



Evaluation of carnauba wax in sustained release Diclofenac sodium tablet formulation

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ABSTRACT

This study was conducted to formulate matrix tablets of diclofenac sodium by melt granulation and to evaluate the effect variation of the concentration of carnauba wax had on the release profile of diclofenac sodium from matrix tablets. Melt granulation of the matrix granules is achieved by mixing a drug powder/or granule with a melt of a wax material (Carnauba wax), with the objective of coating the granules and further retarding drug release from the granules. Four batches of diclofenac sodium granules, DS1, DS2, DS3 and DS4 were prepared by melt granulation using 49.3 %, 43.1 %, 37.0 % and 30.8 % of carnauba wax respectively and then compressed into tablets. The compressed tablets and a control, DSC (Voltaren Retard[®]) were subjected to quality control tests such as friability, weight uniformity test, crushing strength and dissolution test. Friability(%) value was 1.60, 2.00, 2.30 and 2.60 for DS1, DS2 DS3 and DS4 respectively. The mean tablet weight (mg) was 403.8, 404.3, 403.1 and 404.2 for DS1, DS2 DS3 and DS4 respectively. The hardness value(Kgf) was 7.0, 7.9, 7.8 and 7.0 for DS1, DS2 DS3 and DS4 respectively. From the dissolution test, the % drug release after 2 hours was 1.18±0.00, 1.35±0.00, 1.82±0.01, 4.23±0.00 and 4.79±2.63 for DS1, DS2 DS3, DS4 and DSC respectively. The % drug release after 12 hours was 52.03±0.00, 55.09 ±0.08, 70.78±0.93, 73.00±0.15 and 62.28±2.08 for DS1, DS2 DS3, DS4 and DSC respectively. The higher the concentration of carnauba wax, the slower the drug release from the matrix tablet.

Keywords: Melt Granulation, Carnauba Wax, Dissolution Test, Matrix Tablets, Diclofenac Sodium.

INTRODUCTION

Diclofenac is used for long – term symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis [1] . The usual dose of diclofenac sodium in osteoarthritis is 50mg, 2 to 3 times daily and in rheumatoid arthritis, the dose is 50mg 3 to 4 times daily. Compliance is usually a problem. Controlled – release diclofenac sodium 100mg tablet is given once daily. This improves compliance and ultimately therapeutic success.

A sustained – release tablet is a drug product formulation that provides the required dosage initially and then maintains or repeats it at desired intervals. Sustained – release tablets are designed to release the drug slowly after ingestion. The main factor in the more widespread use of these types of dosage forms is that patient compliance is improved, since only one or two tablets need to be taken daily [2].

Reza, reported that in the last two decades, sustained – release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Preparation of drug – embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for manufacturing sustained – release dosage forms because it makes such manufacturing easy. A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. Polymers forming insoluble or skeleton matrices constitute the first category of retarding materials, also classed as plastic matrix systems. The second class represents hydrophobic and water – insoluble materials, which are potentially erodible, while the third group includes polymers that form hydrophilic matrices [3].

Formulation of Sustained – Release Tablets

Sustained – release tablets consist of two parts: an immediately available dose and a sustaining part, containing many times the therapeutic dose for protracted blood drug levels. The immediately available dose is normally directly added to the sustaining part of the tablet or alternatively is incorporated in the tablet coating with the sustaining portion in the core of the tablet [2].

Uncoated sustained – release tablets are prepared by embedding the drug in the tablet matrix. The matrix system can be of three types, namely, plastic matrix system, hydrophobic matrix system and hydrophilic matrix system.

Plastic matrix systems have been widely used for sustaining the release of drug due to their chemical inertness and drug embedding ability. Liquid penetration into the matrix is the rate – limiting step in such systems unless channeling agents are used.

The hydrophobic matrix systems are potentially erodible and control the release of drug through pore diffusion and erosion [4].

The hydrophilic matrix system, when exposed to an aqueous medium does not disintegrate but immediately after hydration develops a highly viscous gelatinous surface barrier which controls the drug release from, and liquid penetration into the centre of the matrix system [5].

Carnauba Wax

Carnauba wax, also called Brazil wax and palm wax is a wax of the leaves of the palm, *Copernicia prunifera*, a plant native to and grown in the northeastern Brazilian states of Piaui, Ceara, Rio Grande do Norte [6]. It is known as “ queen of waxes ” [7] and usually comes in the form of hard yellow – brown flakes. It is obtained from the leaves of the carnauba or fan palm by collecting them, beating them to loosen the wax, then refining and bleaching the wax. Carnauba wax contains mainly esters of fatty acids (80 – 85%), fatty alcohols (10 – 16%), acids (3 -6%) and hydrocarbons (1 – 3%). Specific for carnauba wax is the content of esterified fatty diols (about 20%), hydroxylated fatty acids (about 6%) and cinnamic acid (about 10%). Cinnamic acid, an antioxidant, may be hydroxylated or methoxylated.

It has a melting point of 82 – 86°C (180 – 187°F) which is among the highest of natural waxes.

Its relative density is about 0.97. It is among the hardest of natural waxes, being harder than concrete in its pure form. It is practically insoluble in water. It is soluble on heating in ethylacetate and xylene but practically insoluble in ethyl alcohol. It is used in the pharmaceutical industry as a tablet coating agent.

Mechanism of drug release from wax matrices

The mechanism of drug release from wax matrices has been a matter of controversy since waxy – systems tend to be crude and more heterogeneous than other classes of polymeric systems [8]. In some cases, it has been reported that the mechanism of release from waxy matrices involves the leaching of drug by the eluting medium. Fluid enters through the cracks and pores of the matrix with diffusion of drug through the matrix being insignificant [9,10]. Others reported that release from a typical wax matrix is diffusion – controlled and is best described by Higuchi’s Square root model [11].

Melt Granulation

Melt granulation could be an easy and fast method to formulate sustained release tablets [12]. Melt granulation is a well known process whereby fine powders are agglomerated by means of a molten binder and processed into spherical or nearly spherical granules of homogeneous size. With hydrophobic binders and appropriate fillers, sustained – release systems can be obtained by this process [13].

Melt granulation of the matrix granules is achieved by mixing a drug powder/or granule with a melt of a wax material (Carnauba wax or glyceryl monostearate), with the objective of coating the granules and further retarding drug release from the granules. Thus, matrix granulation and wax coating of the matrix granules are approaches for retarding drug release and hence prolonging the biologic action of drugs with short biologic half life [14].

Melt granulation is one of the most widely applied processing techniques in the array of pharmaceutical manufacturing operations. Melt granulation process is currently applied in the pharmaceutical industry for the manufacture of variety of dosage forms including immediate release and sustained – release pellets, granules and tablets [15].

Melt granulation is used to improve the dissolution rate and bioavailability of the drug by forming a solid dispersion or solid solution. It is used to control or modify the release of drugs.

It is used to mask the bitter taste of active drugs.

Melt granulation has the advantage that neither solvent nor water is used in the process. Also few processing steps are needed as drying steps are eliminated. There are no requirements on the compressibility of active ingredients and the entire procedure is simple, continuous and efficient. Uniform dispersion of fine particles occurs. There is usually good stability at varying pH and moisture levels. Due to their non – swellable and water insoluble nature, they are safe to apply in humans.

EXPERIMENTAL SECTION

Materials

Diclofenac Sodium (Alpha Lab, Germany), Carnauba wax, refined NO 1, yellow (Sigma – Aldrich U.K), Hydrochloric acid 37% (Haig Laboratory Chemical Corporation Wembley, MIDDX, England), Potassium dihydrogen orthophosphate (BDH Chemicals Ltd Poole England). Potassium hydroxide (BDH Chemicals Ltd Poole England), Microcrystalline cellulose (N.B Entrepreneur Nagpur India), Magnesium stearate (Mira Organics and Chemicals Private Ltd Chennai India) and Cab – O – Sil (Hangzhou Ruijiang Chemical Co. Ltd Zhejiang, China).

Preparation of Diclofenac Sodium Granules

Four batches of diclofenac sodium were prepared by melt granulation using the formula in table 1 below. A 20g quantity of Diclofenac sodium was blended thoroughly with the calculated quantity of microcrystalline cellulose in a polyethylene bag. Then the appropriate quantity of Carnauba wax was placed in a beaker and heated to about 88°C using a water – bath. The mixture of Diclofenac sodium and diluent was added to the melted carnauba wax and blended together. This was allowed to cool. The cooled molten mass was passed through a sieve of 100 µm aperture size. This was formulation DS 1 granules. Diclofenac sodium granules for formulations DS 2, DS 3 and DS 4 were prepared in a similar way using the quantities of excipients shown in table 1.

Table 1: Formula for Preparing Diclofenac Sodium Granules

	DS 1 (%)	DS 2 (%)	DS 3 (%)	DS 4 (%)
Diclofenac sodium	24.6	24.6	24.6	24.6
Carnauba wax	49.3	43.1	37.0	30.8
Microcrystalline cellulose	24.6	30.8	36.9	43.1
Magnesium stearate	0.5	0.5	0.5	0.5
Cab –O– Sil	1.0	1.0	1.0	1.0
Total	100.0	100.0	100.0	100.0

Compression of Diclofenac Sodium Granules

A 0.4 g quantity of magnesium stearate and 0.8 g of silicon dioxide were mixed thoroughly with the respective quantities of diclofenac sodium granules in a V – shape laboratory blender (Gemco, New Jersey, USA) for 5 minutes. A 406mg sample of the blend was used to calibrate the die volume and then compressed into tablet using a Cadmach SSF3 single punch tableting machine (Ahmedabad, India) with 12.5 mm punch at a predetermined compression pressure. The granules of batches DS1, DS2, DS3 and DS4 were compressed into tablets using the aforementioned tablet press at a predetermined compression pressure [16].

Evaluation of diclofenac sodium tablets

The compressed tablets were subjected to various quality control tests.

Friability Test: DBK Friability Test Apparatus (DBK Mumbai instruments, India) was used. Ten tablets from batch DS1 were weighed and placed at the right hand side (RHS) of the apparatus while another 10 tablets were weighed and placed at the left hand side (LHS). The apparatus was set to make 100 revolutions in 4 minutes after which the tablets were re – weighed. This was repeated for all the batches.

Uniformity of Weight Test: About 20 tablets from formulations DS1 were weighed and the mean weight determined. This was repeated for formulation DS2, DS3 and DS4. The deviations from mean weight by the individual tablets were calculated.

Crushing Strength: The crushing strengths of the tablets were determined with a tablet hardness tester (Shital Scientific, India) using ten tablets from each batch respectively, immediately after compression.

Dissolution Test Studies: An in – vitro dissolution test was carried out in a six station USP type 1 apparatus, DBK Dissolution Test apparatus (DBK, India) for 12 hours at $37 \pm 1.0^{\circ}\text{C}$ and at 50 rpm. One tablet from each batch was placed in the basket of the respective station of the dissolution test apparatus. Simulated gastric acid medium (0.1N HCl) was used as the dissolution medium for the first 2 hours of the test while for the remaining 10 hours, phosphate buffer was used at pH 6.8 under sink condition. Ten milliliters (10 ml) samples were withdrawn from the dissolution medium and replaced with 10 ml of fresh medium to maintain constant volume every 1 hour. After filtration, the sample solution was analyzed at 270 nm for diclofenac sodium using a DBK UV spectrophotometer (DBK, India). Samples were collected every hour for 12 hours for each of formulations DS1, DS2, DS3, DS4 and DSC. This was repeated in triplicate. The above process was repeated in triplicate for batches DS2', DS4, DS5, DS6 and DSC. Batch DSC was a commercial brand of diclofenac sodium, VOLTAREN RETARD[®] (Norvatis pharma Stein AG, Stein, Switzerland) which served as the control.

Kinetics studies: The dissolution kinetics of Diclofenac sodium from batches DS1, DS2, DS3, DS4 and DSC tablets in phosphate buffer solution of pH 6.8 were determined by the application of the Zero Order [17, 18, 19], First Order [17, 18, 19], Higuchi [19, 20, 21] and Hixson – Crowell's Cuberoot Law [22]. The mechanism of drug release was obtained by fitting the first 60% drug release data into the Korsmeyer – Peppas model [23, 24] as shown below:

Zero Order Model

$$C = K \dots\dots\dots (1)$$

C = %Release, K_0 = Zero Order rate constant expressed in units of concentration/time (t).

First Order Model

$$\text{Log}C_r = \text{Log}C_0 - K_1 t / 2.303 \dots\dots\dots (2)$$

C_r = %Remaining, C_0 = Initial concentration of drug, K_1 = First Order constant, t = Time

Higuchi's Square root Law Model

$$Q = K_H t^{1/2} \dots\dots\dots (3)$$

Q = %Released, K_H = Constant reflecting design variables of the system, t = Time

Hixson – Crowell’s Cuberoot Law Model

$$[(100 - f)/100]^{1/3} = 1 - K_{HC}t \dots \dots \dots (4)$$

f = %Released, K_{HC} = Rate constant, t = Time

Korsmeyer – Peppas Model

$$Mt/M_\infty = Kt^n \dots \dots \dots (5)$$

$$\text{Log } Mt/M = \text{log } K + n \text{ log } t \dots \dots \dots (6)$$

Where, Mt / M_∞ is the fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms for cylindrical shaped matrices as given in table 2 below.

Table 2: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

RESULTS AND DISCUSSION

Table 3: Some physical properties of batches of diclofenac sodium tablets

PROPERTY	BATCHES			
	DS1	DS2	DS3	DS4
Mean tablet weight (mg)	403.8	404.3	403.1	404.2
Hardness (Kgf)	7.0	7.9	7.8	7.0
Friability (%)	1.60	2.00	2.30	2.60
Diameter (mm)	13	13	13	13
Thickness (mm)	3	3	3	3

Friability refers to the tablets ability to withstand abrasion or even breakage during further processing, transportation or storage. Friability values for all the batches were above the official limit of not more than 1%. The friability values increased (1.60 to 2.60) as the concentration of the carnauba wax in the formulation decreased (49.3 % to 30.8%). This showed that there was an inverse relationship between the concentration of carnauba wax in the formulation and the friability.

Tablet hardness is a measure of its resistance to capping, aberration or even breakage under conditions of storage, transportation or handling before usage. Hardness generally increases with normal storage of tablets. It depends on the shape, chemical properties, binding agent and pressure applied during compression. The force required to break tablet is measured in kilograms and a crushing strength of 4 kgf is usually considered to be the minimum for satisfactory tablets. Oral tablets normally have a hardness of 4-10kgf. All the batches had value that were more than 4 kgf, which was necessary for sustained release tablets.

Uniformity of dosage unit is defined as the degree of uniformity in the amount of the drug substance among dosage units. Uniformity of dosage units can be demonstrated by either of two methods; Content Uniformity (by assay test) or Weight Variation.

Tablet weight is mainly affected by factors such as tooling of the compression machine, head pressure, machine speed and flow properties of the powder. Inconsistent powder or granulate density and particle size distribution are common sources of weight variation during compression. Variation between tablet with respect to dose and weight must be reduced to a minimum. Uniformity of weight is an in process test parameter which ensures consistency of dosage units during compression.

None of the tablets from all the batches had a deviation from the mean tablet weight of up to 5%. They were all within the acceptable limit of not more than 5% for tablets weighing 250 mg and above.

Active absorption of oral dosage forms depends on adequate release of the API from the product. Dissolution or solubility of the API play pivotal role in this aspect. Dissolution testing is used as a tool to identify a crucial effect in the bioavailability of the API. Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects. The drug release characteristics of the batches were as shown in figure 1 and table 4. For the four batches, DS1, DS2, DS3, DS4 and the control, DSC, the % drug release at 2 hours was below 5%, confirming the poor solubility of diclofenac sodium at low pH (pH = 1.2). At 12 hours, batches DS1 and DS2 exhibited lower drug release from the matrix tablets than the control, batch DSC while batches DS3 and DS4 showed higher drug release.

Table 4: The % drug release at 2, 8 and 12 hours

TIME (HOUR)	DS1 (%)	DS2 (%)	DS3 (%)	DS4 (%)	DSC (%)
2	1.18 ± 0.00	1.35 ± 0.00	1.82 ± 0.01	4.23 ± 0.00	4.79 ± 2.63
8	36.98 ± 0.08	41.21 ± 0.01	61.18 ± 0.07	60.82 ± 0.08	49.34 ± 0.11
12	52.03 ± 0.00	55.09 ± 0.08	70.78 ± 0.93	73.00 ± 0.15	62.28 ± 2.08

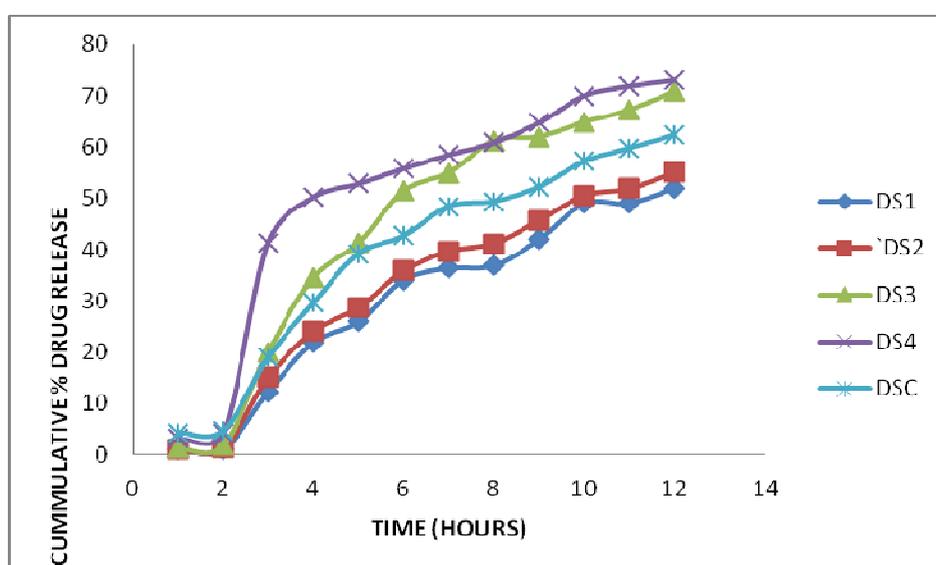


Fig. 1: The Sequential release of Diclofenac Sodium from batches DS1 (100 mg diclofenac sodium, 200 mg carnauba wax), DS2 (100 mg diclofenac sodium, 175 mg carnauba wax), DS3 (100 mg diclofenac sodium, 150 mg carnauba wax), DS4 (100 mg diclofenac sodium, 125 mg carnauba wax) and DSC (Voltaren retard 100 mg) Tablets, in 0.1 N HCl (for 2 h) and phosphate buffer pH 6.8 (10h)

Kinetics of Drug Release

When the in – vitro drug release data were fitted into different release kinetics models, First order kinetics was prevalent in all the batches.

Mechanisms of Drug Release

This was determined by fitting the first 60% drug release data into Korsmeyer – Peppas model.

For all the batches DS 1, DS2, DS3, DS4, and DSC, the application of the Korsmeyer – Peppas equation gave an n – value 1.704, 1.673, 1.733, 1.283 and 1.183 respectively as shown in table 5 below. This showed that their mechanism of release was by super case – II transport. It showed that the drug release was not just by diffusion alone but also by erosion of the matrix structure.

Table 5: Summary of Pharmacokinetic Parameters for the Release of Diclofenac Sodium from Batches DS1, DS2, DS3, DS4, and DSC of Diclofenac Sodium Tablets

Kinetic Model	DS1	DS2	DS3	DS4	DSC
Zero Order Law					
K_0	4.688	5.015	6.748	7.352	5.876
R^2	0.959	0.956	0.921	0.799	0.933
First Order Law					
K_1	-0.029	-0.031	-0.049	-0.049	-0.037
R^2	0.978	0.982	0.971	0.932	0.977
Higuchi's Square Root Law					
K_H	13.27	14.24	19.27	21.4	16.84
R^2	0.793	0.807	0.806	0.818	0.844
Hixson – Crowell's Cube Root Law					
K_{HC}	-0.020	-0.021	-0.031	-0.029	-0.024
R^2	0.970	0.971	0.950	0.877	0.958
Korsmeyer – Peppas					
K	1.109	1.279	1.549	4.395	4.159
n	1.704	1.673	1.733	1.283	1.183
R^2	0.877	0.870	0.864	0.800	0.907

CONCLUSION

The study showed that diclofenac sodium granules prepared by melt granulation can be directly compressed into matrix tablets with sustained – released effects. The higher the concentration of the carnauba wax content of the matrix tablet, the slower the rate of release of diclofenac sodium from it. Batches DS1 and DS2 that contained 49.3 % and 43.1 % of carnauba wax showed higher drug release retardant effect than the control, batch DSC, while batches DS3 and DS4 that contained 37.0 % and 30.8 % of carnauba wax showed lower drug release retardant effect.

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