
Studies on Release of Rifampicin from Modified Pulsincap Technique

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Rifampicin release studies from modified pulsincap preparation were performed using different proportions of various hydrophilic polymers such as guar gum, carbopol 940, sodium alginate, hydroxy propyl methyl cellulose, methyl cellulose, gum karaya and poly vinyl alcohol. The *in vitro* dissolution studies revealed that the release exhibits a Fickian diffusion model. Increasing the hydrophilic polymer content resulted in a reduction in the release rate of rifampicin. Among all the polymers tested, guar gum showed better sustaining capacity even at low concentrations. This technique is more suited for preparing better controlled release formulations.

Controlled release dosage forms are becoming increasingly important since they aid in achieving desired levels of therapeutic activity required for a new drug entity or to extend the life cycle of an existing drug through improved performance or patient compliance¹. Chronic treatment with a conventional drug delivery systems often leads to discontinuation of treatment by a substantial proportion of patients as soon as they begin to feel better².

Rifampicin is a first line drug recommended by WHO for the treatment of tuberculosis³. Relatively high doses of the drug are required to maintain therapeutic concentrations for longer periods, which leads to several side effects⁴. Because of its high cost and adverse side effects it is used mainly in intermittent therapy^{3,5}. Slow release formulations of rifampicin such as those prepared using biodegradable polymers⁶, release micellelamellar phase transition based depot preparation⁴, polydimethylsiloxane shunt⁷, lung specific stealth liposomes⁸, poly (D,L-lactide) microspheres⁹, solid dispersions with Eudragit polymers¹⁰, and rifampicin microcapsules¹¹ were reported in literature.

Hydrophilic polymers as drug carriers have received considerable attention in the last few years; especially from the point of view of cost, biocompatibility and environmental concerns¹². In the present investigation,

we have studied release of rifampicin from a modified pulsincap preparation, prepared using hydrophilic polymers.

Rifampicin IP was obtained from Lupin Laboratories Ltd., Aurangabad. Sodium starch glycolate, Aerosil, hydroxy propyl methyl cellulose, potassium dihydrogen orthophosphate, sodium hydroxide, methyl cellulose, Carbopol 940, sodium alginate and ascorbic acid were procured from S.D. Fine Chem Ltd., Mumbai. Guar gum was procured from Sigma Chemical Co., St. Louis, MO. USA, and gum karaya was procured from Girijan Corporation, Visakhapatnam.

Capsule bodies were exposed to formaldehyde vapor in a desiccator containing formaldehyde solution at the bottom. After exposed for predetermined time intervals, the bodies were removed from the desiccator, exposed to air to remove adhering free formaldehyde and moisture and were finally dried in a vacuum desiccator over fused calcium chloride. The vapor hardened body was cut into small pieces and transferred into a 50 ml volumetric flask. To that 25 ml of 50% v/v sulphuric acid solution was added and kept for 30 min. Then to dissolve the pieces completely, the contents of the volumetric flask were heated on a water bath and the volume was adjusted to the mark with distilled water. One milliliter of this solution was diluted if necessary and 9 ml of chromotropic acid reagent was added. The mixture was then heated on a water bath. An intense purple colour developed to its

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maximum intensity in 30 min, was found to be stable for 36 hr. The content of formaldehyde was estimated spectrophotometrically at 490 nm¹³.

In the present investigation, a mixture of rifampicin 95%, sodium starch glycolate 4.7% (as disintegrant) and Aerosil 0.3% (as lubricant) was taken as a basic mixture for further studies. The above basic mixture was mixed with various hydrophilic polymer such as guar gum, carbopol 940, sodium alginate, hydroxy propyl methyl cellulose, methyl cellulose, and gum karaya in different percentages with respect to basic mixture (i.e., 10, 20, 30) for studying the effect of polymer content and type of polymer on the rifampicin release rate. In all cases, drug content was maintained at 150 mg. Weighed quantity of drug-polymer mixture was filled into the hardened capsule body. The remaining volume of the capsule body was filled with lactose. The soluble cap was locked into the body. Differential scanning calorimetry of rifampicin with or without other additives was performed in the temperature range of 30° to 250° using a Shimadzu DSC-50 Thermal Analyzer. Samples were placed in an aluminum pan and heated at 10°/min with an empty pan as reference.

Dissolution test was carried out using a USP XXI rotating basket method. The stirring rate was 100 rpm. The pH 7.4 phosphate buffer containing ascorbic acid (200 µg/ml) was used as the dissolution medium (900 ml) to prevent degradation of released rifampicin in dissolution medium due to atmospheric oxygen and was maintained at 37±1°. Samples of 5 ml were withdrawn at predetermined time intervals, filtered, diluted suitably and assayed spectrophotometrically. An equal volume of fresh medium was immediately added to maintain the dissolution volume. The samples were analyzed spectrophotometrically at 475 nm using a double beam UV spectrophotometer to assay the amount of rifampicin dissolved at each time interval. Dissolution studies were performed in triplicate and mean values were calculated.

The gelatin capsule bodies were cross-linked with formaldehyde vapors in closed chambers for various time intervals at ambient temperature. This process was done to reduce gelatin solubility. The amino groups in gelatin molecular chain could react with aldehyde groups of formaldehyde by a Schiff's base condensation^{14,15}. In the present study capsules treated with formaldehyde vapors for 12 h were used, since capsules exposed to formaldehyde for 12 h remained intact up to 24 h. The

residual amount of formaldehyde content in hardened capsule body was found to be 0.02% w/w (0.118 mg per 52 mg of average capsule body weight).

Pulsincap was a patented preparation, consisting of hardened capsule body filled with basic drug mixture and sealed with hydrogel plug. After imbibing sufficient quantity of the fluids, the hydrogel plug will be released at predetermined time and the total contents of the capsule will be released into the gastrointestinal fluids. Hence this preparation is regarded as a time-release dosage form. In the present work pulsincap was modified by replacing the drug mixture with drug-polymer mixture in different ratios and filled into the capsule body. The release rate of the drug was controlled by the formation of viscous hydrogel within the capsule body. This technique controls the drug release rate whereas pulsincap preparation controls drug release time.

The dissolution profiles of rifampicin from various formulations were shown in fig. 1. The release of the drug from the polymer drug mixtures was slow compared to the basic mixture. Polymer-basic mixtures containing 10% and 20% of gum karaya, 10% and 20% of sodium alginate; and 10% w/w methyl cellulose failed to retard the drug release. This might be due to a low concentration of the polymer or the low swelling nature of the polymer. But in the case of polymer-basic drug mixture containing 30% of gum karaya, the drug release was significantly retarded. This may be due to formation of a thick gel and gum karaya in higher concentrations preventing the entry of dissolution fluid and subsequent release of the drug. With guar gum though the percentage of gum was increased above 20% there is no significant increase in the retardation of the drug release.

Percent rifampicin released from hardened capsules decreased with increasing polymer content in the hardened capsules. The order of sustaining capacity of the polymers is, Guar gum>HPMC>Carbopo940>gum karaya>sodium alginate>methyl cellulose.

Among all the polymers, guar gum showed more sustaining capacity even at lower concentrations. This is because of rapid hydration capacity of the polymer, which forms a surface barrier quickly. In order to establish the mechanism of drug release from the hardened capsules, the experimental data were fitted to different kinetic models like zero order, first order, spherical and planar matrix models. The linear correlation coefficients of the slopes indicating that the drug release confirm predominantly to case I diffusion (i.e. square root of time

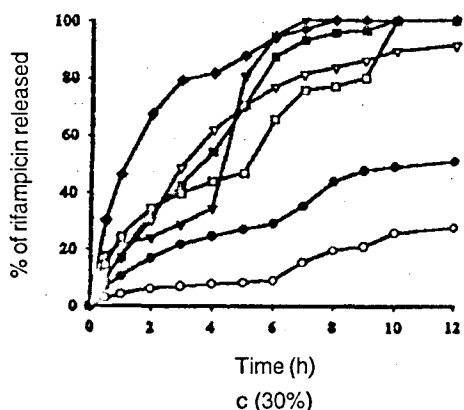
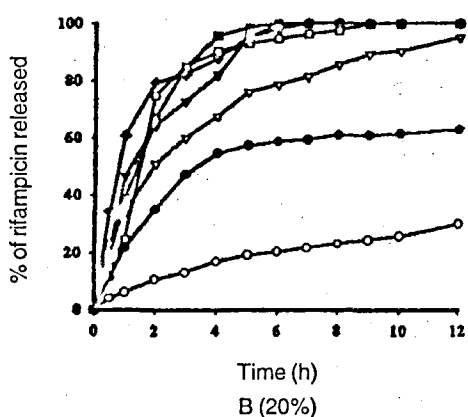
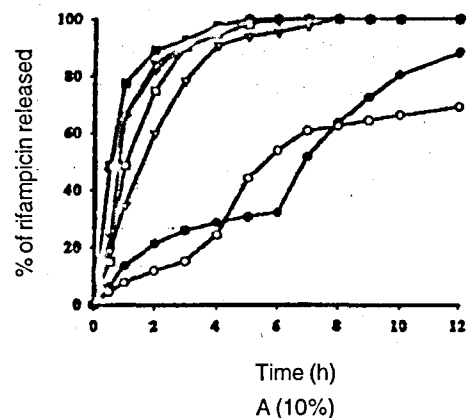


Fig. 1: Dissolution profiles of rifampicin from pulsincaps
 Dissolution profiles of rifampicin from pulsincaps prepared with hydrophilic polymers in 10%, 20% and 30% with respect to basic mixture, HPMC (●-), Guar gum (○-), methyl cellulose (▼-), Carbopol 940 (▽-), Gum karaya (□-), Sodium alginate (◻-), Poly vinyl alcohol (◆-). Each point is a mean of three determinations.

profile). This classical Higuchi type of release mechanism can be explained as a result of the rapid hydration of the polymer molecules on the opening surface of the capsule, which resulted in a gel or highly viscous solution surrounding the opening of the capsule that restricted water penetration into the center. The net result is a reduction of the rate of drug release as a function of time. From the DSC thermograms, it was observed that there is no interaction or complexation of drug with the excipients used during the manufacturing process.

In conclusion, the release of drug from modified pulsincap was found to be proportional to the concentration of the polymer in the case of HPMC, methyl cellulose, gum karaya and carbopol 940, whereas with guar gum there is no such relation. The formulations containing the gum karaya >20%; sodium alginate <10% and methyl cellulose <10% failed to retard the release of the drug. With the formulations containing guar gum there is no significant difference between 20% and 30% in controlling the release of the drug. From this study, it can be concluded that the modified pulsincap preparation is one of the promising formulation techniques for preparing controlled release formulations.

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