Studies on Diclofenac Sodium Loaded Wax/Lipid Microspheres

V.Hanumath Sastry[1*], P.Amareshwar[2], P.Chakravarthi[2], and Mohib Khan[1]
[1] MESCO College of Pharmacy, Hyderabad
[2] University College of Technology, Osmania University, Hyderabad
*Corresponding Author E-mail: - vhsastry@hotmail.com

Abstract

Diclofenac Sodium (DFS) was microencapsulated with stearic acid, cetyl alcohol, white beeswax, paraffin wax, and carnauba wax by melt dispersion technique. The resulting microspheres exhibited tendency to aggregate and the degree of aggregation depended on their melting points. DFS release from the microspheres depended on the physicochemical properties of the wax/lipid coat material. Carnauba wax has shown the maximum retardant effect on DFS release, while stearic acid shown the least among the coat materials employed. DFS release from stearic acid, cetyl alcohol and white beeswax followed fickian diffusion, while that from paraffin wax and carnauba wax followed non- fickian diffusion at a coat: core ratio of 1:1. At a coat: core ratio of 2:1, DFS release from all microspheres followed non- fickian diffusion.

Key words : Diclofenac Sodium, Microencapsulation, Microspheres, Melt Dispersion

Introduction

Diclofenac sodium (DFS) is one of the most popular and widely used Non-steroidal anti-inflammatory drugs (NSAIDs) globally [1, 2].DFS, like majority of NSAIDs is ulcerogenic [3]. Also, its short biological half-life of 1–2 h necessitates multiple dosing for maintaining therapeutic effect throughout the day [4]. Due to these adverse effects and its short biological half life, DFS is an ideal candidate for prolonged release preparations [3]. Microencapsulation by melt dispersion method has been proposed as a simple and useful technique to produce microspheres for achieving sustained release, without using any harmful organic solvents [5]. Waxy materials have major applications in sustained release systems as they have physical properties and behavior suitable to prepare gastro resistant, biocompatible, biodegradable microspheres to release the entrapped drug in the intestinal lumen [6, 7]. There are few reports regarding the microencapsulation of DFS by wax/lipid materials [8, 9]. In the present work, DFS was microencapsulated with various wax/lipid materials by melt dispersion method with an intention to test their suitability for achieving sustained release and to compare the release profile of DFS from the resulting microspheres. Different coat: core ratios were tried and the resulting microspheres were studied for drug content, microencapsulation efficiency, yield percentage, and in-vitro release characteristics.

Corresponding address;
V.Hanumath Sastry
MESCO College of Pharmacy, Hyderabad

Materials

Diclofenac Sodium (gift sample from Amoli Organics, Ahmadabad), Stearic acid (Loba-Chemie), Paraffin wax (Sarabhai M Chemicals), Cetyl alcohol (Loba-Chemie), White Bees wax (Loba-Chemie), and Carnauba wax (Loba-Chemie), Tween 80 (Loba-Chemie) were used. All other chemicals and reagents used were of analytical grade.

Experimental

Preparation of Microspheres: DFS was microencapsulated with various wax / lipid materials like Stearic acid, Paraffin wax, Cetyl alcohol, White Bees wax, and Carnauba wax by melt dispersion method [10]. DFS (1.0 gm) was dispersed in molten wax/lipid material (1.0 gm). The dispersion was then added slowly

in a thin stream to 100 ml of 0.1N Hydrochloric acid, containing 1% Tween 80, maintained at 80-90°C, while stirring at 100 rpm. Stirring was continued for 5 minutes to emulsify the wax dispersion and to form spherical microspheres. The mixture was then cooled to room temperature with ice, while stirring. The encapsulated product was then collected by vacuum filtration and air dried to obtain discrete microspheres.

With each wax/ lipid material, microspheres were prepared at a coat: core ratio of 1:1 and 2:1.

Characterization of Microspheres

Drug Content: An accurately weighed quantity of drug loaded microspheres was pulverized and digested in 0.1N sodium hydroxide. The drug was extracted with the solvent overnight, filtered and the amount of medicament in the filtrate was assayed after appropriate dilution by measuring the absorbance at 276 nm in a UV-visible spectrophotometer (Shimadzu UV 1700 PC, Shimadzu, Japan). The drug content was estimated in triplicate using a calibration curve constructed in the same solvent.

Measurement of Microencapsulation Efficiency: Microencapsulation efficiency was calculated using the following formula:

Microencapsulation efficiency = (estimated percentage drug content/theoretical percentage drug content) × 100 (1)

Yield: The percentage yield of microspheres was calculated using the following formula:

% yield= weight of microspheres (g)/initial weight of DFS (g) + initial weight of wax/lipid (g) × 100 (2)

Evaluation of Dissolution of Diclofenac Sodium: Release of DFS from microspheres (equivalent to 100 mg of medicament was studied using USP [11] Dissolution Type 2 apparatus. Distilled water was used as dissolution medium. The stirring speed was set at 50 rpm and at 37±0.1°C. A 2 ml sample of dissolution medium was withdrawn at different time intervals, suitably diluted and assayed at 276 nm for DFS. The percent of drug released at various time points was calculated and plotted against time. The dissolution studies were conducted in triplicate.

Fitting of Dissolution Data: The kinetics and mechanism of drug release from microspheres was fitted to the following equations:

$Q = Q_0 + k_0 t$ Zero order kinetics equation (3)

$\text{Ln } Q = \text{Ln } Q_0 - k_1 t$ First order kinetics equation (4)

$Q = k_H t^{1/2}$ Higuchi equation (5)

$M_t/M\infty = k_P t^n$ Peppas Equation (6)

Where, Q represents percentage of drug released at time t. In equations (3) and (4) k_0 and k_1 represent respective release rate constants. In Higuchi equation [12] (equation (5) k_H stands for diffusion rate constant. In Peppas equation [13] (equation (6)), $M_t/M\infty$ represents the fractional release of the drug k_P is a constant incorporating structural and geometric characteristics of the release device, and n is the release exponent indicative of mechanism of release.

Results and Discussion

For microencapsulation with various wax/lipid materials melt dispersion method was employed. Due to its poor aqueous solubility [3], DFS was selected as drug candidate to prepare microspheres employing the melt dispersion technique. Tween 80 was used to stabilize the oil in water emulsion by reducing the interfacial tension between the hydrophobic wax dispersion and the external aqueous phase, producing an emulsified oily dispersion, which resulted in drug loaded microspheres on cooling.

The preparation method used in this study was patented [10]. It involves cooling-induced solidification of the lipid phase of a two-phase system. Modifications of the two phases have led to the production of microspheres of both water-soluble and insoluble drugs [14, 15].

Attempts were made to prepare microspheres with three different proportions of coat and core materials. With all coat materials, microspheres could not be prepared at a coat: core ratio of 1:2. At this ratio the melted dispersion of coat and core was very thick and not flowable. Also, aggregate masses were produced during cooling process. It may be due to reduced melting point of the wax/lipid materials. A good flowable melted dispersion was obtained when the proportion of coat material was atleast 50%. With each wax/ lipid material, microspheres were prepared at a coat: core ratio of 1:1 and 2:1.

The microcapsules prepared were found to be discrete and nearly spherical. As no modifiers were included in the formulations, some exhibited tendency to agglomerate, which could be ranked according to their melting points: Cetyl alcohol (52°C)>Paraffin wax (60°C)>White Bees wax (65°C) > Stearic acid (69°C)>Carnauba wax (86°C), where the values in the parentheses indicate the melting points of the respective coat materials.

To characterize the microspheres, three parameters were calculated: the drug content, the microencapsulation efficiency, and the weight yield. These parameters are helpful to ascertain whether the preparation procedure adopted for incorporating a drug into polymeric particles is efficient. Low s.d values in the mean percent drug content ensured uniformity of drug content in each batch of microspheres (Table-1).

Also, microencapsulation efficiency is satisfactory (Table-1). The high values of encapsulation efficiency indicate that DFS got easily wetted and finely dispersed in the molten wax phase prior to emulsification. The production yield of microspheres prepared from all formulations were high (>90%). The slight loss of solids was due to congealed matrix on the glass wall during solidification.

Release of DFS from various microspheres was studied in phosphate buffer of pH 7.4. DFS release from various microspheres was found to be spread over varying periods of time (Fig.1). With all wax/lipid coat materials, drug release was decreased when the coat proportion was increased.

In general, the higher the melting point of lipid coat material, the slower release rate of the active substance was observed, as reported in the case of Potassium chloride sustained release formulations prepared with different kinds and added amounts of Gelucires [16].However, in the present study, the order of drug release from various lipid microspheres was found to follow the following order:

Stearic acid > Cetyl alcohol > White beeswax> Paraffin wax > Carnauba wax

Significantly different dissolution profiles observed from these microspheres can be attributed to the physical and chemical properties of the different wax/ lipid materials employed in this study.

In the case of stearic acid, the enhancement in drug release can be ascribed to the polar carboxylic acid groups in stearic acid, which made the matrix more susceptible to hydration and thereby created a hydrophilic pathway for water molecules to access the drug [15]. This decreased the resistance to diffusion of the dissolution fluid through the wax matrix and increased the drug dissolution. Further, stearic acid ionizes at pH 7.4, and stearate anion decreases the surface tension of the medium and increases the wettability of the dissolving particles [17].

Cetyl alcohol belongs to polar (class I) lipids. The faster release rate observed with cetyl alcohol could be due to the more hydrophilic nature of cetyl alcohol, which allows more rapid penetration of water into the matrix and/or more matrix erosion [18].

Bees wax has hydroxyl and hydroxyl acid groups, which make it more susceptible to hydration in the dissolution medium [19].

Paraffin waxes are made exclusively of hydrocarbons that have little affinity for the dissolution medium. The drug might be entrapped in a compact dense wax matrix that posed a significant hindrance to fluid penetration and passive drug diffusion [19].

Carnauba wax is extremely hydrophobic in nature with lower wettability [20]. Carnauba wax contains lower percentage of free fatty acids and hydroxyl number but contains higher percentage of fatty esters (ester value of 75–85) [21, 22].In addition, Carnauba wax contains 5% of resins [23]. These factors may account for the observed low dissolution behavior of Carnauba wax. Since the microsphere formulations prepared in the present study contained no wax modifiers, formation of pores and cracks did not occur to facilitate drug release and the impervious hydrophobic matrix of Carnauba wax decreased drug release.

The dissolution data of microspheres was fitted to various mathematical models (zero order, first order, Higuchi's square root and Peppas equations) to evaluate the kinetics and mechanism of drug release MS-Excel 2007 software. Coefficient of correlation (r) values were used to select the best fit for the data. The results are shown in Table 2.

It is clear from Table 2 that at 1:1 coat: core ratio the drug release from microspheres followed first order kinetics and diffusion control process is involved. But at 2:1 coat: core ratio the "r" values suggest that the drug release approached zero order kinetics.

Conclusion

DFS could be microencapsulated by various lipid materials used in the present study. A good flowable melted dispersion was obtained when the proportion of coat material was at least 50%. Agglomeration of microspheres and the drug release from them depended on the melting points and the physico-chemical properties respectively, of the lipid coat material employed. At coat: core ratio of 1:1, DFS release from stearic acid, cetyl alcohol, and white beeswax microspheres followed Fickian diffusion, while that from paraffin wax and carnauba wax followed non-Fickian diffusion. At coat: core ratio of 2:1, DFS release from all microspheres followed non-Fickian diffusion. Further extension of the drug release from microspheres prepared with stearic acid, cetyl alcohol, and white beeswax may require tableting. Whilst, drug release from paraffin wax microspheres is inherently sustained, poor drug release from those prepared with carnauba wax my cause severe bioavailability problems, unless a wax modifier is included in the particular formulation.

Table 1

DFS Content, Microencapsulation Efficiency, % Yield, and T_{50} values of Microspheres

ME indicates Microencapsulation Efficiency
All values are averages of three determinations (n=3)
Values in parentheses indicate s.d values

Table 2

Analysis of DFS Dissolution Data: Coefficient of Correlation (r) values and 'n' values in Peppas Equation

Fig.1 Dissolution Profile of DFS from wax/lipid Microspheres (Coat: Core ratio of 1:1)

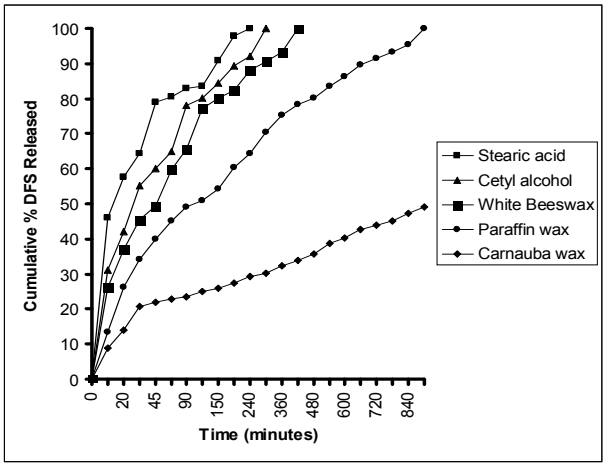
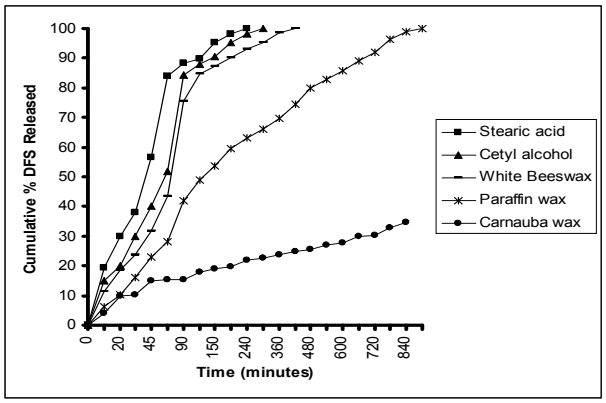


Fig.2 Dissolution Profile of DFS from wax/lipid Microspheres (Coat: Core ratio of 2:1)



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