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Formulation of Nabumetone Controlled Release Tablets Using Hpmc K 4m

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ABSTRACT

Nabumetone [1] is a non-steroidal anti-inflammatory drug used in pain management. The drug release was extended for prolonged duration of period to maintain the drug concentration within therapeutic range, by formulating the controlled release tablets using HPMC K 4M as a release retardant at various concentrations like 25, 31.25 and 37.5 mg per 600 mg Nabumetone tablets, containing 500mg strength. Finally it was observed from in-vitro dissolution data, the release was extended up to 24 h (F1 & F2 formulations).

Keywords: Nabumetone, controlled release, HPMC K 4M.

INTRODUCTION

The major advantage of controlled drug delivery systems is to maintain the drug concentration at the therapeutic concentrations to avoid the peak and valley kind of plasma drug concentration fluctuations and tailoring the drug release such that to maintain at therapeutic concentration for prolonged duration of period which is not possible with conventional dosage forms. Matrix controlled release systems are very potent to prolong the drug release and to extend over a prolonged duration of period. In pharmaceutical field cellulose derivatives are highly employed to form matrix systems, especially hydroxyl propyl methyl cellulose (HPMC) is widely used, which is available in huge number of viscosity grades. In present research HPMC K4M was tried to test the controlled release of medicament over the extended duration.

MATERIALS AND METHODS

Nabumetone, excipients & all chemicals were gifted by SK Health Care Formulations Pvt Ltd., Bolaram, Hyderabad.

Construction of calibration curve: 10 mg of Nabumetone was placed in 10 mL volumetric flask, dissolved and diluted to 10 mL using methanol to get 1000 µg mL^{-1} (dilution 1). From dilution 1, 1 mL

was withdrawn and diluted to 10 ml in a 10 mL volumetric flask using methanol to get 100 µg mL^{-1} concentrations (stock solution). From the stock solution, 1, 1.5, 2, 3, 3.5, 4 mL of solutions were withdrawn individually in series of 10 mL volumetric flasks and diluted to 10 mL using pH 7.4 phosphate buffer to get 10, 15, 20, 30, 35, 40 and 50 µg mL^{-1} concentrations. The solutions were analysed using UV-Spectrophotometer (UV1700–Shimadzu) at 332 nm and using the resultant absorbances the calibration curve was constructed.

Method of preparation of Nabumetone Controlled Release Tablets [2]: Nabumetone and all other ingredients listed in table 1 except magnesium stearate, Talc was passed sieve no 60 to get uniform size particles and weighed accurately. Finally, magnesium stearate, Talc (passed through a 60-mesh/250 micron screen) was introduced to the powder mixture. The final mixture was shaken manually for 5-10 min in a plastic bag. This powder was passed through the hopper of 16 station rotary tabletting machine (Cadmach) and punched into tablets using 8mm s/c. the process is similar for all core formulations, which are prepared by direct compression technique.

Table 1: Formulation Table for Nabumetone CR tablets

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)
Nabumetone	500	500	500
HPMC K4M	25	31.25	37.5
Micro crystalline cellulose	63	56.75	50.5
Magnesium stearate	6	6	6
Talc	6	6	6
Total weight	600	600	600

Evaluation of tablets [3,4] (**Pre-compressional parameters)**

Angle of Repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose of granules was determined by the funnel method. Accurately weighed tablet powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} (h/r)$$

Where: θ = angle of repose, h = height in cm, r = radius in cm

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

Bulk density (BD): It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in g m L^{-1} by the following formula.

Bulk density = weight of powder / Bulk volume.

$$D_b = \frac{M}{V_0}$$

Where, M = mass of the powder, V_0 = bulk volume of the powder

Tapped density (TD): It is the ratio of total mass of powder to the tapped volume of powder Weigh accurately 25 g of granules, which was previously passed through 22# sieved and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula.

Tapped density = Weigh of powder / Tapped volume

$$Dt = (M) / (V_f)$$

Where, M = mass of the powder V_f = tapped volume of the powder.

Carr's Index: Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below:

$$\textbf{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio: Hausner's Ratio is a number that is correlated to the flow ability of a powder

$$\textbf{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Post compression studies

Average weight/Weight Variation: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

Average weight = weight of 20 tablets / 20

%weight variation = {(Average weight – Weight of tablet) / Average weight} ×100

Thickness: Thickness of the tablets (n=3) was determined using a Vernier calipers

Hardness test: Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Friability test: This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min. The difference in the weight is noted and expressed as percentage. It should be preferably between 0.5 to 1.0%.

$$\%\text{Friability} = [(W_1 - W_2)/W_1] \times 100$$

Where, W_1= weight of tablets before test, W_2 = weight of tablets after test

Assay Procedure: Weighed and finely powdered not less than 20 tablets. Transfer an accurately weighed portion of the powder equivalent to about 10mg of model drug into a 10 mL volumetric flask. Add approximately 6mL of pH 7.4 phosphate buffer, shaken and sonicated for 10 min to complete the extraction and volume filled with methanol. 1mL aliquot was pipetted into a 10ml volumetric flask, diluted with methanol to volume, mixed and filtered. From this 1mL aliquot was withdrawn and made up to mark with buffer. Calculate the quantity in mg of model drug in the portion taken by the formula

Assay = {(Test absorbance/Standard absorbance) X (standard concentration/sample concentration) X (purity of drug /100)} X 100.

***In-vitro* Dissolution studies:** *In- vitro* drug release from matrix tablet was studied using USP II apparatus, with 900 mL of dissolution medium phosphate buffer pH 7.4 and rotated at 50 RPM. 5 mL aliquots were withdrawn at one particular interval from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 2 cm apart from bottom of the vessel. Suitable replacement with fresh medium was also made. .The UV absorbance was measured at 332 nm by using (UV1700–Shimadzu) spectrometer after appropriate dilution by dissolution medium. Nabumetone concentrations in the samples were determined from the standard curve of the pure drug. The *In- vitro* dissolution study was performed up to 24 h.

In vitro Release Kinetics Studies: The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from matrix system was described by using zero order kinetics or first order kinetics. The mechanism of drug release from MATRIX SYSTEM was studied by using Higuchi equation and the Peppas-Korsemeyer equation.

Zero Order Release Kinetics: It defines a linear relationship between the fractions of drug released versus time.

$$\mathbf{Q=k_0t.}$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.
A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics: Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$\mathbf{Log\ C= Log\ C_o\text{-}kt/2.303}$$

Where C is the amount of drug dissolved at time t, C_o is the amount of drug dissolved at t=0 and k is the first order rate constant.
A graph of log cumulative of log % drug remaining vs time yields a straight line will be linear if the release obeys the first order release kinetics.

Higuchi equation: It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$$Q=K_2t^{1/2}$$

Where K_2 is release rate constant.
A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

Peppas-Korsemeyer equation (Power Law): In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppas-Korsemeyer equation (Power Law).

$$Mt/\mathbf{M}_\infty = K.t^n$$

Where, Mt is the amount of drug released at time t, M_α is the amount released at time α, M_t/M_α is the fraction of drug released at time t, K is the kinetic constant and n is the diffusion exponent.

To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted. A plot between log drug releases up to 60% against log of time will be linear if the release obeys Peppas-Korsemeyer equation and the slope of this plot represents "n" value. The kinetic data of the formulations were included.
Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using MS EXCEL.

Table 2: Drug release kinetics mechanism

Diffusion exponent(n)	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

Calibration curve for Nabumetone in pH 7.4 phosphate buffer: The results are presented in table 3 and graph is shown in fig.1

Table 3: Results for the graph of Nabumetone in pH 7.4 phosphate buffer

Concentration (µg mL^{-1})	Absorbance (nm)
10	0.183±0.002
15	0.266±0.006
20	0.324±0.002
30	0.528±0.005
35	0.601±0.003
40	0.687±0.008
50	0.853±0.01

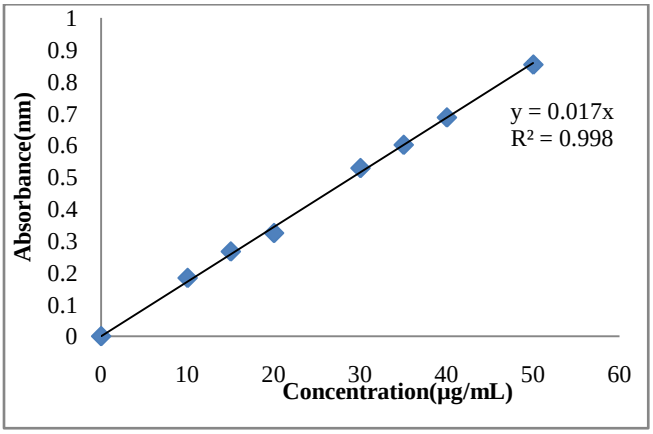

Figure 1: Standard graph of Nabumetone in pH 7.4 phosphate buffer

The standard calibration graph of Nabumetone in pH 7.4 phosphate buffer showed good linearity with r^2 value of 0.987, which suggest that it obeys the "Beer – Lambert" law at concentration range between 10-50 µg mL^{-1}.

Evaluation of tablets

Pre-compressional parameters: The results are given in table 4.

Table 4: Pre-compressional parameters of Nabumetone tablet blends

Formulation code	Angle of repose(θ)	Bulk density (gm/cm^3)	Carr's Index (%)
Pure drug	24º18'	gm/cm^3	16.019%
F1	21º26'±1.84	0.51±0.037	13.88±0.28
F2	23º21'±1.64	0.54±0.044	17.24±0.33
F3	23º47±1.36	0.61±0.038	17.28±0.59

It was observed from the table 4, the angle of repose is between 21-24^{o}, bulk density is between 0.5-0.6 g/cm^{3} and Carr's index is between 13-18 %. All the pre-compression parameters are within passable limits hence can be compressed into a tablet.

Post-compression parameters: The results are given in table 5.

Table 5: Characterization of compressed core tablet

Formulation code	Thickness (mm)	Hardness (kg/cm^{3})	Weight variation (mg)	Friability (%)	%Drug content
F1	4.72±0.1	5.47±0.45	600.35±1.63	0.18	99.33±0.47
F2	4.77±0.1	6.17±0.29	601.5±1.36	0.14	99.70±0.16
F3	4.80±0.2	5.67±0.76	599.8±1.76	0.19	101.40±0.68

From the table 5 it was observed that, the thickness is between 4.7-4.8 mm, hardness is between 5-6.5 kg/cm^{3}, weight is between 599-601.5 mg, friability is between 0.14-0.19% and % drug content is between 99.3-101.4 % for the compressed tablets. All the post-compression parameters for the compressed tablets are in the passable limits.

***In-vitro* dissolution studies:** The results are presented in table 6 and fig.2 shows cumulative percentage drug release of Nabumetone CR tablets.

Table 6: Percentage drug release of F1, F2 and F3

Time (h)	F1	F2	F3
0.5	11±1.21	8.015±1.42	4.8±1.22
1	17.96±1.63	12.23±1.53	7.6±1.25
2	28.13±1.55	15.9±1.26	15.2±1.01
4	38.47±1.03	27.7±1.63	20.07±1.44
6	46.33±1.49	34.48±2.41	26.63±1.09
8	51.86±1.35	42.63±2.11	31.54±1.02
10	59.92±1.69	47.86±1.87	37.96±1.07
12	65.02±1.32	55.3±2.06	42.01±0.92
14	76.31±1.81	60.07±2.62	48.6±1.07
16	84.23±1.03	65.7±1.7	53.32±1.20
18	92.4±2.4	74.87±1.07	57.66±1.23
20	-	80.7±0.7	62.97±1.07
22	-	84.9±1.9	68.83±1.17
24	-	90.23±1.32	76.2±1.2

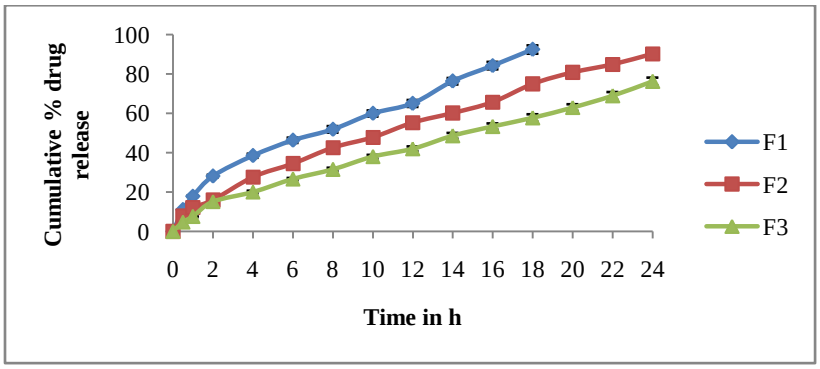

Figure 2: Cumulative percentage drug release of Nabumetone CR tablets

From the dissolution data (table 6) it was observed that, the release is extended up to 18 h by the F1 formulation and 24 h for F2 and F3 formulations. F2 formulation is extending 90 % drug release at 24 h, but F3 is showing only 76 % at 24 h.

Kinetic data: Nabumetone CR Tablets kinetic data was presented in table 7.

Table 7: Kinetic data for Nabumetone CR Tablets

Kinetics	F1	F2	F3
Zero-order (r^2 value)	0.9649	0.9835	0.9888
First-order (r^2 value)	0.9225	0.9551	0.9747
Higuchi (r^2 value)	0.9873	0.9829	0.9735
Korsemeyer-Peppas (n value)	0.6391	0.7676	0.831

From the above table 7, it was observed that all the formulations following zero-order kinetics and diffusion mechanism of release. F2 formulation follows nonfickian diffusion mechanism of release from the Controlled release tablet.

APPLICATIONS

1) Nabumetone Controlled release tablets applicable in pain management like rheumatoid arthritis, rheumatoid pains, and joint stiffness and swelling.
2) It is less gastric irritant compared to other NSAIDS, hence can be safely used in pain management.

CONCLUSIONS

From all the observations, especially from dissolution data F2 formulation was considered as final optimized formulation because it is releasing 90 % drug from the formulation at 24 h, which is showing zero-order release kinetics and non-fickian diffusion as mechanism of drug release.

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