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APPLICATION OF COW GHEE AS HOT-MELT COATING AGENT IN THE DESIGN OF SUSTAINED-RELEASE PELLETS

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ABSTRACT: Coating is one of the effective method used for sustaining the release of dosage form. There are various hydrophilic and hydrophobic polymers which are use to sustain the drug release. Waxes are one of the material which can be use to coat the drug in order to control the release, looking at this fact the present study has been considered the use of cow ghee as an important hot-melt coating agent. The diclofenac sodium was used as a model drug. The pellets were coated with cow ghee composition with ethyl cellulose. Pellets with good surface morphology and smooth texture were produced as a result of hot-melt coating with ghee-ethyl cellulose. Stereomicrography confirmed uniformity of coating of pellets. Coating could be performed with ease and in a very short period of time thus establishing the simplicity and rapidity of processing. Percent yield of coated pellets was excellent since virtually no agglomeration was observed during coating. Dissolution studies of hot-melt coated drug pellets demonstrated that at a given level of coating and for a given pellet size, release from pellets was dependent upon the physicochemical property of the drug, more specifically on the aqueous solubility. The diclofenac sodium pellets showed sustained release of drug for 8hrs with cumulative percent release of 99.8 ± 2.5%. By means of hot-melt coating using cow ghee and ethyl cellulose, sustained-release pellets containing diclofenac sodium were successfully prepared.

Key Words: Cow ghee, Diclofenac sodium, Hot-melt coating, Sustained release, Ethyl cellulose

INTRODUCTION AND EXPERIMENTAL

Hot melt coating technique is defined as the application of fine layer of coating material in molten state over the substrate. Hot melt coating technique is widely used to coat granules, pellets and tablets in order to sustained the drug release, mask the bitter taste of drug, improve stability etc. Hot melt wax coatings have various advantages over wax solution coating. Controlled-release drug pellets are prepared by usually giving a film coat on the drug loaded pellets to control the drug release. Traditionally, almost all coating methods require the use of solvents in which the coating material is either dissolved or dispersed. Initially, organic solvents were in vogue, but stringent regulatory constraints, higher cost of solvents, problems of solvent recovery and concern for residual solvent in the final formulation have been responsible for changing the preference to aqueous-based coating systems.[1,2] Even the latter is not without disadvantages – longer and expensive processing, risk of bacteriological contamination of aqueous dispersions and ability of such dispersions to cause hydrolysis of drug are major limiting factors with the use of such aqueous-based systems.[3]

Toxicity of the organic solvent residues and the influence of environmental protection are major problems associated with solvent coating. So attempts are continuously made to reduce the use of organic solvents in the processing of pharmaceuticals. Various particle size enlargement techniques, which offer freedom from solvents include, melt granulation, melt extrusion, melt dispersion, and pastillation.[4-8] Development of new

lipophilic excipients has provided impetus to the research in the area of processing techniques involving molten state.[9]

Hot-melt coating or solvent-free coating methods offer many advantages over current and conventional coating techniques.[1,3] such as they do not require the use of costly organic solvents, Since there is no solvent to be evaporated, processing times are much shorter, it is tedious process of solvent disposal, treatment or recovery associated with organic solvents is eliminated, since no aqueous medium is used, no risk of bacteriological contamination and hydrolysis of drug, the process is environment friendly, The materials used for solvent-free coating techniques are generally waxes that are much cheaper as compared to costly polymers employed in solvent coatings, The great versatility of waxes in terms of their solubility and ability to solubilize other excipients make them useful in a variety of formulations for different purposes.

Though few, whatever research that has been done in 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. No studies ever employed cow ghee as an agent for hot-melt coating although it is an important component of our daily diet and absolutely free from the hypersensitivity skin and other reactions. Moreover, studies that employed the procedure for preparing sustained-release drug pellets were normally carried out in fluid-bed apparatus which limits the technique as it involves sophistication.[3,10]

The present study has, however, demonstrated that cow ghee could be successfully employed as a sustained release hot-melt coating agent in conjunction with materials such as ethyl cellulose. It is worthy of mentioning that for controlling the release of water-soluble drugs, the method is still advantageous in the sense that prior coating of pellets with this composition followed by final application of a sustained-release film coating with ethyl cellulose or a suitable polymer would lead to faster processing and use of lesser polymer in comparison to formulations where release is primarily controlled by the application of polymeric membrane only.

MATERIALS:

Diclofenac sodium, Nonpareil seeds (20-30 mesh), PVP K-30 and ethyl cellulose were procured from Zim Laboratories Ltd., Kalmeshwar MIDC, Nagpur, India, Cow ghee was obtained from Gourakshan centre, Amravati, India. Solvents and all other reagents used were of analytical grade and were procured locally. Double distilled water was used through out the study.

PREPARATION OF PELLETS:

The process of preparing sustained-release hot-melt coated pellets of diclofenac sodium was carried out in two stages, firstly the preparation of drug pellets by powder drug layering onto nonpareil seeds in a conventional coating pan, and then hot-melt coating of drug pellets in a conventional coating pan. Composition of pellet is indicated in Table 1. Batch size of drug loaded pellets was approximately 330gms. Diclofenac sodium and purified talc were mixed together and sifted through 200 mesh. A 5% solution of PVP K-30 was prepared in isopropyl alcohol for use as binder. The process involved spraying the binder solution onto the rolling nonpareil seeds (in a 12" coating pan equipped with 4 radially arranged baffles, air supply, exhaust system and pneumatic spray system) to uniformly wet the pellet bed followed by addition of diclofenac sodium-talc powder blend in an amount sufficient to allow the pellet bed to roll freely while preventing dust generation to minimize drug loss. The alternate application of binder solution and drug powder dusting was continued until the entire powder blend was layered. After the completion of drug layering process, the pellets were sprayed further with sufficient binder solution to affect adhesion of dusted powder and rolled in the equipment for additional 5min before subjecting to tray drying. The dried pellets were sifted to collect 16-20 mesh fractions while the undersize and oversize were rejected.

Secondly the pellets of fraction 16-20 mesh were coated with ghee-ethyl cellulose (3:1) molten blend in a 12" coating pan equipped with 4 radially arranged baffles and system to heat the pan. The process consisted of first melting the cow ghee, raising the temperature of molten ghee to 80^0C and dissolving ethyl cellulose in the molten ghee with stirring at the same temperature. Diclofenac sodium pellets were then rolled in the coating pan which was heated from outside by convection using room heaters until a bed temperature of 60^0C was attained. The molten coating mass was then ladled onto the hot rolling drug pellets in a slow stream. After the completion of application of coating solution, the pellets were allowed to roll further for 10min during which the bed temperature was allowed to gradually come down. The pellets were then removed and cured in a dryer for 48 hours.

The composition of formulations of pellets is shown in Table 1.

Table 1. Composition of controlled-release hot-melt coated diclofenac sodium pellet formulation

Ingredients	Role in formulation	Qty/capsule
1. Inert Substrate for Deposition of Drug		
Nonpareil seeds (20/30 mesh)	Substrate for drug layering	200 mg
2. Drug Layer		
Diclofenac Sodium (200 mesh)	Active ingredient	100 mg
Purified Talc (200 mesh)	Anti-tack agent	20 mg
PVP K-30	Binding agent	10 mg
3. Sustained-Release Hot-Melt Coating		
Cow Ghee	Release-controlling hot-melt coating agent	24 mg
Ethyl Cellulose	Adjuvant release-controlling, ghee soluble polymer	8 mg
	Total	***362 mg***

EVALUATION OF PELLETS:

The coated pellets were evaluated for Angle of repose, Bulk density, Friability, Hausner's ratio and Drug content as per official procedures. Photomicrography Micrographs of uncoated and coated pellets were taken using Intel play digital microscope QX3 attached to a personal computer. The photographs were used to examine the uniformity of coating and surface of pellets after coating.

The values of different evaluation parameters are given in Table 2 and the stereomicrographs of pellets is given in Figure 1.

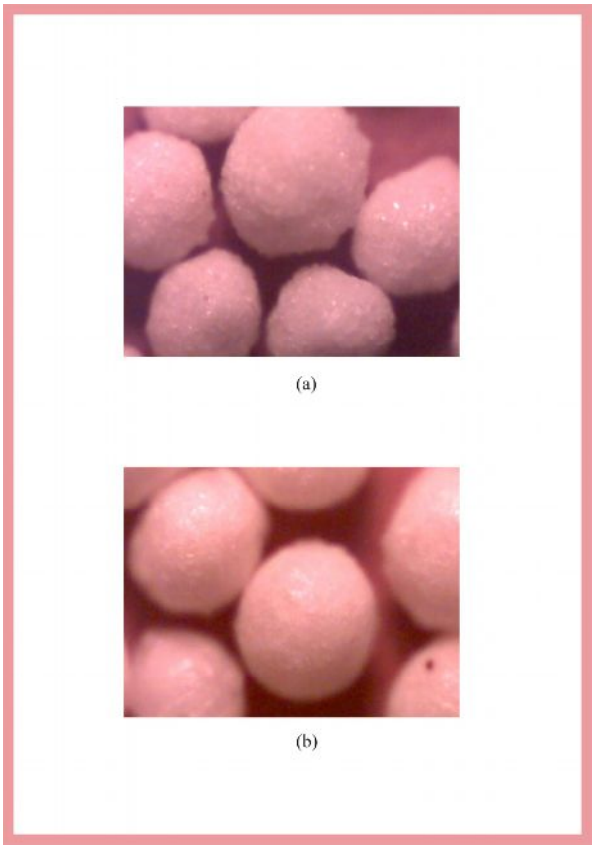

Figure 1. Stereomicrographs of diclofenac sodium pellets - (a) uncoated pellets; (b) hot-melt coated pellets. Magnification: 60X

Table 2. Evaluation parameters for coated Diclofenac sodium pellets

Parameters (Mean ± SD)				
Angle of repose (θ)	**Bulk density (g/cc)**	**Friability (%)**	**Hausner's Ratio**	**Drug Content (%)**
$20.90^0 \pm 0.041$	0.77± 0.0043	0.51± 0.021	1.07± 0.03	97.59±0.18

IN VITRO DRUG RELEASE STUDY:

In vitro release of diclofenac sodium pellets was carried out to evaluate the sustained release characteristics imparted by hot-melt coating with ghee formulations. Dissolution studies were performed using USP 25 apparatus 2 (rotating paddle method), model Electrolab, 6 vessel assembly at 100rpm. The dissolution medium consisted of 900ml simulated gastric fluid (pH 1.2) for first 1hrs followed by simulated intestinal fluid (pH 6.8) from 2 - 8hrs. Temperature was maintained at 37 ± 0.5^0C. Aliquots of 5ml were withdrawn every 1hr interval and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots withdrawn were diluted suitably, filtered and analyzed at 276nm spectrophotometrically[6]. All the release studies were conducted in triplicate and the mean values were plotted versus time with standard deviation less than three indicating reproducibility of result.

The percent cumulative drug release is shown in Table 3 and plot of percentage cumulative drug release against time (Hrs.) is shown in Figure 2.

STABILITY STUDIES OF PELLETS:[12,13]

The pellets were wrapped in aluminium foil, and then placed in umber coloured bottle and was stored at temperature 40^0C ± 2^0C and RH 75% ± 6% for six month. The pellets were evaluated for any changes in physical appearance and percent cumulative drug release after two, four and six month. Result obtained was compared with data obtained for Zero time and room temperature (28^0C ± 2^0C) and relative humidity (42% ± 2%).

The plot of percent cumulative drug release against time (Hrs.) after two, four and six months of stability study is shown in Figure 3

Table 3. Percent cumulative released from the hot-melt coated diclofenac sodium pellets as a function of time.

Time (Hrs)	**Amount of drug released (%) (Mean ± SD)**
1	43.5 ± 3.8
2	69.8 ± 5.6
3	80.0 ± 2.7
4	86.9 ± 6.1
5	91.0 ± 3.9
6	96.0 ± 4.9
7	98.7 ± 1.9
8	99.8 ± 2.5

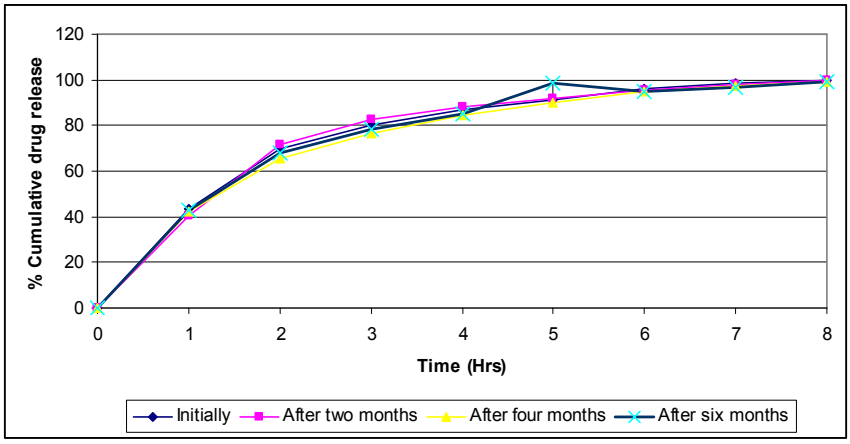

Figure 2. *In vitro* release profile of diclofenac sodium from hot-melt coated pellets as a function of time

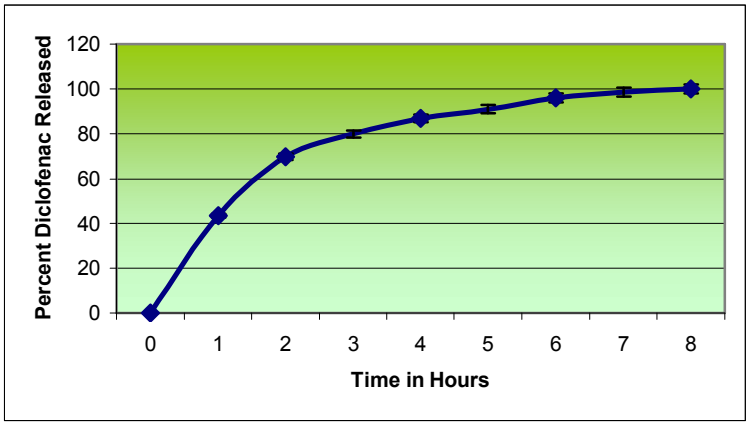

Figure 3. *In vitro* release profile of diclofenac sodiumpellets after stability studies of two, four and six months.

RESULTS AND DISCUSSION

Pellets with good surface morphology and smooth texture were produced as a result of hot-melt coating with ghee formulation. Stereomicrography confirmed uniformity of coating of pellets. Coating could be performed with ease and in a very short period of time thus establishing the simplicity and rapidity of processing. Percent yield of coated pellets was excellent since virtually no agglomeration was observed during coating. Such results were expected since the coating composition was non-tacky and the presence of ghee in fact facilitated free rolling of pellets. The evaluation parameters indicates that the pellets have good flow property with friability of 0.51±0.021 and thus passes the test as per standard pharmacopoeial limit. The drug content in the pellets was found to be 97.59±0.18%.

At a given level of coating and for a given pellet size, the amount of drug released from hot-melt coated pellets is 99.8 ± 2.5 for 8hrs. Drug release from coated pellets was clearly observed to be a function of the physicochemical property of drug. More specifically, the release profile was a reflection of the drug's aqueous solubility. As the diclofenac sodium being more water-soluble its lipid-coated pellets demonstrated more than 80% dissolution in just 4 hours. Since the procedure adopted for hot-melt coating did not facilitate application of more than 10% coating composition, further retardation of diclofenac release could not be achieved. The stability study revealed that there is no significant change in physical characteristics and drug release pattern of pellets. Thus the pellets were stable at accelerated condition.

The results of this study are in unison with studies conducted by different authors but utilizing different lipidic materials *i.e.* for a given wax-coating composition, ability to achieve or prepare sustained release drug pellets utilising a given amount of coating was a factor dependent upon the drugs solubility.[3,10,14] Lower level of coating could sustain release of poorly water soluble drugs such as Theophylline whereas very high amount of deposition of coating could retard release of freely soluble drugs like phenylephrine hydrochloride.

Thus the present composition of ghee could be successfully employed as a sustained-release hot-melt coating agent as any other waxy material such as Compritol [3,10] if the amount of coating deposited on the pellets could be controlled depending on the physicochemical characteristics of the drug. Application of larger quantity of coating material could be made possible by use of more sophisticated equipments and procedures such as fluid-bed coating.[11]

CONCLUSIONS

The present study has demonstrated that cow ghee could be successfully employed as a sustained release hot-melt coating agent in conjunction with materials such as ethyl cellulose. It is worthy of mentioning that for controlling the release of water-soluble drugs, the method is still advantageous in the sense that prior coating of pellets with this composition followed by final application of a sustained-release film coating with ethyl cellulose or a suitable polymer would lead to faster processing and use of lesser polymer in comparison to formulations where release is primarily controlled by the application of polymeric membrane only.

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