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Sustained transdermal release of diltiazem hydrochloride through electron beam irradiated different PVA hydrogel membranes

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ABSTRACT

Extremely fast release of diltiazem hydrochloride (water soluble, anti anginal drug used to treat chest pain) together with its faster erosion has been the primary problem in conventional oral therapy. It has been addressed in this paper by encapsulating the drug in electron beam irradiated various poly (vinyl alcohol) hydrogel membranes and delivering it through transdermal route. Results show excellent control over the release of diltiazem hydrochloride through these membranes subject to their physico-mechanicals.

1. Introduction

In recent years, significant efforts have been devoted on in vitro delivery of small or large molecular weight drugs and other bioactive agents [1,2]. Pharmaceutical technology focuses on formulating therapeutically active agents in biocompatible forms such as nanoparticles, nanocapsules, micellar systems, conjugates and other bio-adhesives for this purpose [3,4]. Besides, latest development of patch therapy investigates controlled/regulated release of very common drugs through polymeric films/membranes. One such experimentation with electron beam irradiated poly (vinyl alcohol) (PVA) hydrogel membranes containing diltiazem hydrochloride has been reported in this paper. Diltiazem is a common, calcium channel blocker, anti-anginal drug used in treatment of angina pectoris (chest pain). It is water soluble and is marketed in tablets of 30, 60, 90 and 120 mg doses. Minimum drug requirement of an adult individual is 180 mg per day and is thus recommended for multiple oral administrations. Burst release together with multiple administrations in conventional therapy often leads to serious problems of drug overdose. The burst release, though sometimes desirable in certain formulations, is known to be the commonest cause of patient side effects and is economically wasteful too since much of the drug released during the burst phase has no therapeutic effect yet reduces longevity of the system [5,6]. Numerous mechanisms have been suggested in the past to minimize or prevent the bursting effect. Few such examples are surface extraction of hydrogels, employing double-walled microspheres, application of extra/additional coating over drug loaded microcapsules, and use of structured composites [7]. Some recent attempts are surface grafting of hydrophilic monomer [8], gamma irradiation of the polymeric drug carrier [9] and insertion of ultrasound tunable component [10]. Idea of selecting PVA as the diltiazem carrier evokes from its ability to immobilize bioactive agents [11]. It has been further treated with electron beam in anticipation of gaining more control over bursting release of diltiazem during application. Electron beam crosslinking is clean and safe technology, especially for biomedical application, since it does not require any external initiators and cross linkers [11], which is harmful and difficult to remove. Previously bursting feature from PVA hydrogel has been modulated by surface crosslinking [12] but authors, until now, are not aware of any literature that discusses on the use of electron beam irradiated PVA hydrogel membranes of widely different molecular weights to study transdermal release behavior of diltiazem hydrochloride. PVA, apart from being biocompatible and biodegradable [13], has wide range of water solubility depending on its grade and molecular weight. It is semi-crystalline; though the crystallinity strongly depends on the extent of water absorption-usually higher water content leads to low crystallinity and vice versa [14]. PVA forms hydrogel with very high gel strength due to extensive intra as well as inter-molecular hydrogen bonding with water. Its excellent fitment with human skin regarding humidity and oxygen permeation properties makes it a strong contender for in vitro drug release membrane application. This paper begins with a comparative discussion on effects of irradiation on physico-mechanicals of different PVA macromers followed by

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trans-dermal release analysis of dilitiazem hydrochloride through selective hydrogel membranes having better balance in overall properties.

2. Experimental

2.1. Materials

Poly (vinyl alcohol) (PVA, 98% hydrolyzed) of widely different molecular weights (number average), 1.15×10^5 (designated as PVA_H) and 1.4×10^4 (designated as PVA_L) was used for the present study. Both the samples were semi-crystalline and were procured from E-Merck, Mumbai, India. Diltiazem hydrochloride (molecular weight 450.98) was a gift sample from Ranbaxy Laboratories Ltd., Gurgoan, Haryana, India.

2.2. Preparation of hydrogel membranes

PVA hydrogel was prepared by dissolving it in distilled water. PVA_H was soluble in boiling water whereas PVA_L dissolved at room temperature. 20% (w/v) PVA solutions were prepared for analysis. After homogeneous mixing of drugs with PVA in stipulated amount stated later, the aqueous gel was placed into polyethylene bags (the thickness of the bags were 5 mm) and was irradiated at different doses under high energy electron beam. The parameters of the accelerator were: electron energy 1.45 MeV; electron beam current 4 mA; scanner width 90 cm and conveyor speed 3.6 m min^{-1}. The post irradiated gels were cast on plane Teflon sheets for spontaneous drying at room temperature. The average thickness of the membranes was maintained at 0.25 cm during casting. Detail of sample composition has been reported in Table 1.

3. Analysis of hydrogels

3.1. Studies on relative measure of crosslinking and chain scission

Measured weight of electron beam irradiated PVA hydrogels were extracted for 24 h from water using soxhlet extraction unit. (100-gel) was considered as sol content and the data was used for comparative study of chain scission and crosslinking with the help of Charlesby-Pinnar plot made from the following equation (Eq. (1)).

$$S + \sqrt{S} = \frac{\mu}{\gamma} + \frac{1}{(\gamma P_{N,0}[I_0])} \quad (1)$$

S denotes sol fraction, μ and γ are the probabilities of chain scission and crosslinking, $P_{N,0}$ is the number average chain length of the original polymer and $[I_0]$ is the irradiation dose. These parameters are calculated from $S + S^{1/2}$ versus $[I_0]$ plot for series of samples.

Table 1
Hydrogel sample composition and drug exponent values.

Sample designation	PVA% (w/v)	Irradiation dose (kGy)	n
PVA_H	20	0	0.3840
$PVA_{H/5}$	20	5	0.3607
$PVA_{H/10}$	20	10	0.6356
$PVA_{H/15}$	20	15	
PVA_L	20	0	0.5808
$PVA_{L/5}$	20	5	0.7356
$PVA_{L/10}$	20	10	0.7210
$PVA_{H/15}$	20	15	

4. Swelling and de-swelling kinetics study

Swelling of irradiated hydrogel membranes was studied after putting samples of uniform dimension ($5 \times 2 \times 0.25$ cm^3) in distilled water at room temperature (27 °C). After stipulated time interval, the samples were taken out of the water, gently wiped in tissue paper to soak surface water and then weighed in an electronic balance (MK 20E, Adair Dutt, India, readability 0.1 mg). The swelling ratio was calculated by dividing swelled weight (S) by dry weight (S_0) after each reading. The experiment was carried out till the samples attained equilibrium. De-swelling experiment was done by periodically recording the decreasing weight of the fully swollen membranes after exposed to ambient air (27 °C, RH: 85) till constant value.

5. Mechanical properties study

Tensile stress–strain properties (tensile strength, modulus and elongation at break) of dry and swelled hydrogel membranes were studied in a Lloyd UTM, USA. All the experiments were carried out at room temperature (27 °C) with membranes cut as per dimensions of ASTM Die C and were pulled at a rate of 10 mm/min. An average of five test results has been reported for analysis.

6. Diltiazem release kinetics study

In vitro diltiazem release studies from selective hydrogels were performed in a Franz diffusion cell (Scheme 1) after loading the drug into hydrogel matrices. 1 mg of the drug was mixed thoroughly with un-irradiated PVA sol for 1 h at room temperature. A dialysis membrane (LA390, average flat width-25.27 mm, average diameter-15.9 mm and capacity approx-1.99 ml/cm) made from cellulose acetate was used as human skin replica for determining diltiazem release from the hydrogel matrix [15]. The membrane was mounted between the donor and receptor compartments of the diffusion cell [16]. The hydrogel membrane was placed on the cellulose acetate membrane and was covered with an aluminum foil. The receptor compartment was filled with phosphate buffer of pH 5.6 to match the skin pH (5.4–6.9) [17]. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was continuously stirred using magnetic beads to maintain a steady temperature at 32 ± 0.5 °C, as the normal skin temperature of human is 32 °C [18]. The aliquots were withdrawn at different time intervals and were replenished with an equal volume of fresh buffer. The diltiazem hydrochloride content in the aliquots was analyzed spectrophotometrically at 236 nm after matching the values with a standard calibration plot.

7. Results and discussions

High energy irradiation on single polymers facilitates two characteristically opposite chemical reactions: crosslinking and chain scission [19]. Charlesby-Pinnar equation (Eq. (1) in the experimental section) gives a good rational measure of that. For each irradiated PVA hydrogels, sol contents were measured and are plotted in Fig. 1 (Charlesby-Pinnar plot) against inverse of irradiation dose. Sol content drops steadily on applying higher irradiation doses. The scattered data points are nicely fitted into a straight line with high accuracy (R^2 values are reported in the figure) on both occasions. High slope of the best fit line interprets low crosslinking while high intercept elucidates high chain degradation probabilities on irradiation. Resultant slope and intercept values of PVA_H and PVA_L are stated in the figure itself. Higher slope of PVA_H enforces smaller $\gamma P_{N,0}$ value in the denominator of Eq. (1). Since $P_{N,0}$ is originally