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RESEARCH ARTICLE

Application of Cow Ghee as an Excipient in Hot – Melt Coating Agent in Controlled Release Rifampicin plus Isoniazid Capsule Formulations

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ABSTRACT

The objective of the present study was to design rifampicin plus isoniazid controlled release pellets using cow ghee (CG) as an important hot melt coating (HMC) agent. The pellets were coated by HMC technique using Cg and ethyl cellulose composition by using conventional coating pan without the use of spray system. The prepared rifampicin plus isoniazid pellets were characterized for drug content, photomicrography, *in- vitro* dissolution studies, flow properties of pellets. Stability studies were performed for a period of 3 months at $40^0 \pm 2^0$C and 75± 5% relative humidity. HMC technique is easy rapid and simple method with no agglomeration seen during coating. *In – vitro* release from pellets at a given level of coating and for present pellets size was dependent upon the physico-chemical properties of the drug. HMC pellets were stable during the course of stability study. Rifampicin plus isoniazid pellets using CG with ethyl cellulose by HMC technique was employed successfully and capsule formulations were prepared.

KEYWORDS

Cow Ghee, Excipient, Hot – Melt Coating Agent, Controlled Release Rifampicin plus Isoniazid Capsule Formulations

INTRODUCTION

Capsule is a solid dosage form in which drug substances are enclosed within either a hard or soft soluble shell, usually formed from gelatin. Capsules may be classified as either hard or soft, depending on the nature of the shell. Soft gelatin capsules are made from a more flexible, plasticized gelatin film than hard gelatin capsules. Hard gelatin capsules allow a degree of flexibility of formulation not obtainable with tablets. However, the problems of powder blending and homogeneity, powder fluidity and lubrication in hard gelatin capsule filling are similar to those encountered in tablet manufacture.

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It is still necessary to measure out an accurate and precise volume of powder or pellets for capsule filling. The ability of such dry solids to uniformly fill into a capsule shell is the determining factor in uniformity of weight and drug content. In one of the earliest reports evaluating the Zanasi machine, Stoyle1 suggested that formulations should have the following characteristics for successful filling[1].

1. Fluidity is important for powder feed from reservoir to the dipping bed and also to permit efficient closing in the hole left by the dosator.
2. A degree of compatibility is important to prevent loss of material from end of the plug during transport to the capsule shell.

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3. Lubricity is needed to permit easy and efficient ejection of the plug.
4. The formulations must have a moderate bulk density. Low bulk density materials or those that contain entrapped air will not consolidate well, and capping similar to what occurs in tabletting may result.

The advantages of multiple unit dosage forms over the single unit ones have been demonstrated by several investigators.[2-5] The coating of particulates such as powders, granules, pellets and tablets to produce controlled release dosage form is becoming increasingly popular, mainly due to the advances in fluidized – bed process as well as availability of new coating materials.[5]

In 1970, the U.S. Environmental protection Agency introduced the Clean Air Act.[6] The hot-melt coating techniques have been shown to avoid the use of solvents and show promising for taste masking, gastric resistance, acid resistance, sustained release or bioavailability enhancement, based upon type of coatingpolymer.[7]

The present study was performed to check the suitability of cow ghee (CG) as a controlled release (CR) hot melt coating agent (HMC) in combination with ethyl cellulose. To prevent the oxidation of CG, α-tocopherol was used as antioxidant in the coating composition.

MATERIAL AND METHODS

Rifampicin was obtained as a gift sample from Lupin Limited, Aurangabad, India. Ethyl cellulose was procured from Themis laboratories Mumbai, India. Cow ghee was obtained from Gourakshan centre Amravati, India. Solvents and all other reagents were of analytical grade and were procured locally.

Method

Table 1: Composition of rifampicin pellets formulations

Sr. No.	Ingredients	Formulations		
		A	B	C
1	Rifampicin	450mg	450mg	450mg
2	Isoniazid	300mg	300mg	300mg
3	Cow ghee	5mg	10mg	15mg
4	Corn starch (dried)	10mg	10mg	10mg
Total		765mg	770mg	775mg

Preparation of Rifampicin Pellets

The various steps involved in the making of rifampicin plus isoniazid pellets are shown below:

Step 1: Rifampicin, isoniazid and dried maize starch were mixed thoroughly.

Step 2: Cow ghee was melted on water bath and added to the mixture of step 1 and mixed thoroughly for 5-10minutes.

Step 3: The blend obtained from step 2 was compressed on single punch Cadmach machine on a 500 tonnes pressure, which converts the material into flakes.

Step 4: The flakes of step 3 were passed from oscillating granulator with 14 mesh.

Step 5: The material obtained from step 4 was again passed through sieve no. 40. The material retained (oversize) on sieve was collected and kept separately.

Step 6: Undersize material of step 5 was again compacted as per step 3 and the steps 4 and 5 were repeated.

Step 7: The 40 mesh oversize materials were mixed thoroughly.

Coating of Rifampicin plus Isoniazid Pellets

The pellets of fraction were coated with ghee – ethyl cellulose molten blend in 12” coating pan equipped with 4 radially arranged baffles and system to heat the pan. The hot melt coating formulation consisted of the following.

The process consisted of first melting the cow ghee, raising the temperature of molten ghee to 80^0C and dissolving the ethyl cellulose in the molten ghee with stirring at the same temperature. The rifampicin pellets were then

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rolled in a bed temperature of 60^{0}C was attained. The molten mass was then added on to the hot rolling drug pellets in a slow stream. After completion of coating solution, the pellets were allowed to roll further for 10 minutes during which time the bed temperature was allowed to gradually come down. The pellets were then removed and cured in a dryer for 48 hours.

Table 2: Rifampicin plus isoniazid pellets coating formulations

Sr. No.	Ingredients	Quantity
1	Cow ghee	75 g
2	Ethyl cellulose	25 g
3	α tochopherol	02 mg

Table 3: Process parameters for HMC of rifampicin plus isoniazid pellets

Process Parameter	Settings
Pellet Charge	500g
Pellet Size	10-20 mesh
Pellet Speed	24 rpm
Amount of coating solution	50g
Core to coat ratio	10:1
Pellet bed temperature	60°C
Relative Humidity	30-50%
Coating time	30 min
Curing time	30°C for 48 hrs

Table 4: Composition of rifampicin capsule formulations

Sr. No.	Ingredients	Formulations		
		A	B	C
1.	Coated rifampicin pellets	841mg	846mg	851mg
2.	Sodium metabisulphite	2mg	2mg	2mg
3.	Magnesium stearate	5mg	5mg	5mg
4.	Corn starch	10mg	10mg	10mg
5.	Colloidal silica (Aerosil)	3mg	3mg	3mg
6.	Sodium lauryl sulphate	2mg	2mg	2mg
Total		863mg	868mg	873mg

Final Blending and Capsule Filling

Step 1: The coated rifampicin pellets were mixed with remaining ingredients i.e. magnesium stearate, starch, colloidal silica, sodium metabisulphite and sodium lauryl sulphate and passed through sieve no. 40 prior to mixing.

Step 2: The resultant blend of step 1 was filled in hard gelatin capsules of size ‘00’. Filling of capsule was done with the help of hand-operated capsule filling machine. For each formulation 600 capsules were prepared.

Evaluation of Capsules

Drug Content Determination

Standard solutions of rifampicin and isoniazid were prepared in 0.01N sodium hydroxide solution (pH 12) separately in concentration of 150µg/ml and 100 µg/ml respectively. They were further diluted with sodium hydroxide solution (pH 12) to concentrations in the range of 2 – 20 µg/ml. The λmax for rifampicin and isoniazid were found to be 327 and 297 nm respectively. The E 1% 1 cm value for both the drugs were obtained at both 327 and 297 nm. The E 1% 1 cm of isoniazid RS and rifampicin RS were found to be 189.0 and 269.33, 325.75 and 199.66, respectively. Absorbances of solutions were taken within 1 hour after the start of the experiment.

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A weighed quantity of the mixed contents of 20 capsules equivalent to 150 mg rifampicin and 100mg isoniazid was dissolved in sodium hydroxide solution (pH 12) and filtered. The filtrate was further diluted with sodium hydroxide solution so that the concentration of rifampicin and isoniazid after final dilution was around 15µg/ml and 10 µg/ml respectively.

Absorbances of samples were recorded at both 297 and 327 nm using sodium hydroxide solution (pH12) as the blank. The percent of rifampicin and isoniazid was calculated by using the following pair of simultaneous equations[8]

$$X = 100 \{(b1s2 - b2s1) / (b1a2 - b2a1)\}$$

$$Y = 100 \{(a1s2 - a2s1) / (a1b2 - b1a2)\}$$

Where, X and Y are the concentrations (% w/w) of isoniazid and of rifampicin;

a1 and a2 represent E1% 1cm of isoniazid at 297 and 327-nm respectively;

b1 and b2 represent E1% 1cm of rifampicin at 297 and 327-nm respectively;

S1 and S2 represent E1% 1cm of the sample at 297 and 327-nm respectively.[9]

In Vitro Dissolution Studies

In Vitro Dissolution of Rifampicin

Dissolution studies were carried out using USP 25 dissolution apparatus 1 (rotating basket method). Dissolution conditions used in the study are indicated below:

Table 5: Dissolution Parameters for Rifampicin

Speed of rotation	100rpm
Temperature	37°C ± 0.5°C
Time	12 hours
Test Medium	Phosphate Buffer pH 7.4 containing 0.02% of ascorbic acid
Volume of test medium	900ml in each Vessel

Samples of 5-ml were withdrawn at regular one-hour intervals for 12 hours. An equal volume of fresh medium was immediately replaced to maintain the dissolution volume. Samples were filtered, diluted adequately and analysed spectrophotometrically at 475 nm to determine the amount of rifampicin released at each time interval. At the end of 12 hours of testing, the drug remains were suspended in 100 ml methanol and the remaining drug content was estimated. This was done to make sure that the amount of drug remained, when added to the cumulative amount of drug released up to twelve hours equals the average drug content of capsules as estimated prior to the drug release studies.

In- Vitro Dissolution of Isoniazid

The dissolution studies were carried out using USP 25 dissolution apparatus 1 (rotating basket method). Dissolution conditions used in the study are indicated below:

Table 6: Dissolution parameters for isoniaizid

Speed of rotation	50 rpm
Temperature	37°C ± 0.5°C
Time	3 hours
Test Medium	Distilled Water
Volume of test medium	900ml in each Vessel

Five ml sample was withdrawn at regular 30 minutes intervals for three hours. An equal volume of fresh medium was immediately replaced to maintain the fresh dissolution medium. Samples were filtered through membrane filter of 0.1µm pore size and suitably diluted with distilled water. Absorbance of the resulting solution was measured spectrophotometrically at 263 nm[10].

Photomicrography

Micrographs of rifampicin plus isoniazid of formulations D, E and F were taken using Intel play digital microscope QX3 attached to a personal computer. The photographs were used

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to examine the surface properties of granules after granulation after coating with cow ghee and ethyl cellulose.

Flow Properties of Powder

The static angle of repose of coated pellets of D, E and F formulations was measured according to fixed funnel and free standing cone method.[11]

Stability Studies

All prepared formulations were packed in polyethylene/aluminium foil pouches and subjected to storage for three months at 40^0C ± $2^0$and relative humidity (RH) 75 ± 5%. After storage at the stated temperature and relative humidity for the period of three month, the capsules were analyzed for determination of drug content.

RESULTS AND DISCUSSION

Drug Content

Results of drug content for the capsules formulations demonstrate that the rifampicin and isoniazid content of formulations D, E and F were within the limit of 100 ± 5 % These results indicate that cow ghee does not interfere with the stability of the drugs under investigation viz. rifampicin.

***In Vitro* Drug Dissolution Studies**

The formulation D that contains 5 mg cow ghee per capsule showed a maximum release of the drug - 97 % rifampicin in 12 hours and 98 % isoniazid in 3 hours. Formulation E containing 10 mg cow ghee per capsule showed 87 % rifampicin and 85 % isoniazid release in 12 hours and 3 hours respectively. A further retardation of release was observed with formulation F containing 15 mg of cow ghee per capsule 58% rifampicin in 12 hours and 76 % isoniazid in 3 hours. The results are recorded graphically in figure 1 and 2 respectively.

Retardation of release of both drugs with an increase in cow ghee concentration in the formulations can be attributed to the hydrophobic nature of cow ghee which not just delays dissolution but also prevents rapid wetting of the active ingredients and slowed partitioning of drug from the lipid matrix to the aqueous dissolution medium.

Slow release of drugs owing to incorporation of cow ghee in capsule formulations demonstrates that the excipient under investigation has the capacity to prevent decomposition of rifampicin in acidic milieu as well as its subsequent interaction with isoniazid.

This in turn may have a positive impact on the bioavailability of rifampicin from such formulations.

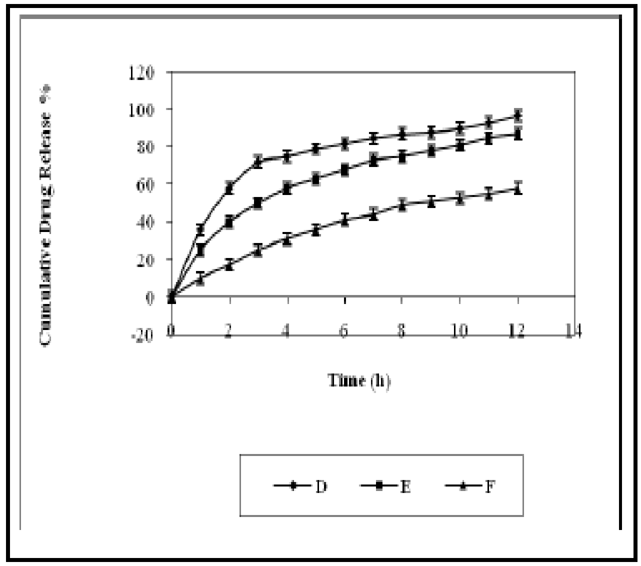

Figure 1: In vitro dissolution of rifampicin from formulations D, E and F

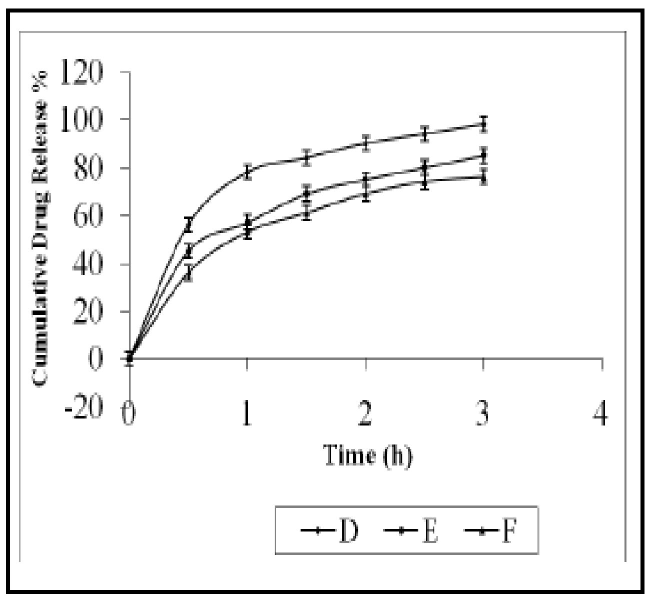

Figure 2: In vitro dissolution of isoniazid from formulations D, E and F

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Photomicrography

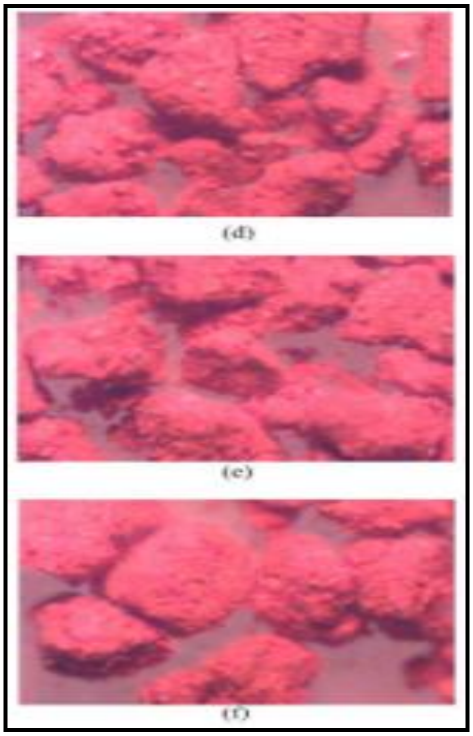

Figure 3: Stereomicrographs of coated pellets of (rifampicin plus isoniazid) formulations Magnification:60X

Photomicrography of granules of various formulations of rifampicin plus isoniazid as depicted in figures 3 shown that granulation of drugs with cow ghee results in product having relatively smooth surface morphology. This fact was reflected in a reduction in repose angle values of granules of all types of formulations indicating that cow ghee is not just a compacting or granulating agent and coating agent, it favorably alters the surface characteristics of granules to facilitate flow properties.

Flow Properties of Powder

It was observed that all the formulations showed excellent flow properties. Formulations D, E and F formed an angle of repose 25.36^0, 23.54^0 and 26.27^0 repose angle values, respectively. This improvement in the angle of repose may be because of the compaction of drug materials and possibility cannot be ruled out that added cow ghee in the formulations increase the adhesion between the particles, which helps to increase the bulk density of the materials. The fatty or waxy nature of cow ghee also promotes slip and slide of granules resulting in further improvement of flow.

Stability Studies

The results of stability studies with group II formulations containing both rifampicin and isoniazid revealed that there were no substantial changes in drug content. Both rifampicin and isoniazid content were above 90% of the original value after storage for 3 months at 40^0C ± $2^0$and relative humidity (RH) 75± 5%.The potency of rifampicin and isoniazid in each after storage at various temperatures are graphically recorded in figures 4 and 5 respectively. These results also indicate that the group II formulations will be sufficiently stable for a period of 2 years as determined from Arrhenius plot.[12]

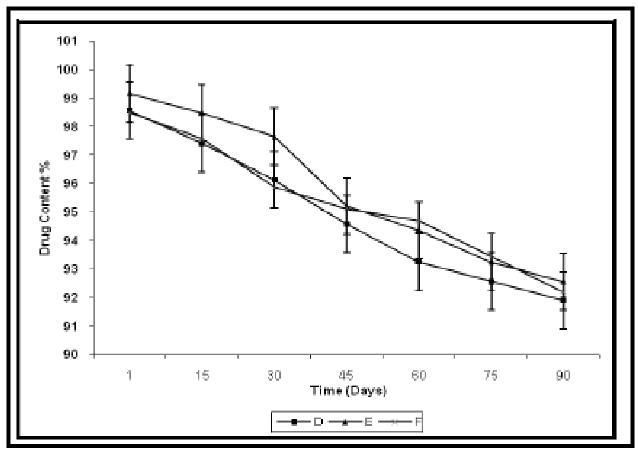

Figure 4: Effect of stability on rifampicin content of D, E and F formulations when stored at 40^0C and relative humidity (RH) 75 ± 5%

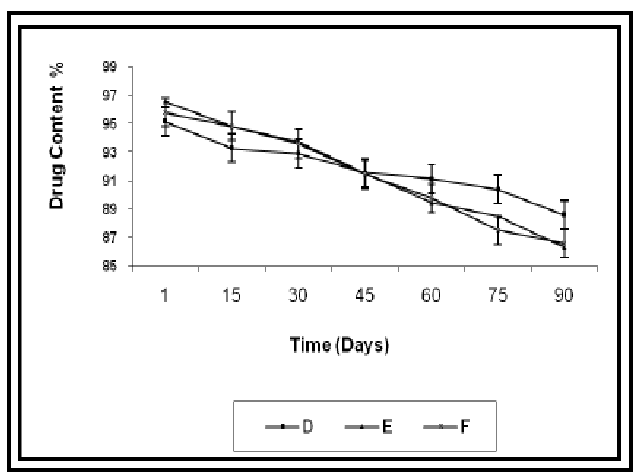

Figure 5: Effect stability on isoniazid content of D, E, and F formulations when stored at 40^0C ± 20 and relative humidity (RH) 75 ± 5%

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CONCLUSION

In conclusion, among the strategies employed for the design of a controlled-release capsule dosage form, use of cow ghee as an excipient during compaction of rifampicin in the formulations and coating of the rifampicin with cow ghee and ethyl cellulose combination seems a promising alternative. It may be possible to employ cow ghee in different combinations to develop the controlled-release capsule dosage forms. This new method for controlling release rates of rifampicin may prove useful in improving oral availability of rifampicin. The cow ghee will be an alternative choice for use as an excipient in compaction method and hot melt coating agent to develop controlled-release dosage forms in the near future.

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