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Development and In-vitro evaluation of poly (lactic acid) films for controlled release studies of Lapatinib: an anticancer drug

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ABSTRACT

Biodegradable poly (lactic acid) films containing Lapatinib were prepared by spreading polymer / Lapatinib solution on the non-solvent surface. Different drug loading polymer films can be obtained by controlling the weight ratios of drug and polymer. The synthesized Lapatinib loaded PLA films were evaluated by different parameters such as drug loading, encapsulation efficiency, surface morphology, differential scanning calorimetry, powder X-ray diffractometry and In vitro drug release kinetics. Various combinations of the polymer-drug weight ratios were used to achieve In vitro release of drug over a period of 30-35 days, with initial burst release < 25% and a steady release rate over the entire period of release. Furthermore the drug release rate of the film could be controlled by the drug loading content and pH of the release medium. Our results suggest that these Lapatinib loaded PLA film formulations could constitute a promising approach for the controlled drug delivery applications. This is the first study which shows the in-vitro release profile of Lapatinib using a polymeric delivery system.

INTRODUCTION

One of the areas that are being actively investigated is the development of biodegradable films from synthetic polymers such as poly (lactic acid) and poly (lactic-co-glycolic acid). Poly lactic acid and its copolymers like poly (lactic-co-glycolic acid) were widely used in controlled drug delivery applications due to their biodegradability, biocompatibility and continue to be popular choices for the development of new drug delivery systems (Khang *et al.,* 2003; Perugini *et al.,* 2003; Ye *et al.,* 2010; Schade *et al.,* 1995; Seigel *et al.,* 2006; Klose *et al.,* 2010). In general, PLA and PLGA micro or nanoparticles are solid particles, which have the disadvantages of low drug incorporation efficiency, easy aggregation and polydispersable particle sizes (Acharya *et al.,* 2010). However various biodegradable polymer films have also been loaded with drugs for controlled release applications due to their promising characteristics such as high surface area, absorbency and easy of fabrication into many desirable product forms (Lewis, 1990; Jacson *et al.,* 2004; Dorta *et al.,* 2002; Dorta *et al.,* 2002; Ma and McHugh, 2010; Knill *et al.,* 2004; Shi *et al.,* 2010). For example gentamicin and tetracycline were released from poly (lactic acid) films (Lee *et al.,* 1997; Park *et al.,* 2000), and ibuprofen, albumin and testosterone were released from poly (lactic-co-glycolic acid) films (Jianmei *et al.,* 2011; Shah *et al.,* 1992) and these systems were studied for potential use in drug delivery applications. A number of methods have been developed for fabrication of polymer films, such as solution casting method (Zilberman, 2005), layer-by-layer technique (Jiang and Li, 2009) and solvent evaporation method (Patel *et al.,* 2009) etc. Lapatinib belongs to signal transduction inhibitor category of targeted therapies.

It particularly interferes with protein tyrosine kinases; Epidermal Growth Factor Receptor (EGFR or HER-1) and Human Epidermal Growth Factor Receptor type-2 (HER-2), which are over express in advanced breast cancer and metastatic breast cancer (MBC) patients. Lapatinib was approved by the FDA for treating advanced and metastatic breast cancers (Medina and Goodin, 2008). Lapatinib has been reported to have anti tumor activity in phase II trials when used as first-line therapy for MBC, in patients with inflammatory breast cancer, and in patients with central nervous system metastases. Lapatinib has also been reported to decrease the percentage of cancer stem cells and improved the long-term survival of patients (Li *et al.,* 2008).

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A long term drug delivery carrier would be an ideal candidate to improve drug adherence and to ensure a continuous supply of optimum doses of the drug. In view of these details, a promising strategy for designing novel drug delivery systems is to combine the merits of both biocompatible and biodegradable polymers.

Poly (lactic acid) is one of the most promising bio-polymer due to the fact that they degrade in the presence of water in to naturally occurring metabolite (lactic acid), which is a weak acid (pKa = 3.86) that reversibly dissociates in water to produce a lactate ion and is capable of entering in to cells via the monocarboxylate transporter (MCT) protein shuttle system (Philip *et al.*, 2005).

Once inside of the cell, lactate can serve as an energy substrate by converting into glucose in the Cori cycle. In addition to its role as energy source for cells, lactic acid has been shown to have an antioxidant property that may serve to protect cells from damage due to free radicals that are naturally produced throughout the cell life cycle (Lampe *et al.*, 2009). Therefore, PLA is an eco-friendly (nontoxic) product with better features for use in the human body.

The objectives of our work are firstly to entrap Lapatinib within the poly (lactic acid) as a single polymer in to films prepared by spreading polymer / lapatinib solution on the nonsolvent surface by controlling the ratio of lapatinib and PLA. Secondly to characterize the formulations in terms of a drug loading and release, surface morphology and in-vitro release studies for their potential applications in controlled drug delivery. These results are presented in this section.

MATERIALS AND EXPERIMENTAL METHODS

Materials

Poly (lactic acid) was purchased from Sigma Aldrich, USA. Lapatinib was procured as a gift sample from Cipla pharma Limited, Bangalore (India). Double distilled water was used in all the experiments. All chemicals were of analytical grade and were used without further purification.

Experimental methods

Preparation of drug loaded PLA films

Polymer films consisting appropriate amounts of poly (lactic acid) and Lapatinib were prepared by spreading polymer/Lapatinib solution on the nonsolvent surface as follows: The components (W_{PLA}/W_{LAP} = 12.5/2.5) were mixed in a solvent (W_{THF} = 85) at room temperature until polymer and drug were dissolved. A pipette was used to take 50 µL of the solution and then the solution was injected on the surface of distilled water in a beaker. The solution spread quickly on the surface of water and solidified into a film within 5 seconds then the film was taken out and washed with distilled water and dried in air at 40^0 C. The process of film formation with different weight ratios were shown in Table. 1

Drug loading and encapsulation efficiency

An appropriate amount of dried films were dissolved in 10 mL of THF, and the absorbance of the solution was measured by using the UV Spectrophotometer (model: UV 3000^+, Lab India®, Mumbai, India). Pure THF was used for a blank experiment before the UV measurement. The results of drug loading and percentage of encapsulation efficiency were calculated using equations 1 & 2 respectively.

$$\% \text{ Drug loading} = \frac{\text{Lapatinib weight in film X 100\%}}{\text{Film weight}}$$

$$\%\text{Encapsulation efficiency} = \frac{\text{Actual weight of Lapatinib X 100\%}}{\text{Theoritical weight of Lapatinib}}$$

Dissolution Experiments

In vitro release studies were performed at 37^0 C using the Tablet dissolution tester (Disso test, Lab India, Mumbai, India) equipped with six paddles at a paddle speed of 100 rpm. About 50 mL of HCL aqueous solution pH=1.2 and phosphate buffer solution (pH=7.4) were used as the dissolution media. The sample was sealed in a dialysis bag, which was suspended in a sealed beaker containing release medium at constant stirring.

At a fixed time intervals, 2 mL of the resultant release medium was sampled for the analysis of lapatinib content, then 2 mL of the fresh release medium was immediately added to maintain the original volume. The amount of lapatinib released was analyzed based on the standard curve using a UV Spectrophotometer at the λ_{max} of 362 nm. The cumulative amount of drug released into the media at each time point was evaluated as the percentage of total drug release to the initial amount of the drug.

Scanning electron microscopy

Scanning electron microscopy (SEM) of drug loaded PLA film surfaces were performed using a jeol JSM 840 A at an accelerating voltage of 5 kV. The SEM samples were Au/Pd sputtered prior to observation.

Differential scanning calorimetry

Differential scanning calorimetry (DSC) measurements were performed using SDT-Q600 thermal system. Weighed samples of 10 mg were placed in alluminium pans under nitrogen at a flow rate of 20 mL/min. the samples were heated from 30 to 800^0 C at a rate of 10^0 C/min.

X-Ray diffractometry

X-Ray diffraction **(**XRD) measurements were performed on a Siemens D 5000 (Germany). The films or powder were placed on the glass sample folder, and measurements were performed using a copper target at 40 mA with a scanning speed of 10^0/min and a 2θ range of $0\text{-}90^0$.

RESULTS AND DISCUSSION

Drug loading and encapsulation efficiency

In the present system under investigation the drug loading and encapsulation efficiencies can be explained by the insolubility of Lapatinib and PLA in water, but their solubility in tetra hydro furan (THF), which is inter-soluble with water. When the mixed solution spreads on the water surface, the THF molecules diffuses in to water phase, leaving the PLA and LAP molecules to quickly solidify due to their insolubility in water. In this case, the Lapatinib and PLA form a thin film on the surface of water.

It is known that Lapatinib and PLA can dissolve well in THF at molecular state, and therefore the drug is distributed homogeneously in the films formed. Thus, high drug loading and encapsulation efficiencies are obtained and presented in Table 1. The values of drug loading contents of the samples with different weight ratios are smaller compared to the corresponding ones in theory. The encapsulation efficiency in all different weight ratios exhibit almost 88%, indicating that the drug can be effectively loaded in to these films at this range.

Table 1: % of drug loading and encapsulation efficiencies at various PLA/LAP weight ratios.

Ratio of *WTHF/WPLA/WLAP*	Drug loading (%)	Theoretical loading (%)	Encapsulation efficiency (%)
85/12.5/2.5	14.2±0.2	16.5	88.0±1.0
85/11.25/3.75	22.2±1.6	26	88.2±6.8
85/10/5	28.6±0.4	32.3	89.2±1.2

Scanning electron microscopy

Fig. 1 shows the SEM images of Lapatinib loaded PLA films with different weight ratios of polymer/drug. Fig. 1A exhibits the top surface of the film with a ratio of W_{PLA}/W_{LAP} =12.5/2.5, which has convex pattern and relatively smooth surface indicating the absence of voids in the film.

The diameter of the convex is 0.80 ± 0.09 µm. Fig. 1B shows the rough surface of the film with a ratio of W_{PLA}/W_{LAP} =11.25/3.75, which indicates the presence of voids in the film. Fig. 1C exhibits the top surface of the film with a ratio of W_{PLA}/W_{LAP} =10/5, which has smooth surface and has no convex pattern. Furthermore, the insert in Fig. 1 C shows the rough cross section surface which indicates the presence of voids in the film.

From the SEM images it is observed that there are voids in the film with higher drug concentration, while there are no voids in the film formed with lower drug concentration. There is convex pattern for the sample of W_{PLA}/W_{LAP} =12.5/2.5, whereas there is no convex pattern in the samples of W_{PLA}/W_{LAP} =11.25/3.75 and W_{PLA}/W_{LAP} =10/5. The thickness of the films with different weight ratios is in the range of 1-5 µm. The results show that the ratio of W_{PLA}/W_{LAP} has a great influence on the surface morphology and structure of the films.

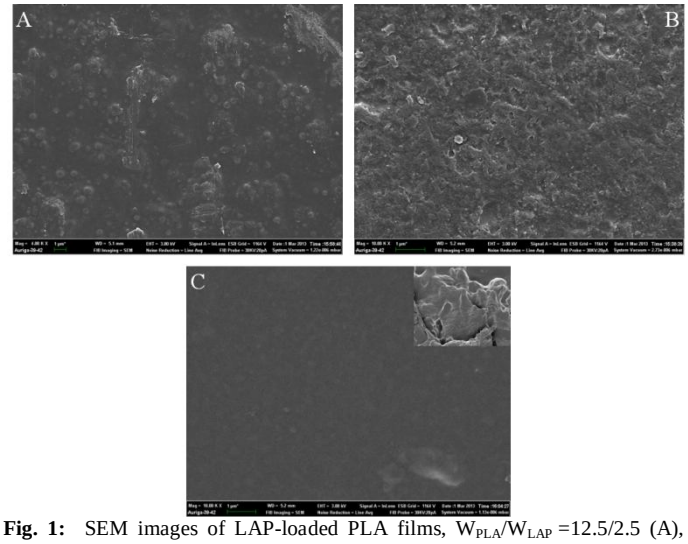

Fig. 1: SEM images of LAP-loaded PLA films, W_{PLA}/W_{LAP} =12.5/2.5 (A), W_{PLA}/W_{LAP} =11.25/3.75 (B) and WPLA/WLAP =10/5 (C).

DSC analysis

The onset melting point of Lapatinib was observed at 98^0C. However, no characteristic peak of Lapatinib was observed in the DSC curve of the Lapatinib loaded PLA-film. Absence of the drug melting peak in DSC thermogram of drug loaded PLA film is sign of molecularly dispersed drug within the polymer matrix. The results are consistent with the PXRD analysis, which reveals that Lapatinib is amorphous in the drug loaded film. This will be explained in the next section.

XRD analysis

The diffraction pattern of Lapatinib exhibits many diffraction peaks, revealing its crystalline state. Whereas the diffraction pattern of Lapatinib loaded PLA film shows the broad and high intense diffraction peak, which was centered at 16.25^o and could be assigned to PLA. This suggests that Lapatinib was transformed from a crystalline state to an amorphous state during film formation.

In vitro release studies

The release profile of Lapatinib from Poly (lactic acid) based films was studied in HCL aqueous solution (pH 1.2) and phosphate buffer (pH 7.4) for 30-35 days and found to be effected by drug loading content and pH of the release medium. The % cumulative release data presented in Fig 4.4 & 4.5 at pH 1.2 and pH 7.4 respectively, indicated that by increasing the pH from 1.2 to 7.4 a considerable decrease in the cumulative release is observed for all formulations. From Fig 4 & 5 it is seen that the W_{PLA}/W_{LAP} =10/5 polymer-drug films have shown higher drug release rates than W_{PLA}/W_{LAP} =11.25/3.75 and W_{PLA}/W_{LAP} =12.5/2.5. The release rate becomes quite slower at the lower amount of drug in the film, due to the availability of more free void spaces through which a lesser amount of drug molecules could transport. Thus drug release rate depends upon the drug loading content as well as pH of the release media.

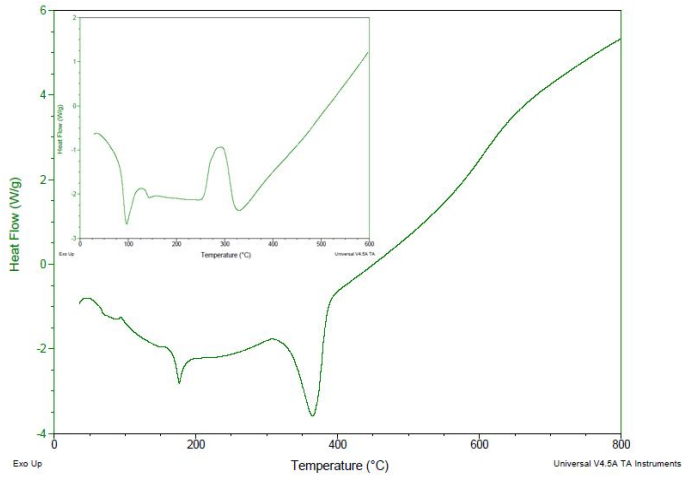

Fig. 2: DSC thermograms of pure drug (a) and drug loaded PLA film (b).

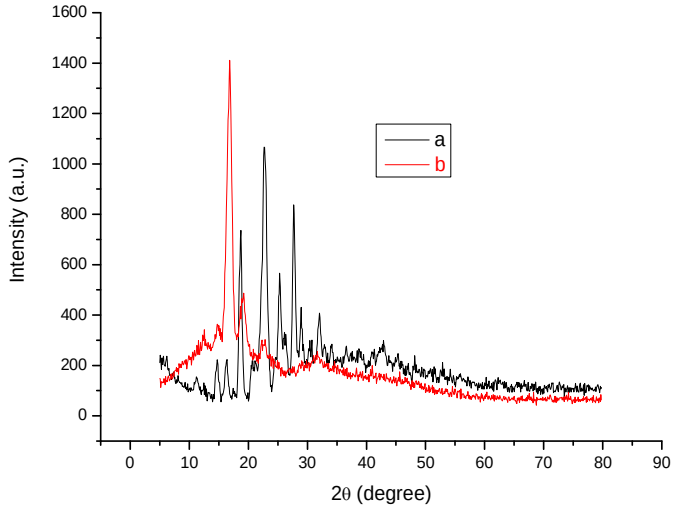

Fig. 3: PXRD patterns of pure drug (a) and drug loaded PLA film (b).

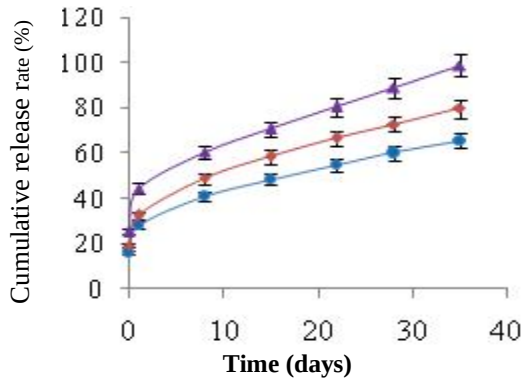

Fig. 4: In vitro release kinetics of lapatinib from the samples with ratios of W_{PLA}/W_{LAP} =12.5/2.5 (•), W_{PLA}/W_{LAP} =11.25/3.75 (♦) and W_{PLA}/W_{LAP} =10/5 (▲) of the films in HCL aqueous solution (pH 1.2).

The formulations containing W_{PLA}/W_{LAP} =12.5/2.5, W_{PLA}/W_{LAP} =11.25/3.75 and W_{PLA}/W_{LAP} =10/5 showed a significant initial burst release of 16, 18 and 25% respectively, in the first day of release and the drug release continued steadily thereafter. This phenomenon is attributed to diffusion of the drug through pre-existing pores in the film surfaces formed during the solvent evaporation process. The remaining of the drug was released slowly as the PLA eroded in the release medium. In films W_{PLA}/W_{LAP} =10/5, the release of the drug was almost completed by 35 days from release media pH 1.2, while it was 80% for W_{PLA}/W_{LAP} =10/5 in pH 7.4 release media. The results suggest that the drug release kinetics is faster at low pH than at high pH. The decreased release rate may have been due to the decreased solubility of Lapatinib in basic media (pH 7.4). The aqueous solubility of Lapatinib is pH dependant, with higher pH resulting in lower solubility.

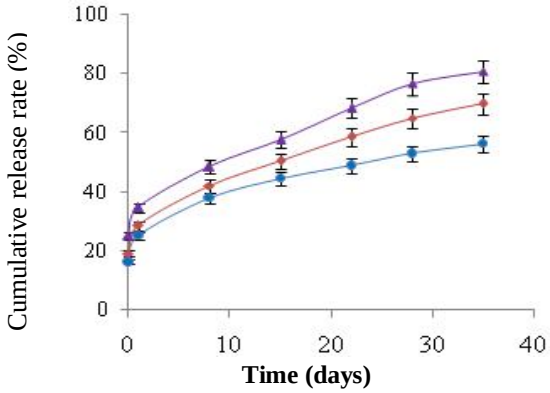

Fig. 5: . In vitro release kinetics of lapatinib from the samples with ratios of W_{PLA}/W_{LAP} =12.5/2.5 (•), W_{PLA}/W_{LAP} =11.25/3.75 (♦) and W_{PLA}/W_{LAP} =10/5 (▲) of the films in phosphate buffer solution (pH 7.4).

Drug Release Kinetics

To know the mechanism of the drug release from the films, the curves obtained from the in vitro dissolution process were fitted in to distinct model equations as follows: Zero order (Cummulative % of drug release Vs time), First order (log cumulative % of drug remaining Vs time), Higuchi release model (Cummulative % of drug release Vs square root of time) and Korsmeyer-Peppas model (log cumulative % of drug release Vs log time). Basing on these models the release kinetics parameter (Regression Coefficient (r^2) value) can be determined for different formulations at pH 1.2 and pH 7.4 and presented in Table 2.

From the samples W_{PLA}/W_{LAP} =10/5 in pH1.2 and W_{PLA}/W_{LAP} =12.5/2.5 in pH 7.4, we observe that r^2 values are larger when fitted to a Higuchi release equation compared with other equations based on Fick's law of diffusion. As for the release of samples W_{PLA}/W_{LAP} =11.25/3.75 in pH 1.2 and W_{PLA}/W_{LAP} =12.5/2.5 in pH 7.4 the r^2 values are higher when fitting to Korsmeyer-peppas release model. When the sample W_{PLA}/W_{LAP} =12.5/2.5 in pH 1.2 and W_{PLA}/W_{LAP} =10/5 in pH7.4 is released, it fits to First order kinetics. The r^2 values are higher when the samples W_{PLA}/W_{LAP} =10/5 in pH1.2 and W_{PLA}/W_{LAP} =12.5/2.5 in pH 7.4 are fitted to the Zero order kinetics. The results show that the drug release mechanism from matrices is usually complex, either diffusion or erosion controlled. However, it is difficult to explain the actual mechanism of release at this stage since, the degradation of polymer starts during the dissolution period. Though some processes may be clearly classified to better understand the drug release from PLA films as mentioned above.

Table 2: Release kinetics parameter (R^2 value) of different formulations at pH 1.2 & pH 7.4.

Ratio of W_{PLA}/W_{LAP}	Zero order		First order		Higuchi		Ritger-Peppas	
	pH 1.2	pH 7.4	pH 1.2	pH 7.4	pH 1.2	pH 7.4	pH 1.2	pH 7.4
12.5/2.5	0.9955	**0.9965**	**0.9956**	0.9792	0.9945	**0.9913**	0.9920	**0.9971**
11.25/3.75	0.9964	0.9911	0.9761	0.9773	**0.9970**	0.9677	0.9806	0.9754
10/5	**0.9967**	0.9830	0.9951	**0.9876**	0.9801	0.9761	**0.9973**	0.9859

CONCLUSIONS

From the present study it was concluded that the Lapatinib loaded poly (lactic acid) films prepared by spreading polymer-Lapatinib solution on the non-solvent surface with different weight ratios was found to show maximum encapsulation efficiency (88.0±1.0 – 89.2±1.2) and the drug release rate monitored by the drug loading content and pH of the release medium. The kinetics of the drug release was investigated based on kinetic parameter (r^2 value) and reported as either diffusion or erosion controlled.

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