

**REVIEW ON SOLVENT EVAPORATION TECHNIQUE: A
PROMISING METHOD FOR MICROENCAPSULATION****Deepa Nag* and Bipul Nath**

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Article Received on
09 April 2018,

Revised on 30 April 2018,
Accepted on 20 May 2018,

DOI: 10.20959/wjpr201811-12438

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ABSTRACT

Microencapsulation is the process of surrounding or enveloping one substance within another substance on a very small scale, yielding capsules ranging from less than one micron to several hundred microns in size. The encapsulation efficiency of the micro particles or microsphere or microcapsule depends upon different factors like concentration of the polymer, solubility of polymer in solvent, rate of solvent removal, solubility of organic solvent in water etc. Microencapsulation is a well-established dedicated to the preparation, properties and uses of individually encapsulated novel small particles, as well as significant improvements to tried-and-tested techniques relevant to micro and nano particles and their use in a wide variety of industrial, engineering, pharmaceutical, biotechnology and research applications. Substances may be microencapsulated with the intention

that the core material be confined within capsule walls for a specific period of time. Alternatively, core materials may be encapsulated so that the core material will be released either gradually through the capsule walls, known as controlled release or diffusion, or when external conditions trigger the capsule walls to rupture, melt, or dissolve. This review article focuses on the use of the Solvent Evaporation technique, for the preparation of polymeric microcapsules, and modifications that have been developed over the years to improve the results obtained with this technique. The author also highlights some of the aspects of choices of process parameters, challenges and limitations of drug microencapsulation in real life. The review covers encapsulation materials, physics of release through the capsule wall and / or desorption from carrier, techniques of preparation, many uses to which microcapsules are put.

KEYWORDS: Microencapsulation, Core Materials, Coating Materials.

INTRODUCTION

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material. The product obtained by this process is called as micro particles, microcapsules. Particles having diameter between 3-800 μm are known as micro particles or microcapsules or microspheres. Particles larger than 1000 μm are known as macro particles. Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and of controlling the release characteristics or availability of coated materials. The uniqueness of microencapsulation is the smallness of the coated particles and their subsequent use and adaptation to a wide variety of dosage forms (Bansode *et al.*, 2010).

In the 21st century, microencapsulation technology has been applied to drug deliveries. Biodegradable polymeric microcapsules have received great attention as potential drug delivery vehicles in consideration of their applications in targeted drug delivery. Microparticles have already been introduced to drug delivery systems with great success. Microcapsule drug carrier systems possess high potential for various applications in therapeutic and pharmaceutical fields, such as anti-inflammation (Bayomi, 2004; Saravenan *et al.*, 2003), antibiotics (Mao *et al.*, 2005), anti-tumor (Zhao *et al.*, 2006; Huang *et al.*, 2010), proteins (Liu *et al.*, 2005; Lu *et al.*, 1995) and vitamins (Rokstad *et al.*, 2012; Shi *et al.*, 2002).

Important aspects of Microencapsulation

- The primary reason for microencapsulation is found to be either for sustained or prolonged drug release.
- This technique has been widely used for masking taste and odor of many drugs to improve patient compliance.
- This technique can be used for converting liquid drugs in a free flowing powder.
- The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation.
- Incompatibility among the drugs can be prevented by microencapsulation.
- Vaporization of many volatile drugs e.g. methyl salicylate and peppermint oil can be prevented by microencapsulation.

- Many drugs have been microencapsulated to reduce toxicity and GI irritation including ferrous sulphate and KCl.
- Alteration in site of absorption can also be achieved by microencapsulation.
- Toxic chemicals such as insecticides may be microencapsulated to reduce the possibility of sensitization of factorial person.

Need for microencapsulation

The primary reason for microencapsulation is found to be either for sustained or prolonged drug release. This technique has been widely used for masking taste and odor of many drugs to improve patient compliance. This technique can be used for converting liquid drugs in a free flowing powder. The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation. Incompatibility among the drugs can be prevented by microencapsulation. Vaporization of many volatile drugs e.g. methyl salicylate and peppermint oil can be prevented by microencapsulation. Many drugs have been microencapsulated to reduce toxicity and GI irritation including ferrous sulphate and KCl. Alteration in site of absorption can also be achieved by microencapsulation. Toxic chemicals such as insecticides may be microencapsulated to reduce the possibility of sensitization of factorial person. Bakan and Anderson reported that microencapsulated vitamin A palmitate had enhanced stability (Wang et al., 2009; Sinha et al., 2004; Jenkins et al., 2006; Moghimi et al., 2001).

Fundamental considerations

The realization of the potential that microencapsulation offers involves a basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials, the stability and release characteristics of the coated materials and the microencapsulation methods.

Advantages of microencapsulation

- Microspheres provide constant and prolonged therapeutic effect.
- Reduces the dosing frequency and thereby improve the patient compliance.
- They could be injected into the body due to the spherical shape and smaller size.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.

- Microsphere morphology allows a controllable variability in degradation and drug release.
- Consumers are unable to taste the added capsules.
- Sensory properties remain unaltered.
- Wider range of specific product for consumer to choose from.

Disadvantages of microencapsulation

- It is an expensive process.
- Requires skill
- Difficult to achieve continuous of uniform film.
- Possible cross reaction may occur between the core and wall material selected.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through gut.
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- Dosage forms of this kind should not be crushed or chewed.

CORE MATERIAL

The core material, defined as the specific material to be coated, can be liquid or solid in nature. The composition of the core material can be varied as the liquid core can include dispersed and/or dissolved material. The solid core can be mixture of active constituents, stabilizers, diluents, excipients and release-rate retardants or accelerators. The ability to vary the core materials composition provides definite flexibility and utilization of this characteristic often allows effectual design and development of the desired microcapsules properties.

Criteria of core material selection for microencapsulation

- The core material is the material to be coated which may be liquid or solid in nature.
- The composition of core material can be varied.
- The liquid core can include dispersed or dissolved material.

Composition of core material

- Drug or Active constituent.
- Additives like diluents.

- Stabilizers.

Coating Materials

The coating material should be capable of forming a film that is cohesive with the core material; be chemically compatible and nonreactive with the core material; and provide the desired coating properties, such as strength, flexibility, impermeability, optical properties, and stability. The coating materials used in microencapsulation methods are amenable, to some extent, to in situ modification.

Ideal properties of coating materials

- Stabilization of core material.
- Inert toward active ingredients.
- Controlled release under specific condition
- Film-coating, tasteless, stable.
- Non-hygroscopic, no high viscosity, economical.
- Soluble in aqueous media or solvent.
- The coating can be flexible, hard, thin etc.

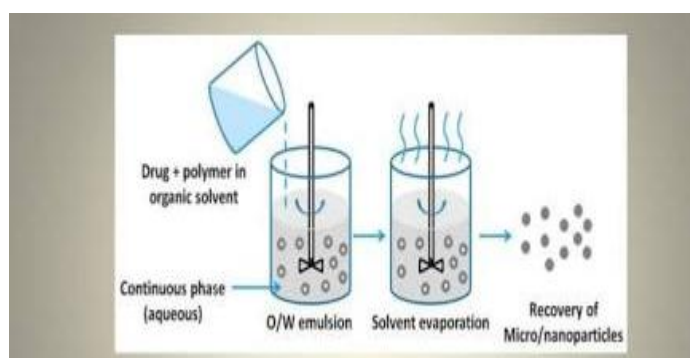
Types of coating materials

- Non-biodegradable materials
 - ❖ Epoxy polymer
 - ❖ Acrolein
 - ❖ Glycidylmethacrylate
- Biodegradable materials
 - ❖ Polyalkylcyanoacrylates
 - ❖ Lactides, glycolides, and their co-polymers
 - ❖ Polyanhydrides
- Natural materials
 - ❖ Carbohydrates: Starch, Agarose,
 - ❖ Proteins: Albumin, Gelatin.
 - ❖ Chemically modified carbohydrates, Poly(acryl)starch
 - ❖ Poly(acryl)dextran

Approaches on the microencapsulation process

- Air suspension
- Coacervation phase separation
- Multiorifice-centrifugal process
- Spray drying and congealing
- Pan coating
- Solvent evaporation techniques
- Polymerization.

Solvent evaporation technique



This method is mainly used for the preparation of microcapsules. In this method, the microcapsule coating is first dispersed in a volatile solvent and is immiscible with the liquid manufacturing volatile phase. The core material to be microencapsulated is dissolved in the coating polymer solution. Then the core material is dispersed in the liquid manufacturing vehicle phase by means of agitation. After that the mixture is heated to evaporate the solvent and to shrink the polymer around the core. The matrix type microcapsules are prepared by dissolving the core material in the coating polymer solution. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase. eg. Evaluation of Sucrose Esters as Alternative Surfactants in Microencapsulation of Proteins by the Solvent Evaporation Method.

LITERATURE OF REVIEW

Hwisa *et al*^[28] studied that in recent times solvent evaporation techniques have gained prominence in microencapsulation process. Solvent evaporation techniques are broadly classified into emulsification solvent- evaporation and extraction methods. Several variations have been developed recently based on this technology. Using solvent evaporation methods we can regulate microsphere morphology and other characteristics to the desired level for the

targeted delivery of bioactives like peptides and vaccines using various biomaterials as carriers. Several methods of solvent evaporation, core and coat materials used, emulsion stabilizers, and process variables were discussed in detail with due interest of recent advancements in this area of research. This technology is showing a promising future for drug targeting and throwing challenges to pharmaceutical scientist such as: scale-up problems, use of non-organic solvents, use of alternative biodegradable polymers, and the application of a viable hybrid technology by amalgamating various techniques of microencapsulation to overcome the problems of peptide degradation during the process and stability of microspheres after the process.

Neeta *et al*^[29] studied the Floating dosage forms are emerging as a promising novel dosage forms, these can be retained in the stomach for a prolonged period of time and release the active ingredient in a predetermined manner. In exploration of this avenue, different novel strategies have been undertaken for the designing of floating systems including floating microspheres. Polymeric floating microspheres are ideal vehicles for many controlled delivery applications due to their ability to encapsulate a variety of drugs, biocompatibility, high bioavailability and prolonged drug release characteristics. To achieve these goals various techniques have been developed for preparation of floating microsphere, among them solvent evaporation is an effective approach. Present review addresses the general description of the floating system, floating microspheres, solvent evaporation process, various research findings based on solvent evaporation technique.

Mushtaque M *et al*^[30] Studied using microspheres constituted by ethyl cellulose and sodium carboxy methyl cellulose Microspheres were prepared using two different solvents, dichloromethane, ethyl acetate and their mixture in 1:1 ratio. The microspheres were prepared using various drug to polymer ratio with the help of solvent evaporation technique and characterized for various parameters. In-vitro drug release/ drug diffusion studies were performed in phosphate buffer (pH 6.4). Ex-vivo study (drug permeation study) was carried out on sheep nasal mucosa. The physical properties, particle size, entrapment efficiency, mucoadhesion time and % drug release depend on the solvent used and on drug to polymer ratio. In order to further investigate the type of drug release mechanism taking place, the % drug release data were plotted according to the four different kinetic models. In-vitro drug release studies showed that peppas and matrix release characteristics were exhibited.

Lee *et al*^[31] studied the Effect of formulation and processing variables on the characteristics of microspheres for water-soluble drugs prepared by w/o/o double emulsion solvent diffusion method. Ethylcellulose, a polymer to microencapsulate a drug by coacervation phase separation technique, emulsion solvent evaporation technique, and spherical crystallization technique.

Pérez *et al*^[34] developed Nondegradable microparticles containing a hydrophilic and/or a lipophilic drug: preparation, characterization and drug release modeling. Eudragit RS and Eudragit RL are biocompatible copolymers synthesized from acrylic and methacrylic acid ester having similar structure that differs only in the extent of the quaternary ammonium substitution and hence high water permeability and hydrophilicity in Eudragit RL as compared to Eudragit RS polymer.

Basu *et al*^[32] reported Preparation and characterization of nitrendipine loaded Eudragit RL 100 Microspheres prepared by an emulsion-solvent evaporation method. The prepared microsphere had shown 79% DEE and 85% drug release at the end of 18 hour.

KOTAGALE *et al*^[33] developed a floating type of dosage form of ranitidine hydrochloride in the form of microspheres capable of floating on simulated gastric fluid was prepared by solvent evaporation technique. Microspheres prepared with ethyl cellulose, Eudragit® RS100 alone or in combination were evaluated for percent yield, drug entrapment, percent buoyancy and drug release and the results demonstrated satisfactory performance. Microspheres exhibited ranitidine hydrochloride release influenced by changing ranitidine hydrochloride-polymer and ranitidine hydrochloride-polymer-polymer ratio. Incorporation of a pH modifier has been the usual strategy employed to enhance the dissolution rate of weakly basic drug from floating microspheres. Further citric acid, fumaric acid, tartaric acid were employed as pH modifiers. Microspheres prepared with ethyl cellulose, Eudragit® RS100 and their combination that showed highest release were utilized to study the effect of pH modifiers on ranitidine hydrochloride release from microspheres which is mainly affected due to modulation of microenvironmental pH. *In vitro* release of ranitidine hydrochloride from microspheres into simulated gastric fluid at 37° showed no significant burst effect. However the amount of release increased with time and significantly enhanced by pH modifiers. 15% w/w concentration of fumaric acid provide significant drug release from ranitidine hydrochloride microspheres prepared with ranitidine hydrochloride: ethyl cellulose (1:3), ranitidine hydrochloride: Eudragit® RS100 (1:2) and ranitidine hydrochloride: ethyl

cellulose: Eudragit® RS100 (1:2:1) whereas citric acid, tartaric acid showed significant cumulative release at 20% w/w. In all this study suggest that ethyl cellulose, Eudragit® RS100 alone or in combination with added pH modifiers can be useful in floating microspheres which can be proved beneficial to enhance the bioavailability of ranitidine hydrochloride.

Pandav *et al*^[35] studied sustained release of Ethylcellulose (300 cps) and Eudragit (RS 100 and RL 100) microparticles containing Propranolol hydrochloride used as a treatment of cardiovascular system, especially hypertension. Propranolol hydrochloride was microencapsulated with different polymers (Ethylcellulose, Eudragit RS, and Eudragit RL) using modified hydrophobic (O/O) solvent evaporation method using 1: 1 combination of acetone and isopropanol as the internal phase. Obtained microparticles were showing higher batch yield with higher encapsulation efficiency. Microparticles were prepared with different ratios of 1 : 1, 1 : 3, 1 : 5, and 1 : 7 (% , wt/wt) using span 80 (% , v/v) as a surfactant. The influence of formulation factors like drug: polymer ratio, internal phase, and type of polymers on obtained microparticles was characterized with respect to particle size distribution, encapsulation efficiency, percentage yield, FTIR, and FE-SEM. Higher encapsulation efficiencies were obtained with various polymers like Ethylcellulose (96.63 ± 0.5) compared to Eudragit RS 100 (83.70 ± 0.6) and RL 100 (89.62 ± 0.6). The in vitro release study was characterized by initial burst. The result of study displays that Ethylcellulose and Eudragit loaded microparticles of Propranolol hydrochloride can be effectively prepared using modified hydrophobic emulsification solvent evaporation technique. Therefore, the modified hydrophobic emulsion technique can also be applied to the preparation of microparticles for low molecular weight and highly water soluble drugs.

Mady *et al*^[36] developed Eudragit RS100 microspheres containing Ibuprofen as an example for acidic drugs was prepared using solvent evaporation technique. It was found that the using of 3% gelatin as an antiaggregating agent in the 0.1N HCl aqueous phase is essential to prevent the appearance of the drug crystals in the aqueous phase during preparation. Also the formulation was individual small particle size microspheres with low mean particle size ($37\mu\text{m}$). The prepared microsphere showed the presence of drug crystal attached to the microspheres surface which supports the antiaggregating mechanism of gelatin. Gelatin is a hydrophilic colloid forming multi-molecular films around the emulsified droplets resulting resists the coalescence of the emulsified microspheres and hindering the rapid diffusion of the

organic phase to the aqueous phase which lead to appearance of the drug crystals swimming in the external phase during preparation. The maximum amount of drug release in 0.1N HCl was 4% in two hrs. The drug release process in phosphate buffer pH 6.8 showed rapid initial and incomplete drug release (45% of actual drug content in 9hr). This is nearly normal of all products prepared by solvent evaporation technique. DSC showed the drug is encapsulated in three forms, solid solution form, drug crystal form and other kind of physico chemical interaction with the polymer.

Agnimitra *et al*^[37] studied the effect of chitosan on the various characteristics of Eudragit RS 100 and ethyl cellulose microspheres which were formulated by o/o emulsion, solvent evaporation method using methanol, acetone, light liquid paraffin system. Effect of chitosan was evaluated on several aspects such as particle size, drug content and entrapment, morphology, drug-polymer interaction and in vitro release study. It was found that chitosan had great influence on the various properties of ethyl cellulose and Eudragit RS 100 microspheres containing lamivudine sulphate as drug candidate.

Patel *et al*^[38] has development of ethyl cellulose microspheres by the o/w emulsification and solvent evaporation method in the presence of tween 80 as an emulsifying agent. The influence of process parameters such as solvent mixture, composition, concentration of the emulsifying agent and speed of stirring has been examined. The microspheres have been analyzed for their size, drug loading capacity and drug release study. Spherical and smooth surfaced microspheres with desired encapsulation efficiencies were obtained. Use of acetone in the oil phase drastically reduced the particle size. Slow drug release from microspheres observed up to 8 h. An optimization procedure was employed to investigate and identify the key parameters affecting the properties of the microspheres

Nethaji *et al*^[39] has developed Ethyl cellulose microspheres of Diclofenac sodium using different drug: polymer ratios by an emulsification solvent evaporation method in presence of Tween 80 as an emulsifying agent and the influence of process parameters such as solvent mixture, composition, concentration of an emulsifying agent and stirring speed has been examined. The microspheres have been analyzed for their size, drug loading capacity and drug release study. The percentage yield is found between 75.34 ± 0.94 percent to 80.34 ± 0.86 % in all formulations. Use of acetone in the oil phase drastically reduced the particle size. Spherical and smooth surfaced microspheres with desired encapsulation efficiencies were obtained. The drug-loaded microspheres (F-I to F-VI) showed the entrapment efficiency of

58.93±0.35% to 90.47±0.93% and shown retarded drug release observed up to 8hrs using phosphate buffer (pH 6.8). All formulated batches indicate compliance with Higuchi's plot and reveals that the drug release followed first order release kinetics. Stability study of best batch showed good results with no-observable physical changes. It could be conclude that the prepared microspheres were shown satisfactory results and suitable for potential therapeutic uses.

Evaluation of microspheres

Yield of microspheres

The % yield was calculated by using the following formula (Berkland et al., 2004).

$$\% \text{ Yield} = \frac{\text{Weight of microsphere}}{\text{Theoritical weight drug and polymer}} \times 100$$

Particle size analysis

Size distribution was determined by sieving the micro particles using a nest of standard BSS sieves (Wang et al., 2007) as well as by optical microscopy using calibrated ocular micrometer (1 ocular division= 14.26 micrometer) with stage micrometer having standard division of 10 micrometer and by counting atleast 100 micro spheres.

Morphology of microspheres

The surface morphologies of microspheres are examined by a scanning electron microscope (XL 30 SEM Philips, Eindhoven, and The Netherlands). The microspheres are mounted onto a copper cylinder (10 mm in diameter, 10 mm in height) by using a double-sided adhesive tape. The specimens are coated at a current of 10 mA for 4 min using an ion sputtering device (Wang et al., 2004; Obeidat et al., 2004).

Density determination

The density of the microspheres can be measured by using a multi volume pycnometer. Accurately weighed sample in a cup is placed into the multi volume pycnometer. Helium is introduced at a constant pressure in the chamber and allowed to expand. This expansion results in a decrease in pressure within the chamber. Two consecutive readings of reduction in pressure at different initial pressure are noted. From two pressure readings the volume and density of the microsphere carrier is determined (Berkland et al., 2004).

Angle of contact

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at degree within a minute of deposition of microspheres (Wua et al., 2003).

Drug entrapment efficiency (DEE)

Microspheres equivalent to defined quantity are crushed and added to 50 mL of suitable solvent media. The resulting mixture is shaken in a mechanical shaker for 3 hr to extract the drug completely. The solution is filtered with a Whatman filter paper and 1 mL of this solution is appropriately diluted to 25 mL using solvent media and analyzed spectrophotometrically at a particular using UV Visible double beam Spectrophotometer (Jyothi et al., 2010).

Following is the equation for drug entrapment efficiency:

$$\% \text{ Entrapment Efficiency} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} \times 100$$

In vitro Drug Release Study

In vitro drug release studies are carried out for all products and for the pure drug in USP type II dissolution test apparatus. Microcapsules equivalent to measured quantity of drug is used for the dissolution studies using 900 ml of dissolution media. Aliquot of samples are withdrawn at predetermined time intervals and filtered. The required dilutions are made with dissolution media and the solution is analyzed for the drug content spectrophotometrically at particular wavelength against suitable blank. Equal volume of the dissolution medium is replaced in the vessel after each withdrawal to maintain sink condition. From the result, the percentage drug release is calculated and plotted against function of time to study the pattern of drug release. The similarity of dissolution profile of the prepared formulations is compared with that of the marketed formulations to arrive at the optimum profile (Chaumeil et al., 1986; Brazel et al., 2000).

Release mechanisms of Microcapsulated product.

Mechanisms of drug release from microspheres are

1. Degradation controlled monolithic system: -

The drug is dissolved in matrix and is distributed uniformly throughout. The drug is strongly attached to the matrix and is released on degradation of the matrix. The diffusion of the drug is slow as compared with degradation of the matrix.

2. Diffusion controlled monolithic system: -

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Rate of release also depend upon where the polymer degrades by homogeneous or heterogeneous mechanism.

3. Diffusion controlled reservoir system: -

Here the active agent is encapsulated by a rate controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix.

4. Erosion: -

Erosion of the coat due to pH and enzymatic hydrolysis causes drug release with certain coat material like glyceryl mono stearate, beeswax and steryl alcohol etc. (S.S Bansode et al,2010)

Application

- Nasal delivery
- Colonic drug delivery
- Protein/Peptide stability
- Drug targeting
- ❖ Passive targeting
- ❖ Active targeting
- Gene delivery
- Microspheres in diagnostic material
- Cell immobilization: In plant cell cultures, Human tissue is turned into bio-artificial organs, in continuous fermentation processes.
- Beverage production
- Protection of molecules from other compounds:

- Drug delivery: Controlled release delivery systems.
- Quality and safety in food, agricultural & environmental sectors.
- Soil inoculation.
- In textiles: means of imparting finishes.
- Protection of liquid crystals.

CONCLUSION

Microencapsulation means packaging an active ingredient inside a capsule ranging in size from one micron to several millimeters. The capsule protects the active ingredient from its surrounding environment until an appropriate time. Then, the material escapes through the capsule wall by various means, including rupture, dissolution, melting or diffusion. Microencapsulation is both an art and a science. There's no one way to do it, and each new application provides a fresh challenge. Solving these riddles requires experience, skill and the mastery of many different technologies.

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