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FORMATION OF INCLUSION COMPLEX OF ANTI-INFLAMMATORY TRITERPENOID CABRALEONE (DN12) WITH HYDROPHILIC BETA CYCLODEXTRIN POLYMER (β-CD-P)

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Keywords:

Inclusion complex, β-Cyclodextrin Polymer, Triterpenoid, Cabraleone, inflammation

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ABSTRACT: The main objective of this study was to improve the solubility of the triterpenoid cabraleone (DN12) and to investigate the anti-inflammatory activity of the complex. DN12 was stabilized by a complex formation with β-cyclodextrin polymer (β-CD-P) in a molar ratio of 1.0:1.0. The DN12 extract and the cyclodextrin complex have been equilibrated in ethanol at 25°C for approximately 24 h. The β-cyclodextrin-polymer complex (β-CD-P-DN12) was characterized by a combination of experimental methods including ultraviolet-visible spectroscopy, differential scanning calorimetry, thermogravimetric analysis, X-ray diffraction, infrared and nuclear magnetic resonance. The formation of the complex with β-cyclodextrin-polymer was confirmed by the use of five analytical tools. *In-vivo* anti-inflammatory activity, using 1 % of the carrageenan-induced rat paw oedema method of the β-CD-P-DN12 complex compared to that of DN12 alone was studied. The results showed that inclusion complex formation β-CD-P-DN12 improved stability and solubility in aqueous solution compared to free DN12. The results of the *in-vivo* study showed that the β-CD-P-DN12 inclusion complex exhibited different pharmacokinetics as compared to free DN12 after injection into the rat paw. The anti-inflammatory activity of DN12 triterpenoid appears earlier when it was complexed within the beta cyclodextrincavity of polymer as compared to free DN12.

INTRODUCTION: Among the various inorganic and organic compounds commonly used as drug carriers, there are cyclodextrins (CDs); a class of biodegradable cyclic oligosaccharides [1]. Due to their hydrophobic inner cavity and hydrophilic outer surface, their unique molecular structure can form supramolecular host-guest complexes with various hydrophobic molecules [2, 3].

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Many studies have already reported the use of cyclodextrins to protect triterpenes and improve their solubility, such as sericoside and azadirachtin which form inclusion complexes with various CDs [4].

In this contribution, the triterpene cabraleone (DN12) **Fig. 1** has been isolated from the leaves of *Combretum glutinosum* [5]. Cabraleone is a molecule with analgesic and anti-inflammatory activity, justifying the use of the *Combretum glutinosum* plant in traditional medicine to manage pain and inflammation [6]. However, the use of cabraleone as a triterpene is severely limited due to its low solubility in water and high sensitivity to environmental stresses such as temperature, light

and oxidation, leading to its chemical degradation and ultimately to a negative impact on the preservation of medical and paramedical formulations. To address this issue, we have initiated a comprehensive study of the encapsulation behavior and stability of CD complexes with DN12, which has not been described yet.

Therefore, the purpose of this work is to study the formation of the β-CD-P-DN12 inclusion complex and to estimate the anti-inflammatory activity of the complex, after the DN12 release. The stoichiometry of the inclusion complex of the β-CD-P-DN12 system in aqueous media is reported. Ultraviolet-visible spectroscopy (UV/VIS) was used to record the absorption spectrum of the β-CD-P-DN12 complex in aqueous solution. In addition, the formation of inclusion complexes was characterized in solid state by differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), thermogravimetric analysis (TGA) and nuclear magnetic resonance spectroscopy (NMR) to verify inclusion complex formation. Finally, anti-inflammatory activity was evaluated by measuring the thickness of inflammatory oedema in rats using calipers. We particularly aim to explore the binding capacity of the resulting inclusion complexes which will provide a useful approach to make new health products which protect us against environmental stresses based on cabraleone (DN12) **Fig. 1.**

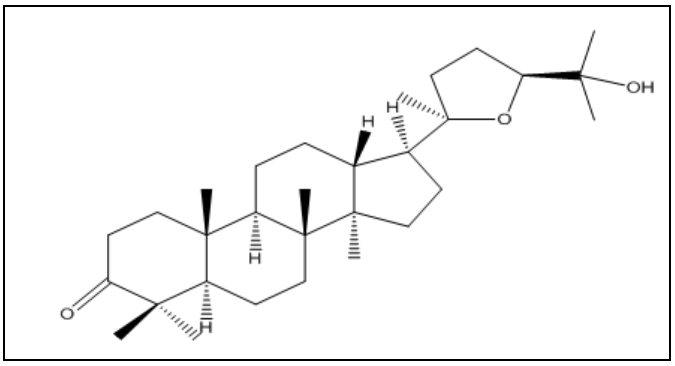

FIG. 1: CHEMICAL STRUCTURE OF CABRALEONE (DN12)

MATERIALS AND METHODS:

Materials: The cabraleone (DN12) used in this work was obtained by extraction, isolation and further characterization according to the protocol described in the literature from the dry leaves of *Combretum glutinosum* harvested in Senegal, particularly in the region of Kaolack [5]. The beta-cyclodextrin polymer (β-CD-P) was synthesized according to a previously reported study [7].

The animal material used for the anti-inflammatory and analgesic activities consisted of male and female Wistar rats weighting between 120 to 200 g on average. The rats were bred in the animal house of the Pharmacology Department of the Faculty of Medicine, Pharmacy and Odontology (FMPO) at Cheikh Anta Diop University (CADU) of Dakar.

Methods:

Preparation of Cabraleone Inclusion Complex (DN12): Cabraleone (0.02 mmol, 9.16 mg) was dissolved in a 95% ethanol solution whereas β-CD-P (0.02 mmol, 22.68 mg) was dissolved in a 20% ethanol solution.

The complex was formed by mixing soluble DN12 with β-CD-P (2ml, v:v 1:1) [8, 9]. The mixture has been stirred for 24 hours at room temperature. The sample mixture was evaporated under reduced pressure and then the sample has been dried in a drying bell for 24h at a temperature of 40°C.

A physical mixture has been prepared which consists of mixing (0.02 mmol, 9.16 mg) mg of DN12 and (0.02 mmol, 22.68 mg) β-CD-P without using solvents.

Ultraviolet-vis Spectroscopy: Solutions containing a fixed DN12 concentration of 2 mmol/L and β-CD-P concentrations ranging from 2 to 10 mmol/L were respectively prepared. The mixtures have been stirred for 2 hours, and the UV absorption spectra were recorded on a VARIAN Cary 50 bio-UV-visible spectrometer UV/VIS spectra of DN12 and β-CD-P were also recorded for comparison. Scans were performed at a speed of 190-800 nm.

Infrared Spectroscopy: Infrared spectroscopic experiments were carried out in a fully automated device controlled by Opus® software, with technical characterization of the 7500-370 cm spectral range^{-1} with a resolution of better than 1 cm^{-1}. This is associated by wavelength accuracy of better than 0.01 cm^{-1} at 2000 cm^{-1}. That enabled our solid samples to be analyzed in the near, mid and far infrared.

X-ray Powder Diffraction Pattern: Experiments were carried out in a powder X-ray diffraction (XRD) apparatus with characterization of D8 DA VINCI with fast LYNXEYE detector and 9-sample changer. Spectra were recorded in an intensity curve of the diffracted X-rays as a function of the diffraction angles between 4 and 80 theta.

Differential Scanning Calorimetry: DSC curves were obtained using a DSC 25 scanning calorimeter thermogram. Masses of approximately 2 mg of each sample were placed in an aluminum container and sealed with an unperforated aluminum cover. An empty non-thermal aluminum tray was used as a reference and nitrogen (grade 4.5) was added at a flow rate of 25 ml/min. DSC curves were measured by heating the samples from -50 to +380°C at an equilibration rate of 20°C/min.

Thermogravimetric Analysis: The Labsys Evo1150 Setaram thermogravimetric analysis (TGA) was used to determine the mass loss or gain on each sample as a function of temperature (from 20°C to 1150°C and at different heating rates) in a controlled atmosphere (Argon).

Nuclear Magnetic Resonance: Bruker's 400MHz ultra-shielded spectrometer controlled by an Avance II console and equipped with a 60-position sample changer, which enables rapid, non-destructive analysis of soluble molecules or macromolecules, was used to compare the chemical shifts of DN12, β-CD-P and the β-CD-P-DN12 inclusion complex.

Anti-inflammatory Activity of the β -CD-P-DN12 Inclusion Complex: Carrageenan-induced Rat Paw: Anti-inflammatory activity was evaluated *in-vivo*, using 1 % of carrageenan-induced rat paw edema method [10]. Then, the rats had been fasted for 12 h before the experiment. They were released in batches of 2: DN12: 1 mg/kg, *per os*) and β-CyclodextrinPolymer-DN12 (P12 or β-CD-P-DN12) (DN12: 1 mg/kg, *per os*).

The anti-inflammatory study was carried out following the method described by Winter [10]. The rats had been fasted for 12 hours before the tests. Before treatment, the initial volume (V_0) of the left hind paw was measured using a water plethysmometer (APELEX 05-7150), Allinde, Bagneux, France. A 100 µl injection of 1 % carrageenan into the foot pad of rat paw was carried out 1 h after gavage of the tested product. The rat paw edema volume was measured at 3 and 5 hours. The significance of edema was assessed by determining the mean percent increase (% INC) in rat paw volume according to the formula:

$$\% \text{ INC} = (V - V_{t0} / V_0) \times 100.$$

V_t = paw volume at time t in hours. V_0 = initial paw volume.

Expression of Results and Statistical Analysis: The results were expressed as mean ± standard error of mean (sem). The student test was used to highlight the existence of a significant difference with a p significance threshold of 0.05. n=5 is the number of experiments in each group.

RESULTS AND DISCUSSION: The aim of this contribution was to improve the solubility of cabraleone (DN12), to protect the triterpene through encapsulationin beta-cyclodextrin polymer (β-CD-P) and to determine their release over time by observing the anti-inflammatory activity of the complex. Different analytical techniques such as UV-visible spectroscopy, IR, XRD, DSC, TGA and H-NMR, were used to demonstrate the inclusion complex formation between the cabraleone (DN12) and the beta-cyclodextrin polymer (β-CD-P). The anti-inflammatory activity of DN12 encapsulated in β-CD-P was also determined in rat paw oedema model.

Ultraviolet-visible Spectroscopy: The inclusion complex of DN12 and β-CD-P in aqueous solution was characterized using UV spectroscopy. **Fig. 2** illustrates the effects of β-CD-P concentration on the spectra of DN12 in aqueous solution. The absorption peak of DN12 in aqueous solution is detected at 283 nm. The absorbance of DN12 significantly varied with the addition of β-CD-P.

Increasing the concentration of β-CD-P from 2 to 10 mmol/L resulted in a decrease in the absorbance of DN12, compared with that of the free DN12 aqueous solution at the same concentration. These changes could be attributed in part to the shielding of chromophore groups in the DN12 molecule, which may be the result of complex formation between DN12 and β-CD-P *via* hydrophobic or vander Waals interactions [11].

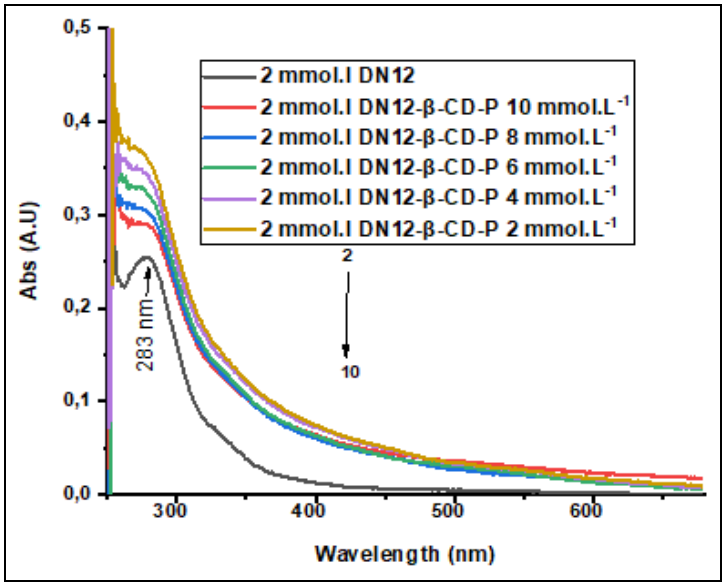

FIG. 2: UV-VISIBLE SPECTRA OF FREE DN12 (BLACK LINE) AND DN12 IN THE PRESENCE OF BETA-CYCLODEXTRIN POLYMER (B-CD-P) AT CONCENTRATION IN THE RANGE 2-10 MMOL.L^{-1}

Dissociation Constant: DN12 is a water-insoluble triterpene, so ethanol was used as a solvent to study the dissociation constant of the β-CD-P-DN12 inclusion complex. We observed that the addition of β-CD-P at different concentrations to DN12 did not change the position of the P-β-CD-DN12 complex characteristic absorption peak. However, as the concentration of P-CD increased, the absorbance of the resulting complex decreased.

Assuming that the stoichiometry of the inclusion complex of DN12 to β-CD units in the β-CD polymer was 1:1, the formation of the inclusion complex could be described by the Benesi-Hildebrand method [12]: where H represented the host, namely the β-CD unit in the polymer, and G was the guest, namely DN12;K_D the dissociation constant of the *P-β-CD* complex.

Applying the different equations from 1 to 3 gives the equation 4.

$$H+G = HG \qquad (1)$$

$$KD = ([G0]-x)\,([H0]-x) / x \qquad (2)$$

$$A= \epsilon H\,([H0]-x) + \epsilon_G\,([G0]-x) + x\epsilon_{HG} \qquad (3)$$

Є: Molar Absorption Coefficient

$$[G0] = [H0]$$

$$[G_0]^{\wedge 2} / \Delta A = k_D/\Delta\varepsilon + [H_0] / \Delta\varepsilon \qquad (4)$$

By plotting $[G]_0^2$ /ΔA as a function of $[H_0]$, a straight line was obtained **Fig. 3**. According to the slope and intersection of the linear dependance, y=6.4x + 19.6, the dissociated constant K_D of the inclusion complex was evaluated at 3.06 10^{-3}mol/L. The result is similar to the formation of the inclusion complex between the guest and beta cyclodextrin polymer [13, 14]. We can therefore conclude that the 1:1 ratio enables us to form the β-CD-P-DN12 inclusion complex.

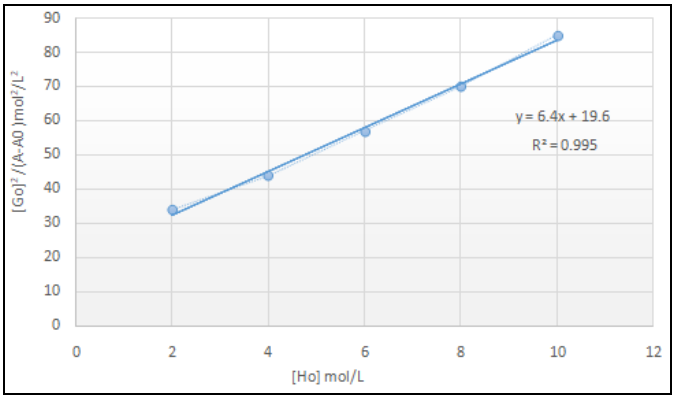

FIG. 3: DETERMINATION OF THE DISSOCIATION CONSTANT BY PLOTTING $[G]_0^2$ /ΔA AS A FUNCTION OF $[H_0]$

Infrared Spectroscopy: Infrared spectroscopy measurements were made on different samples, namely the free triterpene and beta-cyclodextrin polymer as well as on the host-guest inclusion complex and physical mixture with the aim to unambiguously demonstrate the effective inclusion of DN12. The infra-red IR spectra of DN12 (black),β-CD-P(blue), as well as the physical mixture PM β-CD-P-DN12 (red) and the inclusion complex CI β-CD-P-DN12 (green) of the host and

guest are shown in **Fig. 4**. The physical mixture shows the OH peaks of DN12 and β-CD-P (3489 cm^{-1} and 3370 cm^{-1}); the C=O peak of DN12 (1698 cm^{-1}); the spectrum of the physical mixture matched well those of the β-CD-P and DN12 showing the OH band at 3370 cm^{-1} in about 3489 cm^{-1}, respectively and the carbonyl band at about 1681 cm^{-1} in the latter.

These features indicated that the interaction through inclusion complex formation did not occur during simple physical mixing between the two products DN12 and β-CD-P. **Fig. 4** shows also the characteristic bands at 3370 cm^{-1} corresponding to OH groups for the virgin β-CD-P, is shifted to lower wave number at 3331cm^{-1} for the β-CD-P-DN12 inclusion complex. Such effect suggests that interaction between DN12 and the β-CD-Poccurs also out of the interior of the β-CDcavity, which can be rationalized by the large size of DN12.

Then the characteristic C=O band of the virgin DN12 vanishes when forming the complex with the β-CD-P. This shows that the C=O function may be interacting with the β-CD-P. In addition, the intensity and shape of the bands that are clearly observed in the spectrum of the physical mixture are considerably changed in the spectrum of the inclusion complex, showing the disappearance or reduction of the absorption intensities of the corresponding bands [15].

The inclusion complex spectrul resembles the spectrum of pureβ-CD-P. Consequently, we could suggest that some functional groups of DN12 are included in the cavity of the β-CD-P molecules to form the inclusion complex and that the ring with the C=O function may be the part that is inserted into the cavity of the beta-cyclodextrin polymer (β-CD-Pβ) [16, 17].

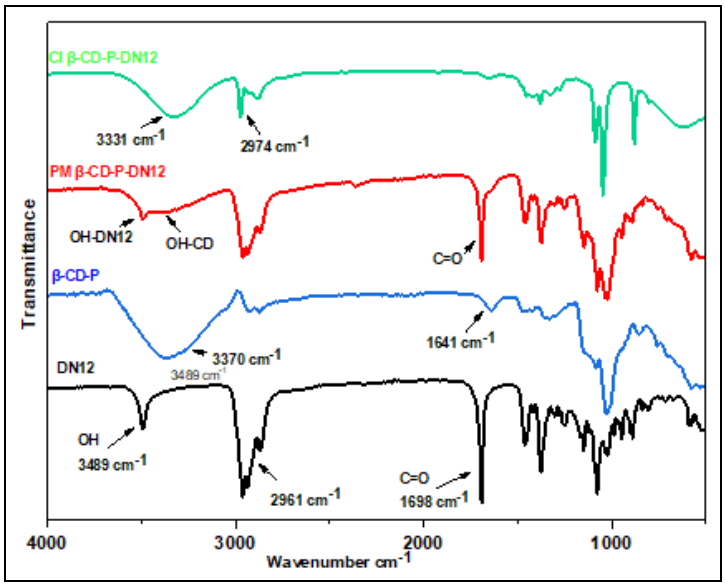

FIG. 4: INFRARED SPECTRA FROM DOWN TO TOP OF DN12 (BLACK), B-CD-P (BLUE), THE PHYSICAL MIXTURE OF DN12 AND B-CD-P (RED) AND THE B-CD-P-DN12 INCLUSION COMPLEX (GREEN)

X-ray Diffraction: X-ray diffraction measurements were carried out before and after the formation of the inclusion complex between the triterpene DN12 and the beta-cyclodextrin polymer (β-CD-P). To evaluate the structure of the different samples, the XRD curves are shown in **Fig. 5** for DN12 (black), β-CD-P (blue), the physical mixture (red) and the β-CD-P-DN12 inclusion complex (green). **Fig. 5** shows that DN12 is in a crystalline state while the beta-cyclodextrin polymer β-CD-P is in an amorphous state. We can notice that the physical mixture between the two products exhibits intense and thin diffraction peaks that can be assigned to the presence of free DN12 in the physical mixture that are superimposed to an amorphous halo assigned to the presence of the β-CD polymer.

However, in the case of the inclusion complex, we observe a change in the XRD profile where the sharp and intense peaks indicating the crystalline state of DN12 are not visible and broad peak is observed indicating the amorphous nature of the inclusion complex [4].

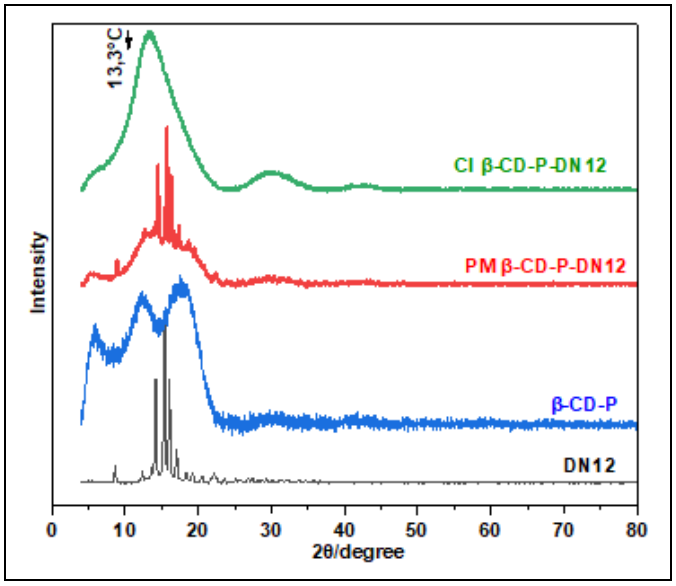

FIG. 5: XRD CURVES FOR DN12 IN BLACK, THE BETA-CYCLODEXTRIN POLYMER (B-CD-P) IN BLUE, THE PHYSICAL MIXTURE IN RED AND THE XRD CURVE FOR THE B-CD-P-DN12 INCLUSION COMPLEX IN GREEN

Differential Scanning Calorimetry (DSC): DSC is a powerful analytical technique to determine the thermal properties of solid cyclodextrin complexes. This technique is widely used to study changes in thermal behavior in the preparation of the inclusion complex [15]. The DSC profiles recorded for the beta-cyclodextrin polymer, the physical mixture and the β-CD-P-DN12 inclusion complex are shown in **Fig. 6**. In general, complexation leads to the disappearance of endothermic peaks, the appearance of new peaks and the broadening or shifting of peaks at different temperatures, indicating a change in the crystal structure [18, 19].

The DSC thermograms of the β-CD-P and of the physical mixture show an endothermic peak at 112.63°C and 150.47°C while the thermogram of the β-CD-P-DN12 inclusion complex shows a peak at 94.90°C. So, it is noticeable that the intensity of the broader endothermic peak has been reduced and the position of the peak has also been shifted. These changes suggest the formation of the inclusion complex and confirms that there is no or less interaction between the two molecules in the physical mixture.

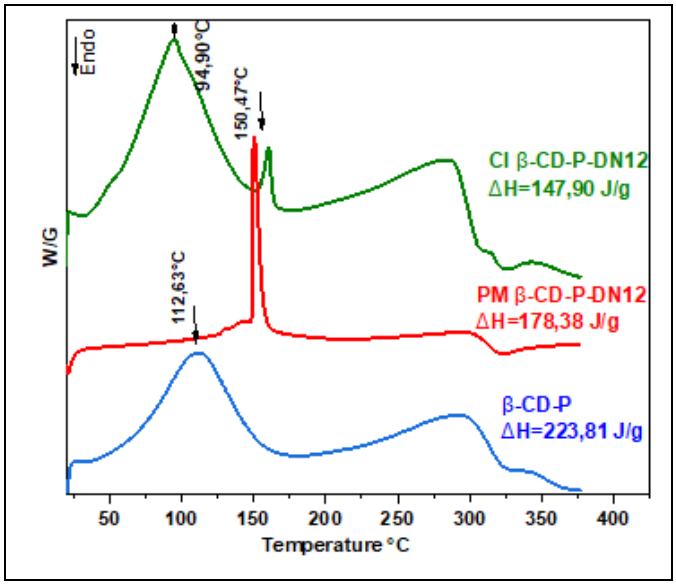

FIG. 6: DSC PROFILES FROM BOTTOM TO TOP OF THE B-CD-P (BLUE), THE PHYSICAL MIXTURE (RED) AND THE B-CD-P-DN12 INCLUSION COMPLEX (GREEN)

Thermogravimetric Analysis (TGA): The thermal stability of the inclusion complex was evaluated by a thermogravimetric analysis over the temperature range of 50-800°C. **Fig. 7** shows the thermograms for DN12 (blue), β-CD-P (red), the physical mixture (green) and the inclusion complex (black). Analysis of the ATG curves shows that DN12 starts decomposing at around 309°C whereasβ-CD-Pstarts decomposing at lower temperature of 274°C.

In **Fig. 7**, the physical mixture and the inclusion complex between DN12 and β-CD-Pstarts decomposing at 281°C and at 294°C respectively, the temperature range follows that of β-CD-P. A weight loss was also observed in the range 400 - 780°C which can be explained by the thermal stability of DN12 in the β-CD-P-DN12 complex and it is also observed that the range moves slowly downwards, which is an expected trend indicating that the thermal stability of the β-CD-P-DN12 complex is better than that of DN12, due to a stronger interaction between DN12 and the β-cyclodextrin polymer (β-CD-P) [20, 21].

It is expected that in β-cyclodextrin polymer powder sample, the hydrophilic inner part of the β-CD cavities is filled with water molecule. The thermogram of the β-CD-P shows a mass loss up to 250°C. An initial mass loss is also observed in the thermogram of the physical mixture confirming that the DN12 is not included with the β-CD cavities.

It is noteworthy that the thermogram recorded for the inclusion complex exhibits a very different behavior in the initial temperature range as no weight loss is observed. This feature suggest that upon inclusion complex formation the water molecules are released from the interior of β-CD cavity filled with a part of the hydrophobic DN12 molecule.

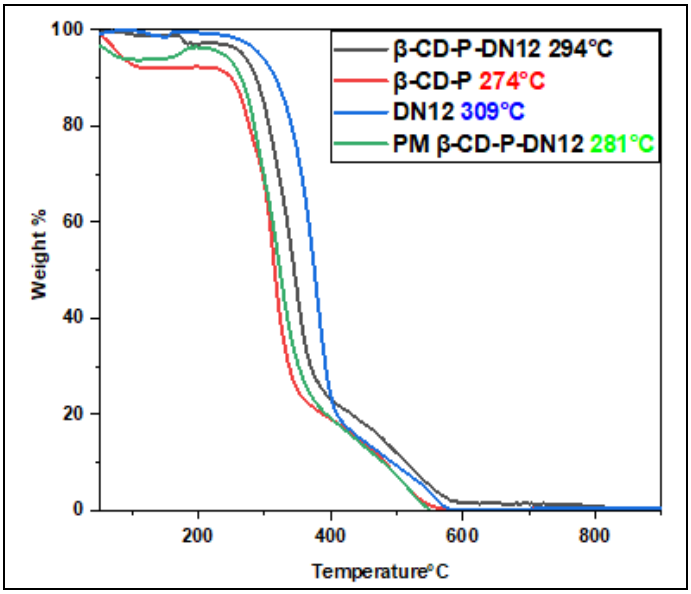

FIG. 7: TGA CURVES FOR FREE DN12 (BLUE) AND B-CD-P (RED), THE PHYSICAL MIXTURE (GREEN) AND THE B-CD-P-DN12 INCLUSION COMPLEX (BLACK)

^{1}H-NMR Spectroscopy: Nuclear magnetic resonance (NMR) is the most effective method for studying the spatial conformation of cyclodextrin inclusions.

Fig. 8 shows that the signals from DN12 in red as protons that are next to the C=O carbonyl have almost disappeared in the spectrum of the β-CD-P-DN12 inclusion complex in green; this reflects the inclusion of the guest compound in the CD-P.

We can see that H-19, H-28, H-29, H-5 and H-2 on DN12 show significant downfield changes in the chemical shift signal (δ), and their range of change is between 0.03 – 0.1 ppm **Table 1**.

In contrast, other hydrogens experience only minor changes in chemical shift. Based on these chemical changes, we can deduce that the inclusion complex of DN12 with β-CD-P has been formed [22, 23].

TABLE 1: CHEMICAL SHIFT OF SOME PROTONS OF DN12 ALONE AND ONCE COMPLEXED WITH THE BETA CYCLODEXTRIN POLYMER (B-CD-P)

	H19	H28	H29	H5	H2
DN12	0,93	1,03	1,07	1,33	2,43
β-CD-P-DN12	0,96	1,05	1,10	1,35	2,34
Δδ	-0,03	-0,02	-0,03	-0,02	0,1

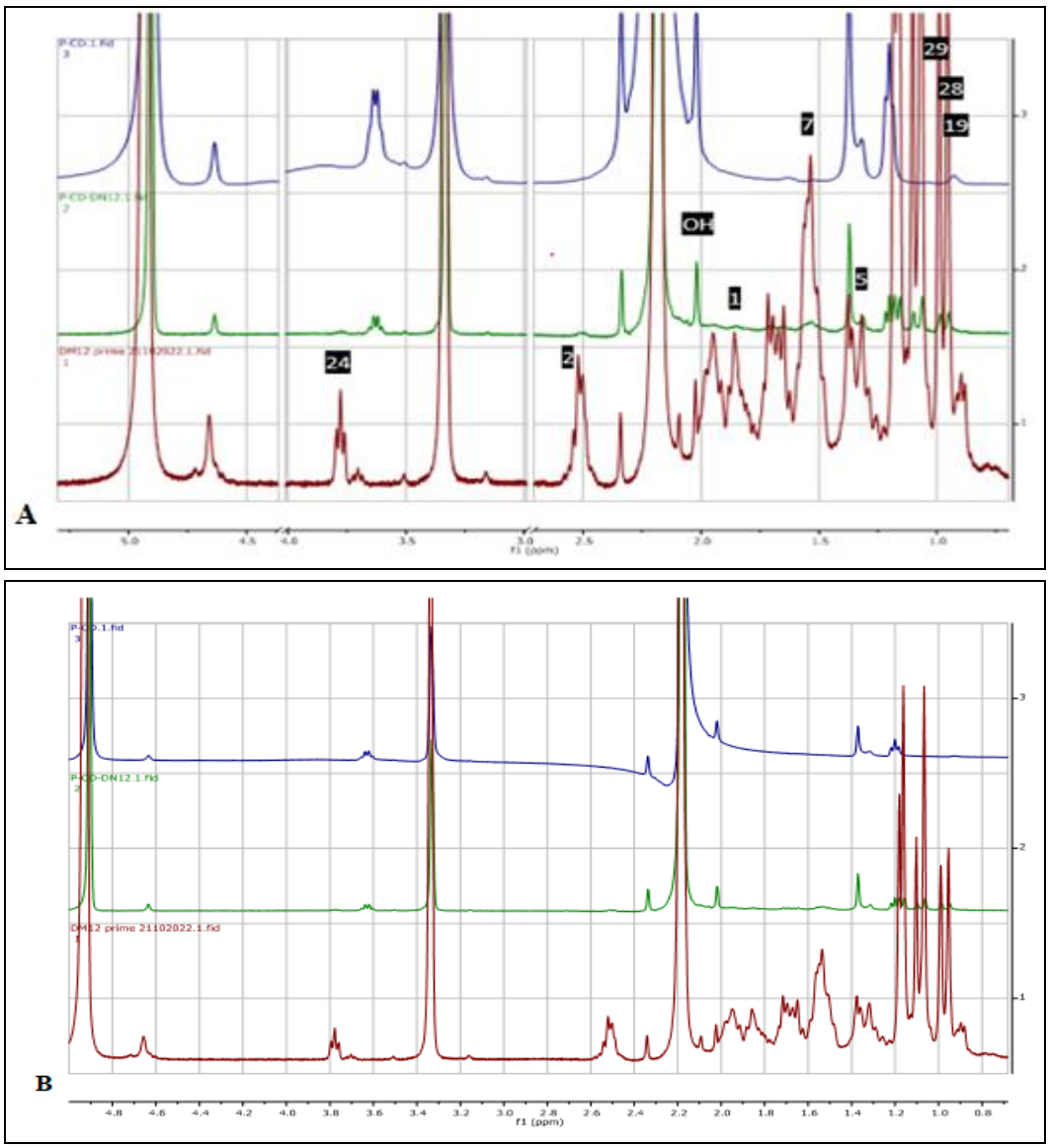

FIG. 8: ^{1}H-NMR SPECTRA OF FREE DN12 (RED) AND B-CD-P (BLUE) AND OF THE B-CD-P-DN12 INCLUSION COMPLEX (GREEN) IN A AND SPECTER TOTAL IN B

Variations of Inflammatory Edema in Carrageenan after β-cyclodextrinpolymer-DN12 (β-CD-P-DN12) Administration: Carrageenan administration in the plantar pad induces inflammatory edema in rats previously treated with β-cyclodextrin (β-CD-P) polymer at a dose of 3 mg/kg *per os*. The variation of edema is 23.20±4.18 % at T1h, 61.80±16.00 % at T3h and 101.33±21.21 % at T5h respectively. The β-cyclodextrin polymer-DN12 (DN12: 1 mg/kg, *per os*), commonly called β-CD-P-DN12, significantly prevents the formation of inflammatory edema after administration of carrageenan. The variations of edema are respectively 10.00±2.42 %, 37.54±3.86 % and 51.41±9.35 %, at T1h, T3h and T5h. These variations are significantly different from that observed in β-cyclodextrinpolymer (β-CD-P) group ($p<0.05$, n=5). The variation of inflammatory edema observed after β-CD-P-DN12 (DN12: 1 mg/kg, *per os*) complex administration, is greater than that observed in DN12 group (1 mg/kg, *per os*) at T3h (37.54±3.86 % vs 50.27±6.26 %)

(P<0.05, n=5). However, the anti-inflammatory activity is identical in β-CD-P-DN12 and DN12 groups at T5H these results suggest a faster absorption of DN12 included in β-CD-P-DN12 that when it is administered alone **Fig. 9**.

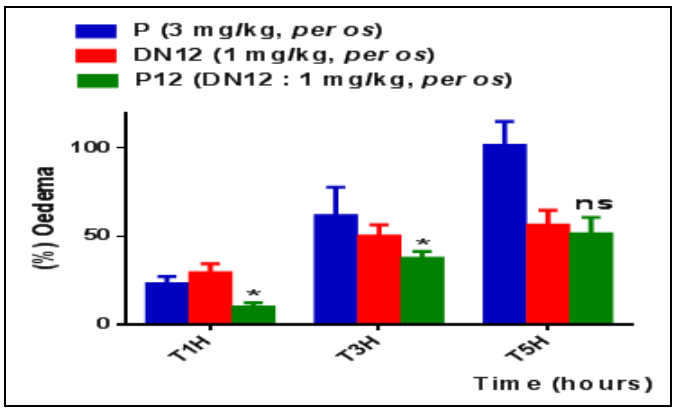

FIG. 9: ANTI-INFLAMMATORY ACTIVITY OF B-CYCLODEXTRIN POLYMER (P)-DN12 COMPLEX (B-CD-P-DN12) IN CARRAGEENAN INDUCED RAT PAW EDEMA. P = B-CYCLODEXTRIN POLYMER, DN12 = CABRALEONE, P12 = B-CYCLODEXTRIN POLYMER (P)-DN12. ** P<0.05 VS DN12. NS: NON SIGNIFICATIF VS DN12*

CONCLUSION: The β-P-CD-DN12 inclusion complex was prepared with a stoichiometric coefficient of 1:1. The various analytical techniques UV visible spectroscopy, IR, DSC, DRX, TGA and NMR confirmed the formation of the P-β-CD-DN12 inclusion complex. The anti-inflammatory activity was also determined on the P-β-CD-DN12 inclusion complex and it was observed that the activity is earlier when the DN12 molecule was complexed within the beta cyclodextrincavity of polymer as compared to free DN12. This is assumed to arise from an increased solubility in its complex form.

ACKNOWLEDGEMENT: Nil

Ethical Issue: The Research Ethics Committee (REC) of Cheikh Anta DIOP University (CADU) in Dakar, Senegal, had approved the use of animal models from the Pharmacology Laboratory of the Faculty of Medicine, Pharmacy and Odontology (FMPO) with the code: 0373/2019/REC/CADU.

CONFLICTS OF INTEREST: There is no conflict of interest.

REFERENCES:

1. Singh J, Dhamija I, Meehenian H, Kumar N, Simran S, Muskan M, Verma ML and Kumar S: Chronicle updates in cyclodextrin-based carriers for drug delivery. Bull Natl Res Cent 2022; 46(1): 202-220.
2. LiJ, Xu F, Dai Y, Zhang J, Shi Y and Lai D: A review of cyclodextrin encapsulation and intelligent response for the release of curcumin. Polym 2022; 14(24): 5421-5439.
3. Xu Y, Rashwan AK, Osman AI, Abd El-Monaem EM, Elgarahy AM, Eltaweil AS, Omar M, Li Y, Mehanni AE, Chen W and Rooney DW: Synthesis and potential applications of cyclodextrin-based metal–organic frameworks: a review. Environ Chem Lett 2023; 21: 447-477.
4. Prodea A, Mioc A, Banciu C, Trandafirescu C, Milan A, Racoviceanu R, Ghiulai R, Mioc M and Soica C: The Role of Cyclodextrins in the Design and Development of Triterpene-Based Therapeutic Agents. Int J Mol Sci 2022; 23(2): 736-768.
5. N'diaye D, Mbaye DM, Gassama A, Lavaud C and Pilard S: Détermination structurale de triterpenoïdes isolés des feuilles de Combretum glutinosium Perr. Ex DC (Combretaceae). Int J Biol Chem Sci 2017; 11(1): 488-498.
6. Sène M, Ndiaye D, Gassama A, Barboza FS, Mbaye MD and SY GY: Analgesic and anti-inflammatory activities of triterpenoid molecules isolated from the leaves of Combretum glutinosum Perr. Ex DC (Combretaceae). J Adv Med Pharm Sci 2019; 19(4): 1-8.
7. Renard E, Deratani A, Volet G and Sebille B: Preparation and characterization of water soluble high molecular weight β-cyclodextrin-epichlorohydrin polymers. Eur Polym J 1997; 33(1): 49-57.
8. Upadhyay C, D'Souza A, Patel P, Verma V, Upadhyay KK and Bharkatiya M: Inclusion complex of ibuprofen-β-cyclodextrin incorporated in gel for mucosal delivery: optimization using an experimental design. AAPS Pharm Sci Tech 2023; 24(4): 100-120.
9. Xu Y, Wang Y, Li C, Han T, Chen H, Chen W, Zhong Q, Pei J, Haenen GRMM, Li Z, Moalin M, Zhang M and Chen W: Preparation, characterization, and biological activity of the inclusion complex of dihydroquercetin and β-Cyclodextrin. AAPS Open 2023; 9: 16-28.
10. Bakshi J, Lathar P, Mehra M, Grewal S, Dhingra D and Kumari S: Evaluation of antiinflammatory response of berberine loaded gum nanocomplees in carrageenan-induced acute edema in rats. Pharmacol Rep 2022; 74(2): 392-405.
11. Lee J, Lee S, Lee S and Oh HB: Noncovalent complexes of cyclodextrin with small organic molecules: applications and insights into host–guest interactions in the gas phase and condensed phase. Molecules 2020; 25: 4048-4075.
12. Li Z, Liu H, Qi C, Yang A and Deng S: Preparation, characterization and molecular modelling of inclusion complex between α-naphthylacetic acid with ethylenediamine-β-cyclodextrin. J Incl Phenom Macrocycl Chem 2019; 93(3): 289-299.
13. Chen M, Wang J, Zhang W, Diao G: Preparation and characterization water-soluble inclusion complexes of imidacloprid-β-cyclodextrin polymer and their electrochemical behavior. J Electroanal Chem 2013; 696: 1-8.
14. Jelić R, Tomović M, Stojanović S, Joksović L, Jakovljević I and Djurdjević P: Study of inclusion complex of β-cyclodextrin and levofloxacin and its effect on the solution equilibria between gadolinium (III) ion and levofloxacin. Monatsh Chem 2015; 146(10): 1621-1630.
15. Pina LTS, Rabelo TK, Trindade GGG, Almeida IKS, Oliveira MA, Dos Santos PL, Souza DS, De Mendes-Filho JER, De Vasconcelos CML, Santos SL, Scotti MT, Araujo

AAS, Quintans JSS, Quintans LJ and Guimaraes AG: γ-Terpinene complexed with β-cyclodextrin attenuates spinal neuroactivity in animals with cancer pain by Ca2+ channel block. J Pharm Pharmacol 2022; 74(11): 1629-1639.

16. Sursyakova VV, Maksimov NG, Levdansky VA and Rubaylo AI: Combination of phase-solubility method and capillary zone electrophoresis to determine binding constants of cyclodextrins with practically water-insoluble compounds. J Pharm Biomed Anal 2018; 160: 12-18.
17. Zhang Y, Li T, Zhao C, Li J, Huang R, Zhang Q, Li Y and Li X: An integrated smart sensor dressing for real-time wound microenvironment monitoring and promoting angiogenesis and wound healing. Front Cell Dev Biol 2021; 9: 1-16.
18. Halder J, Mahanty R, Rajwar TK, Rai VK, Kar B, Ghosh G and Rath G: Nanofibers of glycyrrhizin/hydroxypropyl-β-cyclodextrin inclusion complex: enhanced solubility profile and anti-inflammatory effect of glycyrrhizin. AAPS Pharm Sci Tech 2023; 24(7): 196-210.
19. Hădărugă NG, Bandur GN, David I and Hădărugă DI: A review on thermal analyses of cyclodextrins and cyclodextrin complexes. Environ Chem Lett 2019; 17(1): 349-373.
20. Nerome H, Machmudah S, Wahyudiono, Fukuzato R, Higashiura T, Youn YS, Lee YW and Goto M: Nanoparticle formation of lycopene/β-cyclodextrin inclusion complex using supercritical antisolvent precipitation. J Supercrit Fluids 2013; 83: 97-103.
21. Khatun B, Rather MA, Rohilla S, Borah R, Mandal M and Maji TK: Curcumin hydroxypropyl-$$\beta$$-cyclodextrin complex preparation methods: a comparative study. Chem Papers 2023; 77(8): 4409-4424.
22. Zhang Y, Chen J, Zhang Z, Zhu H, Ma W, Zhao X, Wang M, Wang C, Chen W, Naeem A, Zhang J, Guo T and Wu L: Solvent-Free Loading of Vitamin A Palmitate into β-Cyclodextrin Metal-Organic Frameworks for Stability Enhancement. AAPS Pharm Sci Tech 2023; 24(5): 136-147.
23. Ren L, Jing J, Chen G, Miao Y and Wei P: Preparation, characteristic and pharmacological study on inclusion complex of sulfobutylether-β-cyclodextrin with glaucocalyxin. J Pharm Pharmacol 2014; 66(7): 927-934.

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