FORMULATION AND IN VITRO EVALUATION OF DICLOFENAC SODIUM SUSTAINED RELEASE MATRIX TABLETS USING CARNAUBA WAX AS A MATRIX FORMER

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ABSTRACT

Objective: The main objectives of the present study is to develop sustained release matrix tablet of diclofenac sodium (DS) using carnauba wax (CW) as a matrix former, in addition, polyethylene glycol (PEG-6000) and polyvinyl pyrrolidone (PVP k30) were used as channeling agents to modify and control the release of DS from CW based matrix system.

Methods: The matrix tablet was prepared at different drug-polymer ratio namely 5:2, 5:3, 5:4 and 1:1. The physical properties and post compression parameters of all the prepared formulas were determined and studied. The in vitro dissolution studies were carried out for all formulas and compared to that of a reference marketed product using the similarity factor (f2) equation to choose the best formula.

Results: Formula (F9) showed the highest similarity with the reference marketed product and thus selected as the optimized formula. The release rate of DS from CW based matrix system was found to be affected by many factors including the concentration of the rate retarding polymer in the formula, type and concentration of the channeling agent used, type of filler used, pH of the medium, compression force and method of preparation of the sustained release granules. It was observed that the release rate decreased as the amount of the polymer increased in the formula, also the release rate of DS was highest in formulas contain PEG6000, lactose and in formulas prepared by solvent evaporation method. The dissolution data of the optimized formula were fitted to various release kinetic models in order to determine the principal mechanism responsible for release of DS from CW based matrix system.

Conclusion: Based on the results obtained from this study, it can be concluded that carnauba wax-polyethylene glycol (CW-PEG) system can be used successfully as a matrix former to sustain the release of DS to more than 8hrs. depending on amount of polymer used, PEG/CW ratio, pH of the system and method of preparation.

Keywords: Matrix tablet, Sustained release, Diclofenac Sodium, Carina wax.

INTRODUCTION

Hydrophilic polymers alone are not so efficient in controlling the release of water soluble drugs. Hydrophobic polymers with or without pore forming agents have been extensively investigated for sustaining the release of drugs. They provide several advantages over hydrophilic polymers in that they show good stability profile over a wide pH-range with good drug retarding capacity and high ability to accommodate high drug load [1].

The matrix system is commonly used for manufacturing sustained-release dosage forms because it makes such manufacturing easy. Insoluble-erodible polymers and waxes are commonly utilized as matrix forming components and are extensively used for sustaining the release of drugs [2].

In spite of the recent technological advances in the fabrication of oral controlled-release dosage forms, particular attention has been paid to the regulation of drug release by means of monolithic devices [3].

Embedding a drug within an insoluble matrix provides a convenient mean of controlling the drug release. In such a system, drug release is preceded by penetration of the dissolution medium into the porous matrix to dissolve the drug, followed by diffusion of the dissolved molecules out of the matrix. Solid drug on the matrix surface will be dissolved and released first to provide an immediate shot of the drug. Upon exhaustion of the surface drug, the depletion zone will then increased progressively and sustained drug release is achieved. In such a system, the release rate is a function of the square root of time and liquid penetration to the matrix is the rate limiting step in drug release unless channeling agent is used [4]. Carina wax, due to its ease of handling, safety of application, high drug embedding ability, compatibility and chemical inertness has been chosen and used in this study as rate retarding polymer or matrix former.

DS (sodium 2-[2, 6-dichlorophenyl] amino) phenyl acetate is a sparingly water soluble drug, it is aryl acetic acid derivative having a non-selective COX inhibitor activity. It is a non steroidal anti-inflammatory, antipyretic analgesic official in the Martindale Extra Pharmacopoeia for long term treatment of rheumatoid arthritis, osteoarthritis and other painful and inflammatory conditions. It has a plasma half life of about 1.5 hrs which necessate frequent dosing. The most troublesome side effects are gastrointestinal and are dose related. The dose of DS in adult individuals is 100-300mg/day. The sustained release dosage form is thus required to improve the bioavailability of drug, reduce the severity of side effects and improve the patient compliance by giving the drug on once or twice daily basis [5].

MATERIALS AND METHODS

Materials

DS (Loba laboratories, India), Carina wax (BDH, England). Lactose (The Lactose Co. of New Zealand, New Zealand), PEG6000, PVP K30 (FMC Biopolymer, USA). Dibasic calcium phosphate dihydrate (Harward Pharmaceuticals Limited, Bangalore India). All other reagents used were of analytical grade.

Methods

Preparation of the monolithic system by melt granulation or fusion method

Fusion method is done by melting the rate retarding polymer gradually in beaker on a hot plate (90°C) with continuous mixing, then adding drug material that is pre pulverized and passed through mesh No. 60, dihents and any other additive to the molten mass with continuous stirring until a homogenous mixture is produced, the molten mass is then allowed to cool and solidify at room temperature, crushed and screened (mesh No. 20) to produce granules of wanted size, which stored properly for further studies[6].
Preparation of the monolithic system by solvent evaporation method

Solvent evaporation method is generally done by dissolving the rate retarding polymer in a little amount of chloroform that is pre warmed with mixing until a thin suspension is produced, thereafter DS is dispersed in the mixture by ultrasonication for 15 min. Then transfer exactly 5 ml of the amount equal to one tablet dissolved in 50 ml flask using phosphate buffer (pH 6.8), sonicated for 15 min. Then transfer exactly 5 ml of the above solution to a 100 ml flask and dilute with the buffer to the mark, discard the first few milliliters of filtrate, then the exact amount of t alc is replaced with buffer, thereafter take exactly 300 mg of the above mixture and feed manually to a 9 mm die of flat face single punch tablet press and compress to a tablet using a compression force of 6 tones for 10 seconds, thereafter DS SR matrix tablet is ejected from the die, collected and stored properly for further studies [7].

| Table 1: Different Formulas of Diclofenac Sodium SR matrix tablet |
|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Formula number    | Diclofenac sodium | Car sodium wax | PVP K30 | PEG6000 | Talc | HPC | Lactose | C.F. (ton) | Method | Total Weight |
| F1                | 75 (5:2)         | 5              | 190     | 6      | F    | 300 |
| F2                | 75 (5:3)         | 5              | 175     | 6      | F    | 300 |
| F3                | 75 (5:4)         | 5              | 160     | 6      | F    | 300 |
| F4                | 75 (5:1)         | 5              | 145     | 6      | F    | 300 |
| F5                | 75 (5:1)         | 5              | 130     | 6      | F    | 300 |
| F6                | 75 (5:2)         | 5              | 115     | 6      | F    | 300 |
| F7                | 75 (5:1)         | 5              | 100     | 6      | F    | 300 |
| F8                | 75 (5:1)         | 5              | 130     | 6      | F    | 300 |
| F9                | 75 (5:1)         | 5              | 115     | 6      | F    | 300 |
| F10               | 75 (5:3)         | 5              | 100     | 6      | F    | 300 |
| F11               | 75 (5:1)         | 5              | 145     | 6      | F    | 300 |
| F12               | 75 (5:2)         | 5              | 145     | 7      | F    | 300 |
| F13               | 75 (5:1)         | 5              | 145     | 7      | F    | 300 |
| F14               | 75 (5:2)         | 5              | 115     | 6      | S    | 300 |

[All amounts given in mg and percentage given as w/w]

| Table 2: post compression parameters of DS SR tablets |
|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Formula No.       | % Friability    | Hardness kg.    | % Drug content  |
| F1                | 0.28            | 7.8             | 100.07          |
| F2                | 0.26            | 8.7             | 97.54           |
| F3                | 0.23            | 9.9             | 95.46           |
| F4                | 0.22            | 10.9            | 99.84           |
| F5                | 0.11            | 11.8            | 98.65           |
| F6                | 0.09            | 12.6            | 98.43           |
| F7                | 0.06            | 13.1            | 98.37           |
| F8                | 0.45            | 6.9             | 99.94           |
| F9                | 0.58            | 6.1             | 99.98           |
| F10               | 1.18            | 4.7             | 99.79           |
| F11               | 0.26            | 10.4            | 98.76           |
| F12               | 0.31            | 7.2             | 99.16           |
| F13               | 0.86            | 10.1            | 99.34           |
| F14               | 0.56            | 10.6            | 98.73           |

Assessment of post compression parameters

Hardness Test

The tablet hardness was measured in triplicate using a Monsanto® hardness tester and the force required to break tablets was recorded in kilogram [8].

Friability Test

The friability test was done for the prepared tablet using Roche friabitort for 4 minutes at 25 rpm. 20 tablets were weighed then placed in the friabitort. After their revolution, they are dusted and re-weighed and the friability calculated as percent weight loss according to equation (1) bellow [8].

\[
%F = \frac{\text{initial weight - final weight}}{\text{initial weight}} \times 100 \quad \cdots \cdots (1)
\]

Content Uniformity test

Five tablets were pulverized, passed through mesh 60, then an amount equal to one tablet dissolved in 50 ml flask using phosphate buffer (pH 6.8), sonicated for 15 min. Then transfer exactly 5 ml of the
Variables affecting release profile of DS SR matrix tablet

Effect of polymer concentration

Formulas F1-F4 contain 10%, 15%, 20% and 25% w/w of the total tablet weight were prepared and used for this purpose.

Effect of pH of dissolution medium

All formulas were studied by using 0.1N HCL (pH 1.2) for the first 2hrs and phosphate buffer (pH 6.8) for the rest of the experiment.

Effect of channeling agent type

Formulas F7 and F10, contain two different types of channeling agents namely PVP K30 and PEG 1500 in concentration of 15% (w/w) of the total tablet weight were used for this purpose.

Effect of channeling agent concentration

Formulas (F5-F10) were used for this purpose. F5, F6 and F7 contain (PVP K30) at a concentration of 5%, 10% and 15% w/w of the total tablet weight respectively and F8, F9 and F10 contain (PEG 1500) in the same concentration mentioned above were used.

Effect of changing the diluents type

Formulas F4 and F11 which contain the same amount of DCP and lactose respectively were used for this purpose.

Effect of changing the compression force

Formulas F4, F12 and F13 prepared at a compression force of 6, 5 and 7 tons, respectively were used for this purpose.

Effect of changing the method of preparation

Formulas F9 and F14 prepared by melt-granulation and solvent evaporation methods, respectively, were used for this purpose.

Comparative dissolution study and selection of best formula

The best formula was chosen according to comparative dissolution study with a reference marketed product of DS SR tablet (Divon SR), employing the similarity factor equation (F2) introduced by Moore and Flanner [10], as shown in equation (2) below.

\[
F_2 = 1 - \frac{1}{n} \sum_{i=1}^{n} \left| R_t - T_t \right|^2 \times 100
\]

\[
R_t = 50 \times \log \left( \frac{1 + \frac{1}{n} \sum_{i=1}^{n} \left| R_t - T_t \right|^2}{2} \right)
\]

Where n is the number of dissolution time points, Rt and Tt are the reference and test dissolution values at time t, respectively.

Analysis of release kinetics for the optimized formula

The cumulative amount of DS released from the selected formula at different time intervals were fitted to zero order, first order, Higuchi and Korsmeyer–Peppas models to characterize the release kinetics and propose a mechanism of drug release [11].

Results and Discussion

Assessment of post compression parameters for the prepared tablets

Table (2) shows the results obtained for friability, hardness and % drug content of DS SR tablets. All the prepared formulas (except than F10) showed acceptable weight loss (less than 1%), this result may be attributed to the presence of retarding polymers in considerable amount (10-25% w/w) of the total tablet weight which improve the compressibility and hence physical parameters of the tablets [12].

Content uniformity test

All the prepared formulas of DS SR matrix tablet showed a % drug content between 95.46% to 100.07%. These results complied with USP specification for tablet monographs which is 90% to 110% of drug content [9].

Variables affecting Diclofenac Sodium release from SR tablet

Effect of concentration of rate retarding polymer

The effect of polymer content on DS release as a function of time was found to be significantly different (P<0.05) among different concentrations of CW as shown in figure (1) below. It can be observed that (regardless to the type of the rate retarding polymer used) the drug release is inversely proportional to the level of rate retarding polymer present in the matrix system [5].

Effect of pH of the dissolution medium

The pH of the dissolution medium was found to affect significantly (P<0.05) on the release rate of DS from the matrix system. In fact, all formulas show a characteristic biphasic release profile characterized by a very slow initial release phase at pH 1.2 (0.1N HCl) followed by a rapid, sharp and bursting release phase at pH 6.8 (phosphate buffer). This finding can be attributed to the very low aqueous solubility of DS at acidic pH (due to very poor wettability) which becomes more soluble at pH 6.8 [13].

Effect of type of channeling agent

The investigation was undertaken to observe the effect of using different types of channeling agents (PVP K30 and PEG1500) on DS release from wax based matrix tablets in formulas F4 contains no channeling agent, F7 contains 15% w/w PVP and F10 contains 15% w/w PEG1500. From figure (2) below, the rate and extent of DS released were found to be significantly different (P<0.05) among these three formulas and were found to be governed by the type and content of the channeling agents. It was observed that without the presence of channeling agent, drug release from the formula (F4) was very slow, this effect was due to the fact that carnauba wax is extremely hydrophobic in nature with low wettability; leading to a decrease in the effective interfacial area between the drug and the dissolution medium; which results in a reduction of the matrix wettability [14,15], whereas in formulas F7 and F10 the presence of channeling agents remarkably improve drug release due to improved matrix wettability.

![Fig. 1: effect of concentration of CW on DS release](image1)

![Fig. 2: effect of channeling agent type on DS release](image2)
10% and 5% w/w of the total layer weight and showed 90% DR in about 11.5 and 12hrs, respectively. On the other hand, F10 containing PEG6000 in concentration of 15% w/w of the total layer weight had been disintegrated in less than 5hrs. and showed 90% DR in about 5.5hrs. compared to F9 and F8 containing PEG6000 in concentration of 10% and 5% w/w of the total layer weight and showed 90%DR in about 9.5 and 11.5hrs, respectively. These results suggest that the matrix with higher channeling agent concentration provides less tortuous and/or more porous pathway, leading to formation of hard tablet. The channeling agents act by creating void spaces in the hydrophobic matrix of CW [17], causes the formation of channels/pores for entry of the dissolution medium [18].

In this study, F11 containing lactose as diluent was designed and the release rate and extent from this formula were compared with those obtained from the corresponding F4 that contain DCP as a diluent, as shown in figure (5) below. It was found that the drug release was increased from 79.1% in F4 containing dibasic calcium phosphate dihydrate to 94.4% in F11 containing lactose at the end of 12hrs. This finding can be explained simply by the fact that lactose is soluble except for and dissolve rapidly when come in contact with the dissolution medium leaving behind pores and micro cavities which lead to decreasing the total matrix tortuosity and/or porosity, i.e. acting as channeling agent. Also, by its osmogenic impact, lactose will dissolve and produce a local increase in the osmotic pressure within the matrix system causing solvent drag leading to more drug to be dissolved and released [20].

Effect of changing the compression force

Different compression force have been found to pose a great impact on the release characteristics and found significantly (P<0.05) affect on release rate of DS from CW based matrix system as shown in figure (6) below.

CW is a water insoluble, non swellable, non digestible and slowly erodible matrix former; therefore, the compression force is a very important factor that controls the rate of drug release from such a polymer. It was observed that at a constant die fill, an increase in the compression force to a certain limit results in a proportional increase in tablet hardness and decrease in tablet thickness, usually associated by a decrease in drug release rate [21].

This finding can be explained as following; at low compression force there might be insufficient tablet strength and a great level of porosity which allow for larger amount of solvent to get access to the matrix system, leading to increasing the drug diffusivity out of the system. Once a sufficient compression force is applied, optimal tablet hardness is reached and continuous matrix is formed, beyond this point further increase in the compression force is not necessarily accompanied by a significant change in the release rate of DS but instead may accompanied by some tablet problems like chipping and lamination [22,23].

**Effect of changing the diluents type**

The effect of different fillers have been extensively studied and in many situations found to be of little effect on release rate for drugs that are embedded with hydrophilic polymers like HPMC. However, switching of an insoluble filler by a more soluble one (as in case of DCP and lactose) have found to possess a large impact and play an important role in drug release from waxy based matrices as in case of carnauba wax [17,19].

**Effect of Changing Method of Preparing the Sustained Release Granules**

It was observed that the method of preparation of the sustained release DS granules (F9 and F14) was significantly (P<0.05) affect the release rate and extent of the drug from CW based matrix system as shown in figure (7) below. Heat treatment of the tablets made by melt granulation in F9 further retarded drug release because heat treatment above the melting point of the carnauba wax redistributed the wax, producing thermal binder forming a new matrix system with higher tortuosity [24].

Heat treatment of the wax seemed to cause one or more of the following effects [24]:

- Formation of a thermal binder.
• Formation of welded bonds.
• Formation of recrystallizing bonds.

While for formula F34 which was prepared by solvent evaporation method, it seems that chloroform making carnauba wax more wettable and easily dispersible in the dissolution medium, causing formula F14 to disintegrate in few hours releasing more than 98% of DS incorporated [25].

Fig. 7: Effect of different methods of preparation on DS release

Comparative Dissolution Study and Selection of the Best Formula

Figure (8) below shows the similarity in the dissolution profile of the selected formula (F9) and the reference marketed product of DS.

Fig. 8: Similarity between F9 and marketed product

Formulas F3, F4, F5, F6, F7, F8, F9, F11, F12 and F13 all showed a dissolution profile extended for 8hrs. or more and appeared to be promising for SR DS matrix tablet. All these formulas were subjected to the similarity factor (f2) test and compared with marketed product for this purpose. Among all of these formulas, F9 appeared to have the highest similarity (67.41) with the reference marketed product and thus was selected as the best formula for SR DS matrix tablet.

Mathematical Analysis of Release Kinetics

The release kinetics of DS from the selected formula (F9) was determined by finding the best fitting of the dissolution data to the mathematical models of drug release. Correlation of dissolution data to these models revealed a good fitting of F9 to Higuchi model with \( R^2 = 0.976 \) [26,27]. The release mechanism was further confirmed by Peppas model which revealed a super case II transport indicating that two or more mechanisms were involved in the process of drug release, including diffusion [28].

REFERENCES


