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Electron beam irradiation: a novel technology for the development of transdermal system of isosorbide dinitrate

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Abstract

The development of a transdermal delivery system for isosorbide dinitrate (ISDN) using electron beam irradiation was studied. The solid state stability of the drug to irradiation was assessed. The drug was dissolved in 2-ethylhexylacrylate (EHA)-acrylic acid (AA) system and this solution was directly irradiated on a backing membrane (Scotchpak®1006) at different doses to get transdermal patches. The developed systems were evaluated for residual monomer content, equilibrium weight swelling ratios (EWSR), differential scanning calorimetry (DSC), weight uniformity, thickness uniformity, drug content and content uniformity, peel strength, in vitro release, skin permeation kinetics and skin irritation potential. The developed system possessed excellent adhesive properties. Increase in the irradiation doses did not have a significant effect on the peel strength values. The systems exhibited promising skin permeation kinetics and no skin irritating potential, both of which are important properties for transdermal drug delivery. The ISDN-EHA-AA system developed at an irradiation dose of 50 kGy showed a higher skin permeation profile as compared to an internationally marketed transdermal matrix system of ISDN.

Keywords: Electron beam irradiation; Radiation polymerization; Acrylates; Isosorbide dinitrate; Transdermal

1. Introduction

Isosorbide dinitrate (ISDN) is an organic nitrate and is widely used in the treatment and prophylaxis of coronary vessel diseases. Its short elimination half-life, high first pass metabolism after oral administration, low molecular weight and lipophilic properties makes it an ideal candidate for transdermal drug delivery via e.g. ointment, micro-emulsion, transdermal spray or transdermal therapeutic system (TTS) (Laufen and Leitold, 1992; Kietzmann et al., 1995). ISDN administration in transdermal as well as buccal forms circumvents the hepatic first pass metabolism associated with its oral administration (Danjo et al., 1994; Nozaki et al., 1996, 1997).

The use of radiation technology in biomedical sciences is well known due to its potential in producing several applications and diagnostic devices. Radiation has proven to be an effective tool for synthesis of polymer matrices for immobilization of many drugs at room temperature (Langer and Peppas, 1983) as well as low temperature (Yoshida et al., 1979; Kaetsu et al., 1986). Alpha particle irradiation has been used to develop nuclear track microporous membranes, which

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is used as drug release rate controlling membranes for TTS (Wu et al., 1993). Radiation cross-linked biodegradable and synthetic hydrogels have been used for hemostasis, tissue augmentation, tissue engineering and other medical applications (Cruise, 2002). Adhesives for transdermal (Kishi, 1991) and buccal tapes (Horiuchi et al., 1988) have also been synthesized by radiation polymerization.

Radiation polymerization is preferred over the thermo-chemical polymerization method for these applications because of some very unique features of radiation polymerization, viz., the final matrix is free of any residual initiator, the process can be carried out in broad temperature range and it also provides an opportunity for simultaneous sterilization of the product (Kaetsu, 1994). The overall activation energy for the radiation polymerization process has been reported to be 1/3 of the thermo-chemical process (Woods and Pikaev, 1994), hence is more energy efficient. In addition, it eliminates the use of solvents thereby contributing to environmental safety, decreasing cost and simplifying the manufacturing process (Dowbenk, 1989). As no solvents are involved, there are no chain transfer reactions, resulting in polymers of high molecular weight with improved properties.

In the present work, the electron beam irradiation has been used to fabricate transdermal patches of ISDN in EHA-AA matrices directly on a backing membrane. The effect of varying irradiation doses on system properties was studied. A HPLC analytical technique was standardized to estimate the drug in the presence of monomers and its degradation product. The peel strength data, release and the permeation pattern of the drug from the developed patches have also been reported. The skin permeation parameters of the developed systems were also compared with an international marketed transdermal matrix system of ISDN.

2. Materials and methods

2.1. Materials

ISDN (Chin-Chem Laboratories, India), backing membrane (Scotchpak®1006, 3M Pharmaceuticals, USA), Release Liner (Scotchpak®1022, 3M Pharmaceuticals, USA) were used as received. 2-Ethylhexylacrylate (EHA) obtained from Aldrich was made free of inhibitor by washing with 5% sodium hydroxide solution saturated with sodium chloride. It was subsequently washed with water to remove traces of alkali and dried over anhydrous sodium sulfate before use. Acrylic acid (AA) was purified by vacuum distillation. All chemicals and reagents employed were of AnalaR grade from Ranbaxy Chemicals Ltd., India. Nanopure water (conductivity 0.6 μS/cm) obtained by passing distilled water through a Branstead Nanopure purifying system was used for all experiments.

2.2. Analytical method for ISDN

A stability indicating HPLC method was developed for the estimation of ISDN from its degradation product, isosorbide mononitrate (ISMN). This method also gave good separation of ISDN from the two monomers employed, EHA and AA. The chromatographic conditions employed included a Lichrospher RP-18 column (5 μm, 125 mm × 4.6 mm, Merck), with a mobile phase of acetonitrile:water (6:4) at a flow rate of 1 ml/min and detection wavelength of 215 nm. A sample loop of 20 μl was employed and integration was done using Borwin V 1.21 chromatography software. Working standards were used for routine analysis.

2.3. Determination of ISDN solubility in EHA-AA system

Solubility of ISDN in EHA-AA was determined by taking excess quantity of drug (500 mg) in EHA-AA (9.5:0.5, w/w) mixture. The solutions were than equilibrated at 37 °C with gentle shaking in a constant temperature water bath for 24 h. The undissolved drug was removed by filtration and the filtrate was suitably diluted and analyzed by the HPLC method as discussed in Section 2.2.

2.4. Electron beam irradiation

The high power electron beam (EB) accelerator ILU-6 from Institute of Nuclear Physics, Novosibirsk, USSR was used for irradiation purpose. Prior to carrying out irradiation the electrical parameters and the conveyor speed were synchronized in such a way that 10 kGy of radiation dose could be delivered to the samples in each pass. This was done by Nylon film

dosimetry. The samples to be irradiated were placed in a chamber equipped with efficient cooling arrangement and inert gas atmosphere. This chamber was then placed on a conveyor, which passed below the EB horn for irradiation. The irradiation parameters employed were energy = 1.8 MeV, current = 2 mA, at a pulse rate of 10 pulses/s and conveyor speed = 13 mm/s which delivered a dose of 10 kGy/pass. Thus, to irradiate a system with a dose of 150 kGy, 15 such passes would be required.

2.5. Stability of ISDN to electron beam irradiation

The solid state stability of ISDN was determined by exposing the drug to varying doses of electron beam irradiation, viz., 30, 50, 70, 100 and 150 kGy. The drug was then analyzed by the HPLC method as discussed in Section 2.2. The chromatogram was observed for the peak corresponding to the degradation product.

2.6. Development of monolithic systems of ISDN

Aluminium moulds, 3 cm in diameter and 1 mm in depth were fabricated for preparing transdermal systems of ISDN. The mould contained a thin layer of poly(EHA) to act as a base adhesive. The backing membrane (Scotchpak®1006) was then fixed on to this adhesive. A solution of ISDN in EHA-AA at a concentration of 30 mg/ml was prepared. The volume was titrated so as to obtain a drug concentration of 1 mg/cm^2 of the patch. This volume was then transferred accurately by means of a pipette on to the backing membrane. The moulds were then placed in a chamber continuously purged with nitrogen and allowed to pass below the electron beam for irradiation. The effects of varying irradiation doses, viz., 30, 50, 70, 100 and 150 kGy were studied. In this case, formation of adhesive would occur directly on the substrate (in this case the backing membrane). The backing membrane containing the drug loaded polymeric film was then easily peeled off from the base adhesive and covered with a release liner (Scotchpak®1022).

2.7. Evaluation of drug loaded transdermal systems

The developed systems were evaluated for residual monomer content, equilibrium weight swelling ratio (EWSR), differential scanning calorimetry (DSC), weight uniformity, thickness uniformity, drug content and content uniformity, peel strength, in vitro drug release and skin permeation kinetics. The skin irritation potential of the systems was also assessed. For evaluation of these physico-chemical parameters, six systems were considered ($n = 6$).

The residual monomer content (EHA and AA) in the developed monolithic systems of ISDN was determined by the HPLC method. The films obtained after irradiation were weighed and then sonicated in mobile phase to extract the residual monomers. The extract was suitably diluted and subjected to HPLC analysis. The percent monomer content was determined. Films were also kept in a vacuum dessicator to remove residual monomer traces. They were kept for a period of 2, 4, 6 and 8 h and the decrease in the residual monomer content was determined at each time interval using the same procedure mentioned above.

In the determination of EWSR, accurately weighed polymeric film (on 1 cm^2 area of backing membrane) was placed in about 50 ml of chloroform at 37 °C in a stoppered conical flask for a period of 12 h till a constant increase in weight was obtained. The EWSR was then expressed as a ratio of weight of the swollen mass and weight of the dry mass.

The DSC thermograms of pure ISDN, placebo EHA-AA film and ISDN-EHA-AA films were recorded using a Mettler TA 4000 thermal analyzer. The samples were heated in sealed aluminum pans at the rate of 10 °C/min over a temperature range of −100 to +100 °C. Alumina was employed as the reference standard.

In the weight uniformity studies, the weights of six individual patches and the standard deviation between them were determined. The thickness of prepared TTS was determined by a dial thickness gauge at five strategic positions and the standard deviation within the patch and between patches was computed.

In the drug content studies, a patch size of 1 cm^2 was extracted in mobile phase, acetonitrile:water (6:4). The patch was sonicated for 1 h to facilitate extraction of the drug from the polymeric matrix. The extract was then filtered and suitably diluted. This solution was then estimated for drug content by HPLC as discussed in Section 2.2. In addition, to ensure content uniformity throughout the polymeric matrix, content was determined at four opposite sites of the patch (corresponding to an area of 1 cm^2).

The peel strength is indicative of the adhesive nature of the system. The peel strength of the TTS (1 cm^2) was determined by using a 180° peel strength tester (Martin, 1987). The tester consists of a stainless steel plate on to which a release liner was fixed. The release liner was peeled off from the test patch and the adhesive side was then fixed on to the release liner on the stainless steel plate. The test patch was then pulled from the substrate (release liner) at 180° angle at a fixed rate of 300 mm/min by means of a hook attached to a spring balance. The point at which detachment begins to occur was taken as the peel strength expressed in g/cm^2. The peel strength on human skin was determined on six healthy human volunteers. In this case, the forearm of each volunteer was kept in parallel to the stainless steel plate. The test patch was applied to the forearm instead of the steel plate and the test was conducted exactly in the same manner as for the peel strength with respect to the release liner.

The in vitro release pattern was studied using Keshary-Chien type diffusion cells having a volume of 10 ml and effective area of 1 cm^2. The recipient compartment was water-jacketed and the temperature was maintained at 37 ± 0.5 °C using a circulating water-bath (Siskin-Julabo, Germany). A patch of 1 cm^2 was taken for the study with distilled water as the diffusion medium. Aliquots (1 ml) were withdrawn at 0.5, 1, 2, 3, 4, 6, 8 and 10-h intervals and replaced with fresh medium. The samples were analyzed by HPLC method as discussed in Section 2.2 and the amount of drug released at each time point was calculated. The percent cumulative release in each case was determined and plotted against time in hours to obtain release profile for each transdermal system. The in vitro release studies were done on a set of six systems.

The drug permeation from the transdermal systems through excised abdominal guinea pig skin was studied ($n = 6$). A Keshary-Chien type diffusion cell of volume 10 ml was employed for the study, onto which the skin was mounted. The donor area was 100.6 mm^2 on which transdermal system of size 1 cm^2 was applied in direct contact with the epidermis. A constant temperature of 32 ± 0.5 °C was maintained throughout the experiment using a circulating water-bath (Siskin-Julabo, Germany). Samples (1 ml) were withdrawn over a period of 1, 2, 3, 4, 6, 8, 10, 12 and 24 h and replaced with fresh medium. The drug concentration at each time point was determined by the HPLC method as stated in Section 2.2. The cumulative amount of drug permeated per centimeter square was plotted versus time in hours to obtain the permeation profile for each formulation. The data for percent cumulative permeated against time was analyzed and the coefficient of regression (r) and the release rate constant (slope) were computed. Diffusion coefficient was determined using the equation described by Higuchi (1963) as given below.

$$Q = 2C_0 A \left(\frac{Dt}{\pi}\right)^{1/2} \quad (1)$$

where Q is the amount of drug diffused, C_0 is the initial concentration of the drug, A is the area of application, D is the diffusion coefficient (cm^2/day), and t is the time of application of product (days).

"D" can be calculated on simplification of Eq. (1).

$$Q = k(t)^{1/2}$$

where $k = 2\,C_0\,A(\sqrt{D}/\sqrt{\pi})$.

The permeability coefficient was calculated using Ficks law of diffusion

$$Q = P \times A \times C_0 \times t \quad (2)$$

where P is the permeability coefficient (cm/day).

The partition coefficient K_p (between formulation and receptor fluid) was calculated using the expression: $K_p = P/D \times h$; where, K_p is the partition coefficient, P is permeability coefficient, D is diffusion coefficient and h is the thickness of the barrier membrane in centimeters. The skin permeation parameters of the developed systems were compared to those of an internationally marketed matrix system of ISDN obtained under similar experimental conditions (Bharti, 1997).

Two systems ISDN-EHA-AA (50 and 150 kGy) were evaluated for its skin irritation potential by the Draize test (Draize et al., 1944). Six healthy female albino rabbits weighing between 2 and 3 kg were used for each system tested. The positive control applied was 0.8% w/v solution of formalin and the negative control was a blank backing membrane. The hair on the dorsal surface of the skin of the rabbits was first trimmed using a pair of scissors. The remaining hair was then removed by use of a depilatory cream. Care was taken to avoid any injury or abrasion on to the

skin. The rabbits were then kept in quarantine to aid the healing of any possible injury inflicted during the hair removal process. The control systems were placed on the left dorsal side of the rabbits. Three rabbits were tested with the positive control and the other three with the negative control. The test patch was placed on the right dorsal side of the rabbit. The patches were kept in place for a period of 24 h after which they were removed and the site was observed for any signs of skin irritation. Scoring was done according to the Draize scale: irritation due to formalin control (score 4, very severe), no erythema/edema (score 0, no irritation), very slight edema/erythema (score 1, slight irritation), well defined erythema/edema (score 2, moderate irritation), moderate erythema/edema (score 3, severe irritation), severe erythema/edema (score 4, very severe irritation).

3. Results and discussion

The developed analytical method gave good resolution of ISDN from its degradation product ISMN with retention times of 2.26 ± 0.02 min and 1.27 ± 0.03 min, respectively. The method also gave well separated peaks of ISDN from 2-EHA and AA with retention times of 2.26 ± 0.02 min, 12.77 ± 0.05 min and 1.15 ± 0.02 min, respectively. The solid state ISDN was found to be stable at all experimental doses of electron beam irradiation, viz., 10, 30, 50, 70, 100 and 150 kGy. The chromatograms did not reveal peak corresponding to the degradation product.

The determination of drug solubility in monomer system was essential, as the prime objective was to incorporate the drug into the monomer matrix followed by exposure to irradiation to yield a drug-in-adhesive system. An idea of the drug solubility would help to achieve desirable drug loading in the polymeric system. The solubility of ISDN was found to be 49.76 ± 0.98 mg/ml in EHA-AA system.

In the case of ISDN-EHA-AA system, a minimum dose of 50 kGy was essential to obtain polymeric films of EHA-AA. At 30 kGy, the irradiation dose was insufficient to bring about polymerization and no adhesive film was obtained. Hence, the systems fabricated at 30 kGy were not considered for any further evaluation. The films obtained at 50 kGy had good tack and adhesion. Further increase in the irradiation dose from 50 to 150 kGy did not bring about any change in the adhesive property of the film.

Table 1
EWSR data for ISDN-EHA-AA systems at varying doses

Irradiation dose (kGy)	ISDN-EHA-AA (±S.D.)
50	29.327 ± 2.56
70	26.452 ± 1.25
100	20.549 ± 0.45
150	19.000 ± 0.85

EWSR: equilibrium weight swelling ratio [weight of swollen mass (g)/weight of dry mass (g)].

The residual EHA content in the drug-loaded films was found to decrease from $2.15 \pm 0.12\%$ to $0.30 \pm 0.01\%$ with increase in the irradiation dose from 50 to 150 kGy. Further exposure of the films in a vacuum dessicator, for a period of 6 h led to a significant reduction in the EHA content and no peak of EHA was observed on HPLC analysis. This indicates that the EHA content was negligible and if present was below the analytical detection limit of 500 ng. No peak of AA was observed at any irradiation dose. The detection limit for AA was 200 ng.

The results of the EWSR are as depicted in Table 1 for ISDN-EHA-AA systems. This indicates the maximum swelling of the polymer in chloroform. At higher radiation doses, there was a decrease in the equilibrium swelling ratio. This was attributed to the cross-linked nature of the polymer, thereby offering a greater resistance to the swelling phenomenon. These results are in consonance with the theoretical consideration that high irradiation dose increases the cross-link density of the polymer.

The DSC thermograms of the drug-loaded films irradiated at doses ranging from 50 to 150 kGy did not show the exotherm corresponding to ISDN. This suggested that the drug was molecularly dispersed in the polymeric matrix. The DSC thermograms of ISDN, placebo EHA-AA film (150 kGy) and ISDN-EHA-AA film (150 kGy) are depicted in Fig. 1.

The films of ISDN-EHA-AA complied with the tests for weight and thickness uniformity. The data for the weight and thickness uniformity are represented in Table 2. All the systems complied with the tests for content uniformity and the drug content values were in the range of 97–99% w/w of the theoretical content.

The peel strength value is indicative of the adhesive nature of the formulation. All the developed systems

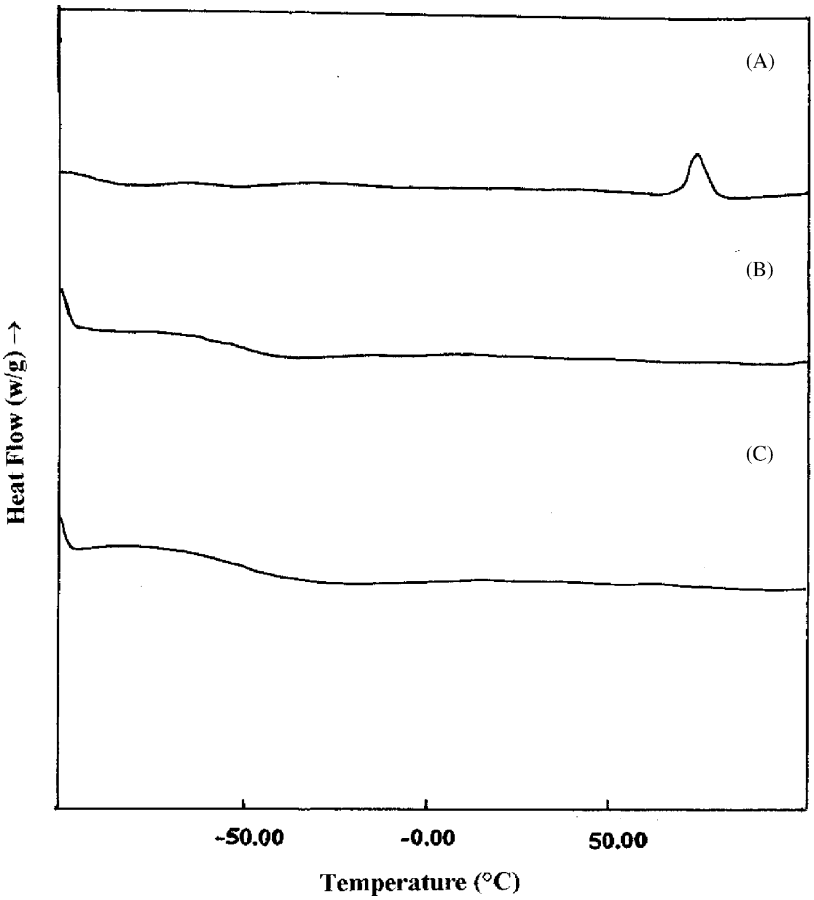

Fig. 1. Differential scanning calorimetric thermograms. (A) ISDN, (B) placebo EHA-AA (150 kGy), (C) ISDN-EHA-AA (150 kGy).

gave different peel strength value with respect to the release liner in comparison to the peel strength with respect to the skin. There was no significant increase in the peel strength of the patches with increasing irradiation doses. The results of the peel strength studies are as depicted in Fig. 2. Insignificant variation in the peel strength values between patches was observed

Table 2
Data for weight and thickness uniformity

ISDN-EHA-AA systems (kGy)	Weight (mg) (mean ± S.D.)	Thickness (μm) (mean ± S.D.)
50	42.44 ± 1.02	465 ± 4.65
70	47.12 ± 0.48	470 ± 6.54
100	51.66 ± 0.86	455 ± 5.68
150	49.28 ± 1.54	460 ± 3.47

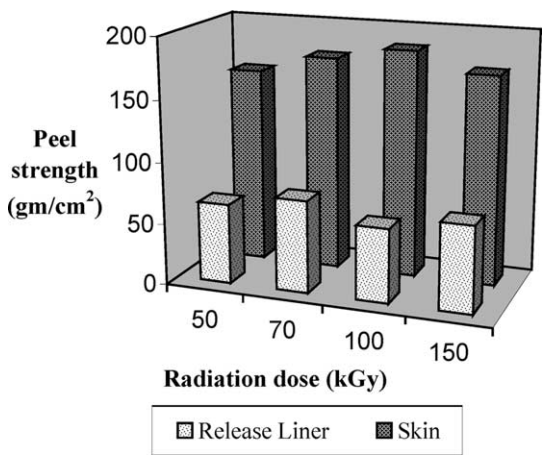

Fig. 2. Peel strength data of ISDN-EHA-AA systems with respect to release liner and skin at varying irradiation doses.

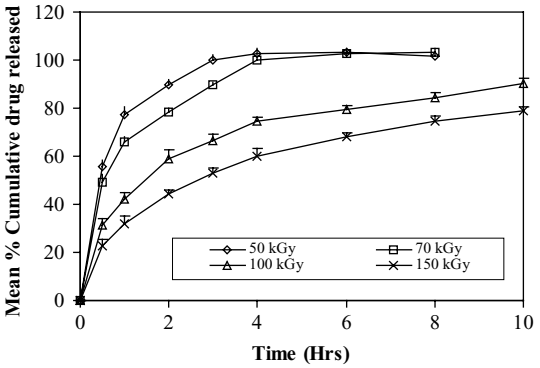

Fig. 3. In vitro release of ISDN from ISDN-EHA-AA systems: effect of varying irradiation doses.

and hence the error bars have not been indicated in the figure.

In vitro release test is widely used for its simplicity and reproducibility and is a useful tool in quality control of finished transdermal systems (Van Buskirk et al., 1987). It is known that the in vitro drug release from transdermals may not correlate with the in vivo release. In the in vitro release studies, no additional peaks from the polymeric matrix at or near the retention time of ISDN were found. It was observed that in the ISDN-EHA-AA system, as the dose of irradiation increased there was a significant reduction in the release of ISDN from the polymeric matrix. As it is observed with an irradiation dose of 50 kGy, 100% of the drug was released in a period of 3 h whereas with a dose of 150 kGy considerable retardation was obtained. The in vitro release profiles for the same are as illustrated in Fig. 3.

The skin permeation data from ISDN-EHA-AA systems indicated a substantial decrease in the skin permeation profile when the irradiation dose was increased from 50 to 70 kGy. Further increase in the irradiation dose from 70 to 150 kGy did not affect the permeation significantly. Systems fabricated at an irradiation dose of 50 kGy followed a zero order kinetics for up to 12 h, after which it leveled off. At all higher doses, a zero-order type permeation pattern was observed. There was a decrease in the diffusivity and permeability coefficient with a parallel increase in the vehicle/skin partition coefficient with increasing doses. It should be noted, however, that the decrease is not very significant which could be due to the fact that the stratum corneum of the skin acts as the rate-limiting step governing the mechanism of permeation. The skin permeation parameters for all systems are listed in Table 3 and the permeation profiles for the same are as shown in Fig. 4. The permeation data available (Bharti, 1997) for the international marketed matrix system of ISDN was flux = 21.8212 μg/cm^2/h, diffusivity coefficient = 11.87×10^{-3} cm^2/h, permeability coefficient = 0.0218 cm/h and vehicle/skin partition coefficient = 0.0919. These permeation parameters were calculated for the mean skin permeation data obtained for the marketed system (mean of

Table 3
Fit of various kinetic models and comparison of permeation parameters for ISDN-EHA-AA systems at varying irradiation doses

Parameters	50 kGy	70 kGy	100 kGy	150 kGy
Zero order				
r	0.9714	0.9987	0.9981	0.9991
Rate[a]	2.8595	1.3154	1.3714	1.4418
First order				
r	0.9948	0.9950	0.9949	0.9960
Rate	−0.0196	−0.0068	−0.0071	−0.0076
Higuchi				
r	0.9725	0.9324	0.9310	0.9372
Rate	14.7498	6.3271	6.5902	6.9680
J[b]	28.5950	13.1547	13.7141	14.4184
D[c]	0.0171	0.0031	0.0034	0.0038
P[d]	0.0285	0.0131	0.0137	0.0144
K_p[e]	0.0837	0.2092	0.2011	0.1891

[a] Rate constant (h^{-1}).
[b] Flux (μg/cm^2/h).
[c] Diffusivity coefficient (cm^2/h).
[d] Permeability coefficient (cm/h).
[e] Partition coefficient.

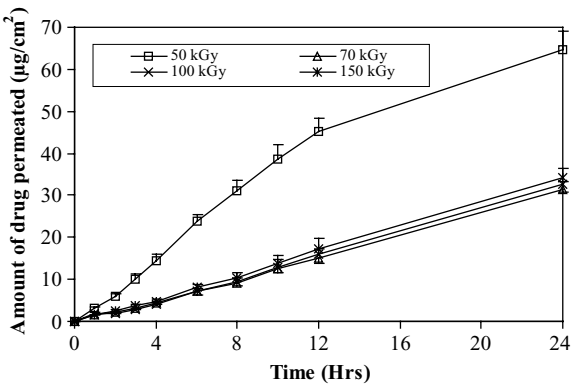

Fig. 4. Skin permeation of ISDN from ISDN-EHA-AA systems: effect of varying irradiation doses.

six systems tested). A comparison of the permeation parameters indicates that the ISDN-EHA-AA system irradiated at a dose of 50 kGy showed higher skin permeation as compared to the marketed TTS.

In the skin irritation study, the tested formulations did not show any signs of erythema/edema at the site of application during the period of the study. Thus, promising results were obtained for the ISDN-EHA-AA system irradiated at 50 kGy when compared to the marketed TTS of the same size. However, further in vivo studies in human subjects needs to be carried out.

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