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FORMULATION DEVELOPMENT OF RIFAMPICIN CR MATRIX TABLET WITH DIFERENT VISCOSITY GRADES OF HPMC

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Abstract

Tuberculosis (TB), widely occurring, is still one of the most deadly infectious diseases worldwide. Rifampicin is a well-known candidate for its excellent antitubercular activity. But it suffers from such many drawbacks as a poorly soluble drug, short half-life, severe adverse effects of the drugs during long-term therapy, pH-dependent degradation, potential bioavailability problems associated with drugs, and poor patient compliance. Design and development of controlled release (CR) formulations has been and continues to be of greater interest to formulation scientists and pharmaceutical industry. They offers many advantages, such as improved patient compliance, less dose, minimized side effects, reduced or no fluctuation of drug in the blood, and cost effectiveness. Therefore in this present research work, an attempt was made to formulate and characterize hydrophilic controlled release matrix tablets of rifampicin have been formulated using Hydroxypropyl methylcellulose (HPMC) polymer (medium and high viscosity) by direct compression method. Influence of formulation variables such as drug: HPMC ratio, viscosity grade of HPMC on the formulation characters and drug release has been studied. Our results indicated that the release rate of the drug and the mechanism of release from the HPMC matrices are mainly controlled by the drug: HPMC ratio and viscosity grade of the HPMC. The formulations were found to be stable and reproducible.

Keywords: Controlled release matrix tablet, Rifampicin, HPMC, Tuberculosis.

Introduction:

Controlled release dosage forms cover a wide range of prolonged action formulations, which provide continuous release of the active ingredients at a predetermined rate and for a predetermined time. The most important objective for the development of these systems is to furnish an extended duration of action and thus assure greater patient compliance Pharmacokinetically, it is often desirable to administer a single dose of medication, which release the active ingredient over an extended period of time rather than to administer a number of single doses at regular intervals. Drug absorption at the desired rate means, first to reach the effective plasma level within an acceptable short time period, second, to avoid an over shoot in the case of rapidly absorbed drugs and third to maintain effective plasma levels over the desired time period.[2] Although the intensity of pharmacological effect is related to the drug concentration at the site of action, which is in turn, related to the plasma drug concentration, an ideal situation is obtained when the concentration is continuously maintained between minimum effective and maximum safe levels (Therapeutic index).

Various approaches of controlled drug delivery system:

Gastroretentive drug delivery systems [1,3]

- Site Specific drug delivery systems
- Colon specific drug delivery systems
- Transdermal drug delivery system
- Pulsatile drug delivery system

Advantages of controlled release preparations:

- Controlled release drug products offer several important advantages over immediate release conventional dosage form of the same drug.
- a) More efficient drug utilization by the body.
- b) Better patient compliance.
- c) Decreased frequency of administration.

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d) Elimination of peak and valley plasma levels so that drug concentration is
maintained constant over a long period of time. Hence reduction in severity
and frequency of untoward side effects.
e) Safety margin of potent drug is increased.
f) Avoidance of night-time dosing.
g) Reduction in GIT irritation and other dose related side effects.
h) A greater selectivity of pharmacological activity.

Disadvantage of controlled release preparations:
1. Dose dumping: There is always the possibility of sudden release of the total dose administered i.e. dose dumping, which may result in some toxic manifestations.
2. Less flexibility in dose adjustments: It is very difficult to adjust the dose of control release products to a patient's response. The physician has less flexibility in adjusting the dosage regimens.
3. Side effects: For some drug requiring repeated administration during the course of day the use of sustained release system can result in reduction in therapeutic efficacy and increase in side effect; in particular for drugs which are subject to large metabolic degradation due to first pass effect. e. g. Levodopa.
4. The cost of unit dose of controlled therapeutic system is higher than the regular conventional dosage forms.
5. Drug that react with receptors that are inactivated by prolong stimulus so shows tolerance hence decreased in efficacy. e.g. Nitrates.
6. A gradual release can result in greater degradation and consequently less bioavailability.
7. Unpredictable and often poor 'In vitro-In vivo' correlation [3].

Rifampicin or rifampin (USAN) is a bactericidal antibiotic drug of the rifamycin group [4]. It is a semisynthetic compound derived from Amycolatopsis rifamycinica (formerly known as Amycolatopsis mediterranei and Streptomyces mediterranei) [5].

Rifampicin is an intensely red solid, and the small fraction which reaches body fluids is known for imparting a harmless red-orange color to the urine (and to a lesser extent, also sweat and tears) of users, for a few hours after a dose. Maximal concentrations in the blood are decreased by about a third when the antibiotic is taken with food [6]. Rifampicin is a well-known candidate for its excellent antitubercular activity. But it suffers from such many drawbacks as a poorly soluble drug, short half-life, severe adverse effects of the drugs during long-term therapy, pH-dependent degradation, potential bioavailability problems associated with drugs, and poor patient compliance.

Objective:

The aim of this present research work is to formulate and characterize CR tablets of rifampicin by using two different viscosity grades of HPMC polymer by direct compression method.

Experimental Methods:

1. PREPARATION OF CR TABLET FORMULATION:

Controlled release rifampicin tablets were formulated using HPMC polymers by direct compression method using a single station tablet compression machine using 12 mm standard concave punches [7]. The compression force was kept at a constant level to produce tablets of 5-6 kg/cm^2 hardness. The details of formulation batches were given in table:1.

2. EVALUATION OF CR TABLET FORMULATION:

A] Physical Characterization of Formulations

The weight variation, hardness, Friability and drug content of each tablet from different batches of the formulations were determined as per the procedure given in the Indian Pharmacopoeia (1996) [7,8].

B] Release Rate Studies

Release rate was studied using USP type 1 (basket method) in 900 ml 7.4 pH phosphate buffer containing 0.02% w/v of ascorbic acid, at 37 ± 1° C at 100 rpm. Sample was analyzed by ultraviolet spectrophotometric method at 475 nm.

Figure 1: Hypothetical drug concentration profiles of multiple doses of an immediate release drug delivery system

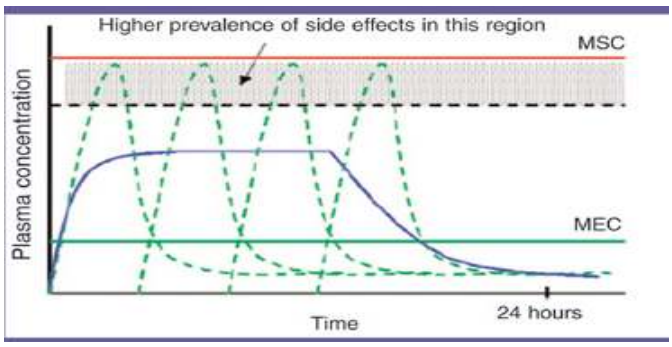

Figure 2: Rifampicin

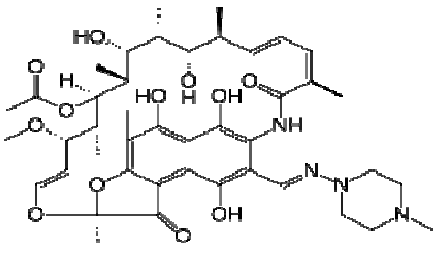

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TABLE:1 FORMULATION COMPONENTS AND PHYSICAL PROPERTIES DIFFERENT FORMULATIONS

F.C.	Drug (mg)	HPMC K4M (%w/w)	HPMC K15M (%w/w)	Drug content (% l C) [a]	Weight variation (%)[b]	Hardness (kg/cm^2)[c]	Friability (%)
F-1	450	50	-	102.1± 0.7	±2.8	6.6 ± 0.7	< 0.9
F-2	450	40	-	100.2± 0.3	±2.6	6.4 ± 0.6	< 0.9
F-3	450	30	-	99.6 ± 0.9	±2.1	6.8 ± 0.5	< 0.9
F-4	450	-	30	100.7± 1.4	±2.5	6.9 ± 0.7	< 0.9
F-5	450	-	40	98.9 ± 1.2	±2.3	6.6 ± 0.7	< 0.9
F-6	450	-	50	101.2± 1.2	±2.8	6.8 ± 0.5	< 0.9
F-7	450	20	20	99.6 ± 0.9	±2.5	6.6 ± 0.7	< 0.9
F-8	450	10	40	100.3± 1.4	±2.8	6.7 ± 0.9	< 0.9
F-9	450	30	10	99.9 ± 1.2	±2.1	6.9 ± 0.7	< 0.9
F-10	450	10	20	100.5± 1.3	±1.4	6.9 ± 0.5	< 0.9

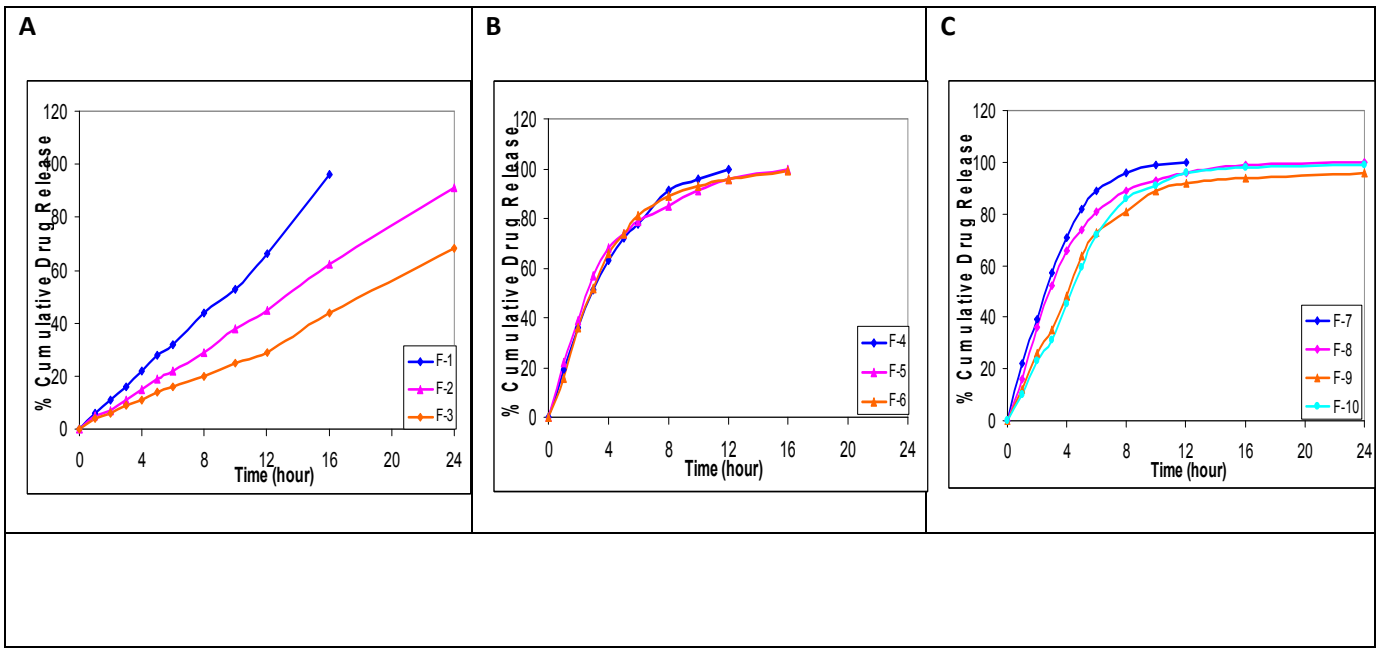
[a]mean of triplicate with SD;

[b] ± max % variation from the mean;.

[c]mean of 20 tablets

*Also contains 0.6% w/w of talc and 0.4% w/w of magnesium stearate as additives.

Figure 3: Release profile of rifampicin from formulations A] F-1 to F-3 B] F-4 to F-6 C] F-7 to F-10



Conclusion:

This study showed that the medium and high viscosity grade HPMC K4M and K15M could be used successfully in combination as a matrix material in proper ratio to design CR formulations of a poor water soluble drug like rifampicin, with desired quality and release characteristics. The tablets formulated showed good physical properties indicating that the direct compression method employed for the formulation development was satisfactory. The tablet manufacturing method was relatively simple and can be easily adopted in conventional tablet manufacturing units in industries on a commercial scale.

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