RESEARCH ARTICLE

Studies on Characterizations, Solubility and Dissolution of Multicompoent Inclusion Complex of Domperidone using Cyclodextrin/Cyclodextrin Derivatives with Different Auxiliary Agents

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ABSTRACT

Domperidone (DOMP) is an antiemetic drug, although it has low bioavailability and isn't very soluble. Our solution to these issues is the Multicompoent inclusion complex (MCIC), which we would make by combining cyclodextrin and its derivatives with various auxiliary agents/auxiliary substances (AXAs), such as citric acid, mannose, and L-arginine, among others. Compared to β-CD and H-β-CD, first tests reveal that Domperidone with M-β-Cyclodextrin produces better results. Auxiliary agents, such as citric acid, were chosen for use in multicomponent inclusion complexes. In order to determine whether method was more effective in increasing domperidone solubility, researchers compared the physical mixing method with the kneading method for preparing the multicomposite inclusion complex. Phase solubility experiments for multicompoent inclusion complexes revealed considerable improvements in complexation efficiency and stability constants. In order to characterize the multicompoent inclusion, XRD, DSC, FT-IR, and NMR were employed. When compared to the pure medication alone, the complexes demonstrated an increase in drug solubility and release through in vitro dissolving and saturation solubility experiments. This study concluded that AXAs and methyl-β-cyclodextrin have a synergistic action that increases the solubility of DOMP and, perhaps, its bioavailability.

Keywords: Domperidone, Multicompoent-inclusion-complex, M-β-Cyclodextrin, Auxiliary agent.

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INTRODUCTION

Rate of dissolution and oral bioavailability are impacted by low solubility of drugs in water soluble, which are categorised as BCS CLASS II drugs. For the better therapeutic effect drug should be present in its solubilised form to get absorbed through passive diffusion method. The several methods are used for enrichment of solubility of drug which results in improvement in the bioavailability.[1-2] For the medicine to be more soluble in water, it is essential that beta-cyclodextrin (β-CD) forms an inclusion complex. Inclusion complex modifies drug's chemical, biological, and physical properties. In order to create new cyclodextrin derivatives, the chemical modification process involves adding functional groups to the original molecule. Along with advantages β-CD has the limitation of high molecular weight, cost, required in large concentration to achieve required result because of low complexation efficiency.[3-7] This problem is overcome by forming multicomponent inclusion complex (MCIC) by adding different categories of Auxiliary agents (AXAs) to the drug-cyclodextrin inclusion complexes. The various auxiliary agent such as hydroxyl acids, sugar alcohol, amino acids used for synergistic consequence on solubility and complexation effectiveness of drug- cyclodextrin inclusion composite.[8-9] Domperidone (DOMP) is antiemetic drug has low oral bioavailability, due to various dissolution problem and body is require to expose high quantity of drug to overcome this, multicomponent inclusion complex is prepared with various auxiliary agent. This study also shows the effect of various category of auxiliary agent on the solubility improvement of DOMP.[10]

MATERIAL AND METHOD

Domperiodne (DOMP), M-β-CD (Methyl-beta-cyclodextrin), β-CD (Beta-cyclodextrin),CTA (Citric acid), HP-β-CD (Hydroxy-propyl-beta-cyclodetrin), L-ARN (L-Arginine), D-MNT (D- Mannitol) was procured from Yarrow Chem Products, Mumbai, India. All these chemical agents and reagent used were of analytical grade.

Screening of AXAs

To choose appropriate AXAs, DOMP was used to screen a number of auxiliary agents in the absence of CD and its derivatives. A variety of AXAs, including sugar alcohols, hydroxy acids, and amino acids (D-mannitol, CTA, L-arginine, etc.), were tested for their capability to rise solubility of DOMP.[11]

Determination of concentration of AXAs

The concentrations of the AXAs, specifically CTA, that were chosen experimentally were measured in the ternary complex. Saturation solubility tests were conducted after

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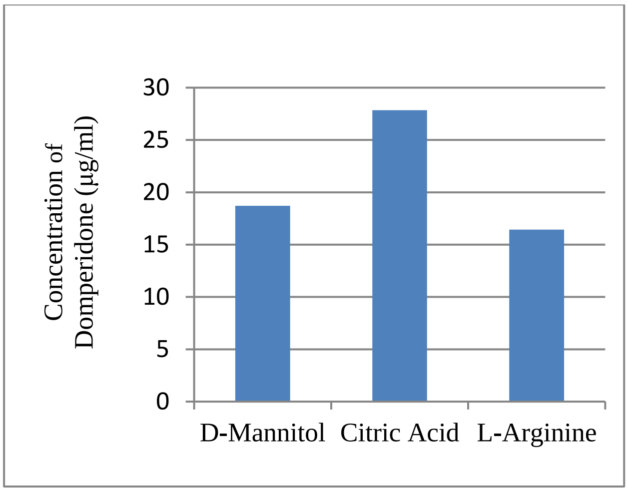

Figure 1: Solubility of DOMP in several AXAs

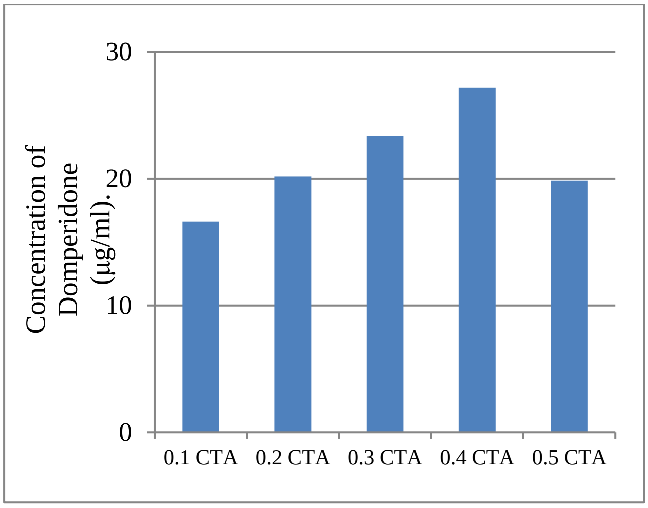

Figure 2: Various Concentration of Citric acids

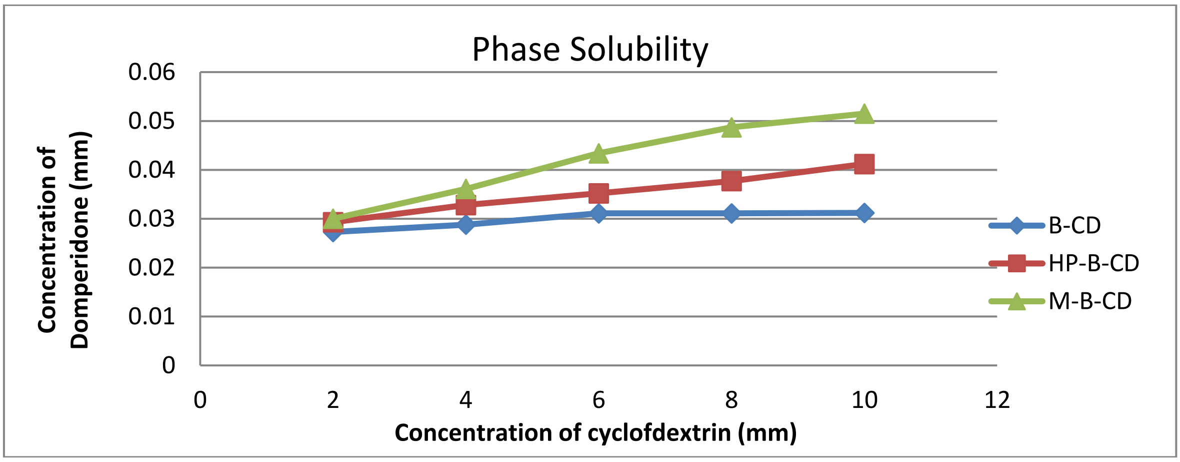

Figure 3: Phase solubility diagram with DOMP with HP- β-CD, β-CD, and M-β-CD

five solutions ranging from 0.1 to 0.5% were produced in water.[11]

Phase solubility

This approach designated by Higuchi and Connors [9-12] was used to conduct phase solubility studies for the binary system. In 10-milliliter screw-capped bottles, a surplus of DOMP (10 mg) was mixed with 10 milliliters of distilled water that contained increasing volumes of M-β-CD, β-CD, and HP-β-CD solutions at altered concentrations (ranging from 0.001-0.01 M). For 72 hours, the contents were mixed using a rotary flask shaker set at 37°C. We used a 2401-PC UV spectrophotometer to measure absorbance at 284 nm after achieving equilibrium. If needed, we diluted the samples before filtering them using Whatman filter paper no. 42. As a comparison to the binary system, ternary system, phase solubility tests were conducted.[10] 10 milliliters of distilled water with increasing concentrations of (0.001 to 0.01 M) M-β-CD solutions was mixed with an excess of ten milligrams of DOMP in 10-milliliter screw-capped bottles containing a constant amount of AXAs agent, specifically 0.4% citric acid, the third component.[10]

We calculated stability constant (Kc) for binary and ternary systems by sloping phase solubility graph in water. From first straight line in phase solubility diagram, we were able to determine drug's intrinsic solubility (S0) and apparent stability constant (S) using following equation:

$$Stability\ Constat\ (Kc) = \frac{Slope}{So(1 - Slope)}$$

Obtaining CE standards for CDs, which were obtained by following formula, is convenient for selection of complexation conditions.[12, 22]

$$Compexition\ efficiency\ (CE) = \frac{Slope}{(1 - Slope)}$$

Inclusion complexes of DOMP preparation

Since physical mixing, kneading procedure was found to provide maximal solubility. It was used to prepare the inclusion complexes. Physical mixing method was used to create Binary inclusion complex (DOMP-PM-B) by evenly mixing DOMP and M-β-CD in a mortar with a 1:1 molar ratio. The MCIC (DOMP-PM-T) was made by evenly mixing DOMP and M-β-CD (1:1) in a mortar. During trituration, each component was supplemented with CTA at a ratio of 1:1:0.4% by weight. The complexes were dried and subsequently passed through a filter with a mesh size of 85. The complexes that were created were placed in glass vials and utilized for subsequent research.[13]

Kneading approach was used to formulate binary inclusion complex (DOMP-IC-B) by placing the necessary amounts of DOMP and M- β-CD (1:1) into glass mortar i. A

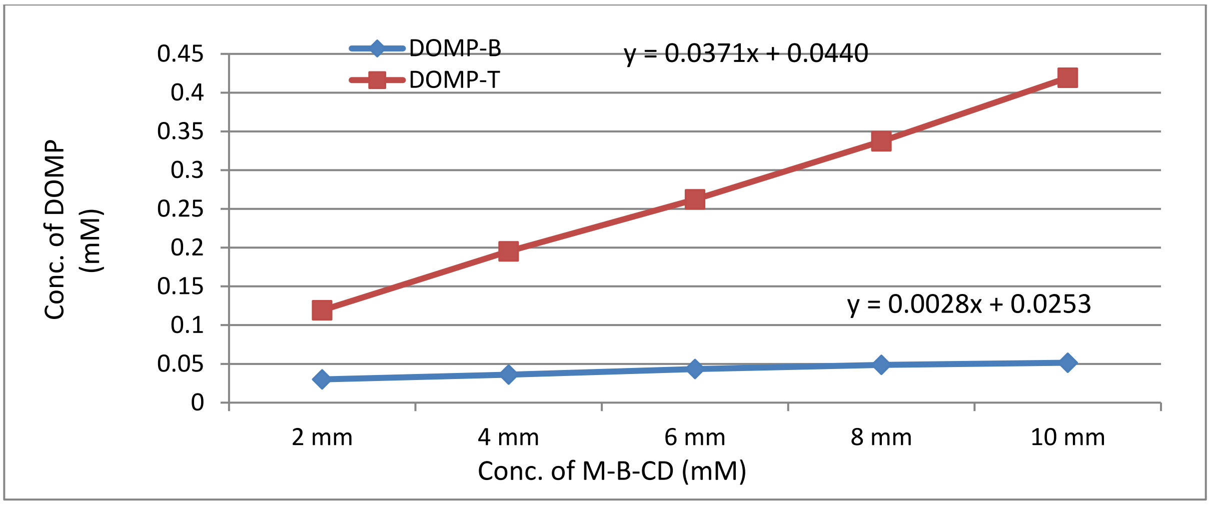

Figure 4: Phase solubility diagram for DOMP-B and DOMP-T

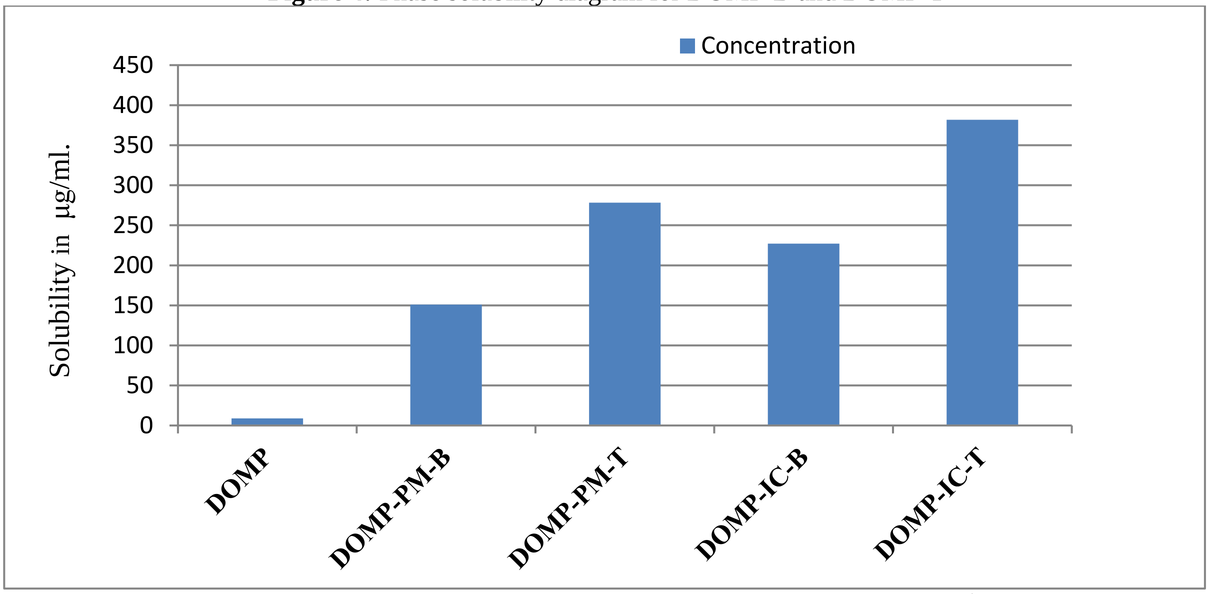

Figure 5: Saturated Solubility of binary, ternary complexes and DOMP in water at 25 ± 2^0C. DOMP-PM-B: Binary inclusion complex by physical mixing method, DOMP-PM-T: Ternary Inclusion complex by Physical mixing method, DOMP-IC-B: Binary inclusion complex by kneading method, DOMP-IC-T: Ternary inclusion complex by kneading method

mixture of one part ethanol and one part water was added, and mixture was stirred until it became a smooth paste. After that, mixture was kneaded for approximately hour. The suitable amount of solvent was supplied during kneading to keep the product consistency. The goods were dehydrated, filtered through #85 sieves, and stored in a desiccator until needed again. Prepared Ternary inclusion complex was with a progressive addition of CTA in a 1:1:0.4% molar ratio, the MCIC (DOMP-IC-T) was produced.[14,15]

Characterization of MCIC

Saturation Solubility

The saturation solubility method was used to regulate aqueous solubility of DOMP and MCICs in water. To individual vials containing 10 ml of water (solvents), MCIC, namely DOMP-IC-T, DOMP-PM-T, DOMP-IC-B, DOMP-PM-B and DOMP, were added in excess. After 24 hours of being shaken at 25°C and 100 rpm, the sealed vials were emptied and the contents filtered by Whatman filter paper. Appropriate dilutions of samples were then used for estimate.[10-11, 22]

Table 1: Binary and Ternary System Phase solubility study

Parameters	DOMP-B	DOMP-T
CE	0.0028	0.0385
$K_C(M^{-1})$	137.25	603.84

Fourier Transform Infrared spectroscopy

Prepared KBr pellets were analyzed using an 8400S FTIR spectrophotometer (Shimadzu Corporation, Japan) to obtain FT-IR of M-β-CD, pure drug, and all formulations. The Sangli, ABCP was site of this investigation.

X-Ray diffraction studies

XRD from PAN Analytical Spectris Pvt. Ltd. in Singapore was used for the powder X-ray diffractometry, which involved a copper target.

Differential scanning calorimetry

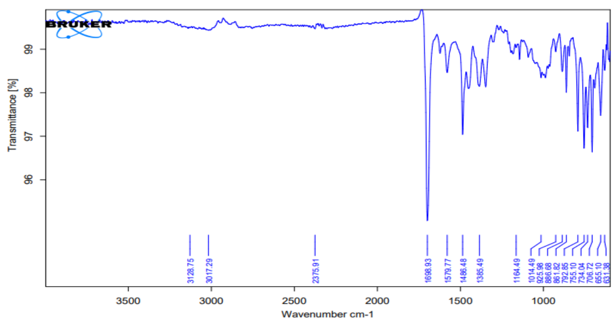

Figure 6: FTIR of Pure Drug DOMP

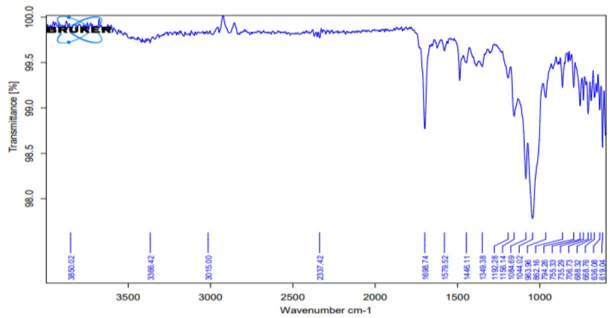

Figure 7: FTIR of DOMP-IC-T

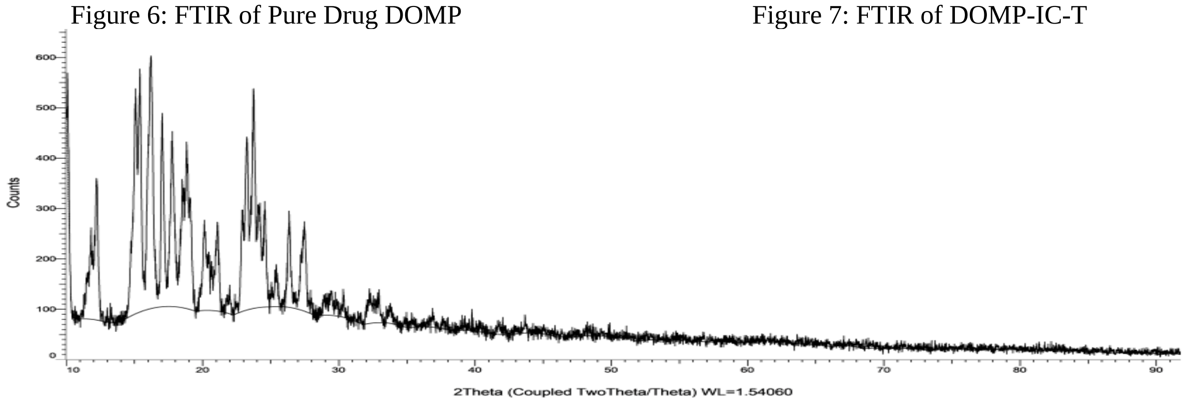

Figure 8: XRD of DOMP

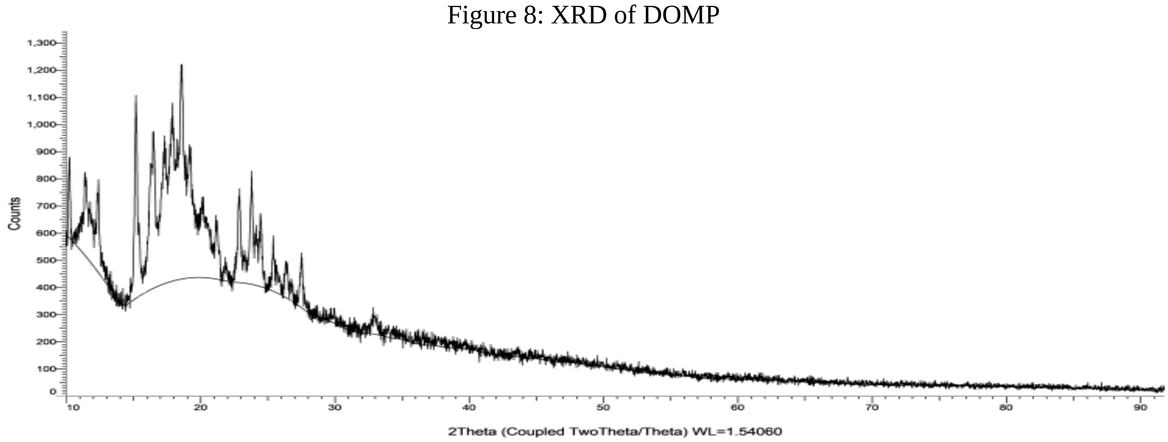

Figure 9: XRD of DOMP-IC-T

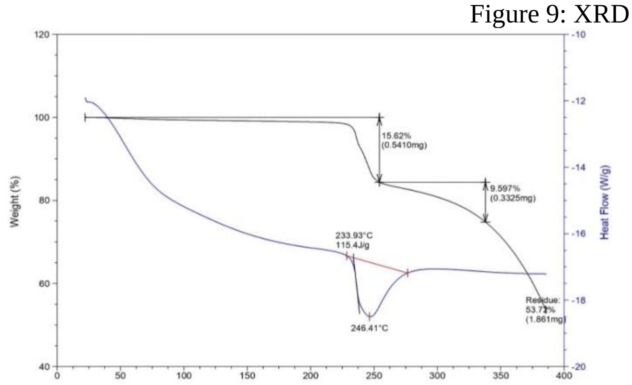

Figure 10: DSC of Pure Drug

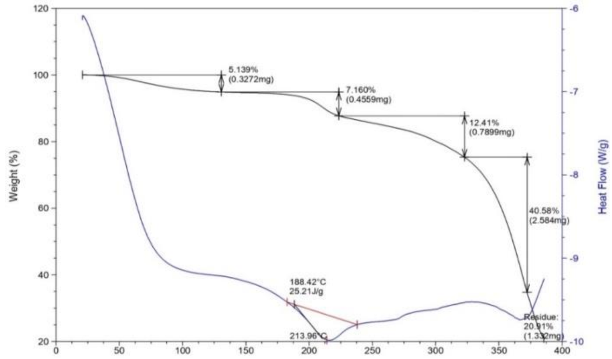

Figure 11: DSC of DOMP-IC-T

The inclusion complexes and pure drugs were both studied using DSC. Using a nitrogen atmosphere and a heating (10°C/min), DSC examination was accomplished using an SDT Q600 from TA Instruments USA. 0-400°C was temperature range that was utilized.

Proton Nuclear Magnetic Resonance Spectroscopy

A Bruker II 400 NMR Spectrometer was used to analyze the DOMP and MCIC samples for 1 H NMR in order to detect presence of any complexes. We used DMSO d as our solvent. The research took place at Solapur's PAH Solapur University.

In-vitro Dissolution studies

Dissolution investigation were conducted on both pure drug and MCIC, which is equivalent to 10 mg of medication. Here is what dissolution test conditions were: The operating conditions phosphate buffer (pH 6.8) 900 mL, 100 rpm of speed, 37 ± 0.5°C of temperature, and a USP class II rotating paddle device. At 5, 30, and 60-minute interludes during dissolving research, 5-milliliter aliquots were removed and replaced with 5-milliliter volumes of fresh medium. A blank made of phosphate buffer was used to measure absorbance at 284.00 nm after the extracted materials were filtered by Whatman's filter paper. At each time point, we calculated the cumulative percentage of medication dissolved and plotted that against the passage of time in minutes.[10]

RESULTS AND DISCUSSION

Screening of auxiliary agent and its Concentration

Solubility was improved to a maximum of 27.18 in AA screening study, as shown in Fig. 1, by CTA. It also shows that of three AXAs tested, CTA increased DOMP solubility the most. Figure 2 shows that DOMP's solubility increases linearly with increasing AXA

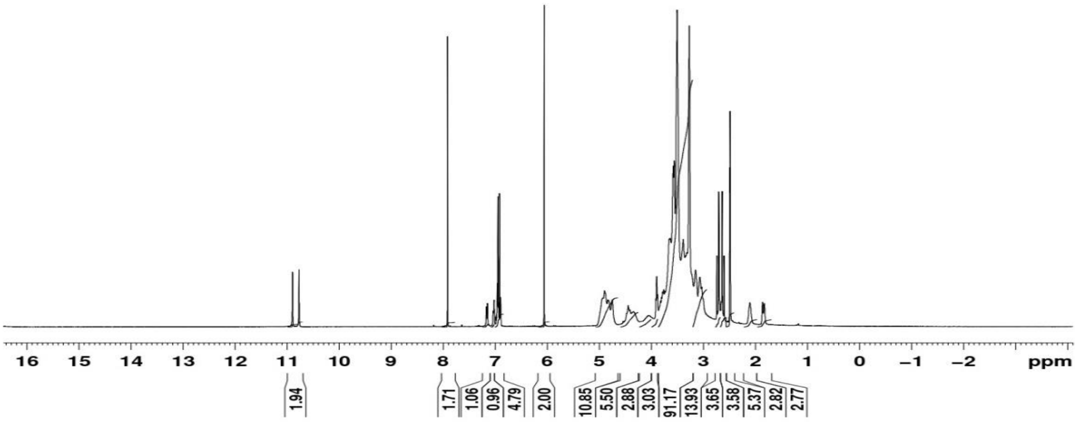

Figure 12: NMR of DOMP

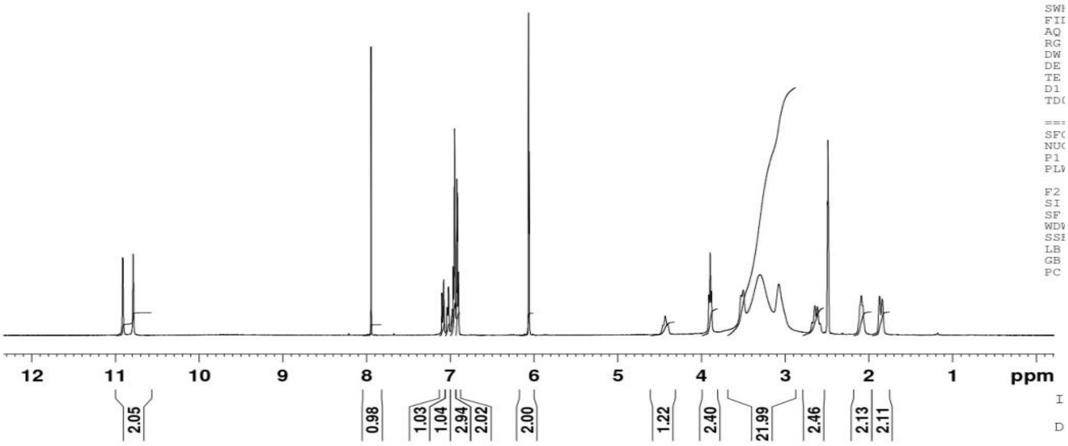

Figure 13: NMR of DOMP-IC-T

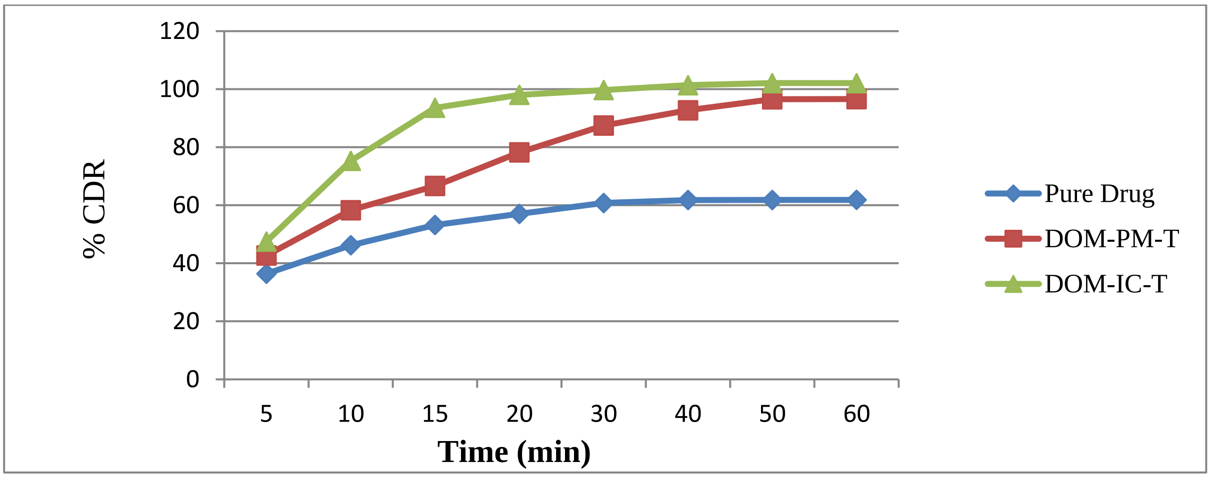

Figure 14: Pure DOMP and other complexes in-vitro dissolution profile

concentrations up to 0.4%, but thereafter it stopped increasing significantly. Therefore, in order to conduct phase solubility investigations and create ternary complexes, 0.4% CTA was utilized as the third component.

Phase solubility studies

Binary system: The results suggest that HP-β-CD and M-β-CD have a solubility curve that is similar to the AL type, suggesting that DOMP is more soluble in these compounds than in β-CD (Figure 3). Additional research using M-β-CD shown even greater enhancement in the solubility of DOMP. Challa et al. provide strong evidence for this claim.[16]

Binary and Ternary system: The stability constant (Kc) for 1:1 complex of DOMP-B was found to be 137.25 M^{-1}, while for DOMP-T it was 603.84 M^{-1}, according to slope of straight line in AL type solubility diagram (Figure 4). To expand bioavailability of medications that are poorly soluble in water, Kc values that were determined are sufficient for formation of inclusion complexes.[23] Table 1 shows the Binary and Ternary System Phase solubility study.

Saturation solubility study

Saturation solubility tests were performed on binary, ternary complexes and DOMP, in water, and the results are displayed in Figure 5. Development of binary and ternary complexes by M-β-CD and citric acid amended aqueous solubility of DOMP. DOMP-IC-T ternary complex increased DOMP solubility more than the DOMP-PM-T complex or the binary complex did. A solubility 8.770 µg/ml was determined for DOMP in water. Solubility was observed to increase in all cases, according to the data (Figure 5). However, inclusion complexes formed by M-β-CD and citric acid in 1:1:0.4% ratios by kneading method showed the largest rise, 42 times advanced than pure drug.[24]

FTIR Spectroscopy

In order to determine existence of various functional groups, FTIR spectra were tracked. Figure 6 and 7 display the FTIR spectra of DOMP and DOM-IC-T, respectively. The stretching vibration bands of C=O, C-N, N-H, and two C-O are observed in FTIR spectra at 3128.75, 1698.93, 1486.48, 1385.49, and 1164.49 cm^{-1}, respectively. There was no evidence of drug-polymer interaction in the spectra of DOMP-IC-T, as nearly all drug characteristic peaks (3015.00, 1698.74, 1446.11, 1349.36 and 1156.14 cm^{-1}) were present. [10,17-18]

X-ray diffractometry Studies (XRD)

The crystalline nature of DOMP, M-β-CD and citric acid was evaluated by X-ray diffraction studies. DOMP shows the sharp and less diffused characteristic peak in diffraction pattern of drug which indicate crystalline nature of drug (Fig: 8). Diffraction pattern of DOMP-IC-T shows the less sharp and highly diffused characteristic peak. The decreased intensity of characteristic peak in diffraction pattern of DOM-IC-T shows the decreased in crystalline nature of drug and formation of amorphous MCIC formation (Fig: 9).[17, 19]

Differential scanning calorimetry

The fact that DOMP's thermal curve showed its crystalline anhydrous condition (Tpeak = 246.51°C, ΔH=115.4 J/g) is evident. The drug melting endotherm's peak temperature (Tpeak=213.96°C, ΔH=25.21.4 J/g), as well as its area, broadening, and downward shifting, are all revealed by the DOMP-IC-T (Figure 10 and 11). The latter occurrence was produced by development of inclusion complexes and/or amorphization of DOMP. The findings clearly point to the presence of robust physical interactions among M-β-CD, DOMP, and AAs (CTA), and establishment of a stable ternary complex.[20-21]

Proton nuclear magnetic resonance spectroscopy (1H NMR)

Chemical shifts in NMR spectra are based on the number of protons contributing to a signal. Spectral peaks between 0 and 3 ppm correspond to protons in alkyl chains, while peaks around 3 to 5 ppm are associated with protons attached to carbons bonded to electronegative atoms. Protons between 6 and 8 ppm are likely aromatic, indicating a benzene or aromatic ring. Signals above 8 ppm often correspond to aldehyde or carboxylic acid protons. Multiplicity is caused by neighboring hydrogens, with peaks often n+1. The dominant peaks around 7-8 ppm suggest aromatic rings, alkyl chains, and ethers, alcohols, or amine functionalities Fig.12. The spectrum of a compound reveals a carboxylic acid (-COOH) group, aromatic rings, alkyl chains, and possibly an oxygen-containing group. The 12-ppm peak indicates a carboxylic acid proton, while the 7-8 ppm range indicates aromatic protons. The 4-5 ppm peak may indicate protons attached to carbons bonded to electronegative atoms like oxygen, suggesting alcohol, ether, or ester functionality. The 0-3 ppm range includes aliphatic protons and alkyl chains. Other significant peaks are attributed to protons adjacent to electronegative atoms or double bonds Fig.13.

In-vitro Dissolution studies

The purpose of the in vitro dissolution investigation was to examine how the complexes' release behaviour was affected by the increased solubility of DOMP. In Figure 14, we can see the outcomes of the in vitro dissolving experiment. In the first ten minutes of dissolution, 36.41% of DOMP was released in pH 6.8 phosphate buffers. Maximal drug release of 61.81% was achieved after 60 minutes.

Atend of 10 minutes, drug release from DOMP-PM-T was 58.10%, while the release from DOMP-IC-T was 75.30%. The order of drug release, consistent with saturation solubility data, was observed to be pure DOMP < DOMP-PM-T < DOMP-IC-T at the end of 60 minutes. Ternary complexes that included citric acid and were made using the kneading approach outperformed the other complex in terms of drug release and rate of dissolution of DOMP. Solubilizing activity of M-β-CD is improved by adding AXAs because of their hydrophilicity and capacity to create hydrogen bonds in the MCIC.[25-30]

CONCLUSION

Solubility and dissolution profile of DOMP were considerably enhanced by the creation of ternary inclusion complexes utilizing M-β-CD and citric acid, as this investigation indicated. Solubility was improved by a factor of 42 when compared to pure DOMP, thanks in large part to the kneading procedure. The drug release p of ternary complexes was shown to be superior to that of binary complexes and pure DOMP in vitro dissolution studies. A possible strategy for increasing bioavailability of pharmaceuticals like DOMP that are not very water-soluble is to form ternary inclusion complexes with citric acid as an auxiliary agent, according to the results. Investigating the formulation's potential for clinical uses and improving it could be the subject of future research.

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