ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

Recent advancement in wound healing dressing material

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Article History:

Received on: 07.05.2019
Revised on: 13.08.2019
Accepted on: 18.08.2019

Keywords:

biodegradation,
dermal patch,
Poly (lactic acid),
woundhealing

ABSTRACT

Wounds have been occurring as long as the existence of life. Presently available advanced wound care products for dressing are beyond the reach of the majority Indian population, and they also do not completely fulfil the required benefits of therapeutic value. The dermal patch technology is the best-known and widely used approach for delivering drugs. It has been proven to be the fastest, easiest, safest and most economical way for drug delivery. The use of biodegradable polymers in wound management has been brought into prominence with new innovations in drug delivery system. Thus with a new dimension for the use of polymeric materials in or as wound healing, drug delivery devices involves incorporation of biodegradability into the drug delivery system. A number of degradable polymers are potentially useful for drug delivery including a variety of synthetic and natural substances such as Poly Lactic acid, Poly Crypolactone, Chitosen etc. Among all these Poly (lactic acid) (PLA) is the most readily biodegradable polymer in the surgical field. The biodegradable polymers have gained growing importance in the medical area, and these have been used in a wide number of applications in the human body, such as surgical sutures, controlled drug release systems, artificial skins, guides for nerves, veins and artificial arteries and orthopaedic devices. Biodegradable polymers have several physical and chemical characteristics, such as molecular mass average and distribution, glass transition and/or melting temperatures, monomer ratios and sequencing for copolymers. The knowledge of physicochemical characteristics of Poly Lactic acid polymers essential to understand its thermo-mechanical performance. In order to achieve appropriate wound healing, sustained release of the drug from the bio-degradable patch is necessary. So the assessment of the interaction between the drug and polymer is indispensable.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v10i3.1512

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INTRODUCTION

In ayurvedic literatures, many drugs and preparations for the management of chronic non-healing ulcer are described. Out of all these drugs, some have shodhan (wound debridement/wound cleansing) properties, and some others have ropana (wound healing) properties. There is an apparent requirement for a combination of the drug for proper management of the wound. Hence, there is the use of a polyherbal preparation for the management of infective wound, which have both wound cleansing and wound healing properties.

Acharya Sushruta has mentioned a group of barks of five trees known as "Panchavalkala" for wound healing which consists of Vata (Nyagrodha), Udumbara, Ashwatha, Parishpippaland Plaksha (Shastri and Sthan, 2010a). Parishpippal as described in Nighantu granthas, interpreted by Dalhan as Gardbhand is a controversial drug and not easily available (Shastri and Sthan, 2010b). Therefore, in the present study, the compound ayurvedic drug(CAD) consists of aqueous extract of stem bark of four Ficus species of Vata (*Ficus bengalensis* Linn.), Ashwatha (*Ficus religiosa* Linn.), Udumbara (*Ficus glomerata* Roxb.), Plaksha (*Ficus lacor* Buch-Ham.).

Nanoparticles are considered as one of the most promising dosage forms as potential formulations for site-specific drug delivery system, including drug targeting (Soppimath *et al.*, 2001). Colloidal polymeric particles used as drug carriers can be made of synthetic or natural polymers, which must be biocompatible and biodegradable polymers in drug delivery systems (Ding, 2006).

The wound healing dermal patch was designed on a bio-polymeric membrane material, and it was the carrier for the compound ayurvedic drug along with suitable additives which include diluents and binders (Mainardes and Silva, 2004). The use of biodegradable polymers in wound management has been brought into prominence with new innovations in drug delivery systems (Arayne and Sultana, 2006). Biodegradation is a natural process by which organic chemicals in the environment are converted into simpler compounds. Biodegradation can only occur within the biosphere as microorganisms play a central role in the biodegradation process.

Thus with a new dimension for the use of polymeric materials as drug delivery devices involves incorporation of biodegradability into the drug delivery system. However, a number of degradable polymers are potentially useful for this purpose including a variety of synthetic and natural substances in all these Poly(lactic acid) (PLA) is the most readily biodegradable polymers (Ahmed and Discher, 2004). The proposed wound healing dermal patch was bilayer, where in the first layer supports moisture balance and the second layer for controlling wound infection and cell proliferation.

Poly (lactic acid) (PLA) has been used worldwide as a biodegradable substrate for nano-drug delivery so for preparation of biodegradable patch, poly (lactic acid) (PLA) was used as a substrate for wound dressing material for impregnation of active ingredients of the compound Ayurvedic drug. PLA provides a wide range of degradation rates, from months to years, depending on its composition and molecular weight, the lactide polymers chains are cleaved by hydrolysis to form natural metabolites (lactic acids), which are eliminated from the body through the citric acid cycle (Mainardes *et al.*, 2006). The presence of the ester linkage makes these polymers hydrolytically unstable. This means that they can be degraded when in contact with the body fluids, resulting in products that are reabsorbed by the organism, as part of the carbohydrates metabolism (Beiser and Kanat, 1990). It is known that the molar mass, polydispersion, crystalline degree, morphology, thermal history and chemical structure of the polymers are factors that influence the degradation rate considerably (Dumitriu, 1996).

Biodegradable polymers have several physical and chemical characteristics, such as molecular mass average and distribution, glass transition and/or melting temperatures, monomer ratios and sequencing for copolymers. All these properties can influence the physical behaviour of raw polymers (Cilurzo *et al.*, 2008).

The mobility of a polymeric chain determines the physical characteristics of the final product. The mobility is a function of atoms agitation in the molecules, being directly proportional to the temperature. Therefore, the knowledge of the physicochemical characteristics of a polymer is fundamental to understand its thermo-mechanical performance (Canevarolo and Babetto, 2002).

When polymers are used as controlled drug delivery systems, additional qualities, such as surface area, bulk density, surface morphology and particle size are included and may affect both degradation and drug release from the polymeric system (Devarajan and Sonavane, 2007). The study of the in-vitro interaction between Compound Ayurvedic Drug (CAD)and the polymer was done by keeping Poly (Lactic Acid)(PLA) as a polymer.

MATERIALS AND METHODS

Preparation of biodegradable patch by solvent casting method

In the present study, an aqueous extract of all four drugs (CAD) was together grinded, and the powdered drug were put through sieve no. 100 to fix the particle size of the drug to 100 microns. The poly (lactic acid) polymer was taken with Dichloromethane solution. 25%W/W Compound Ayurvedic Drug was mixed with dichloromethane solution and kept over ultrasonicator for dispersion. After ultrasonication, 25%W/W Compound Ayurvedic Drug was mixed with a polymer solution and kept over rotator having 1500rpm for mixing.

Table 1: Physicochemical evaluation of the polymer solution

Physicochemical parameter	Polysaccharide biopolymer solution
Specific gravity	1.25
Viscosity	0.55-0.75
pH	6.80
Total bacterial count (per g)	Absent

Standard Film applicator was taken to make the film of a standard size of 100-micron thickness. The Solution of Compound Ayurvedic drug and Polymer was pasted over the glass sheet in a cold room at 4°C. The Film applicator was moved over the solution, and a film of 100-micron standard thickness was made. Dichloromethane, being a volatile substance got evaporated and Biodegradable film having 25% W/W drug and polymer remained in the patch. The biodegradable patch was finally made after evaporation of the solvent. The prepared films were peeled from the plates, and the films showed the good film-forming property (filmogenicity).

RESULTS AND DISCUSSION

Biodegradable Patch

The prepared biodegradable films were evaluated for their physicochemical properties. The pH, viscosity and total bacterial count of the polymer solution is tabulated in Table 1.

Table 2: Physicochemical evaluation of the dermal patch

Sample uniformity of weight (10 × 10cm) (mg)	4.35 mg
Thickness (mm)	100 micron
Melting point (°C)	58°C
Moisture content (%)	18.68%

The formulated biopolymer dermal films were tested for uniformity of weight, thickness, melting point and moisture content. The average weight of the patches (10 × 10cm) were found to be 4.35mg with a thickness of 100 microns. The moisture content of the film was found to be ranging from 16.81% -18.68%and the results are shown in Table 2.

In vitro drug release kinetics

In vitro drug release kinetics was investigated in phosphate buffer solution (pH-7.4) at 37°C from the drug-loaded polymer matrix.

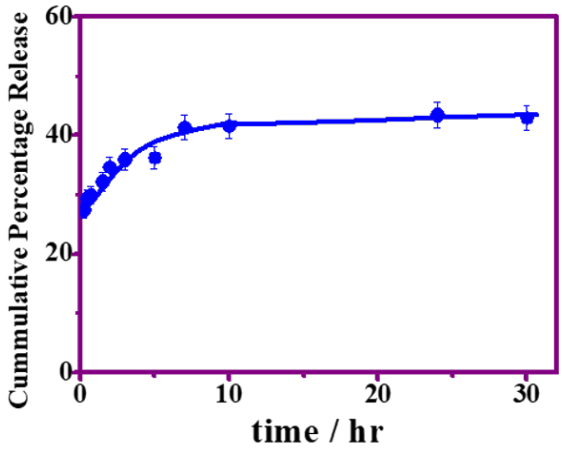

Figure 1: In Vitro Release of The Drug

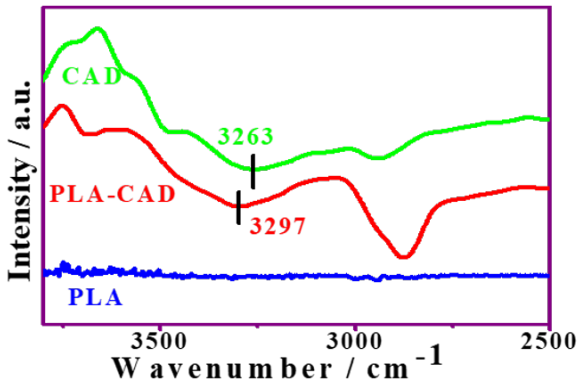

Figure 2: IR spectroscopy of shifting of –NH group

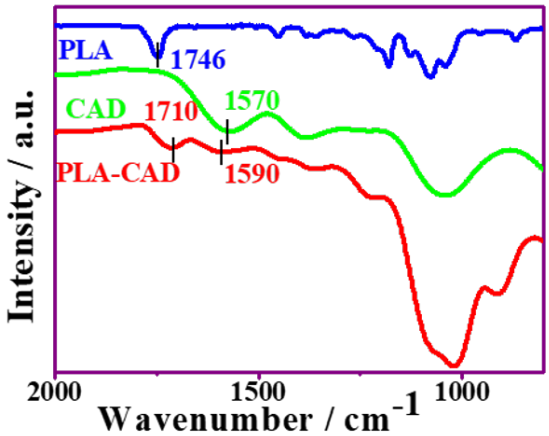

Figure 3: IR spectroscopy of shifting of carbonyl group

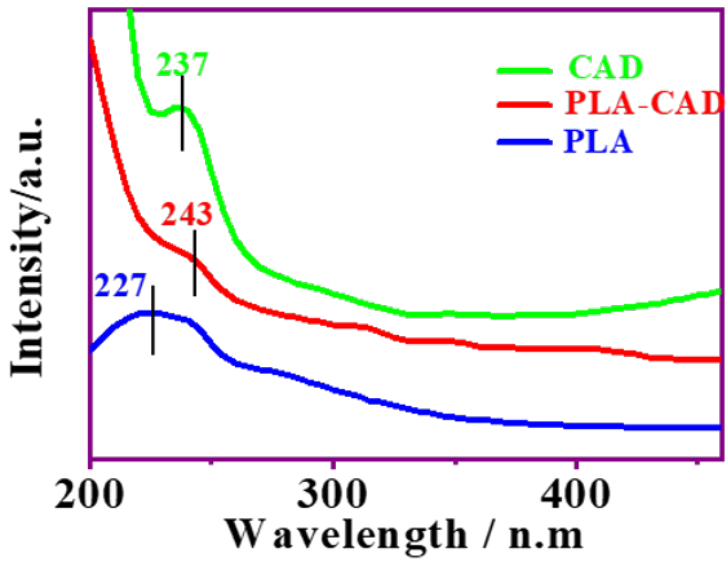

Figure 4: UV spectroscopy

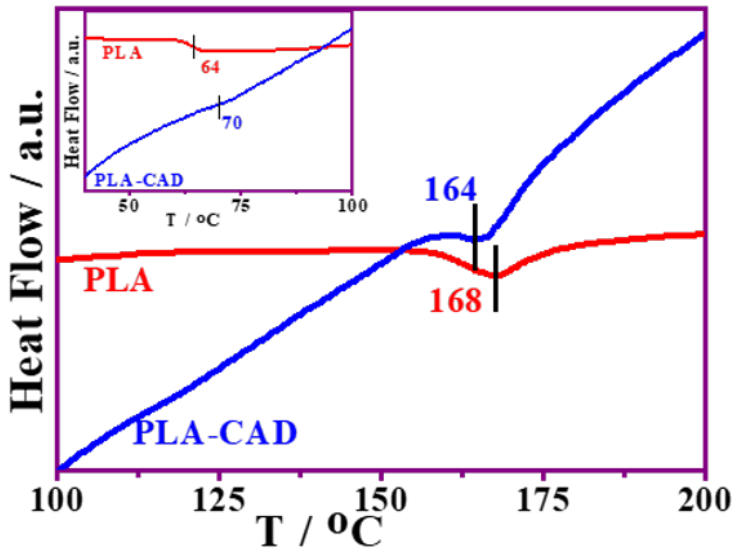

Figure 5: Increase in Glass Transition Temperature

The concentration of released drug was measured by UV-VIS spectroscopic studies. The main object of a sustained drug release system in wound healing is to deliver a biologically active molecule at a rate needed by the wound environment for therapeutic effect over a desired time frame.

The drug release kinetics depends on (a) liquid penetration into the matrix (b) dissolution and (c) diffusion of the drug, and all these factors were the rate-determining step for drug release. The diffusion is a slow process, and it depends on the interaction between the polymer matrix and the drug as in Figure 1.

The relative interaction between the polymer matrix and the drug has been confirmed through the shifting in –NH frequency which are Stretching at 3263 cm^{-1} to 3297 cm^{-1} in (Figure 2) and bending at1570 cm^{-1} to 1590 cm^{-1} (Figure 3) also indicates greater interaction between CAD and polymer.

The relative interaction between the polymer matrix and the drug has been confirmed through the shifting of stretching frequency of carbonyl group in the lower IR range, i.e. From 1746 cm^{-1} to 1710 cm^{-1} (*i.e.*, decrease in energy of carbonyl group and greater stability of PLA -CAD) (Figure 3).

The drug shows an absorption peak in uv-vis spectroscopy at 237 nm and is due to p-p* transition. Now in Compound Ayurvedic drug impregnated

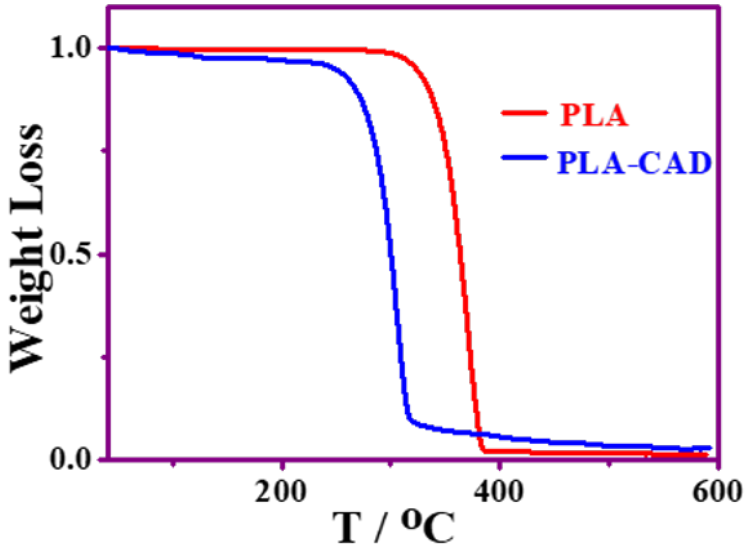

Figure 6: Temperature increased, the degradation rate of PLA-CAD was found more in comparison to PLA

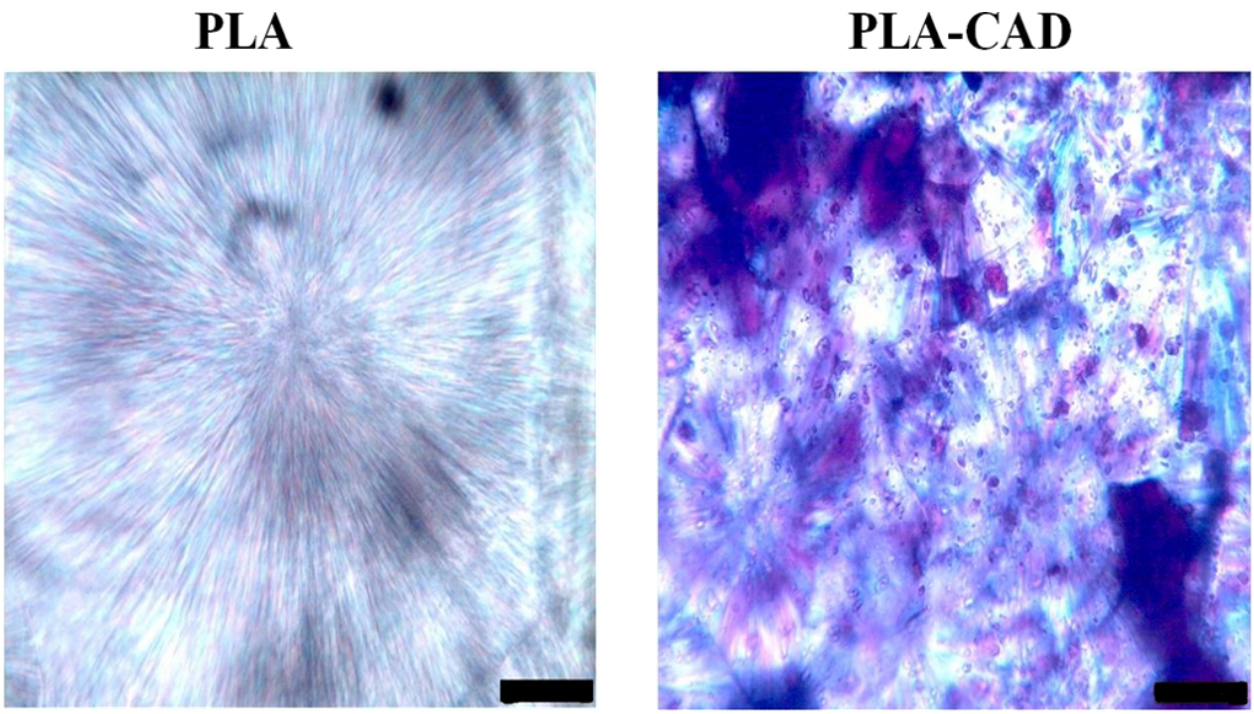

Figure 7: Radius of spherulite (~200 micron), Radius of spherulite (~75 micron)

with PLA, the peak shifts to 243 nm due to the interaction between drug and PLA, which lowers the energy gap between p and p* orbitals (Figure 4).

The increase in glass transition temperature by 6^{o}C (64^{o}C to 70^{o}C)in PLA-CAD as compared to PLA due to restricted chain movement in presence of CAD (Figure 5).

Depression in Melting Point

The depression in melting point 4^{o}C (168^{o}C to164^{o}C)in PLA-CAD strongly indicate the interaction between PLA and CAD (Figure 5).

As the temperature increased, the degradation rate of PLA-CAD was found more in comparison to PLA, as shown in Figure 6.

Polarizing optical micro graphs of PLA and PLA-CAD

The Samples were crystallized at 130°C up to full Solidification. The nucleating phenomena have also been observed in polarizing optical micrographs (Figure 7). The average spherulitic radius are 200

microns and 75 microns for pure PLA and PLA-CAD, respectively. Here CAD acts as a nucleating agent. The enhanced interaction between PLA and CAD restricts the crystal growth rate of the matrix.

CONCLUSION

Each drug present in Compound Ayurvedic drugs (i.e. combination of 4 Ficus species) is a well-known drug for wound healing since ancient times. In order to have its better acceptability, a newer approach of preparing a biodegradable patch by impregnating the drug in Poly(lactic acid) polymer was done.

Selection of polymer is very important during drug designing for drug delivery carriers. There are many biodegradable polymers, but the selection was based on facts like the interaction of drug and polymer, sustained drug release from the carrier, degradation rate, cost-effectivity and easy availability. After several trials, it was found that the interaction of Compound Ayurvedic drug and Poly (lactic acid) was significant.

Polymeric three-dimensional structured material which was selected as a drug carrier allowed the continuous and controlled localized therapeutic drug release within the desired time limit.

The relative interaction between the polymer matrix and the Compound Ayurvedic drug was confirmed by IR spectroscopy of shifting of –NH group and shifting of carbonyl group*, i.e.* decrease in energy of carbonyl group and greater stability of PLA -CAD.

The Compound Ayurvedic drug(CAD) shows absorption peak in UV spectroscopy at 237 nm but after impregnation, i.e. in PLA-CAD the peak shifts to 243 nm due to the interaction between CAD and PLA, which lowers the energy gap between p and p* orbitals and shows greater stability of PLA –CAD.

The increase in glass transition temperature by 6^oC (64^oC to 70^oC) in PLA-CAD as compared to PLA strongly indicates the interaction between PLA and CAD.

The depression in melting point 4^oC (168^oC to164^oC) in PLA-CAD strongly indicates the interaction between PLA and CAD. As the temperature increased, the degradation rate of PLA-CAD was found more in comparison to PLA.

The average spherulitic radius are 200 microns and 75 microns for pure PLA and PLA-CAD, respectively. The enhanced interaction between PLA and CAD restricts the crystal growth rate of the matrix.

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