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Studies on rifampicin release from ethylcellulose coated nonpareil beads

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Abstract

The rifampicin release studies from ethylcellulose coated nonpareil beads were studied. Propylene glycol and Castor oil were used as plasticizers. The in vitro dissolution studies revealed that the release rate is inversely proportional to percent of coating thickness. The release rate also depends on the type of plasticizer used in the coating polymer. The mechanism of drug release follows Higuchi diffusion model. Water vapour permeation studies indicated that the water vapour transport rate through free films is directly related to the drug release rate. DSC thermograms and IR spectras revealed that there is no interaction between rifampicin and other additives. SEM photographs of coated beads, before dissolution and after dissolution, also indicates that the drug release mechanism follows diffusion model.

Keywords: Rifampicin; Propylene glycol; Castor oil; Nonpareil beads; Higuchi model

1. Introduction

Many controlled release systems have been developed for the purpose of maintaining a therapeutically effective concentration of drug in systemic circulation for a longer period of time, as well as to reduce side effects. Oral controlled release systems are mainly grouped into three types, viz. reservoir, monolithic and matrix types. A number of methods and techniques have been used in the manufacture of oral controlled release dosage forms.

The importance of beads in drug dosage form design and development is indisputable. Beads have been successfully used to provide flexibility in dose strength, maximisation of drug absorption, minimisation of local irritation of the gastrointestinal tract and control of the bioavailability of the active drug (Ghebre-Sellassie and Knock, 1995). In addition, beads have a low surface area-to-volume ratio, thus providing an ideal shape for the application of film coating. Film coatings are applied to beads to mask the undesirable tastes, odours and colours, to control the release of active ingredient, to provide stability during storage and transportation and to impart protection against air, moisture and light.

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Ethylcellulose (EC) is one of the most widely-used water insoluble polymer in film coating because of many advantages it affords formulators, such as good film formability, excellent physiochemical stability, minimum toxicity, etc. Especially, an increasing interest in the controlled release dosage form has led many researchers to attempt extending the use of EC to various dosage forms. The major aim of EC film coating is to provide an effective means for rate control of drug release, such dosage forms are commonly termed as 'capsule-type controlled release system', 'diffusion-controlled reservoir devices' or membrane moderated controlled release systems (Sainji et al., 1993).

Rifampicin is the semi synthetic hydrazine derivative of rifampicin B. Rifampicin is a first line drug recommended by WHO in the treatment of tuberculosis. Relatively high doses of the drug are required to maintain therapeutic concentrations for longer periods, which leads to several side effects. Due to its high cost and adverse side effects it is used mainly in intermittent therapy (Girling and Hitze, 1979; Jopling, 1983). The biological half-life varies from 1.5 to 5 h. The prolonged treatment of tuberculosis with conventional chemotherapy of rifampicin and its adverse side effects promoted the development of controlled release formulations.

In the last several years many different types of rifampicin controlled release formulations have been developed to improve clinical efficacy of drug and patient compliance (Mathur et al., 1985; Uppadhyay et al., 1997; Schierholz, 1997; Deol and Khuller, 1997; Denkbas et al., 1995; Amar and Khalil, 1997; Nakhare and Vyas, 1995; Khopade et al., 1996; Barik et al., 1993). In the present study, ethylcellulose coated nonpareil beads were prepared and evaluated.

Table 1
Composition of drug layering solution

Ingredients	Quantities
Rifampicin	10 g
PVP K-30	0.25 g
Dichloromethane:methanol (4:1)	100 ml

2. Experimental

2.1. Materials

Rifampicin I.P. was obtained from Aristo Pharmaceuticals Ltd., India; Ethylcellulose (S.D. Fine Chem. Ltd; India), non-pareil starch beads were gifted from Natco Pharma Ltd. India, propylene glycol, castor oil (Loba Chemie India), methanol (Qualigen Fine Chemicals, India) dichloromethane (Qualigen Fine Chemicals, India); acetone (Qualigen Fine Chemicals, India); polyvinyl pirrolidone K-30 (PVP-K 30) gift sample from VECO pharma, India, sodium hydroxide (Qualigen Fine Chemicals, India); potassium dihydrogen orthophosphate (S.D. Fine Chem. Ltd; India), and ascorbic acid (S.D. Fine Chem. Ltd; India).

3. Methods

3.1. Drug layering

Approximately 2500 g of non-pareil beads (mesh No. 22/24) was used as initial cores for drug loading. Table 1 shows the coating composition used for drug layering. Rifampicin and PVP were dissolved in dichloromethane–methanol mixture and sprayed radially using spray gun under pressure onto the rotating nonpareil bead in the coating pan. PVP was used as a binder. Methanol and dichloromethane mixture was taken as a solvent for easy drying after drug layering.

A laboratory size Kaiweka (Cadmach Machinery Co. Pvt. Ltd., India) coater was used for loading the drug solution. The flow rate of the solution was maintained constant at 25 ml/min, which prevents the agglomeration of beads during coating process. The inlet air temperature (Silencio 1000 drier, Braun, a division of Gillette, New Delhi, India) was 45 °C and the drying time after each application was 2 min. The speed of the coating pan was 32 rpm.

3.2. Film coating

Approximately 1000 g of drug loaded beads, were used for film coating. A 5% w/v solution of ethyl cellulose in acetone was prepared. To this 30% w/w of propylene glycol or castor oil was added with respect to polymer weight. The drug-loaded beads were coated using pan coating (Kalweka). The polymer solution was sprayed radially using spray gun (Uniques India Ltd., India) under pressure onto the rotating rifampicin loaded nonpareil beads at the flow rate of 25 ml/min. The inlet air temperature (Silencio 1000 drier, Braun, a division of Gillette, New Delhi, India) was 45 °C and the drying time after each application was 2.5 min. The speed of the coating pan was 32 rpm. Samples were taken periodically throughout a run to give different coating thickness. The coating level is the quotient of the dry weight of polymer and the weight of the uncoated drug loaded beads, expressed as a percentage. All beads were stored in plastic bags at room temperature until required.

3.3. Drug assay

One hundred milligrams of rifampicin loaded beads were ground into fine powder and all the powder was transferred into a 100 ml volumetric flask and dissolved in 100 ml methanol. Then 1 ml samples were taken, filtered, diluted suitably and assayed spectrophotometrically at 475 nm. The experiment was performed in triplicate and mean values were taken and are reported.

3.4. Differential scanning calorimetry (DSC)

DSC scans were performed using Shimadzu DSC-50 thermal analyser to obtain the melting endotherms of pure rifampicin and the optimised formulations. Approximately 5 mg of each sample was weighed into small aluminium pans. Samples were heated from 30 to 250 °C at a rate of 100 °C/min with an empty pan as reference.

3.5. Infrared spectroscopy

Infrared spectra of the pure rifampicin, and ethylcellulose coated nonpareil beads, which was loaded with rifampicin, were determined from mineral acid mull using Perkin–Elmer 841 IR spectrophotometer The scanning range used was 4000–600 per cm

3.6. Scanning electron microscopy (SEM)

SEM photographs of the 6.5% EC coated nonpareil beads taken before and after drug release studies using JEOL JSM-T330A Scanning microscopy. The coated beads (before and after dissolution) were loaded on studs and applied fine gold coating with gold for 5 min at 10 mA ion current under a pressure of 0.1 Torr using JEOL JFC-1100E Ion sputter. The coated beads were scanned and the micrographs were examined.

3.7. Preparation of polymer films

About 5% w/v of ethylcellulose polymer solution was prepared in acetone. Propylene glycol and castor oil (Graha Cole et al., 1995) in a concentration of 30% w/w of the polymer was incorporated as a plasticizer. Polymer solution 4 ml was poured within glass bangle (5.3 cm diameter) placed on mercury surface in a petridish (Utsumi et al., 1961). The rate of evaporation was controlled by inverting a funnel over the petridish. After 24 h, the dried films were taken out and stored between sheets of wax paper in a desiccator. The prepared films were evaluated for uniformity of thickness and water vapour transmission.

3.8. Film thickness

Film thickness was measured by a Dial Gauge (Exceed, Tokyo) at nine different points on the film. The average of the nine readings was calculated.

3.9. Water vapour transmission studies

For water vapour transmission studies, glass vials of equal diameter (1.32 cm) were used as transmission cells. These transmission cells were

Table 2
Water vapour transmission data of ethylcellulose films

Time (h)	Amount of water vapour ($\pm$S.D.) ($n=3$) transmitted (mg) through EC polymer films containing plasticizers (g cm/cm^2 24 h)	
	Propylene glycol	Castor oil
6	7.84 ± 2.361	7.01 ± 3.016
12	15.04 ± 3.104	14.15 ± 2.165
24	26.83 ± 2.842	24.34 ± 1.016
48	54.23 ± 3.321	49.86 ± 2.104
72	80.70 ± 2.706	76.14 ± 2.315
90	101.35 ± 2.511	98.64 ± 3.154
120	133.16 ± 2.564	127.74 ± 3.361

washed thoroughly and dried in an oven. About 2 g of fused calcium chloride was taken in the cells and the polymer films were fixed over the brim with the help of an adhesive. Then the cells were accurately weighed and kept in a closed desiccator containing saturated solution of potassium chloride. The humidity inside the desiccator was measured by a hygrometer and was found to be 84% RH. The cells were taken out and weighed after 6, 12, 24, 48, 72, 96 and 120 h of storage. The increase in weight at each time interval is used for the calculation of quantity of water vapour transmitted through these films. The water vapour transmission is usually expressed as the number of grams of water permeating at a steady state each 24 h per 1 cm film thickness per square centimetre. From the data obtained, water vapour transmission (Q) was calculated using the formula $Q = WL/S$ where W is grams of water vapour per 24 h, L is the thickness of polymer film (in cm) and S is the surface area exposed to the polymer film (in cm^2) (Utsumi et al., 1961). The results are given in Table 2.

3.10. Dissolution medium

The pH 7.4 phosphate buffer containing 0.02% w/v of ascorbic acid was used as dissolution medium to prevent the degradation of released rifampicin in dissolution medium due to atmospheric oxygen.

3.11. In vitro dissolution studies

Ethyl cellulose coated beads equivalent to 300 mg of rifampicin was taken in a basket of the USP XXI dissolution apparatus 1. The stirring rate was 100 rpm. pH 7.4 phosphate buffer containing ascorbic acid (200 μg/ml) was used as dissolution medium (900 ml) and was maintained at 37 ± 1 °C. Samples of 5 ml were withdrawn at predetermined time intervals with a pipette fitted with a filter. The collected samples were diluted suitably, if necessary, and were analysed for the rifampicin content by UV spectrophotometric (Shimadzu UV-160-02 Double beam Spectrophotometer) method at 475 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Each dissolution study was performed in triplicate.

At the end of 12 h of dissolution testing, the remaining beads were collected and suspended in methanol and the remaining drug content was estimated. This is to make sure that the amount of drug remaining adds to the drug release to give total mass balance of drug content.

4. Results and discussion

Generally pancoater is used for sugar coating or active filler coating but we have tried to utilisation of the pancoater for functional film coating. We have calibrated the procedure for applying uniform coating thickness by conducting the reproducibility between batch to batch. Basing on that we have fixed the parameters.

Percent of drug loaded on nonpareil beads was found to be 52%. Rifampicin release from all the coated beads was found to be low (Figs. 1 and 2). The drug release from coated beads depends on proportion of coating material in the coated beads. The release rate constants showed in Tables 3 and 4, revealed that the release rate decreased as the proportion of ethyl cellulose increased. Higher concentration of polymer causes relatively more retardation in drug release. The higher coating volume applied, increases the thickness of the membrane and thus causes a relatively higher retardation in release

Rifampicin release from all the coated beads followed first-order kinetics. The first order release plots are shown in Figs. 3 and 4. In almost all the cases straight lines were observed from second hour onwards when log percent drug remaining values were plotted against time. In the initial period up to 2 h, the release rate was higher in 2, 3, 4 and 4.5% EC coated beads. This increase might be due to improper coating formation around the drug loaded beads and might be due to solubility of loaded drug into polymeric film during coating process. The first order release kinetics were further confirmed by the linear correlation coefficients of slopes, shown in Tables 3 and 4. The higher release in the first 2 h might have served the purpose of loading dose of controlled release products. The MIC of rifampicin is 0.02–0.1 μg/ml (Reynolds, J.E.F., 1993). For obtaining the therapeutic concentration 90 mg of the drug has to be released within 2 h.

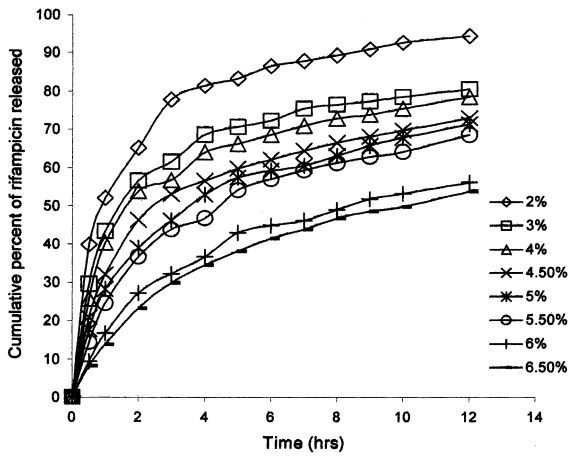


Fig. 1. In vitro dissolution profiles of rifampicin from ethylcellulose coated nonpareil beads (propylene glycol as plasticizer), ($n = 3$).

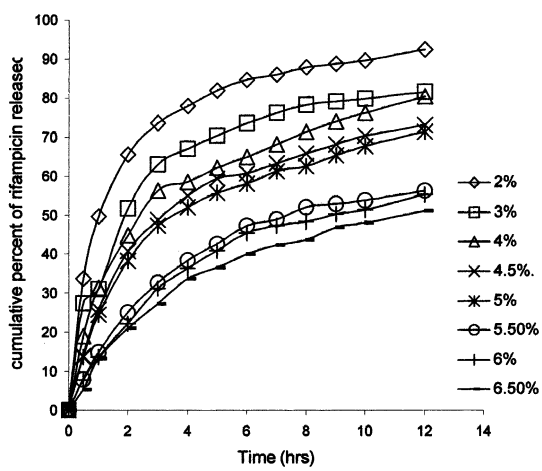


Fig. 2. In vitro dissolution profiles of rifampicin from ethylcellulose coated nonpareil beads (castor oil as plasticizer), ($n = 3$).

Plot of cumulative amount of drug released versus square root time were found to be linear in all the cases with both plasticizers, i.e. propylene glycol and castor oil, indicating that the drug release mechanism from these coated beads might be of diffusion type as proposed by Higuchi (1961) for insoluble matrices. Accordingly, drug release from these coated beads involves penetration of the dissolution fluid, dissolution of the drug in the dissolution fluid and leaching out of the drug through interstitial channels or pores. Thus the over all release rate depends on (1) the rate at which the dissolution fluid penetrates the wall material, (2) the rate at which the drug dissolves in the dissolution fluid and (3) the rate at which the dissolved drug can penetrate the wall and disperse from the surface. Drug release mechanism from matrix dosage forms has been described by Higuchi as follows:

$$Q = \sqrt{D(2W - C_s)C_s t}$$

In the above equation, D is the diffusion coefficient of the drug in the matrix, W is the total amount of the drug per unit volume of the matrix, C_s is the solubility of the drug in the matrix and t is the drug release time. When $W \gg C_s$. The above equation can be simplified to the following:

$$Q = \sqrt{2WDC_s t}$$

This equation indicates that the amount of drug released is proportional to the square root of time from the diffusional release of a drug from a matrix-type system. The linear correlation coefficients of the slopes, shown in Tables 3 and 4 indicating that the drug release from EC coated nonpareil beads is Higuchi diffusion. This fact supports the conclusion that the drug is released by a diffusion mechanism process with first order release kinetics. The dissolution profiles of the

Table 3
Coefficients and release rate constants of drug release functions from ethylcellulose coated nonpareil beads (castor oil as plasticizer)

Formulation	First order plot				Higuchi plot			Baker–Lonsdale model
	r^2	r^{2a}	r^{2b}	K/h^b	r^2	r^{2a}	r^{2b}	r^2
2% EC	0.969	0.977	0.997	1.9604	0.941	0.947	0.969	0.702
3% EC	0.937	0.941	0.988	0.4649	0.959	0.929	0.957	0.769
4% EC	0.970	0.987	0.992	0.4753	0.980	0.980	0.989	0.784
4.5% EC	0.957	0.971	0.997	0.3764	0.978	0.971	0.985	0.777
5% EC	0.960	0.975	0.987	0.3551	0.982	0.976	0.988	0.794
5.5% EC	0.959	0.959	0.988	0.2684	0.988	0.977	0.975	0.838
6% EC	0.963	0.963	0.989	0.2600	0.989	0.979	0.975	0.852
6.5% EC	0.969	0.975	0.996	0.2032	0.992	0.989	0.988	0.847
2:2:1 ratio of 6:4:2%	0.976	0.988	0.997	0.4380	0.990	0.987	0.992	0.826
2:2:1 ratio of 2:3:4%	0.956	0.980	0.998	0.5200	0.964	0.975	0.974	0.768

[a] Calculated from first hour onwards.
[b] Calculated from second hour onwards.

Table 4
Coefficients and release rate constants of drug release functions from ethylcellulose coated nonpareil beads (propylene glycol as plasticizer)

Formulation	First order plot				Higuchi plot			Baker–Lonsdale model
	r	r^{2a}	r^{2b}	K/h^b	r^2	r^{2a}	r^{2b}	r^2
2% EC	0.964	0.981	0.993	0.8273	0.933	0.942	0.948	0.726
3% EC	0.921	0.954	0.990	0.3901	0.949	0.957	0.970	0.750
4% EC	0.933	0.972	0.996	0.3724	0.953	0.972	0.986	0.760
4.5% EC	0.938	0.967	0.999	0.3223	0.965	0.969	0.992	0.783
5% EC	0.960	0.977	0.995	0.3546	0.982	0.982	0.985	0.810
5.5% EC	0.964	0.975	0.996	0.2513	0.992	0.987	0.990	0.816
6% EC	0.960	0.975	0.995	0.3354	0.985	0.982	0.986	0.850
6.5% EC	0.972	0.979	0.999	0.2442	0.994	0.991	0.994	0.865
2:2:1 ratio of 6:4:2%	0.947	0.973	0.996	0.3351	0.973	0.978	0.986	0.800
2:2:1 ratio of 2:3:4%	0.964	0.982	0.999	0.6033	0.965	0.973	0.974	0.769

[a] Calculated from first hour onwards.
[b] Calculated from second hour onwards.

above formulations were also fitted to Baker–Lonsdale model (Baker and Lonsdale, 1987) for determining the diffusion coefficient. The linear correlation coefficients of the slopes indicated that the release profiles were not fitted to Baker–Lonsdale model.

In conclusion, the drug release pattern did not follow the dissolution mechanism or erosion mechanism or Baker–Lonsdale diffusion mechanism, it followed the Higuchi's diffusion mechanism. The kinetics of the release followed the first order release rate but not the zero order release rate. This judgement was made on the basis of respective r^2 values.

4.1. Comparison of rifampicin release from ethyl cellulose coated beads containing propylene glycol and castor oil as plasticizers

A comparative evaluation of the effect of two plasticizers on the release of rifampicin from ethylcellulose coated beads was performed using

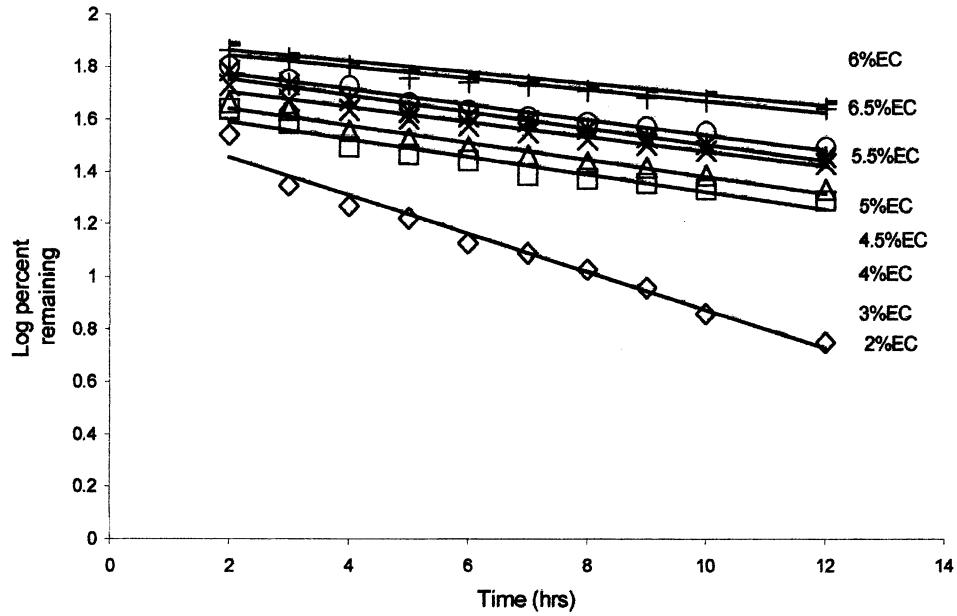


Fig. 3. First order plots of percent rifampicin undissolved versus time of ethylcellulose coated nonpareil beads (propylene glycol as plasticizer).

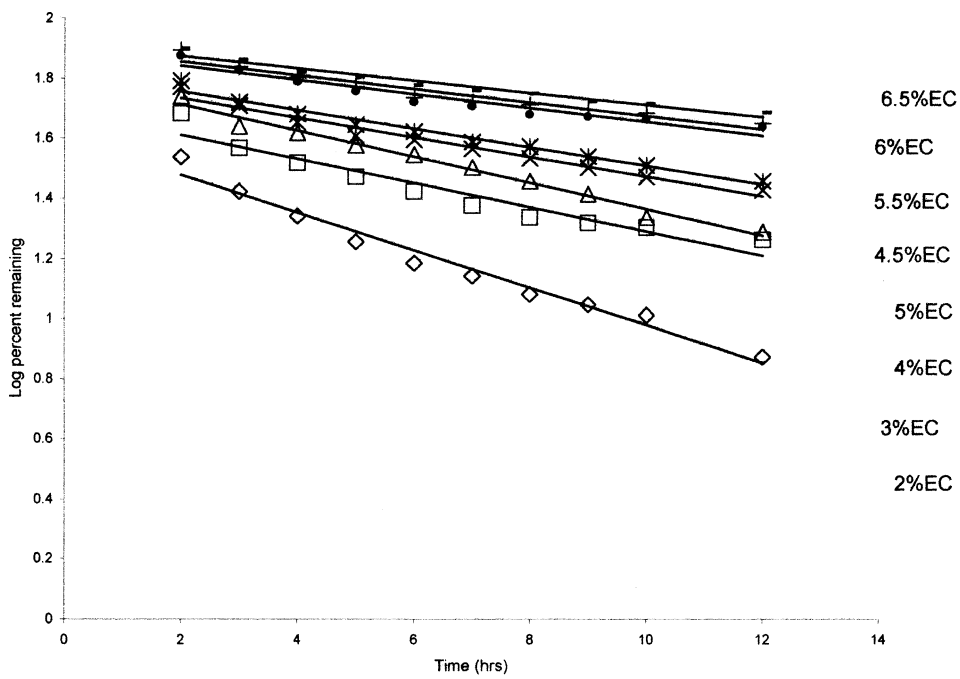


Fig. 4. First order plots of percent rifampicin undissolved versus time of ethylcellulose coated nonpareil beads (castor oil as plasticizer)

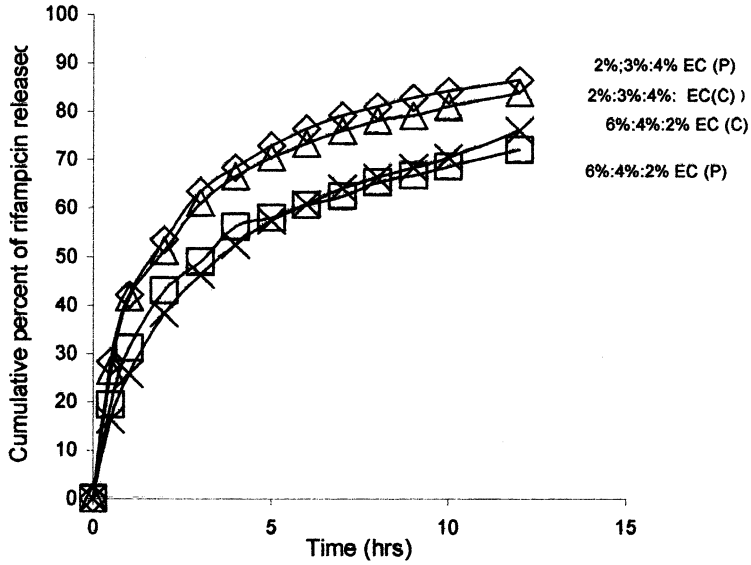


Fig. 5. In vitro dissolution profiles of rifampicin from ethylcellulose coated nonpareil beads (2:2:1 ratio), ($n = 3$).

propylene glycol and castor oil as plasticizers during film coating. Rifampicin release rates (K, per h) from various coating thickness beads are summarised in Tables 3 and 4. Among the two plasticizers, coated beads containing propylene glycol (hydrophilic) as plasticizer gave relatively rapid release of rifampicin when compared with the corresponding coated beads containing castor oil (hydrophobic) as plasticizer. The plasticising properties of castor oil was determined by using TG/DTA analysis (not shown). The Tg value of free EC film showed 171.1 °C but in the case of EC film containing castor oil showed no Tg value indicating that the castor oil acted as plasticizer.

The following formulations were prepared using blends of coated beads:

1. 2:2:1 ratio of 2:3:4% EC coated nonpareil beads (propylene glycol as plasticizer);
2. 2:2:1 ratio of 2:3:4% EC coated nonpareil beads (castor oil as plasticizer);
3. 2:2:1 ratio of 6:4:2% EC coated nonpareil beads (propylene glycol as plasticizer);
4. 2:2:1 ratio of 6:4:2% EC coated nonpareil beads (castor oil as plasticizer).

In each case coated beads equivalent to 300 mg of rifampicin were taken for dissolution studies.

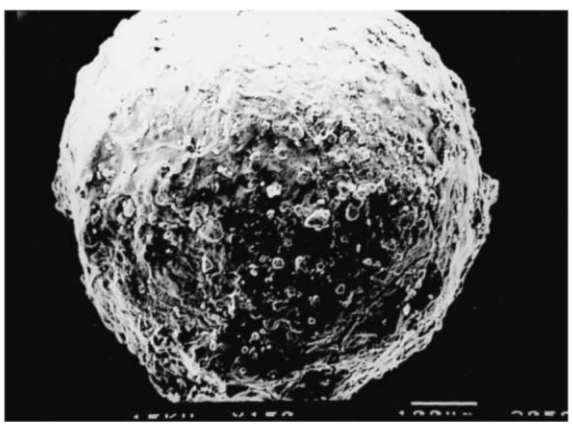
Rifampicin release from the above four formulations was studied in 7.4 pH phosphate buffer containing 0.02% w/v ascorbic acid using USP apparatus 1. Dissolution rate test apparatus as described earlier over a period of 12 h, shown in Fig. 5. The correlation coefficients shown in Tables 3 and 4, indicated that the above formulations also obey the Higuchi's diffusion mechanism with first order release kinetics.

SEM photographs of 6.5% EC coated nonpareil beads taken before and after drug release studies are shown in Figs. 6 and 7. The SEM photographs of coated beads indicated that the coated beads retained their size and shape even after completed the dissolution study for 12 h. This observation also confirmed that the drug release mechanism from these coated beads is by diffusion mechanism. The SEM photographs of the coated beads after dissolution show the coating to be cracked upon dissolution. This might be due to poor plasticisation of the ethylcellulose film.

DSC scans of the pure rifampicin (not shown) indicated that the pure drug showed a sharp melting peak at 184.1 °C. The melting peak of rifampicin in coated nonpareil beads was at 181.6 °C. Rifampicin in the coated nonpareil beads showed no shift in the characteristic peak in comparison with the pure rifampicin. The DSC

thermograms revealed that there is no interaction between rifampicin and the other additives or no degradation in rifampicin molecule.

The IR spectras of the pure rifampicin (not shown), indicated that the characteristic absorption stretch for C=O group at 1572 per cm and broad bands between 2800 and 2300 per cm for N–H stretch are obtained. The finger print region IR spectra showed a characteristic sharp peak at 1281 and 1040 per cm for C–O–C acetyl group. In comparison with pure drug, the absorption peak of the spectra for rifampicin in coated nonpareil beads showed no shift and no disappearance of characteristic peaks suggesting that there is no interaction between rifampicin and other additives or no degradation in rifampicin molecule.



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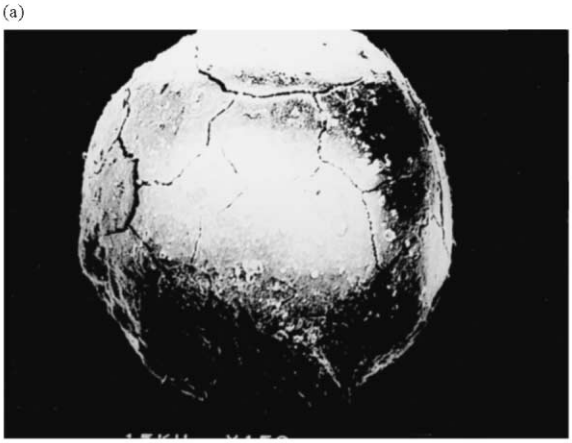
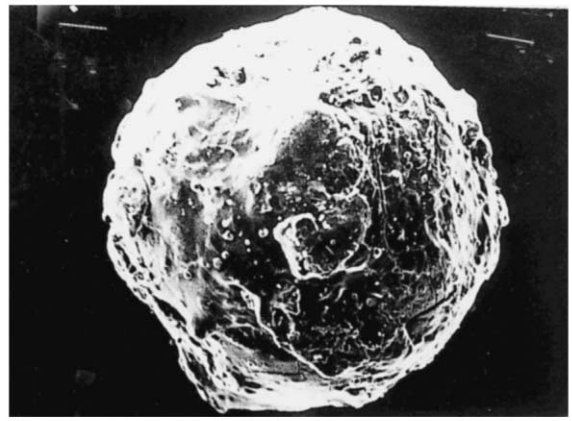
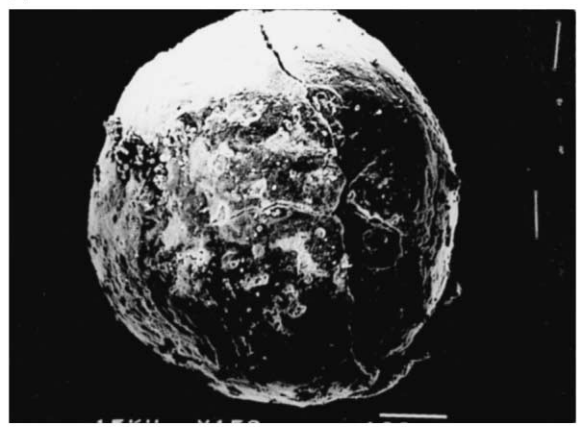


(b)

Fig. 6. SEM photographs of ethylcellulose coated nonpareil beads (A) before dissolution, (B) after 12 h dissolution, (propylene glycol as plasticizer).



(a)



(b)

Fig. 7. SEM photographs of ethylcellulose coated nonpareil beads (A) before dissolution, (B) after 12 h dissolution, (castor oil as plasticizer).

Water vapour permeation of free film tests was carried out to gather additional information possibly leading to predictive correlations on the behaviour of the coating shells. Rifampicin release from coated beads is varying with the type of plasticizer employed, the relative permeability characteristics of ethylcellulose films containing plasticizers, i.e. propylene glycol and castor oil were evaluated. Both the two films gave thin uniform and flexible films. The thickness of each film was measured at nine different points on the film and the average thickness was calculated. The average thickness of these films are 86.93 (μg), 87.16 (μg) for the films containing propylene glycol and castor oil as plasticizers, respectively.

The water vapour permeation values were found to be 3.444 and 3.174 g cm/cm^2 24 h for ethylcellulose films containing propylene glycol and castor oil as plasticizer, respectively. Thus, the order of the increasing permeability of ethylcellulose films containing two plasticizers is as follows:

Propylene glycol > castor oil

It was observed that this order of increasing permeability of films is same as the order of increasing rifampicin release rate from ethylcellulose coated beads with these plasticizers.

The above results indicate that the rifampicin release from the coated beads depends on the permeability of the polymer used in ethylcellulose film coating on rifampicin loaded nonpareil beads, propylene glycol was found to be more permeable and hence gave relatively rapid but controlled and nearly complete release of the contained medicament over a period of 12 h.

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