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Application of hot-melt coating for sustained release pellets of fenoverine

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ABSTRACT

Hot-melt coating (HMC) techniques are widely used to provide drug protection, to improve aesthetic value of products, to reduce acidity of vitamins, to provide lubrication and to modify drug release. Lipid coating can regulate the drug release from the pellets. In the present study, fenoverine (anti-spasmodic drug) was used as model drug. The application of cow ghee and mixture of cow ghee-caurnauba wax in various ratios were used as drug release regulators for fenoverine pellets. The kinetics of drug release from pellet formulations was investigated. Fenoverine pellets of 16:20 mesh size were prepared by extrusion-spheronization technique and coated with the molten coating materials at various ratios in a modified pan coater without spray system. The dissolution of coated pellet was decreased with the increases in quantity of caurnauba wax in coating composition. Formulation F4 was selected as optimized formulation based on difference factor (f_1) and similarity factor (f_2) values (6.65 and 64.66 respectively). Drug release from the sustained release pellets occurred by diffusion, which was reflect from Higuchi model. The 'n' value of Peppas equation for release of drug from coated pellets were lies between 0.5-1.0, hence the drug release mechanism can be concluded as non-Fickian diffusion. The results signify that drug release could be adjusted by varying the ratio of cow ghee to caurnauba wax.

Keywords: Difference factor, Extrusion-spheronization, Hot-melt coating, Sustained release, Similarity factor.

INTRODUCTION

Oral solid dosage forms for sustained drug release has the major attention amongst all the controlled drug delivery systems due to its conventional usage. Polymeric film coatings have been utilized widely for controlled release of an active substance from pharmaceutical dosage forms because the coated dosage forms enable the sustained and precise release of drug with good reproducibility. The performance of these drug delivery systems is evaluated primarily in terms of their release kinetics and overall ease of administration. Methods that release drug with zero order kinetics for an extended time period is usually considered optimal [1, 2]. Multi-unit dosage forms like beads, granules, larger particles, pellets, spherules and mini-tablets are less affected by variation in the gastric emptying rate and overall gastrointestinal transit time compared to a single unit such as tablets. The advantages of multiple-unit dosage forms over the single-unit ones have been demonstrated by several investigators [3-6]. The multi-unit sustained release dosage forms are usually manufactured by coating the drug-loaded pellets or granules with gastrointestinal fluid-insoluble polymers. The drug release is controlled by diffusion through the pores of polymer film. The coating of particulates such as powders, granules, pellets and tablets to produce sustained release dosage form is becoming increasingly popular, mainly due to the advances in fluidized-bed process as well as availability of new coating materials [7].

Film coating processes often require solvent such as water, organic solvents or mixture. The use of organic solvents may lead to environmental problems, solvent residues and excessive costs of recovery. The aqueous solvent generally prolongs the duration of the coating process as well as leads to microbial contamination or hydrolysis of drug. Therefore, hot-melt coating is a smart alternative for organic and water based coating. Hot-melt coating

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technique defined as the application of fine layer of coating material in molten state over the substrate [8]. The hotmelt 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 material [9]. Fenoverine is an anti-spasmodic drug that restores smooth muscle motility and relieves the distressing symptoms associated with irritable bowel syndrome and primary dysmenorrhoea [10]. Animal fats are not commonly used as pharmaceutical excipients; however cow ghee is a clarified butter with a high melting point and has been described as a sustained release agent. Hot-melt coating employed waxes such as cetyl alcohol, beeswax, lanolin etc. which have definite disadvantages such as ability to demonstrate hypersensitivity or immunogenic responses in certain individuals. But cow ghee is an important component of our daily diet and absolutely free from the hypersensitivity skin and other reactions [11].

The main objective of this study was to investigate possibility of using cow ghee and mixture of cow gheecaurnauba wax as coating films on fenoverine pellets using hot-melt coating technique in a modified conventional coating pan with four radially arranged baffles without spray system and to evaluate their release characteristics. Caurnauba wax provides mechanical strength to the coating. Whereas, α - tocopherol was used as antioxidant as coating material may undergoes oxidation during process or storage of dosage form. Titanium dioxide is an opacifier.

MATERIALS AND METHODS

Materials

Fenoverine was used as model drug gifted by Euro Drug Laboratories Ltd. Hyderabad (AP) India. Cow ghee and caurnauba wax were used as coating waxes. Cow ghee was purchased from Gourakshan Dham, Akola (MS) India. Caurnauba wax was procured from Zim Laboratories Ltd, Kalmeshwar, Nagpur (MS) India, purified talc and titanium dioxide was purchased from S.D. Fine Chemicals, Mumbai (MS) India. All other chemicals used were of laboratory and reagent grade.

Preparation and hot-melt coating of pellets

Fenoverine pellets were prepared by extrusion-spheronization [12, 13]. Accurately weighed 500 g of fenoverine and sucrose solution were blended together in a suitable bowl for 10 min and immediately passed through #16 mesh to form extrudates. The wet extrudate was transfer into the rotary shaker pelletizer and the equipment was operated for 10 min at 200 r/min speed to produce drug pellets. Then the pellets were dried at 60°C for 3 hr. The dried pellets were then sifted to collect 16-20 mesh fractions. Undersize and oversize pellets were rejected. Pellets of fraction 16-20 mesh were coated with cow ghee-caurnauba wax molten blend in a coating pan equipped with 4 radially arranged baffles and system to heat the pan. The coating systems used in this study was cow ghee and mixture cow ghee-caurnauba wax at the ratio at the 9:1, 8:2, 7:3 and 6:4 [Table1].

Ingradiants (mg)	Formulation						
mgreulents (mg)	F1	F2	F3	F4	F5		
Cow ghee	20	18	16	14	12		
Caurnauba wax		2	4	6	8		
α-Tocopherol	0.5	0.5	0.5	0.5	0.5		
Titanium dioxide	0.5	0.5	0.5	0.5	0.5		

Table 1: Composition of modified release	hot-melt coating material
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A 500 g batch of 16:20 mesh pellets was loaded into the coating pan for coating without spray system. The critical process parameters required for coating were shown in [Table 2].

Table 2: Process parameters	for hot-melt coating	of fenoverine pellets
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Process Parameters	Settings
Pellet charge	500 g
Pellet size	16 - 20 mesh
Pan speed	25 r/min
Amount of coating solution	50 g
Pellet bed temperature	60°C
Relative humidity	30-50%
Coating time	30 min
Curing conditions	30 °C for 48 hr

Theoretical release profile

Approximately, 45%, 60%, 75% and > 90% drug should be release in 2, 4, 6 and 8 hr respectively. Initial burst release of fenoverine help in achieving the therapeutic level and remaining amount act as maintenance dose.

Evaluations of fenoverine pellets

Pellet size determination

Size determination was carried out using sieve analysis method. Approximately 200 g of pellets was placed into a sieve shaker equipped with 8-, 12-, 16-, 18-, 20-, 30- and 40-mesh US standard sieves (Acmas Tachnocracy[®], India) and shaken for 20 min. Each weight fraction was recorded. The mean size was determined. Shape and surface morphology view of the gold-treated pellets were photographed using a scanning electron microscope (Jeol[®], Japan) [14].

Angle of Repose

Accurately weighed 50 g of hot-melt coated pellets were poured gently through glass funnel on the graph paper. The height of pile and diameter were noted and angle of repose for uncoated and coated pellets were calculated.

Hardness and friability

The hardness of uncoated and hot-melt coated pellets was examined by Veego digital dial type hardness tester (Veego Scientific[®], India). For the friability study, 10.0 g pre-weighed pellets, collected on sieve having 0.85 mm aperture with 25 glass beads of 3mm diameter were placed in Roche's friabilator (Veego Scientific[®], India) for 100 revolutions at 25 r/min speed. The mass of pellets placed on sieve with 0.85 mm aperture. The smaller particles were allowed to pass through the sieve and pellets were reweighed. The friability was determined as percentage loss of mass of pellets after test was recorded [15], [16].

Determination of fenoverine content

An accurately weighed portion of pellets, equivalent to about 200 mg of fenoverine, was dissolved in absolute methanol, filtered and adjusted to the desired concentration with 0.1N HCl. The UV absorbance of the solution was determined at 261 nm. The percent drug content was calculated [17].

Dissolution of fenoverine pellets

An automated dissolution setup comprised a dissolution apparatus, a six-channel peristaltic pump, a UV-Visible spectrophotometer equipped with six 1-cm quartz flow cells. For both uncoated and coated pellets the dissolution test was carried out. Release of fenoverine from coated pellets was carried in 900 ml of 0.1 N hydrochloric acid using dissolution test apparatus 2 USP XXIV (Electrolab[®], India). A six station dissolution test apparatus was used. One capsule containing 200 mg of fenoverine coated pellets, a speed 100 r/min and a temperature of $37 \pm 0.5^{\circ}$ C were employed in each test; samples were withdrawn through a filter at different time intervals, suitably diluted and assayed for fenoverine at 261 nm using double beam UV-Visible spectrophotometer (Schimadzu[®] UV-1601, Japan). Drug release studies were conducted using sample size six [17].

Stability studies

Optimized formulation was kept in the humidity chamber (Lab Top[®], India) maintained at 40°C and 75 % relative humidity for 3 mon. At the end of studies, the formulation was subjected to drug content, hardness, friability and *in vitro* dissolution studies. For the comparison of release profiles of initial and aged samples, the difference factor (f_1) and similarity factor (f_2) were calculated [18], [19].

RESULTS AND DISCUSSION

Preparation of fenoverine pellets

Hot-melt coating has been adopted because it is faster and cheaper than the conventional coating techniques where evaporation and/or recovery of solvent can be expensive, tedious and time consuming. The modified pan coater is recommended for this purpose because of its ability to operate at the production temperature close to the congealing temperature of the molten mass, which is essential for producing a continuous coating on the particles. In addition, this coating technique enhances stability and provides taste masking and sustained release characteristics to the pellets. In this study, pellets containing fenoverine, a poorly water soluble drug, were prepared by direct pelletization using a by extrusion-spheronization in a rotatory shake pelletizer. Both core and hot-melt coated pellets were successfully prepared.

Evaluation of fenoverine pellets

Physical characterization of pellets

The average size of the uncoated pellets is 840 μ m. Sieve analysis revealed that most coated pellet size was found in a range of 864-912 μ m as shown in [Table 3]. The uncoated pellet as shown in [Fig.1] appeared to possess spherical shape and smooth surface. Fig.1 shows the shape and surface of the coated pellets. It could be seen that the coated pellets were not as spherical as the uncoated ones. It could be due to premature solidification of some molten coating material and non-uniform coating pattern. However, the surface roughness appeared to diminish with the application of coating wax [Fig. 2]. The pellets have good flow property with low friability and sufficient crushing strength [Table 3].



Fig. 1: Scanning electron photomicrographs of uncoated pellets (50X)



Fig. 2: Scanning electron photomicrographs of hot-melt-coated pellets (50X)

Determination of fenoverine contents

Fenoverine contents in uncoated and coated pellets were determined by using UV-Visible spectrophotometer. [Table 3] shows the content in any preparation was in a range of 98.64 % and 100.35%. The results implied that present pelletization could produce the pellets with good reproducibility of drug content. The drug content in the pellets was also found to be within Pharmacopoeial limit.

Dissolution of fenoverine pellets

The release of fenoverine from the uncoated fenoverine pellets was quite rapid. More than 90% of drug release was achieved at 20 min, and the drug release was markedly decreased with the increase in the amount of caurnauba wax

[Figure 3]. With cow ghee: caurnauba wax ratio 6:4, only 68.19% drug release was obtained at 8 hr. The results indicated that could significantly retard the release of poorly water soluble drug. Formulation F4 was selected as optimized formulation as it shows difference factor (f_1) and similarity factor (f_2) values were 6.65 and 66.62 respectively, when compared with theoretical release profile.

Formulation	Mean size (µm)	Angle of repose ^a (°)	Hardness ^a (kg/cm ²)	Friability ^a (%)	Drug Content ^a (%)
F1	864	26.75 ± 0.027	2.40 ± 0.20	0.21 ± 0.00	98.64 ± 0.045
F2	877	23.13 ± 0.015	2.60 ± 0.15	0.17 ± 0.011	99.160 ± 0.062
F3	890	22.34 ± 0.025	2.75 ± 0.25	0.14 ± 0.008	97.14 ± 0.177
F4	897	17.78 ± 0.050	2.85 ± 0.20	0.13 ± 0.003	100.35 ± 0.333
F5	912	16.80 ± 0.036	3.05 ± 0.15	0.11 ± 0.009	98.83 ± 0.270
F0	840	18.75 ± 0.047	1.65 ± 0.25	0.31 ± 0.010	100.01 ± 0.121
Fs	880	17.83 ± 0.034	2.80 ± 0.20	0.12 ± 0.004	100.03 ± 0.113

Table 3: Physico-chemical	characterization of pellets
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Where, ^a indicates values are (mean ± SD) when sample size is in triplicate, F0 indicates uncoated pellets and Fs indicates formulation F4 kept for stability study as per ICH guidelines for 3 mon



Fig. 3: *In-vitro* dissolution of fenoverine from hot-melt coated pellet formulations (Mean \pm SD, n = 6)

The dissolution profiles of all coated pellets prepared under these experimental conditions indicated that the drug release follows majorly Higuchi model. The initial fast release could be due to both dissolution and diffusion from the surface and outer zone of the pellets. As the drug in the outer zone was depleted, the drug particles in the inner area diffused through the coated film at slower rate. In an attempt to describe the kinetics of drug release, several mathematical models were used to express the drug release [20]. Drug release from the sustained release pellets occurred by diffusion, which was reflect from Higuchi model. [Table 4] illustrates the coefficients of determination obtained from various mathematical models. The 'n' value for formulation F1 to F5 were lies between 0.5-1.0, the drug release mechanism can be concluded as non-Fickian diffusion (anomalous transport) mechanism.

Table 4:	Kinetic	analysis	of data	obtained.
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Formulation	Zero order Fir		First order Higuchi Model		Korsmeyer-Peppas Equation		Hixon- Crowell Model	
	\mathbf{R}^2	\mathbf{k}_0	\mathbf{R}^2	\mathbf{k}_1	\mathbf{R}^2	\mathbf{R}^2	ʻn'	\mathbb{R}^2
F1	0.395	8.848	0.617	- 0.5113	0.663	0.669 ^b	0.907	0.475
F2	0.538	7.823	0.807	- 0.3915	0.795 ^b	0.714	0.912	0.756
F3	0.823	10.710	0.915	- 0.6195	0.970 ^b	0.803	0.939	0.958
F4	0.949	11.010	0.868	- 0.4168	0.994 ^b	0.885	0.950	0.969
F5	0.967	7.943	0.976	- 0.1313	0.980 ^b	0.958	0.920	0.981

Where, ^b Best fitted model for the formulation, R^2 - regression coefficient, k_0 - zero order release rate constant, k_1 - first order release rate constant, and n- exponent for Korsmeyer-Peppas equation.

Stability studies

In view of the potential utility of the formulation, stability studies were carried out at 40 °C and 75 % RH for 3 mon (for accelerated testing) to assess their long-term stability. Analysis of the dissolution data [Fig. 4], after storage for 3 mon, showed no significant change in the release pattern indicating that the two dissolution profiles were similar ($f_2 > 50$). The other parameters evaluated were comparable with initial values.



Fig. 4: Dissolution profile of fenoverine pellets after storage at 40 °C and 75 % RH (Mean ± SD, *n* =6)

CONCLUSION

Fenoverine pellets were successfully prepared by direct pelletization process using by extrusion-spheronization. The pellets prepared by this mean were spherical in shape and had relatively smooth surface. A narrow particle size distribution was achieved. The fenoverine pellets were coated with mixture of cow ghee and caurnauba wax using hot-melt coating technique in a modified conventional pan coater and proven to be successful. Hot-melt coating technique presents an easy, economic, rapid and simple choice compared to conventional coating methods where solvent evaporation and recovery could become very expensive and time consuming.

Dissolution study of the coated fenoverine pellets showed that the release rate could be controlled using appropriate coating materials, i.e., cow ghee and caurnauba wax. The dissolution rate can be regulated by varying the composition of the coating material. Drug release from the sustained release pellets occurred by diffusion, which was reflect from Higuchi model. More specifically from 'n' value of Peppas equation, the drug release mechanism can be concluded as non-Fickian diffusion. The results signify that drug release could be adjusted by varying the ratio of cow ghee to caurnauba wax. A further *in vivo* study has to be carried out to assess the bioavailability of the drug form the multi-unit dosage form.

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