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Effect of wax on the release pattern of drugs from the sustained release fatty matrix tablet

Swati Jagdale*, Swapnil Ghorpade, Dhaval Bhavsar, Bhanudas Kuchekar and Aniruddha Chabukswar

MAEER's, Maharashtra Institute of Pharmacy, Kothrud, Pune, Maharashtra, India

Abstract

The sustained release fatty matrix tablet of Diclofenac sodium and Theophyllinee were prepared using melt granulation technique. The tablets were prepared using carnauba wax (CW) and stearic acid (SA) / emulsifying wax (EW) in the varying ratios. The evaluation of granules was done for angle of repose, Hausner`s ratio, Carr`s compressibility index, and sieve analysis. Tablets were evaluated for hardness, friability, content uniformity, weight variation and dissolution test. The dissolution study show the controlled release of the drug from tablets depending on concentration of wax. The invitro dissolution study show that for the formulation of Diclofenac prepared by using highest concentration of carnauba wax show maximum sustained activity whereas for tablets of Theophylline, the formulation containing highest concentration of stearic acid show maximum sustained release activity.

Keywords: Melt granulation, sustained release, matrix tablet, carnauba wax, stearic acid, emulsifying wax.

Introduction

Diclofenac sodium (sodium 2-[2, 6-dichlorophenyl) amino**]** phenyl) acetate is a sparingly water soluble drug. Diclofenac sodium is aryl acetic acid derivative having a nonselective COX inhibitor activity. It is a non steroidal anti-inflammatory and antipyretic-analgesic agent used in the treatment of rheumatoid arthritis and osteoarthritis. It has the plasma half life about 2 hrs with good tissue penetrability. The dose of Diclofenac sodium in healthy individual is 100-

300mg/day. The sustained release dosage form is required to improve the bioavailability of drug and the patient compliance.

Theophylline (1, 3- dimethyl-3, 7- dihydro-1 H-purine- 2, 6- dione), is a slightly water soluble drug. Theophylline is the methyl xanthine derivative used as a bronchodilator in the treatment of bronchial asthma and chronic obstructive pulmonary disease (COPD). The elimination half life of Theophylline in adults is 7-12 hours. Theophylline has the narrow margin of safety, as the concentration of drug in the blood increases above 25-30µg/ml it may cause severe side effects. The dose of Theophylline is 100-300 mg. Hence, to avoid the side effects the sustained release dosage form is required which release the drug in controlled manner and maintain the concentration of the drug in therapeutic range. [1-3]

Sustained release dosage form has various advantages over conventional dosage form in aspects of clinical efficacy and patient compliance. The matrix system is commonly used for manufacturing sustained release tablet dosage form. Melt granulation has various advantages over the conventional wet granulation method as the liquid addition and subsequent drying steps are omitted. Melt granulation technique involves the formation of fatty wax matrix in which drug is embedded resulting in controlled release of the drug from the fatty matrix. The carnauba wax, emulsifying wax and stearic acid in various concentration mixtures are used to form the dissolution rate controlled release tablets. The fatty wax excipients have a melting range between 50^0 -80^0 C. Hence attempts have been made to develop extended release matrix tablets of Diclofenac sodium and Theophylline separately, using wax such as carnauba wax, emulsifying wax and stearic acid. [4, 5]

Materials and Methods

Materials

Diclofenac sodium and Theophylline was obtained from JCPL, Jalgaon as a gift sample. Carnauba wax (CW), stearic acid (SA) and emulsifying wax (EW) were of the pharmaceutical grades.

Methods

a) Preparation of Diclofenac Na and Theophylline tablets:-

Preparation of matrices by melt granulation method:-

The tablets containing varying concentrations of the wax are prepared according to the formula given in Table 1 and 2.

For preparation of granules by melt granulation method, the appropriate quantities of drug and excipients were weighed on the analytical balance. The carnauba wax and stearic acid/ emulsifying wax were mixed in the petri plate and melted at 80-85^0c. Then the drug and other excipients were added to the molten mixture of wax and allowed to cool. The granules of uniform size were prepared from the solid mass and were passed through sieve no.18. The granules were compressed in the 8 station rotary press tablet compression machine. [5]

Table 1 Formulation of Diclofenac sodium tablets

Sr.No.	Formulation	Drug	Carnauba wax	Stearic acid	Emulsifying wax	Silicon dioxide	Magnesium stearate
1.	DS-1	110	110	110	-	20	40
2.	DS-2	110	100	120	-	20	40
3.	DS-3	110	120	100	-	20	40
4.	DE-1	110	110	-	110	20	40
5.	DE-2	110	100	-	120	20	40
6.	DE-3	110	120	-	100	20	40

(All the quantities are in mg.)

Table 2 Formulation of Theophylline tablets

Sr.No.	Formulation	Drug	Carnauba wax	Stearic acid	Emulsifying wax	Silicon dioxide	Magnesium stearate
1.	TS-1	175	87.5	175	-	20	40
2.	TS-2	175	175	87.5	-	20	40
3.	TS-3	175	131.5	131.5	-	20	40
4.	TE-1	175	87.5	-	175	20	40
5.	TE-2	175	175	-	87.5	20	40
6.	TE-3	175	131.5	-	131.5	20	40

(All the quantities are in mg.)

b) Characterization of granules

The granules were evaluated for various parameters such as angle of repose, hausner`s ratio, Carr`s compressibility index, and sieve analysis.

Angle of repose:-

The angle of repose is a relatively simple technique for estimation of the flow property of a powder. Powders with low angle of repose are free flowing and those with a high angle of repose are poorly flowing powders [6, 7]

10 gm of granules were passed through funnel and the pile was formed. The height and weight of the pile was measured and the angle of repose was calculated by using the formula:-

Angle of repose (θ) = $\tan^{-1}$ height /radius.

Carr`s compressibility index:-

The Carr's compressibility index was calculated by calculating the tapped and bulk density using the 100 ml measuring cylinder. Compressibility is calculated by the formula.

$$\text{Carr`s compressibility index} = \frac{\text{bulk density - tapped density}}{\text{Bulk density}} \times 100$$

A carr`s index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

Particle Size distribution:-
The particle size distribution of granules was evaluated by sieve analysis using standard sieves in the range of sieve no. 10-36. The fraction was collected and weighed.

c) Characterization of tablets
The characterization of tablets is done for various parameters such as thickness, hardness, friability, content uniformity, weight variation and dissolution test.

Thickness:-
Thickness of tablets was determined using vernier caliper. Five tablets of each batch were used and average values were calculated.

Hardness:-
For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester.

Friability:-
For each formulation, the friability of 20 tablets was determined using the Roche friabilator. In this test tablets were subject to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighted 20 tablets was placed in Roche friabilator which was then operated for 100 revolution i.e. 4 mins. The tablets were then dusted and reweighed. Percent friability (%F) was calculated as follows,

$$\% F = (\text{loss in weight} / \text{initial weight}) \times 100.$$ [6-9]

Drug content and percentage yield:-
To calculate the drug content and percentage yield, the tablets were triturated in the morter. Ten milligrams of the tablet powder was added to 10 mL of distilled water and drug solution was filtered through Whatman paper no.1. The sample was analyzed for drug content by UV spectrophotometry (Varian Cary 100) at 276.28 nm for Diclofenac and 271.60nm for Theophylline after suitable dilutions. Drug stability in the dissolution medium and distilled water was checked for a period of 8 hours. Percentage yield of each formulation was calculated. [5]

In Vitro Dissolution Studies
The release rate of drug from the tablets was determined using *United States pharmacopeia (USP)* 24 Dissolution Testing Apparatus type-2 (paddle method). Initially the dissolution test was performed in 0.1N HCl for 2 hours. Then the dissolution medium was replaced with 900 mL of phosphate buffer pH 7.4 and the dissolution test was carried out at 37 ± 0.5°C at 60 rpm. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus hourly for 8 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 micron membrane filter and diluted to a suitable concentration with respective dissolution

method. Absorbance of these solutions was measured at 276.28 nm for Diclofenac and 271.60nm for Theophylline using a varian cary100 double beam UV spectroscopy. Cumulative percentage drug release was calculated using an equation obtained from a standard curve and using PCP Disso v3 software. [4-6]

Table 3 Evaluation of granules

Sr. No.	Formulation	Angle of repose	Hausner`s ratio	Carr`s compressibility index
1.	DS-1	21.11^{o}	1.174	14.447
2.	DS-2	18.886^{o}	1.186	14.943
3.	DS-3	17.96^{o}	1.137	11.568
4.	DE-1	19.86^{o}	1.153	13.294
5.	DE-2	20.863^{o}	1.200	16.686
6.	DE-3	18.756^{o}	1.112	10.084
7.	TS-1	21.11^{o}	1.098	9.0077
8.	TS-2	18.886^{o}	1.07	6.6859
9.	TS-3	17.96^{o}	1.111	9.9352
10.	TE-1	19.86^{o}	1.124	11.6860
11.	TE-2	20.86^{o}	1.085	8.9874
12.	TE-3	18.75^{o}	1.112	10.084

Table 4 Evaluation of tablets

Sr. No.	Formulation	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)
1.	DS-1	52	3.7	0.5	98.96
2.	DS-2	53	4.0	0.5	101.43
3.	DS-3	53	3.9	0.6	97.92
4.	DE-1	52	4.1	0.5	96.78
5.	DE-2	51	4.5	0.6	102.17
6.	DE-3	52	3.9	0.7	101.70
7.	TS-1	64	3.5	0.7	99.30
8.	TS-2	63	3.8	0.7	98.56
9.	TS-3	64	3.6	0.5	96.25
10.	TE-1	62	4.0	0.4	100.06
11.	TE-2	66	4.2	0.8	98.27
12.	TE-3	64	4.2	0.6	96.78

Results and Discussion

The granules thus prepared using various wax concentrations were evaluated and the results thus obtained are given in table 3.

From the evaluation of granules it was observed that the angle of repose was found between 17-21^{o}. This indicates that the granules have the good flow property. Also, the carr`s compressibility index of all the granules was found below 15. This is also the indicator of the good flowability.

The hardness of the tablets was found between 3.5 and 4.5. This indicates the sufficient hardness imparted by the wax to the tablets. The percent drug content was also observed within the desired range between 96-102 %. From the observed evaluation parameters, DS-2 and TE-1 shows the most satisfactory results for hardness, friability and content uniformity.
In vitro drug release profile:-

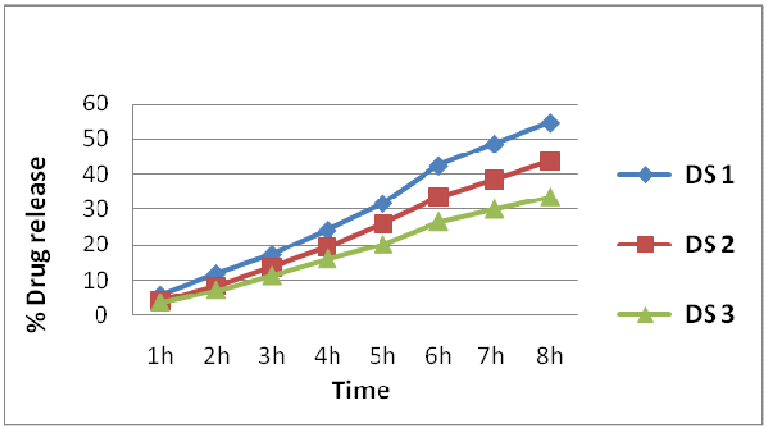

Fig 1 Dissolution Profile of Diclofenac sodium tablets containing CW and SA

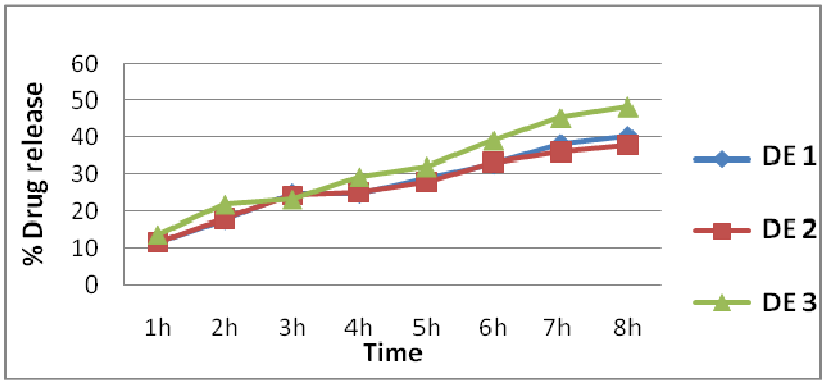

Fig 2 Dissolution Profile of Diclofenac sodium tablets containing CW and EW

For the formulation containing Diclofenac sodium, the % drug release in the tablets containing SA was observed in the order: DS-3> DS-2> DS-1.This indicates that the formulation containing

more concentration of CW shows least quantity of drug released and the formulation containing equal amount of CW and SA show maximum drug release after 8 hrs.

Whereas, for the formulation containing EW, the % drug release was observed in the order: DE-2> DE-1>DE-3. Maximum drug release was observed in the formulation containing minimum concentration of EW and formulation containing highest concentration of EW shows minimum drug release. This indicates that EW retards the drug release from the formulation.

For the formulation containing Theophylline, the % drug release in the tablets containing CW and SA was observed in the order: TS-1> TS-3> TS-2. This indicates that the SA retards the drug release from formulation as it shows minimum drug release after 8 hrs. Also for the tablets containing CW and EW, the % drug release pattern was observed in the order: TE-3 > TE-1> TE-2. Hence, it was observed that the formulation containing least quantity of EW shows more drug release within 8 hrs.

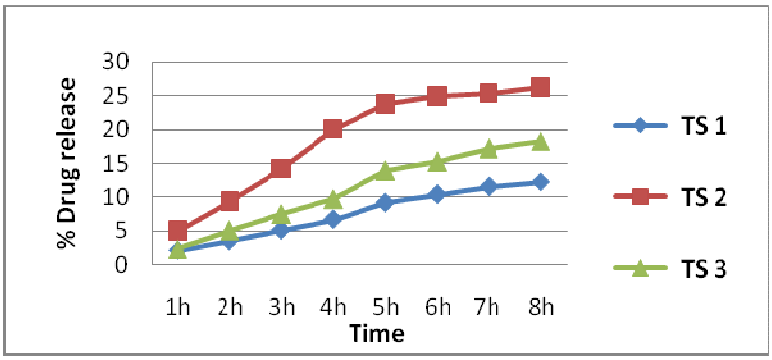

Fig 3 Dissolution Profile Theophyllinee tablets containing CW and SA

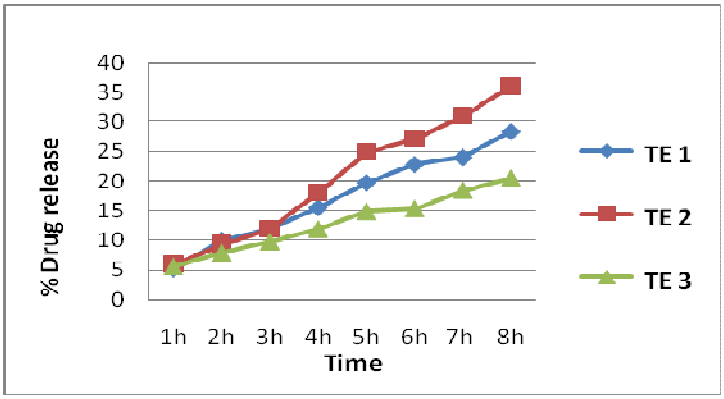

Fig 4 Dissolution Profile of Theophylline tablets containing CW and EW

Release Experiments:-

In order to gain insight into the drug release mechanism from the tablets, release data of selected tablets were examined according to the zero-order, first-order and Higuchi's square root of time mathematical models, Hixson and Crowell powder dissolution method, Korsmeyer and Peppas

model and the release exponent n was calculated using PCP Disso v3 software. Table 5 shows the data for kinetics of tablets.

Table 5 Kinetic release data

Sr. No.	Formulation no.	R^2 Value for formulation					Best Fitting model
		Zero order	First order	Matrix	Korsmeyer - peppas	Hixson-crowell	
1.	DS-1	0.9966	0.9766	0.9545	0.9900	0.9868	Zero order
2.	DS-2	0.9988	0.9925	0.9596	0.9968	0.9959	Zero order
3.	DS-3	0.9973	0.9946	0.9633	0.9955	0.9963	Zero order
4.	DE-1	0.9690	0.9542	0.9547	0.9470	0.9624	Zero order
5.	DE-2	0.9514	0.9723	0.9902	0.9783	0.9669	Matrix
6.	DE-3	0.9674	0.9865	0.9906	0.9707	0.9823	Matrix
7.	TS-1	0.9933	0.9948	0.9660	0.9962	0.9944	Peppas
8.	TS-2	0.9616	0.9720	0.9727	0.9833	0.9691	Peppas
9.	TS-3	0.9968	0.9961	0.9607	0.9973	0.9959	Peppas
10.	TE-1	0.9940	0.9950	0.9746	0.9962	0.9963	Hix-Crowell
11.	TE-2	0.9966	0.983	0.9530	0.9937	0.9909	Zero order
12.	TE-3	0.9863	0.9947	0.9843	0.9969	0.9937	Peppas

From the release experiments, it was observed that in diclofenac tablets, zero order was the best fitting model for DS-1, DS-2, DS-3 and DE-4 whereas matrix was observed as the best fitting model for DE-2 and DE-3. It was further observed that the best release pattern was observed for DS-2.

In the formulation of Theophylline, korsmeyer and peppas was observed as the best fittimg model for TS-1, TS-2, TS-3 and TE-3. Hixson and crowell was observed as the best fitting model for for TE-1, Zero order release was observed as the best fitting model for TE-2. TE-1 shows the best drug release pattern from formulation.

Conclusion

From the present study it can be concluded that the waxy material can be successfully used for the formulation of sustained release dosage form. The waxy material such as carnauba wax and emulsifying wax are efficient matrix forming agents and can control the release of drug from the formulation. From the tablets of diclofenac sodium, DS-2 was observed as the best formulation in regards of evaluation parameters and release pattern. Whereas, TE-1 was observed as the best formulation in the tablets of Theophylline. The release retarding agents are cheap, readily available, safe and easy to handle. The melt granulation method is best suited for wax forming material as the melting point of such material is low. The formulation containing stearic acid shows more sustained release action as compared to the formulation containing Emulsifying wax.

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