

SYNTHESIS, CHARACTERIZATION, AND PRELIMINARY RELEASE STUDIES OF CLOTRIMAZOLE DRUGS FROM POLYMER DERIVATIVE FROM EUGENOL

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ABSTRACT

The aim of this work was to focus on the modification of the chemical structure of eugenol by the incorporation of a polymerizable group, e.g., carboxylic group or amid group. This approach will allow the eugenol derivative to participate in polymerization reactions rather than to inhibit them and will be more efficacious in the field of drug delivery. In this paper I report on the synthesis of three eugenol derivatives, which differ in the spacer group between two, three eugenol molecules, their homopolymerization characterization by FTIR spectroscopy. . Also the release behavior of the hydrogels was studied. The release studies showed that the basic parameter affecting the drug release behavior of the hydrogels were pH of the solution.

KEYWORDS: Eugenol, Drug Release, Clotrimazole

INTRODUCTION

Controlled drug delivery technology represents one of the most rapidly advancing areas of science in which chemists and chemical engineers are contributing to human health care. Such delivery systems offer numerous advantages compared to conventional dosage forms including improved efficacy ¹.

Hydrogels are crosslinked hydrophilic polymers capable of imbibing large volumes of water, but swellable when immersed. The water retaining capacity of these materials is due to the presence of hydrophilic functional groups such as –OH, –COOH, –CONH₂, –CONH, –SO₃H along the polymer chains. ^{2,3}

Hydrogels are known as good candidates for the controlled release formulations for pharmaceutical applications mostly due to their high biocompatibility. In recent years, these polymeric carriers have been extensively considered in sustained and controlled release devices for the delivery of water-soluble drugs. ^{4,5}

The various properties of hydrogels such as biocompatibility, hydrophilicity, flexibility all make it ideal for use as drug delivery matrix. Hydrogels show good compatibility with blood and other body fluids, thus are used as materials for contact lenses, burn wound dressings, membranes, and as coating applied to living surfaces. ⁶

Eugenol (4-allyl-2-methoxy phenol) is a naturally occurring allyl benzene which has been reported to show a number of biological activities. Eugenol is considered to be non-mutagenic and non-carcinogenic and is generally accepted as safe by the Food and Drug Administration. Human exposure to eugenol occurs through its use in dentistry as an analgesic and local anesthetic and its presence in foods and spices . In traditional medicine, eugenol has been used against gastrointestinal diseases and chronic diarrhea. Several investigations also indicated that eugenol has antioxidant

and antimutagenic activities. Eugenol can regulate an array of cellular biochemical processes such as inhibition of lipid peroxidation, cyclooxygenase-2 gene expression and reactive oxygen species. 7

Eugenol derivatives or methoxyphenol derivatives in wider classification are used in perfumery and flavouring. They are used in formulating insect attractants, analgesics, biocides and antiseptics. 8,9

MATERIALS AND METHODS

Materials

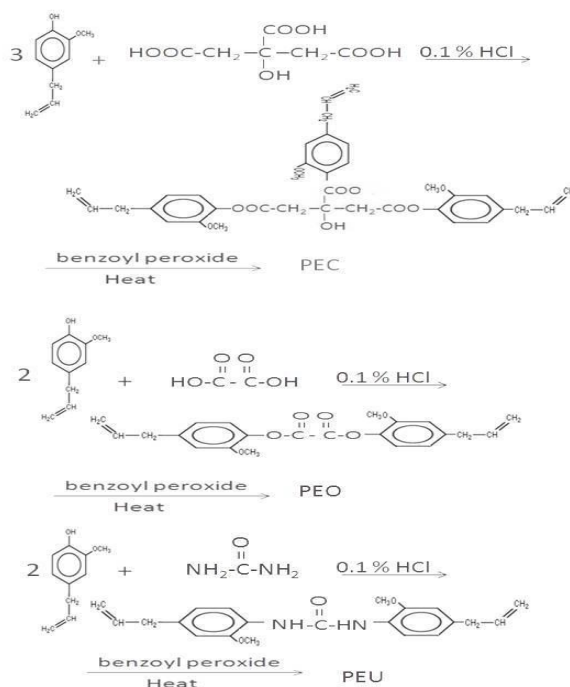
Eugenol was obtained from Prevest Denpro Limited. Citric acid, oxalic acid, NaHCO_3 , urea, and benzoyl peroxide was purchased from Thomas Baker (Chemicals) Pvt. Ltd. Mumbai. Clotrimazole was purchased from Al Arak Aleppo. and HCl purchased from Aldrich.

Preparation of monomer

Three types of monomer are prepared by condensation reaction: three moles of eugenol with one mole of citric acid, and two moles of eugenol with one mole of oxalic acid and urea by adding 5 drops of diluted 0.1% HCl as catalyst. The reaction mixture was stirred for 1 hour at 100°C . Then the reaction mixture was cooled and neutralized by washed with 0.1% of NaHCO_3 then with water.

Preparation of polymer

Polyester (eugenol-citric acid), (eugenol-oxalic acid) and polyamide (eugenol-urea) were prepared by direct polyaddition reaction of eugenol double bond by using benzoyl peroxide as initiator. The reaction mixture was stirred for 3 hours at 100°C .



Samples of PEC, PEO and PEU were loaded with clotrimazole. The drugs were added and mixed into the melt of PEC, PEO, and PEU after incorporation, the melt was molded into tablets (10mm diameter, 3mm height) which were immersed in 100ml buffer solutions at pH 4, 7 and 9 at 37°C. The release was followed by ultraviolet spectroscopy. Samples of 0.5 to 1ml were taken at various time intervals, their absorption intensity was measured in a Apel PD-303 (Japan) UV-spectrometer, at 748 nm .¹⁰

Swelling and hydrolysis studies

Swelling experiments were performed at several pH conditions using different buffer solutions including the following: (a) pH 4.0, (b) pH 7.4, and (c) pH 9.0. Swelling studies were carried out in triplicate by placing dried hydrogel samples into a 20-mL screw-capped glass vials containing 20 mL of appropriate buffer solutions. The samples were maintained at 37.0°C and shaken at 60 cycles/min. At specific time intervals, the hydrogel samples were removed from the solution, gently dried to remove excess liquid from the surface and then weighed by Denver instrument (Germany) Balance . The swelling ratio (SR) was estimated as the ratio of the wet hydrogel (M wet) to the dry mass (M dry) :

$$SR = (M_{wet} - M_{dry} / M_{dry}) * 100 \% .^{11}$$

RESULTS

POLYMER CHARACTERIZATION by Infrared spectra

Infrared spectra of the synthesized polymers in KBr pellets were obtained from Shimadzu FTIR-8400s spectrophotometer. Whereas in case of eugenol and the monomers , being a liquid, a thin film was cast over the NaCl block and its FTIR was recorded in laboratory of State of petrochemical company . The FTIR study showed characteristic peak as shown in figure 1, 2 and 3.

DISCUSSIONS

The FTIR spectra was characterized peaks of eugenol, citric acid, urea, oxalic acid monomers and polymeric blends as shows in figure (1, 2 and 3). The FTIR spectrum of eugenol showed the presence of alcohol group at 3523 cm⁻¹ and c=c at 1149 cm⁻¹.

When, hydroxyl peaks of eugenol derivative monomers, was very weak due to chemical reaction between hydroxyl group for eugenol and carboxyl groups of citric acid, oxalic acid and amine group for urea. At same figures when distinguish the peaks of c=c before and after polymerization reactions, we see the peak absence due to addition polymerization to double bond.

Time-dependent swelling behavior of PEC, PEO and PEU was observed with changes in pH of buffer solution. Swelling kinetics of hydrogels in pH (4, 7 and 9) buffer solution, at 37°C are plotted in figures (4, 5 and 6) as average of three trials. The PEC swelled and reach equilibrium within 48 hrs, while PEO within and PEU. The pH dependent swelling behavior was observed with change in pH buffer solution. The SR increase at pH increase.

Figure (7, 8 and 9) shows the release profiles of clotrimazole drugs from polymer derivative from eugenol. For all polymers, the clotrimazole release increases rapidly at first and then gradually reaches an equilibrium value in approximately

48 hr. The figures also shows that the release percent of clotrimazole for PEC was higher than for PEU and PEO, in pH 4 and 9 while PEO higher than PEC and PEU in pH 7 .

REFERENCES

1. Kathryn E. Uhrich , Scott M. Kevin M. Shakesheff, Cannizzaro and Robert S. Langer Polymeric Systems for Controlled Drug Release: Chem. Rev., 99, 3181-3198, 1999.
2. Peppas NA, Mikos AG. In Hydrogels in Medicine and Pharmacy, vol. 1, Peppas NA (ed). CRC Press: Boca Raton, FL, 1986; 1.
3. Kudela V. Encyclopedia of Polymer Science and Engineering (2nd edn, vol. 7). Wiley: New York, 1987; 783–789.
4. Korsmeyer RW, Peppas NA. Swelling-controlled delivery systems for pharmaceutical application. In Controlled Release Delivery Systems. Marcel Dekker: New York, 77–90 ;1983 .
5. Peppas NA, Gurny R, Doelker E, Buri P. Modelling of drug diffusion through swellable polymeric systems. J. Membr. Sci.; 7: 201. 1980.
6. Ajji, Z., I. Othman, and J.M. Rosiak, Production of hydrogel wound dressings using gamma radiation. Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms, 229(3-4): p. 375-380. 2005.
7. N Vidhya & S Niranjali Devaraj: Induction of apoptosis by eugenol in human breast cancer cells, Indian Journal of Experimental Biology, Vol. 49, pp. 871-878, 2011.
8. Mosciano, Gerard (1996), Methyl eugenol, <http://www.alanwood.net/pesticides.html>
9. Eugenol(2005): <http://www.wikipedia.com>
10. P.A. Tarantili, A.G. Andreopoulos Design of biodegradable polymer systems for drug release applications, Proceeding of the 8th Polymers for Advanced Technologies International Symposium Budapest, Hungary, 13-16 September 2005.
11. Zhiqiang Yang, Yuehua Zhang, Peter Markland, Victor C. Yang Poly(glutamic acid) poly(ethylene glycol) hydrogels prepared by photoinduced polymerization: Synthesis, characterization, and preliminary release studies of protein drugs , 2002 Wiley Periodicals, Inc.
12. Spectral database for organic compounds http://riodb01.ibase.aist.go.jp/sdbs/egi-bin/cre_index.cgi?lang=eng.

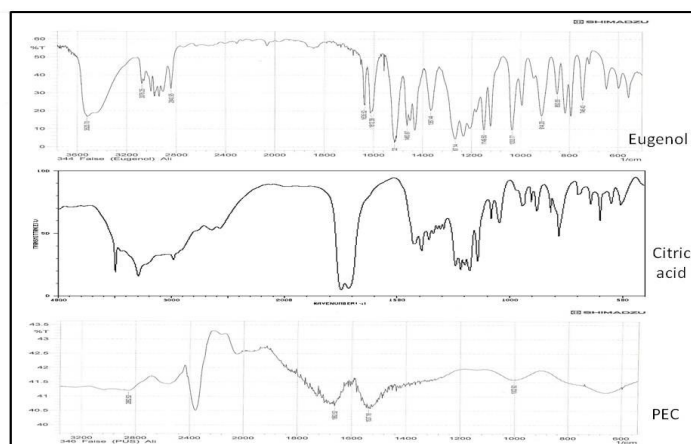


Figure 1: The FTIR Spectra for Eugenol, Citric Acid ¹² and PEC

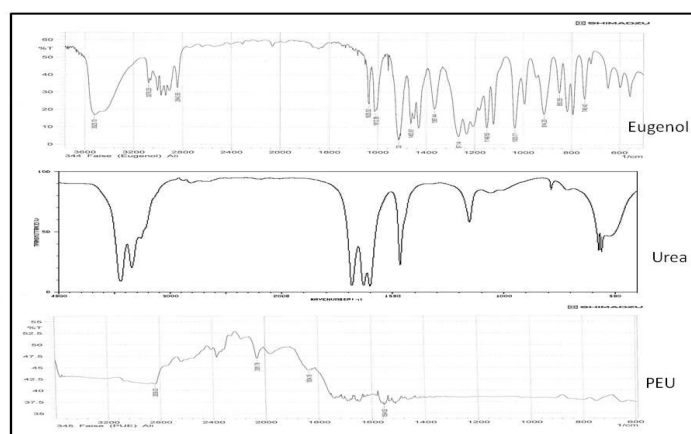


Figure 2: The FTIR Spectra for Eugenol, Urea ¹² and PEU

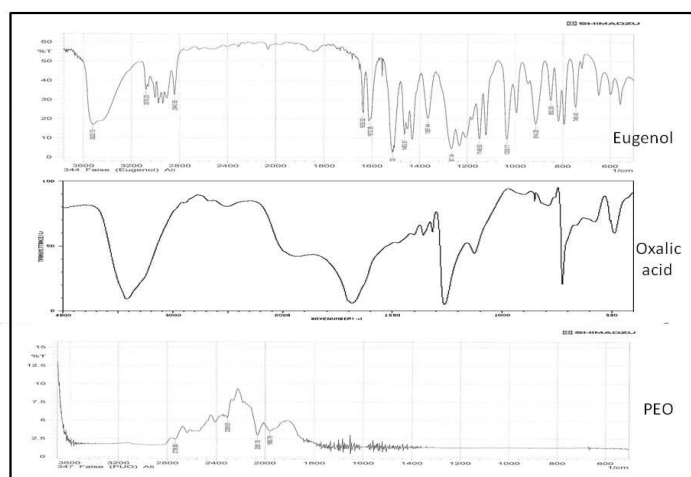


Figure 3: The FTIR Spectra for Eugenol, Oxalic Acid ¹² and PEO

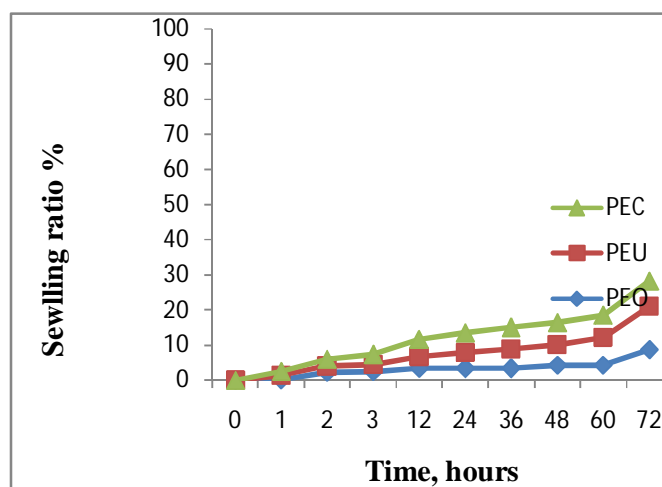


Figure 4: Swelling Behavior Over Time of PEC, PEU and PEO. at pH 4

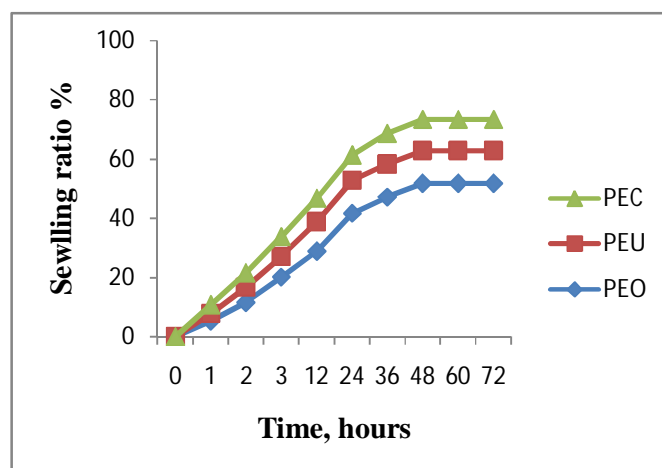


Figure 5: Swelling Behavior Over Time of PEC, PEU and PEO . at pH 7

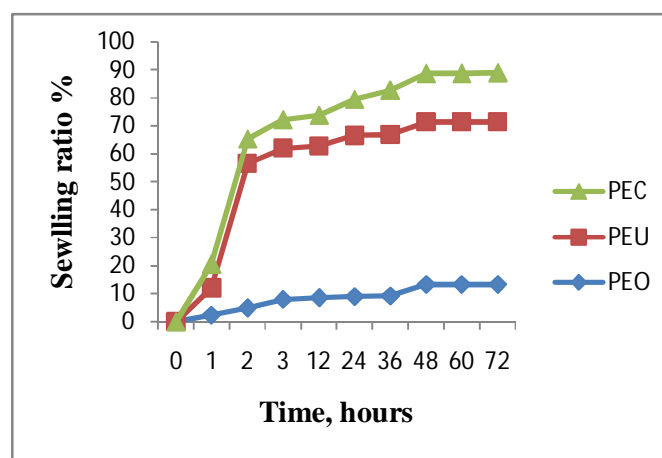


Figure 6: Swelling Behavior Over Time of PEC, PEU and PEO . at pH 9

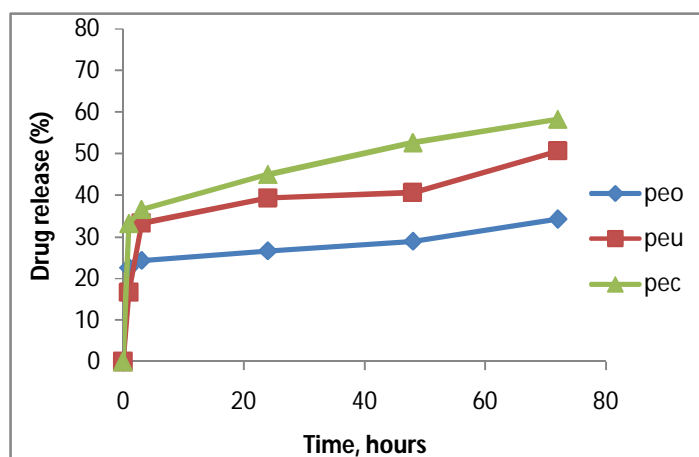


Figure 7: Drug Release % Over Time of PEC, PEU and PEO . at pH 4

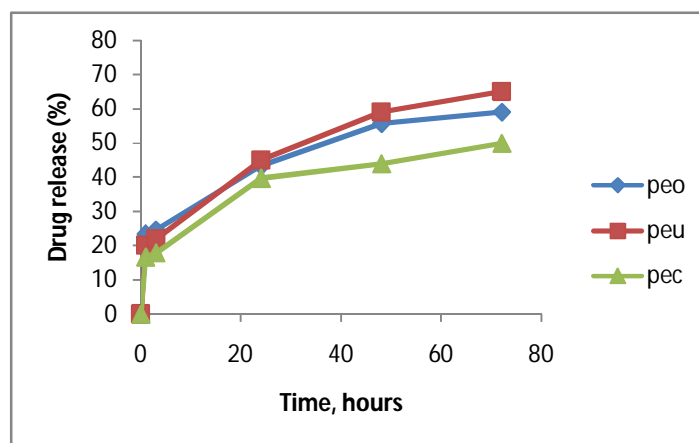


Figure 8: Drug Release % Over Time Of PEC, PEU And PEO, at pH 7

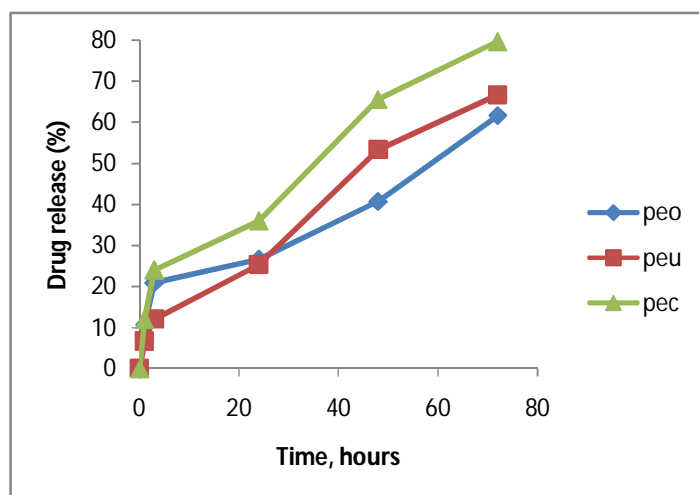


Figure 9: Drug Release % Over Time of PEC, PEU and PEO . at pH 9

