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Application of Cow Ghee as an excipient in Hot – Melt Coating agent in controlled release rifampicin capsule formulations

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Abstract: The objective of the present study was to design rifampicin 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 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 pellets using CG with ethyl cellulose by HMC technique was employed successfully and capsule formulations were prepared.

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. 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, Stoyle[1] 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.
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.

Tha 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 coating polymer.[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.

Materials

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.	Cow ghee	5mg	10mg	15mg
3.	Corn starch (dried)	10mg	10mg	10mg
Total		465mg	470mg	475mg

Preparation of rifampicin pellets

The various steps involved in the making of rifampicin pellets are shown below –

- ***Step 1.*** Rifampicin 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 5-10 minutes.
- ***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:

Table 2. Rifampicin plus isoniazid pellets coating formulations

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

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 rolled in a bed temperature of 60^0C 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.3. Process parameters for HMC of rifampicin pellets

Process parameters	**Settings**
Pellet charge	500g
Pellet size	10-20 mesh
Pan speed	24rpm
Amount of coating solution	50g
Core to coat ratio	10:1
Pellet bed temperature	60^0C
Relative humidity	30-50%
Coating time	30 min
Curing conditions	30^0C for 48h

Table 4. Composition of rifampicin capsule formulations

Sr. No.	**Ingredients**	**Formulations**		
		A	**B**	**C**
1.	Coated rifampicin pellets	511mg	516mg	521mg
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		533mg	538mg	543mg

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 '0'. 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

Mixed contents of 20 capsules equivalent to 0.1g of rifampicin, was weighed accurately and shaken with methanol, volume made upto 100 ml and the resulting solution filtered. Two ml of the filtrate was diluted to 100 ml with phosphate buffer of pH 7.4 and absorbance of the resulting solution was measured spectrometrically at 475 nm[8] (Shimadzu UV 1601 Japan).

Table 5. Dissolution process parameters for prepared rifampicin capsules

Speed of rotation	: 100rpm
Temperature	: 37 ^{0} C ± 0.5 ^{0} C
Time	: 12 hours
Test medium	: Phosphate buffer (pH 7.4) containing 0.02 % of ascorbic acid
Volume of test medium	: 900 ml 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[8] 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.

Photomicrography

Micrographs of granules of formulations A, B and C were taken using Intelplay digital microscope QX3 attached to a personal computer. The photographs were used 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 A, B and C formulations was measured according to fixed funnel and free standing cone method.[9]

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 said period, the capsules were analysed for determination of drug content.

Results and discussion

Drug Content

Results of drug content for the capsules formulations demonstrate that the rifampicin content of formulations 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 A, which contained the cow ghee (5 mg per capsule) showed a maximum release of the drug (98 % in 12 hours). Formulation B having composition of cow ghee 10 mg per capsule showed a moderate release (84 % in 12 hours). Formulation C containing 15 mg cow ghee per capsule showed slowest release a maximum of 57 % in 12 hours.

The low dissolution of the drug in aqueous medium may presumably be owing to the fatty or hydrophobic nature of cow ghee, which may obstruct the drug to dissolve in to the dissolution medium. It is reasonable to assume that drug-partitioning form the lipoidal matrix of ghee into the aqueous dissolution medium would be low. Dissolution studies revealed that release rate was inversely related to cow ghee content, the results are shown in fig.2. This suggested that ghee slows down the dissolution rate. This fact is advantageous for rifampicin preparations since a protracted release would prevent drug from decomposition in acidic pH of stomach. Possibility of slow releasing complex formation cannot be ruled out.

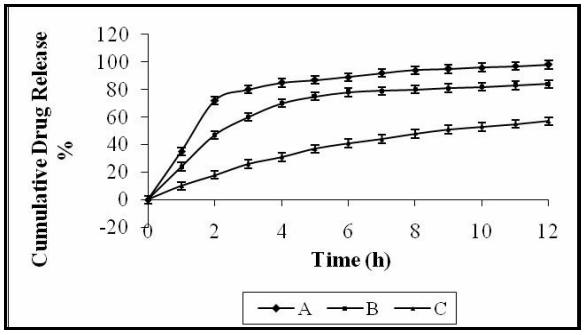

Figure 2. *In vitro* dissolution of rifampicin from formulations A, B and C

Photomicrography

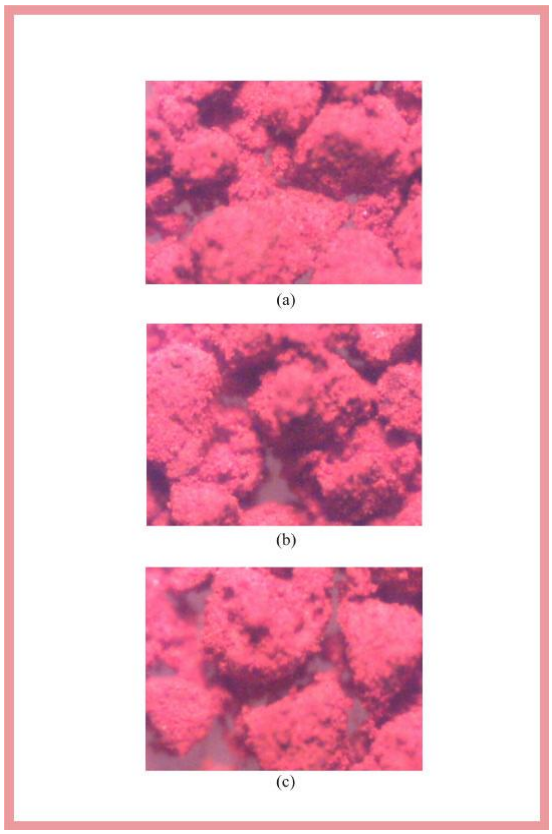

Figure 1. Stereomicrographs of coated pellets of (rifampicin) formulations. Magnification: 60X

Photomicrography of granules of various formulations of rifampicin as depicted in figures 1 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 favourably 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 A, B and C formed an angle of repose 23.65^0, 25.58^0 and 22.34^0 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 product stability studies revealed that there were no substantial changes in the drug content. The potency of rifampicin in each formulation was found in the range of 99 % to 91 % for the storage conditions as shown graphically recorded in figures 3. This indicated that the formulations prepared with cow ghee were sufficiently stable and there was no deleterious impact or interaction of cow ghee with the drug materials in the formulation during storage at 40^0C. ± 2^0 and relative humidity (RH) 75± 5%. Since the potency of the active(s) in the formulations was found to remain above 90 % of the original concentration after storage at specific condition for a certain period of time (*i.e.* 3 months in the present investigation), there is good assurance that the formulations will have a shelf life of 2 years as determined from Arrhenius plot.[10]

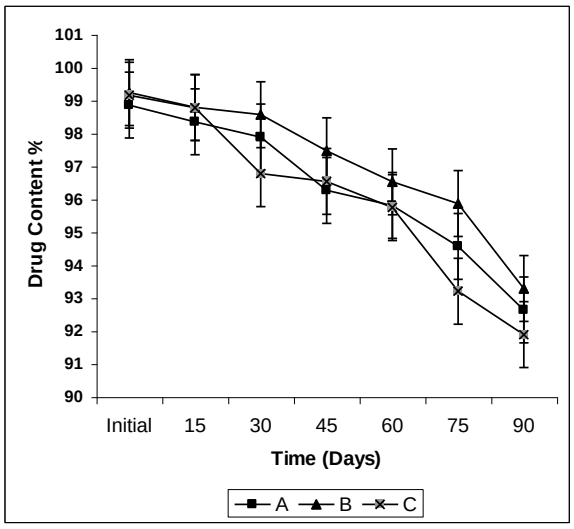

Figure 3. Effect stability on rifampicin content of A, B, and C formulations when stored at 40^0C. ± 2^0 and relative humidity (RH) 75 ± 5%.

Conclusions

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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