

Original Research Article

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Evaluation of the Release Profiles of Ibuprofen Formulated from Carnuba Wax and Homolipid *Capra hircus*

Abstract

Purpose: To investigate the sustained release characteristics of ibuprofen lipospheres made from *Capra hircus* (GF) and carnauba wax (CW) in comparison with conventional granules as standard.

Methods: Ibuprofen (90 g) and the lipid (30 g) were prepared by melt dispersion technique. Conventional granules of ibuprofen were prepared with starch mucilage, 20% w/v. Resulting lipospheres were characterized with respect to sizes, flow property, bulk and tap densities, encapsulated in hard gelatin capsules and evaluated for drug release profiles.

Results: Dissolution profile for lipospheres were a maximum drug release of 97% in 1 hr (conventional granules), 23% in 4 hr (GF), 60% in 2 hr (CW) and 40% in admixtures of fats (GC). Admixing the fats enhanced flow properties of the lipospheres. Inclusion of a surfactant enhanced the release profiles from the lipospheres.

Conclusion: Formulation of ibuprofen into lipospheres modified the release profile, which has implications in the formulation of sustained release multiunit dosage forms.

Keywords: Carnuba wax, *Capra hircus*, Ibuprofen lipospheres, Dissolution profiles.

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Introduction

Various approaches have been adopted over the years to achieve sustained and/or extended release formulations of bioactive substances with short biologic half-life ($t^{1/2}$). Such drugs require frequent administration, which results in certain drawbacks such as lack of compliance to dosage regime and increased chances of unwanted side effects [1-3]. The commonest approach to sustain the release of drugs is spherionization followed by film coating; film coating with water insoluble

polymers such as acrylatemethacrylate copolymers and ethylcellulose. However, film coating with organic solvents are cumbersome, expensive and they are not environmentally friendly [4-7].

In order to minimize the cumbersome problems of frequent dosing and side effects, the need to prolong the plasma half-life ($t^{1/2}$) of the drug by formulation into sustained release preparation becomes very crucial for such drugs. Ibuprofen is a non-steroidal anti-inflammatory drug

(NSAIDs) used extensively in the treatment and management of rheumatoid arthritis and osteoarthritis conditions. Its short biologic half-life is only 1.8 - 2 hours and it is often administered orally at a dose of 200 - 400mg every four to six hours daily and its dosing frequency makes it an ideal drug candidate that requires sustained release formulation. Side effects frequently reported of NSAIDs include gastrointestinal irritation, nausea and dyspepsia, thrombocytopenia [8-9]. Hence the objective of this study was to design sustained release formulation of ibuprofen into lipospheres using carnuba wax (CW) and/or homolipids extracted from *Capra hircus* (goat; GF) for sustained release system. Lipospheres are solid microparticulate dispersion composed of a hydrophobic fat and drug of size range 0.2 – 1000 µm [10]. The influence of inclusion of surfactant on the release profile, the packing and flow properties will also be investigated.

Materials and Methods

Materials

The test drug Ibuprofen was received as a gift from Emzor Pharmaceutical Company Ltd, Lagos Nigeria. Carnuba wax (Halewood Chemicals Ltd, England) a fine waxy solid, pale yellow in colour, with melting point 80-88°C was used as a standard pharmaceutical wax. The homolipid fat from *Capra hircus* (GF) was obtained locally from an abattoir in Benin City, Nigeria. All other reagents were of analytical grade.

Extraction and purification of the homolipid from *Capra hircus* (GF)

The homolipid extraction followed the modified procedure described in an earlier study [11]. The extraneous materials were manually separated from the adipose tissue that was grated and subjected to moist heat by boiling with half its weight of water in a stainless steel vessel immersed in a water bath maintained at 90 °C for 45 mins. The molten fat was separated from the aqueous phase after filtration. The fat obtained was deodorized by treatment with activated

charcoal to obtain a dull-whitish clump fat stable and suitable for drug delivery.

Preparation of the lipospheres

Batches containing the appropriate quantities of the drugs (90 g) and the lipids (30 g) (CW or GF or the admixture of both) in the proportional ratio of 3:1 (i.e. drug: lipid) and/or the surfactant (tween 80) were melted together to form a homogenous mixture. The mixture was precipitated with water over ice chips in a water bath maintained at 4 °C to form the lipospheres [12] while conventional granules were made with 20% w/v starch mucilage. The resulting lipospheres were filtered out, washed with more water and dried at room temperature 28 °C for 48 hours and stored in an airtight desiccator activated with silica gel overnight before their evaluation. Lipospheres were evaluated for their physical and micromeritic properties as follows:

Evaluation of degree of entrapment efficiency

Lipospheres (100 g) were soaked in 100ml of distilled water maintained at 40 °C over night with occasional stirring. The resulting solution was cooled to 0 °C in a refrigerator and analysed spectrophotometrically at 265 nm for ibuprofen content. The percentage efficiency was obtained from the equation:

$$\% \text{ entrapment efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad (1)$$

Determination of tapped and bulk densities

The bulk and tapped densities (BD and TD) were determined by standard procedures and the data substituted into the following equation to obtain the compressibility index (CI) [13]:

$$CI = \frac{(TD - BD) \times 100\%}{TD} \quad (2)$$

Flow properties of the lipospheres

The flow characteristics of lipospheres was evaluated by funnel method which determined the angle of repose obtained when a sample of powder (10 g) was allowed to fall freely from the

Table 1: Physical properties of lipospheres and conventional granules

Parameters evaluated	Conventional granule	Goat fat (GF)	Carnuba wax (CW)	Admixture (GC)	GC +T.80
Angle of repose (θ^0)	15.13	38.13±2.1	27.3±1.3	21.6	23.10
Bulk density (gcm^{-3})	0.32±0.02	0.27	0.476	0.370	0.321
Tapped density (g.cm^{-3})	0.51±0.03	0.318	0.588	0.446	0.407
Compressibility index (CI)	37.25±2.1	15.09	19.05	17.01	21.10
Entrapment efficiency (%)	--	23.0	69.0	85.6	72.0

stem of a funnel to a horizontal surface [14]. The radius (r) and height (H) of the powder bed were determined and the angle of repose (θ) was estimated using the expression:

$$\theta = \arctan \frac{H}{r} \quad (3)$$

Particle size distribution

The size distribution of lipospheres and conventional granules were carried out by sieve analysis mounting a series of test sieves ranging in pore size 212 μm –1.7mm in a sieve shaker (Endicott's Ltd, UK). Fractions retained on each sieve were weighed and the percentage frequency for each size distribution determined.

Encapsulation of the granules and lipospheres

A 200mg sample of the granules or lipospheres was filled manually into empty hard gelatin shells of 250mg capacity. The capsules were stored over night in airtight containers before the dissolution studies.

Dissolution studies

Each capsule (200 mg) of the lipospheres or the granules was placed in a cylindrical basket (aperture size 425 μm , diameter 20 mm, and height 30 mm) and immersed in 1000 ml 0.1N HCl maintained at 37 ± 1 °C and stirred at 100 rpm with a single blade stirrer (GallenKamp stirrer; model APP N0 4B 5784A. Cat N0: SS530). At selected intervals, 5 ml samples were withdrawn with a pipette fitted with a cotton plug, diluted and analysed spectrophotometrically

at λ_{max} 265nm for ibuprofen content (PG Instruments Ltd England, model T70). In the case of the lipospheres, samples were refrigerated over night to allow solidification of the leached fat before assaying for ibuprofen content. All determinations were carried out in triplicate, and the amounts of drug released were expressed as percentage of initial drug content and mean values are reported.

Results

Physical properties of the lipospheres and the granules

Treatment of the extracted goat fat (GF) with activated charcoal brought about a remarkable reduction in the innocuous odour. Results of the physical properties of lipospheres and the conventional granules are shown in Table 1. The percentage entrapment efficiency obtained from GF lipospheres alone was very low (i.e. < 25%). CW wax alone, their admixture (GC) and with surfactant GC+T.₈₀ gave higher percentage entrapment efficiencies (i.e. 69, 86 and 72%, respectively). The conventional granules exhibited satisfactory flow properties as revealed by the low angle of repose (<15⁰), while the lipospheres exhibited very poor flow properties with angle of repose ranging from 31-35⁰. Carr index (CI) values of the liposomes were <23% which were low when compared with the conventional granules with CI value > 40%. Generally, the particle size ranged from 212 – 1700 μm for both conventional granules and the lipospheres. The modal class size generally was 1000 μm . Data of release profiles from conventional granules and lipospheres are shown

in figure 1. The conventional granules gave the highest release with a maximum release of 97% of the total pay load and the time taken to achieve this maximum release (t_{∞}) was 1hr. GF lipospheres exhibited very low percentage entrapment efficiency (< 25%) again the release rates were markedly retarded. Generally, the release from lipospheres made from CW and/or the admixture (GC) were markedly retarded, and the dissolution rates $\%h^{-1}$; (Table 2) ranged as follows: 21.6 (conventional granules), 14.1 (CW lipospheres), 6.3 (GF lipospheres), 5.6 (GC admixture lipospheres) and 14.7 (GC +T.₈₀) respectively.

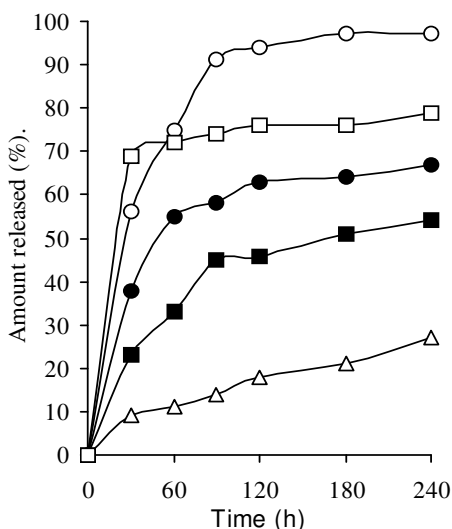


Figure 1: Dissolution profiles of ibuprofen released from the 250mg capsules: (O) Conventional granules, (●) CW only, (Δ) GF only, (■) Admixture GC, and (□) GC +T.₈₀

Table 2: Dissolution rate profiles of conventional granules and lipospheres

Granule type	Dissolution rate ($\%h^{-1}$)
Conventional granules	21.6
Goat alone (GF)	6.3
Carnauba wax alone (CW)	14.1
Admixture (goat & carnauba fats; GC)	5.6
Admixture + surfactant (GC+T. ₈₀)	14.7

Discussion

Low entrapment efficiency from GF have been observed in this study that may be attributed to the stiff consistency of GF. The admixture GC (3:1) yielded the highest entrapment efficiency which may be attributed to the texture and/or consistency modification. It does appear that the poor flow property which was more remarkably low with GF than CW is due to the clustering and sticking behaviour observed in the lipospheres prepared with GF. Preliminary investigations of the texture and structural compositions of the fats as revealed by the viscosity indices showed that GF was of a stiffer consistency than CW and/or their admixtures GC. Their viscosity indices were in the following range: GF (4800s) >>CW (3200s) > GC (2600s) respectively.

Carr index (CI) value (Table 1) showed that the lipospheres were not compressible since earlier preliminary investigations revealed poor flow properties, sticking and clustering.

Particle size distribution

There was a slight difference in the particle size distribution between the conventional granules and the lipospheres which was not statistically significant. Also, the composition of the fat had no significant influence on the size distribution of the lipospheres.

Drug release characteristics

Generally, the lipospheres displayed retarded drug release while the conventional granules displayed a rapid dissolution of the drug from the surface of the granules. The retarded release exhibited by the lipospheres may be attributed to the poor influx of the aqueous leaching fluid into the matrix core of the lipospheres. Fats and waxes being hydrophobic in nature impair rapid influx of the leaching fluid into such matrix-structured core. However, the inclusion of surfactant (Tween 80; T.₈₀) is known to enhance the release of drugs from the lipospheres. The presence of a surfactant in the core of the lipospheres promoted the release of the hydrophobic drug from the core

of the liposphere by enhancing the solubilization of the drug in the aqueous leaching medium.

Conclusion

Formulation of ibuprofen into lipospheres using homolipid fat from *Capra hircus* (goat fat) causes low drug entrapment efficiency and the resulting lipospheres may display poor flow properties compared with the standard pharmaceutical fat, carnauba wax. The admixtures of the fats will produce higher percentage entrapment efficiency and produce flow properties quite similar to those of carnauba wax.

The enhanced release profiles exhibited by the inclusion of surfactant has important implications in the formulation of sustained release where a prompt onset of action may be desired followed by extended maintenance release especially in conditions of excruciating painful conditions such as arthritis.

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Contribution of Authors

We declare that the Authors in this article did this work and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. FEE conceived, designed and prepared the manuscript; JEI collected and analyzed data obtained while MA carried out all laboratory procedures. All Authors gave their consent to preparation and publication of the manuscript.

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