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Preparation, Characterization and Dissolution Behaviour of Freeze Dried Complexes of Curcumin-Gamma Cyclodextrin

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

The aim of the current research was to develop and characterize curcumin-gamma cyclodextrin inclusion complexes in order to enhance solubility and rate of dissolution of poorly soluble curcumin. Based on the stoichiometric ratio of 1:1, the inclusion complexes of curcumin with γ-cyclodextrin were prepared by freeze drying method. The prepared dried and solidified inclusion complexes were characterized with the help of infrared spectroscopy, differential scanning calorimetry, and X-ray diffractometry. The comparative evaluation of solubility and rate of dissolution were investigated and compared with pure curcumin. Dissolution study demonstrated only 10% release from pure curcumin at 1 hour as opposed of approximately 72% release form freeze dried curcumin complexes. The freeze dried complexes exhibited almost complete release after 5 hours while only 34% release was observed from the pure curcumin during the same time period. Therefore, the freeze dried complex provided approximately 3 to 7-fold enhancement in the dissolution and release of curcumin over a period of 6 hours of dissolution testing. The kinetics of the *in vitro* release behaviors of the curcumin and curcumin complexes were investigated by

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applying various models such as zero order, first order, Higuchi and Peppas models. The release of the curcumin was observed to follow the first order release kinetics, since the correlation coefficient (R2) for the first order was the highest in comparison to other kinetic models.

Keywords: Curcumin; γ-cyclodextrin; freeze dried inclusion complexes; dissolution; release kinetics.

1. INTRODUCTION

Curcumin is one of the most extensively studied natural compounds as herbal medicine. It is one of the main polyphenols of the widely used house hold spice, turmeric, obtained from *Curcuma longa* (Family. *Zinziberaceae*) [1]. Curcumin is a small molecule with molecular weight of 368.4 g/mol and empirical molecular formula of $C_{21}H_{20}O_6$ Fig. 1. Due to polyphenolic nucleolus, curcumin has been reported to have strong antioxidative and anti-inflammatory activities [2,3]. Furthermore, it has been shown to possess other pharmacological actions such as anti-arthritic [4,5], anti-alzhiemer [6,7], anti-bacterial [8,9], anti-cancer [10,11], anti-diabetic [12,13], anti-viral [14-16], hepatoprotective [17-19] and nephroprotective actions [20-22]. Despite of several pharmacological action, curcumin fails to exhibit potential therapeutic benefits due to its poor bioavailability [23-25]. The bioavailability of curcumin has been reported to be as low as 1% or even undetectable and poor water solubility (0.6-8 µg/ml) has been reported to be the main reason of poor bioavailability [26-28].

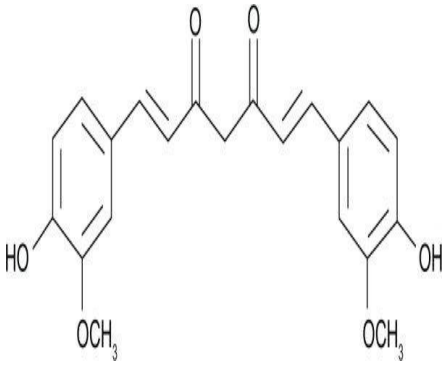

Fig. 1. Chemical structure of curcumin (diferuloylmethane): (1E, 6E)-1,7-bis (4-hydroxy- 3-methoxyphenyl) -1,6- heptadiene-3,5-dione

The development of inclusion complexes of poorly soluble drugs with cyclodexrtrins is considered as one of the most commonly used techniques of solubility and bioavailability enhancement. These are several reports of inclusion complexes of curcumin with alpha and beta-cyclodextrin or their derivatives [29-33]. However, there are few reports with gamma-cyclodextrin [34,35]. The current study reports the development and characterization of solid inclusion complexes of curcumin with γ-cyclodextrin for the improvement of solubility and dissolution of curcumin.

2. MATERIALS AND METHODS

Curcumin and gamma-cyclodextrin were purchased from Loba chemicals (Banglore, India.), and S. D. Fine Chemicals (India) respectively. Other chemicals and solvents used in this study were of analytical reagent grade.

3. PREPARATION OF INCLUSION COMPLEXES

The solid inclusion complexes were prepared in a molar ratio of 1:1 curcumin: cyclodextrin because the phase solubility diagram resulted in A_L type correlation [36]. The complexes were prepared by freeze drying method as reported earlier [37]. Briefly, an accurately weighed equimolar quantities of curcumin and gamma-cyclodextrin were mixed and dissolved in distilled water basified with 27% ammonia solution in order to facilitate the dissolution of curcumin. The resulting solution was kept in the freezer overnight. The frozen mixture was then freeze dried in the Lyph-lock 6 freeze drier (Labconco, MO, USA) for 8 hours. The freeze dried powder was passed through 100-mesh sieve to get homogenous product and stored in a desiccator for further characterization and investigation.

4. CHARACTERIZATION OF INCLUSION COMPLEXES

4.1 X-ray Diffraction Study

The X-ray diffraction study of pure curcumin and its inclusion complexes with γ-cyclodextrin was performed by using X-Ray diffractrometer (PW 1830, Phillips, Japan). The sufficient amount of sample was taken and scanned continuously at °2θ between 5-50° at an interval of 0.020 per

second, keeping the generator tension and current at 30 kV and 25 mA respectively. The The X-RD traces of pure curcumin and freeze dried inclusion complexes were compared with regard to peak position and relative intensity, peak shifting and presence or lack of peaks in certain regions of °2θ values.

4.2 Differential Scanning Calorimetry (DSC)

The differential scanning calorimetry of the pure curcumin, γ-cyclodextrin and freeze dried inclusion complex of curcumin was performed using differential scanning calorimeter (Pyris 6 DSC, Perkin Elmer, MA, USA). The sufficient quantity of samples (approximately 5 mg) were accurately weighed and crimped in the aluminium pans (Perkin Elmer) to get the pallets. All the samples were then scanned between 50-400^{o}C at 10^{o}C/min keeping flow rate of inert nitrogen gas at 20 ml/min.

4.3 Fourier Transform Infra Red spectroscopy (FT-IR)

The FT-IR spectroscopy of pure curcumin and freeze dried inclusion complex were studied by using FT-IR instrument (Win-IR, Bio-Rad, California, USA). The samples were prepared by mixing curcumin or inclusion complex with potassium bromide in a clean glass pestle and mortar and compressed to get pellet. The pellets were scanned between wave number range of 5000-500 cm^{-1} after base line correction.

4.4 In Vitro Dissolution Study

The *in vitro* dissolution study was performed by using USP apparatus I, the basket method. The samples were prepared by filling of pure curcumin (20 mg) or inclusion complexes (equivalent to 20 mg curcumin) in the hard gelatin shells. The dissolution was carried out in 900 ml of simulated gastric fluid (SGF) without pepsin, stabilized at 37 ± 0.5^{o}C with the basket rotating at 75 rpm. The solublizer, 1% w/v of SLS was added in the dissolution medium to maintain the sink condition. The dissolution profiles of all the molecular inclusion complexes were subjected to the kinetic analysis to establish the drug-release mechanism. The release data were fitted to zero order, first order, matrix (Higuchi model), and Peppas models to ascertain the kinetic modeling of drug release [38].

5. RESULTS AND DISCUSSION

5.1 X-Ray Diffraction of Solid Complexes

The X-ray diffraction (XRD) analysis of cyclodextrin based inclusion complexes has been extensively reported as one of the widely used techniques to characterize the formation of amorphous inclusion complexes [39,40]. X-ray diffractogram of curcumin showed various peaks at different angles with most intense one at an angle of 17.68°(100%) followed by 17.62°(92%) and 9.22°(80%) respectively, revealing the crystalline nature of curcumin, as shown in Fig. 2. X-ray diffractogram of γ-CD also showed crystalline nature with peaks at 9.4°(89%), 9.5°(96%), 12.8°(69%), 23°(100%) and 32°(75%) respectively whereas inclusion complex of curcumin-γ-CD showed humps only, suggesting amorphous nature of the complex. These findings are in agreement with the available findings of cucumin-beta-cyclodextrin inclusion complexes [41,42].

5.2 FT-IR Spectral Analysis

The Fourier Transform Infra-Red spectroscopy (FTIR) of cyclodextrin based inclusion complexes has been extensively reported as one of the widely used techniques to characterize the formation of amorphous inclusion complexes [43, 44]. Curcumin has a carbonyl-stretching band at 1629 cm^{-1} and –OH band at 3511 cm^{-1}, therefore, FT-IR could be used to detect guest interactions. The carbonyl-stretching region of IR spectra of curcumin and its complex with γ-CD are presented in Fig. 3. The IR spectra of cyclodextrin showed the peaks corresponding to the nature and position of functional groups present. The spectra of curcumin- γ CD inclusion complex did not show new peaks indicating that no chemical bonds were created in the formed complexes. Though, IR C=O stretching band was instead highly diminished, broader and shifted to lower frequency suggesting the inclusion of the drug in the cyclodextrin cavity. These observations are in agreement with those reported by other group of researchers [45,46].

5.3 Differential Scanning Calorimetry (DSC)

The Differential Scanning Calorimetry (DSC) of cyclodextrin based inclusion complexes has been extensively reported as one of the widely used techniques to characterize the formation of

amorphous inclusion complexes [47,48]. A comparative DSC thermograms of curcumin and inclusion complexes are shown in the Fig. 4. The thermal curve of pure curcumin was typical of a crystalline anhydrous substance with a sharp endothermic peak at 176^{o}C corresponding to the melting point of the drug as shown in Fig. 4a. The DSC curve of cyclodextrin showed the liberation of crystal water as an endothermal effect peaked between 80-150°C, followed by a peak at 287°C corresponding to melting point of γ-cyclodextrin Fig. 4b. The complete disappearance of the drug endothermal effect was observed with all curcumin-γ-cyclodextrin complexes suggesting inclusion of the drug and formation of amorphous compounds. These observations are in agreement with those reported by other group of researchers [49,50].

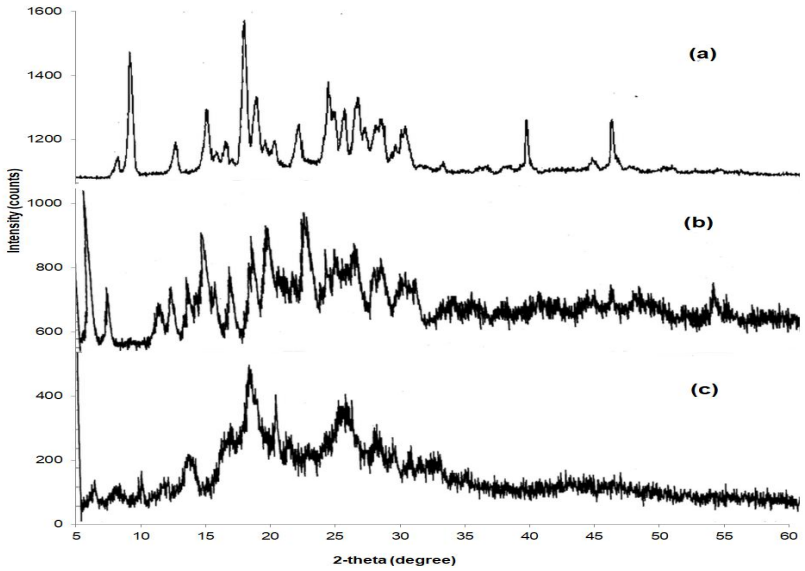

Fig. 2. Comparative X-ray differacto grams of curcumin gamma cyclodextrin and their freeze dried inclusion complexes

(a) Curcumin, (b) γ-CD, (c) curcumin-γ-CD Freeze dried complex

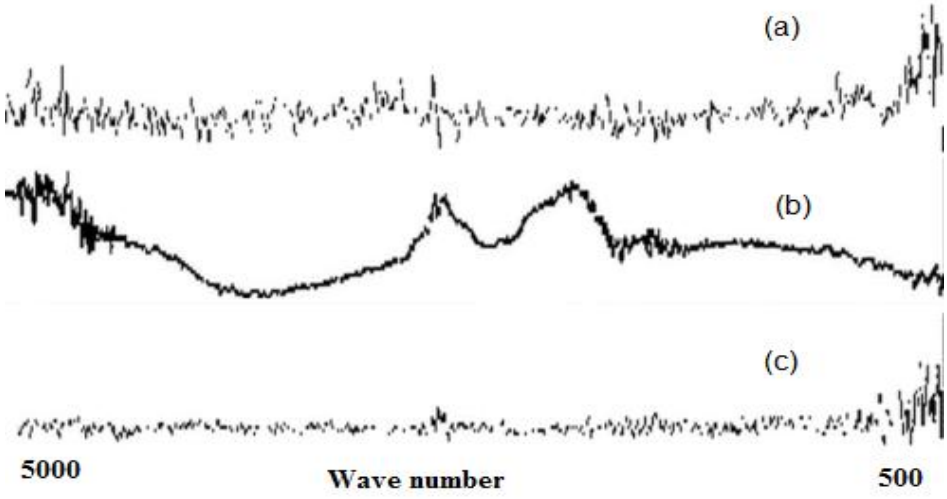

Fig. 3. Comparative FT-IR spectra of curcumin, gamma cyclodextrin and their freeze dried inclusion complexes

curcumin, (b) γ-CD, (c) curcumin-γ-CD freeze dried complex

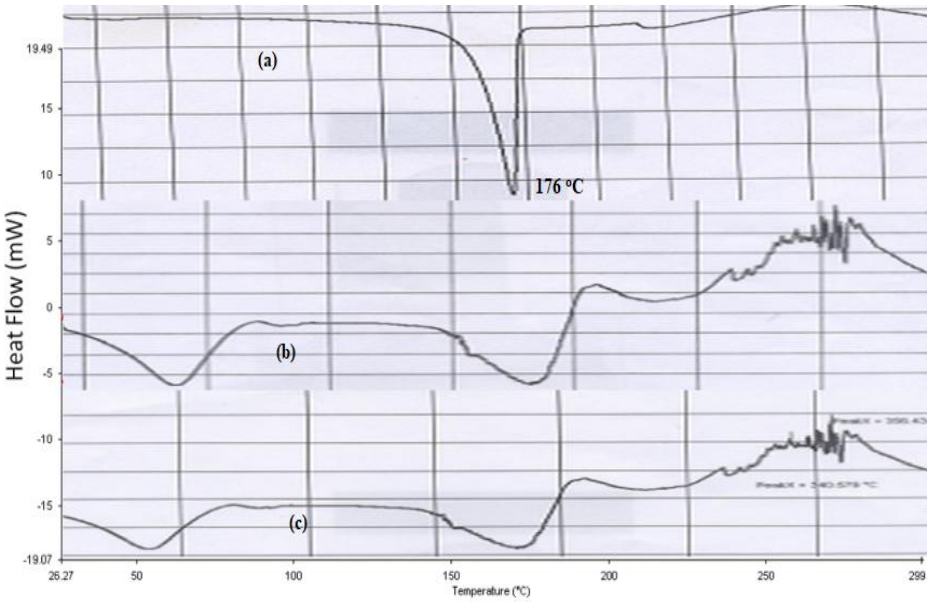

Fig. 4. Comparative DSC thermo grams of curcumin, gamma cyclodextrin and their freeze dried inclusion complexes

(a) curcumin, (b) γ-CD, (c) curcumin-γ-CD freeze dried complex

5.4 Dissolution Rate Profile of Curcumin and Curcumin Complexes

The dissolution medium was optimized first by investigating UV responses of curcumin (10 µg/ml) diluted with dissolved in 30% alcohol, 1% SLS (sodium lauryl sulphate), 0.1% Tween 20 and 0.1% Tween 80. Based on preliminary investigate, 1% SLS was used as the co-solvent in the dissolution media. The dissolution profiles of curcumin and curcumin complexes are shown in Fig. 5. The dissolution study revealed that release of curcumin form the complexes were faster as compared to curcumin alone. At one hour only 10.5% release of curcumin was observed from pure curcumin sample while curcumin complexes exhibited approximately 30% (physical mixture of curcumin and gamma cyclodextrin) and 72% release in the same time period (freeze dried complex of curcumin and gamma cyclodextrin). The freeze dried complexes exhibited almost complete release after 5 hours while only 34% release was observed from the pure curcumin during the same time period. Therefore, the freeze dried complex provided approximately 3-fold enhancement in the dissolution and release of curcumin. The curcumin-gamma cyclodextrin complexes investigated in this research provided may be considered better than other inclusion complexes of curcumin reported earlier [51-54]. For instance, Radjaram et al. 2013, reported only 8% release of curcumin from curcumin complex after 1 hour as compared to 72% release in this investigation [51]. Likewise, Jantarat et al, 2014, also reported approximately 6% release of curcumin from freeze dried complexes of curcumin with hydroxypropyl betacyclodextrin [52]. Moreover, Mohammad et al, 2020 reported only 58% release of curcumin from curcumin-beta-cyclodextrin complexes after 6 hours of release study while we have observed complete release of curcumin from gamma cyclodextrin complexes at 5 hours [53].

The kinetics of the *in vitro* release behaviors of the curcumin and curcumin complexes were investigated by applying various models. The release kinetics of curcumin and curcumin complexes applied to zero order, first order, Higuchi and Peppas models are shown in the Figs. 6, 7, 8 and 9 respectively. The release of the curcumin was observed to follow the first order release kinetics, since the correlation coefficient (R2) for the first order was highest in comparison to other kinetic models as shown in Tables 1.

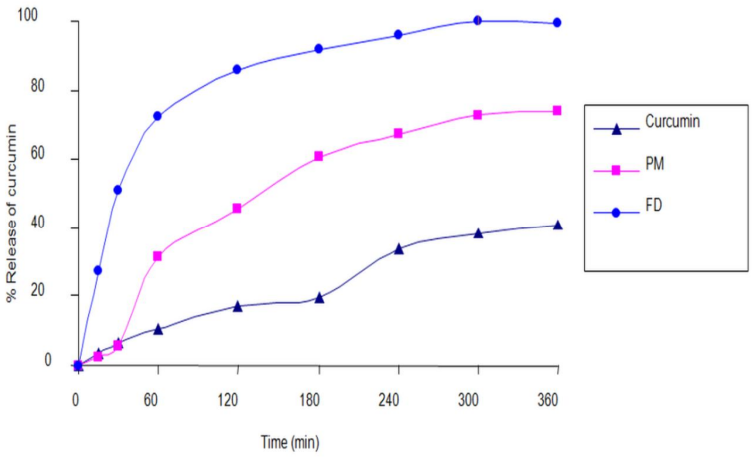

Fig. 5. Release profile of curcumin and curcumin-γ-CD complexes in simulated gastric fluid without pepsin with 1% (w/v) of sodium lauryl sulphate

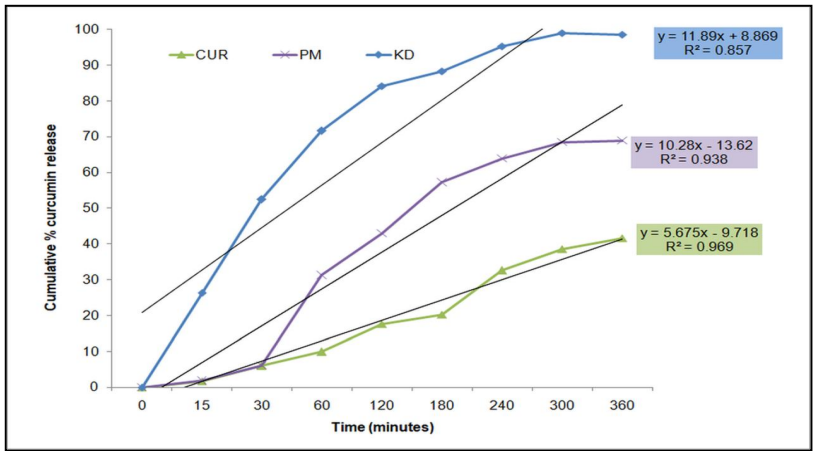

Fig. 6. Zero order kinetic release of curcumin and curcumin complexes

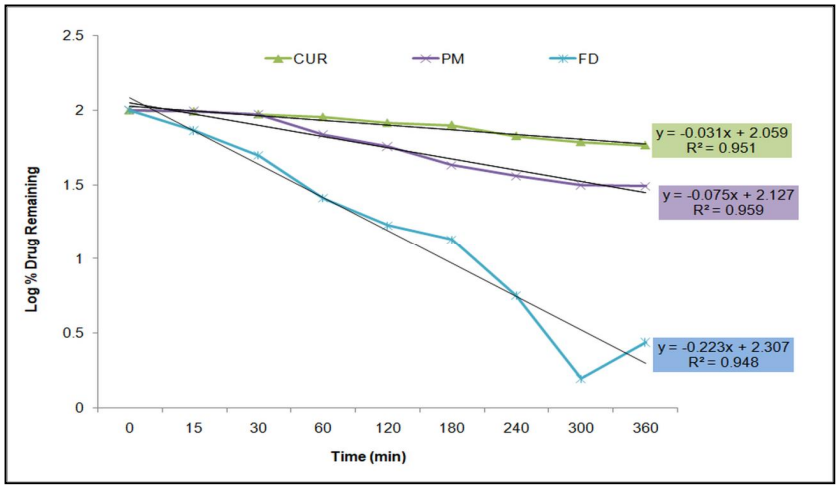

Fig. 7. First order kinetic release of curcumin and curcumin complexes

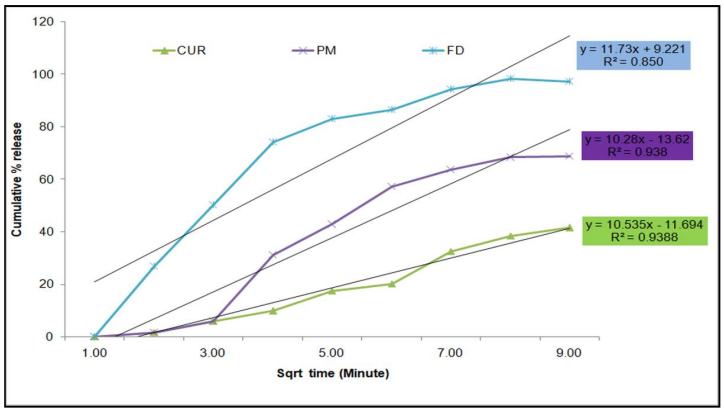

Fig. 8. Higuchi model kinetic release of curcumin and curcumin complexes

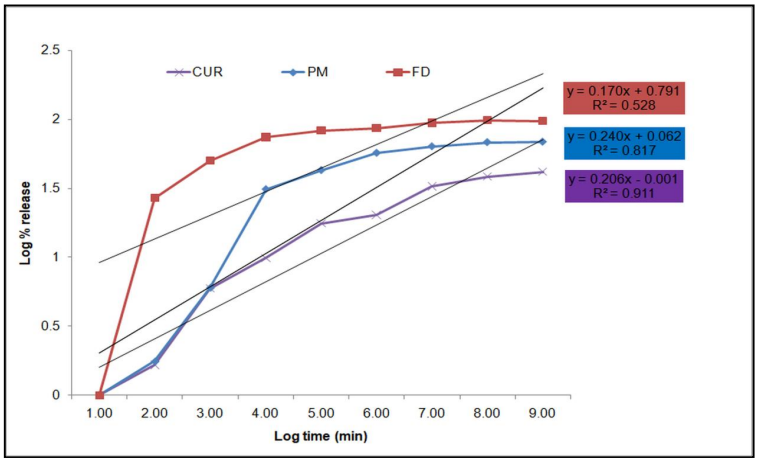

Fig. 9. Peppeas model kinetic release of curcumin and curcumin complexes

6. CONCLUSION

The results obtained in the present investigation are significant from the point of view that freeze dried complex of curcumin-gamma cyclodextrin complexes have much better solubility and dissolution as compared to the pure curcumin. Inclusion complex formation resulted in amorphous compounds with improved solubility and dissolution of curcumin. The developed freeze died complexes of curcumin and cyclodextrin may further be explored for industrial applications.

CONSENT

It is not applicable

ETHICAL APPROVAL

It is not applicable

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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