PerkinElmer Spectrum 100 and Omnic software) analysis, tests were conducted in ATR mode using diamond crystal at RT. The background was initially scanned and subsequently, the samples were placed on the diamond crystal and scanned. The contact between the sample and the crystal was ensured by adjusting the force applied. 4 scans from 4000-650 nm were conducted before the data was finally recorded [27].

In Silico Molecular Docking Study: In silico molecular docking study using AutoDock vina: Auto dock was utilized to investigate the four proteins with the following PDB entry codes: acetylcholinesterase (4EY7), beta-secretase cleavage enzyme (2HM1), monoamine oxidase (2Z5X), and N-methyl-D-aspartate receptor (1PBQ) [28]. These proteins play an important role in controlling Alzheimer's disease. AChE plays a role in the metabolism of acetylcholine, BACE1 is involved in the formation of amyloid-beta plaques, MAOs are enzymes associated with neurotransmitter metabolism, and NMDA receptors are involved in synaptic plasticity [29]. The procedure followed in studying these proteins using Auto Dock involved several steps: Preparation of Protein Targets: The X-ray crystallographic structures of the

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target proteins were downloaded from the Protein Data Bank (PDB). The proteins were then prepared in Discovery Studio and AutoDock, which included processes such as adding hydrogen to the protein, assigning bond orders, deleting unnecessary associated molecules, adding missing atoms, and energy minimization using AutoDock. Ligand Dataset Preparation: The ligands were prepared for docking studies. The ligands with the best binding scores were exported as mol2 files, and their interactions with the protein targets were investigated using the Discovery Studio Visualizer. Docking Studies: The ligands with the best binding scores were docked using AutoDock vina. The binding poses are generated in the form of PDBQT files, and the interactions are seen in Discovery Studio. [30]. Molecular Interaction Analysis: The molecular interactions of specific ligands with their respective target proteins were studied. The docking scores and interactions, such as hydrogen bonding and pi-pi stacking, were analysed. Overall, AutoDock vina was used in this study to perform docking simulations and analyse the binding interactions of the ligands with the proteins of interest. It played a crucial role in evaluating the inhibitory potential of the Celecoxib ligand against these AD-related proteins.

4. Results

In this section, the results of % yield of microencapsulated celecoxib, % drug load, particle morphology and size by SEM, melting temperature after microencapsulation, dissolution profile, functional group FTIR spectroscopy method, and molecular docking studies have been discussed.

Determination of solvent evaporation yield and Drug loading: The percentage yield and drug loading of solvent-evaporated microencapsulated CXB are presented in Table 2. The yield percentage varied depending on the polymer used for encapsulation, ranging from 92 to 99%. The percentage of Drug load varied between 60 to 98%. The formula ME-1 and ME-2 show relatively higher % yield and drug load (Table-2).

Table 2. Formulation of Celecoxib Microencapsulation

Sl. No	Formulation code	% Yield	% Drug load
1	ME-1	98.9	87.7
2	ME-2	99.6	98.3
3	ME-3	92.3	85.7
4	ME-4	92.2	59.5

SEM results: The surface morphologies of pure CXB, pure polymers, and solvent-evaporated microencapsulated CXB samples were examined by SEM. SEM was employed to examine the impact of the solvent evaporation process on the morphology of the samples obtained. SEM images of pure CXB revealed a rod-shaped morphology (Fig. 2. a) and after microencapsulation with polymers showed irregular shape and particle size varied from 10 to 550 µ (Fig. 2: a to i).

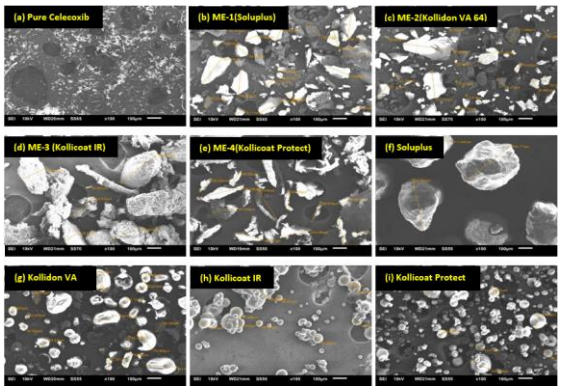

Fig. 2. SEM images of Microencapsulated CXB

Differential Scanning Calorimetry (DSC) results: The DSC thermograms of pure CXB and microencapsulated CXB with polymers were presented in Figure 2 and Table 3. The melting point of pure celecoxib was found to be approximately 164 °C, consistent with previously reported data, with a sharp endothermic peak observed at this temperature. In the thermogram (Figure 3), all microencapsulated samples exhibited endothermic peaks around 90 to 100°C.

Table 3. DSC of pure CXB and microencapsulated CXB

Sl. No	Formulation code	Tm in °C
1	Pure Celecoxib	164
2	ME-1	85
3	ME-2	56 & 94
4	ME-3	85
5	ME-4	92

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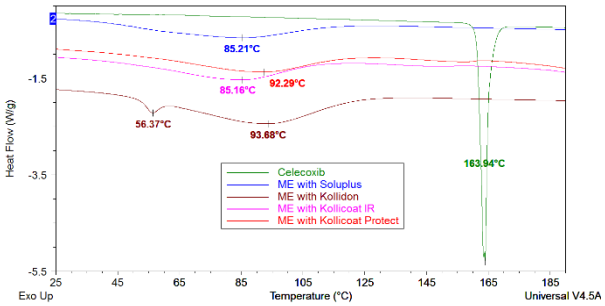


Fig. 3. DSC thermogram of Pure Celecoxib and after microencapsulation.

Dissolution studies: The dissolution profile of Pure Celecoxib and microencapsulated CXB formulations was studied employing SLS as a wetting and solubilizing agent in the dissolution medium to mimic the gastrointestinal tract's sink effect. The dissolution profiles of pure Celecoxib and microencapsulated CXB are depicted in Fig. 4. Pure Celecoxib exhibits the slowest rate and extent of dissolution across all time intervals, attributed to its poor solubility and wettability. The ME-1 and ME-2 demonstrate the highest dissolution when compared to ME-3 and ME-4.

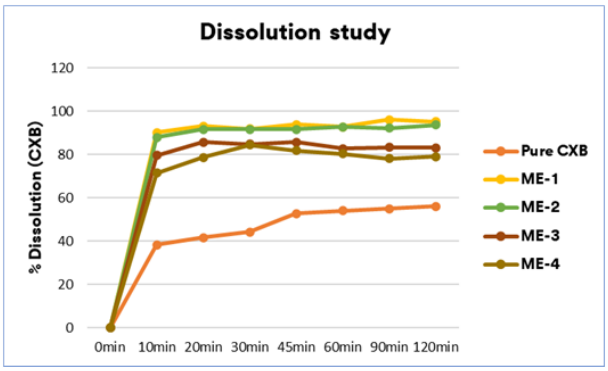


Fig. 4. % Dissolution of Pure Celecoxib and after microencapsulation.

Identification of Drug-Polymer Interaction by Fourier Transform Infrared Spectroscopy: The IR spectra of Pure CXB, Pure polymers, and microencapsulated CXB mixtures were compared (Fig. 5). The IR spectrum of plain CXB showed characteristic peaks at 3400 to 3250 cm−1, which were assigned to the drug–NH symmetric stretching vibration and peak at 3098 corresponds to C-H stretch bond. The other characteristic bands may be attributed to the following group vibrations: 1157 and 1345 cm−1 (S=O stretching), 1560 cm−1 (NH bends), and 780 cm–1 (aromatic –CH bend). From plain polymer IR spectra, the major peaks are 3500 to 3300 cm-1 corresponding to the O-H stretch bond, and peaks from 3000-2850 cm-1 corresponding to the C-H stretch bond. The peaks around 1730 cm-1 are assigned to the C=O stretch bond. specific absorption bands present within the 1690–1630 cm-1 band due to Amide C=O stretch. And same peaks are observed in the IR spectra of microencapsulated CXB.

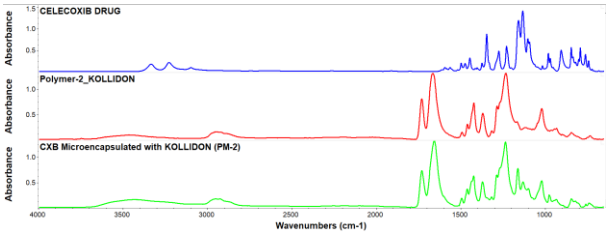
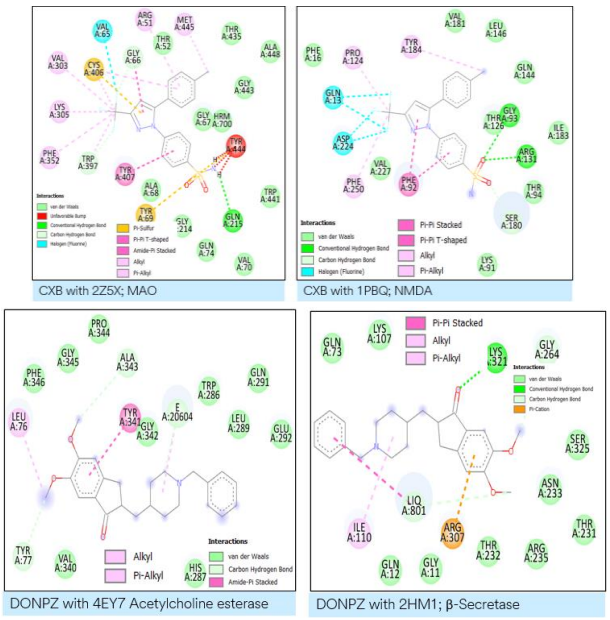


Fig. 5. % Dissolution of Pure Celecoxib and after microencapsulation.

Molecular Docking: The primary goal of the molecular docking study is to identify the interaction of celecoxib with selected AD protein targets in selected active sites. Celecoxib's docking score was calculated as −6.3 for AChE (4EY7), −6.5 in BACE 1 (2HM1), −5.1 in MAO (2Z5X), and −9.1 with NMDA (1PBQ). The docking score for donepezil was obtained as −5.5 for AChE (4EY7), −7.6 in BACE 1 (β-Secretase) (2HM1), −7.0 in MAO-A (2Z5X), and −8.6 with NMDA (1PBQ). The associated amino acids for each protein are discussed below (Fig.6 and Table 4).



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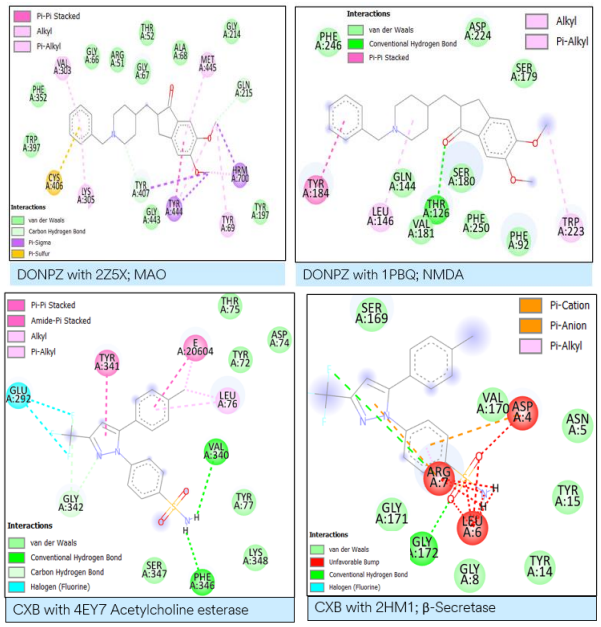

Fig. 6. 1Binding interaction of CXB and donepezil with acetylcholine esterase, β-Secretase, monoamine oxidase, and NMDA

Table 4. Comparison of docking score of celecoxib and donepezil with AD related proteins

Sl No	Protein and PDB ID	Ligand	Score
1	4EY7 Acetylcholine esterase	Celecoxib	-6.3
		Donepezil	-5.5
2	2HM1 beta-secretase	Celecoxib	-6.5
		Donepezil	-7.6
3	2Z5X monoamine oxidase	Celecoxib	-5.1
		Donepezil	-7.0
4	1PBQ N-methyl-D-aspartate	Celecoxib	-9.1
		Donepezil	-8.6

5. Discussion

Neurodegeneration is marked by the gradual deterioration of brain function [31]. There are many neurodegenerative diseases, including Huntington's disease, Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. [32, 33]. CXB is used to manage autoimmune diseases like arthritis, and rheumatoid arthritis [34]. CXB prevents cognitive impairment and neuroinflammation in rats treated with soluble amyloid β. [35]. Further, CXB is a selective COX-2 inhibitor that also ameliorates neuroinflammation [36]. However, there are still several challenges regarding the solubility and permeability of drugs toward brain cells. Thus, microencapsulation of CXB was created to improve its solubility.

The solubility of any drug substance to target any disease or disorder is a matter of challenge. Many drugs failed due to their poor bioavailability though they have great potency [37,38,39]. In the current study, we performed microencapsulation of CXB not only to enhance the solubility profile we also to increase the availability of CXB towards CNS. This strategy may help counter neurodegenerative diseases like Alzheimer's Disease. Here the microencapsulation method has many advantages inhibiting unfavorable chemical interactions, masking aroma, and tastes, and mainly increasing solubility the method like solvent evaporation method of microencapsulation is simple to follow and is a low-cost method.

The solvent-evaporated microencapsulated CXB mixtures show a greater % yield for ME-1 & ME-2 than ME-3 & ME-4, (Table-2) this may be because of the chemical composition with Silicone which makes it less hydrophilic. Similarly, the % drug load (Table 2) was higher for ME-2 when compared to other polymer microencapsulated CXBs specifically ME-3 & ME-4. and drug loading are tabulated in Table 2. SEM images of pure Celecoxib showed rod shape morphology (Figure: a) and after microencapsulation the shape of the sample became irregular shape which is due to pulverization and the particle size was seen as less than 1000 μ which would help in increasing the solubility (Figure: a to i).

In the Microencapsulated CXB samples, CXB is dissolved in ethanol and is converted to an amorphous state after microencapsulation with polymers. DSC results have clearly shown the amorphous state of CXB in these matrices. The overall exothermic peaks were observed at less than 100°C after microencapsulation. (Table-2 & Figure-2) These results indicated the presence of CXB and polymers in an amorphous state [29]. Pure Celecoxib demonstrates the lowest rate and extent of dissolution at all time intervals due to its poor

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solubility and wettability. The ME-1 and ME-2 demonstrate the highest dissolution when compared to ME-3 and ME-4. Numerous prior studies have demonstrated that encapsulated amorphous solids are more soluble than pure drug formulations.

The IR spectra show the interaction between polymer and drug is observed at a specific region 1160 cm-1 which is due to S=O bond from CXB. The changes in IR spectra of microencapsulated CXB indicate the formation of hydrogen bond between the carbonyl and hydroxy group present in the polymer and the CXB. The ester and amide functional groups of Soluplus and Kollidon VA 64 could be involved in hydrogen bonding. These interactions by forming a hydrogen bond stabilizes the drug-polymer microencapsulated samples which improves the drug dissolution rate [39].

The molecular docking study of CXB with protein related to neurodegeneration revealed the potency of the compounds against neurodegeneration. The binding energy score simulates the potential energy change that occurs when the protein and ligand interact. This means that a higher negative score indicates a stronger binding. The proteins involved in the docking study of AD are acetylcholinesterase (AChE), which plays a role in the metabolism of acetylcholine, β-secretase (BACE1), BACE1 is involved in the formation of amyloid-beta plaques, monoamine oxidases (MAO), MAOs are enzymes associated with neurotransmitter metabolism and the N-Methyl-D-aspartate receptor (NMDA). NMDA receptors are involved in synaptic plasticity [40]. For all the above proteins with CXB are found to be observed with optimum single decimal negative binding scores. This indicates the strong binding with proteins of various targets. The binding score values are equivalent to donepezil, a well-known Acetylcholine inhibitory drug used in the treatment of AD [41].

From the above observation further Animal studies would be planned to assess the efficiency of microencapsulated CXB for the management of AD

6. Conclusion

The microencapsulation of CXB with polymers altered the physicochemical properties of CXB, resulting in increased dissolution rate and solubility, particularly notable in the ME-2 formulation. Solvent evaporation produced uniform micronized particles with a higher dissolution rate compared to pure CXB. Furthermore, microencapsulation of CXB led to the formation of an amorphous state, typically associated with improved dissolution rates. It can also be concluded that microencapsulation of CXB has several benefits, including decreasing undesirable chemical interactions, and masking unpleasant aromas and tastes. So, in this connection, it can be concluded that microencapsulated CXB significantly enhanced the solubility and permeability of brain. The improved solubility and permeability of microencapsulated CXB may be a catalytic agent for the management of neurodegenerative-associated disorders.

In this study, microencapsulation of CXB with various polymers was effectively carried out using the solvent evaporation method. The microencapsulated CXB formulations showed improved solubility and dissolution rates compared to pure CXB and this enhancement was more pronounced in ME-2 formulated sample. SEM analysis revealed irregular particle shapes and sizes after microencapsulation. DSC results indicated the amorphous state of CXB in the solid dispersion matrices. FTIR spectra demonstrated the formation of hydrogen bonds between CXB and the polymers, enhancing CXB solubility.

The molecular docking study of CXB with protein related to neurodegeneration revealed the potency of the compounds against neurodegeneration. The binding energy score simulates the potential energy change that occurs when the protein and ligand interact. This means that a higher negative score indicates a stronger binding.

From the above observation further Animal studies would be planned to assess the efficiency of microencapsulated CXB for the management of AD.

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Abbreviations

ME-1, ME-2, ME-3, ME-4: Microencapsulated with Polymer-1, 2,3 & 4.

CXB: Celecoxib

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DSC: Differential Scanning Calorimetry

FTIR: Fourier Transform Infrared Spectroscopy

SEM: Scanning Electron Microscopy

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