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Formulation and in Vitro Evaluation of Nabumetone Pulsatile Drug Delivery

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ABSTRACT

The present study aimed to design and evaluate an oral pulsatile drug delivery system (Pulsincap) for Nabumetone, a nonsteroidal anti-inflammatory drug (NSAID) used in the management of rheumatoid arthritis (RA), osteoarthritis (OA), and juvenile rheumatoid arthritis. The Pulsincap system consists of a water-insoluble hard gelatin capsule body cross-linked with formaldehyde vapors, filled with an optimized Nabumetone tablet blend, and sealed with a hydrogel plug prepared from Ethyl Cellulose and HPMC K15M in varying ratios. Twelve tablet formulations (F1–F12) were prepared using different super-disintegrants (Crospovidone, Ludiflash, Lycoat). Formulation F12 (Lycoat 20 mg) was selected as optimized, showing maximum drug release of 98.16% within 30 minutes. Capsule bodies exposed to formaldehyde for 6 hours maintained the required 6-hour lag time. Among five pulsincap formulations (P1F12–P5F12), P5F12 — containing Ethyl Cellulose:HPMC K15M (2:1) — was identified as optimal, achieving 99.84% drug release after a 6-hour lag time. Drug release followed Korsmeyer-Peppas kinetics with super case-II transport. Stability studies at 40°C/75% RH for 3 months confirmed formulation stability. This system offers a promising chronotherapeutic approach for timed drug delivery aligned with the circadian pattern of arthritic symptoms.

Keywords: *Pulsatile drug delivery, Nabumetone, Pulsincap, Chronopharmaceutics, HPMC K15M, Ethyl Cellulose, Rheumatoid Arthritis, Lag time*

1. INTRODUCTION

Controlled drug delivery systems have become central to modern pharmaceutical research. Circadian rhythms significantly influence the pharmacokinetics and pharmacodynamics of many drugs, as well as the intensity of several disease states. Conditions such as rheumatoid arthritis, bronchial asthma, angina pectoris, and myocardial infarction exhibit strong circadian patterns — symptoms are most severe in the early morning hours upon waking.

Pulsatile drug delivery systems (PDDS) are designed to release a drug after a predetermined lag time, followed by a rapid burst release. The Pulsincap system — developed by R. P. Scherer International Corporation — employs a water-insoluble gelatin capsule body sealed with a swellable hydrogel plug. The plug controls lag time by swelling, eroding, or both upon contact with gastrointestinal fluid, after which the drug is rapidly released.

Nabumetone (a prodrug NSAID, COX-2 preferential inhibitor) is metabolized to its active form 6-methoxy-2-naphthylacetic acid (6-MNA) and is indicated for RA and OA. Its longer half-life (~20 hours) and once-daily dosing requirement make it an ideal candidate for chronotherapeutic pulsatile delivery — taken at bedtime to achieve peak plasma levels at the time of maximal arthritic symptoms in the early morning.

2. MATERIALS AND METHODS

2.1 Materials

Nabumetone (Spectrum Pharma Labs, Hyderabad), Crospovidone, Ludiflash, Lycoat, Microcrystalline Cellulose (MCC), Magnesium Stearate, Talc, Ethyl Cellulose, HPMC K15M, and Formaldehyde were procured from standard suppliers. All reagents were of pharmaceutical/LR grade.

2.2 Preformulation Studies

Solubility of Nabumetone was assessed in 0.1 N HCl, pH 6.8, and pH 7.4 phosphate buffer. Drug-excipient compatibility was determined by FTIR spectroscopy (IR-Affinity-1, Shimadzu). The UV λmax was identified using a T-60 UV-Visible Spectrophotometer and standard calibration curves were established at pH 1.2 (358 nm) and pH 7.4 (359 nm).

2.3 Formaldehyde Treatment of Capsule Bodies

Hard gelatin capsules (size '0') were exposed to formaldehyde vapors (15% v/v, with $KMnO_4$) in a closed desiccator for 2, 4, 6, 8, and 10 hours. Post-exposure capsules were dried for 24 hours. Optimization was performed by disintegration testing in pH 1.2 (2 hrs) and pH 7.4 media. Six-hour treated capsule bodies maintained the required 6-hour lag time and were selected for further studies.

2.4 Formulation of Nabumetone Tablets (F1–F12)

Twelve formulations were prepared by direct compression using Nabumetone (15 mg), super-disintegrant (Crospovidone/Ludiflash/Lycoat at 5, 10, 15, 20 mg), MCC, Magnesium Stearate, and Talc (total tablet weight: 100 mg). Tablets were evaluated for hardness, friability, weight variation, drug content, disintegration time, and in vitro dissolution (USP Type I, pH 7.4, 100 rpm, 37°C).

2.5 Pulsincap Assembly

The optimized F12 tablet was placed in the 6-hour formaldehyde-treated capsule body. A hydrogel plug (100 mg) was prepared from Ethyl Cellulose:HPMC K15M in ratios 1:1, 2:1, and 1:2, compressed and placed at the capsule opening. Five pulsincap formulations (P1F12–P5F12) were assembled and the joint sealed with 1% Ethyl Cellulose ethanolic solution.

2.6 Evaluation of Pulsincap

In vitro release was studied using the Sequential pH Change Method (pH 1.2 for 2 hrs, pH 7.4 for 7 hrs) at 100 rpm, 37°C. Drug release was quantified by UV absorbance at 359 nm. Release kinetics were analyzed by Zero Order, First Order, Higuchi, and Korsmeyer-Peppas models. Stability studies were conducted at 40°C/75% RH for 1 and 3 months.

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

Nabumetone showed highest solubility in pH 7.4 buffer (1.248 µg/mL) compared to 0.1 N HCl (1.168 µg/mL) and pH 6.8 buffer (0.858 µg/mL). FTIR analysis confirmed no chemical interaction between Nabumetone and excipients — characteristic peaks remained unaltered in the formulation spectra. The UV λmax was confirmed at 359 nm.

Table 1. Solubility of Nabumetone in Various Solvents

Solvent	Solubility (µg/mL)
0.1 N HCl	1.168
pH 6.8 Buffer	0.858
pH 7.4 Buffer	1.248

3.2 Powder Flow Properties

All blends demonstrated good flow properties. Angle of repose ranged from 25.74° to 29.84°, Carr's index from 12.54% to 20.25%, and Hausner's ratio from 1.12 to 1.22, indicating consistent, free-flowing blends suitable for direct compression.

3.3 Tablet Characterization

All 12 tablet formulations met pharmacopoeial standards. Hardness ranged from 5.1 to 6.8 kg/cm², friability was below 1% for all batches, and drug content ranged from 96.15% to 99.64%. F12 showed the fastest and most complete dissolution (98.16% in 30 min), attributed to the high concentration of Lycoat (20 mg), a superior film-forming hydroxypropyl pea starch that enhances disintegration.

Table 2. Characterization of Selected Tablet Formulations

Formulation	Hardness (kg/cm²)	Friability (%)	Drug Content (%)	Disint. Time (s)
F1	6.8±1.1	0.70±0.02	96.15±1.24	20
F4	6.8±1.6	0.65±0.07	95.76±1.34	29
F8	5.9±1.4	0.61±0.04	96.85±1.20	18
F12	6.4±1.2	0.36±0.02	99.64±1.75	11

3.4 Formaldehyde Treatment Optimization

Capsule bodies treated for 6 hours maintained integrity in pH 1.2 for 2 hours and disintegrated at 6 hours in pH 7.4 — matching the required lag time. Bodies treated for 8 and 10 hours showed lag times of 9 and 12 hours respectively and were excluded. The 6-hour treatment was thus optimal for chronotherapeutic dosing at bedtime.

Table 3. Disintegration Times of Formaldehyde-Treated Capsule Bodies

Exposure Time (hrs)	pH 1.2 (2 hrs)	pH 7.4 Disint. Time (hrs)
2	Intact	—
4	Intact	1
6	Intact	6
8	Intact	9
10	Intact	12

3.5 In Vitro Release from Pulsincap Formulations

All five pulsincap formulations showed negligible drug release during the lag phase (0–5 hrs), followed by rapid burst release. Increasing HPMC K15M content in the plug prolonged the lag time. P5F12 (Ethyl Cellulose:HPMC K15M = 2:1) achieved 99.84% drug release after a 6-hour lag — the optimal balance between lag time maintenance and complete burst release.

Table 4. In Vitro Dissolution Data — Pulsincap Formulations (% CDR)

Time (hrs)	P1F12	P2F12	P3F12	P4F12	P5F12
0	0	0	0	0	0
2	0.16±1.08	0.42±1.74	0.75±1.74	1.05±1.26	1.29±1.54
4	1.26±1.45	2.95±1.64	1.48±2.25	1.43±1.51	6.42±1.48
6	96.43±1.48	89.12±1.22	5.48±1.20	7.26±1.20	27.74±1.48
7	99.63±1.52	97.35±1.28	65.46±1.52	35.86±1.85	66.19±1.67
8	—	98.12±1.44	88.96±1.48	83.49±1.25	93.51±1.75
9	—	—	98.43±1.26	98.42±1.62	99.84±1.58

3.6 Release Kinetics

Drug release data from the optimized P5F12 formulation was fitted to kinetic models. The Korsmeyer-Peppas model yielded the highest correlation coefficient (R=0.909), indicating super case-II transport (n > 0.89), characteristic of swelling-controlled release. Zero order (R=0.824) fit better than first order (R=0.566) and Higuchi (R=0.536), confirming concentration-independent, timed release.

Table 5. Release Kinetics — Optimized Formulation P5F12

Kinetic Model	R Value	Interpretation
Zero Order	0.824	Moderate fit — time-dependent release
First Order	0.566	Poor fit
Higuchi	0.536	Poor fit — not diffusion controlled
Korsmeyer-Peppas	0.909	Best fit — Super Case-II transport (n > 0.89)

3.7 Stability Studies

Stability studies at 40°C/75% RH for up to 3 months showed no significant changes in hardness, friability, drug content, or dissolution profiles for either F12 tablets or P5F12 pulsincaps. Drug content remained above 99.27% and in vitro dissolution above 97.89% after 3 months, confirming excellent physicochemical stability.

Table 6. Stability Data — F12 and P5F12 (40°C/75% RH)

Parameter	Formulation	Initial	1 Month	3 Months
Hardness (kg/cm²)	F12	6.4±1.2	6.2±1.7	6.0±1.6
Friability (%)	F12	0.36±0.02	0.39±0.08	0.42±0.05
Drug Content (%)	F12	99.64±1.75	99.48±1.18	99.27±1.19
In Vitro Release (%)	F12	98.16±1.89	98.05±1.48	97.89±1.75
In Vitro Dissolution (%)	P5F12	99.84±1.58	99.67±1.29	99.46±1.20

4. CONCLUSION

A chronopharmaceutical Pulsincap dosage form of Nabumetone was successfully designed and evaluated. The optimized formulation P5F12 — comprising an F12 tablet core (Lycoat 20 mg, 15 mg Nabumetone) encapsulated in a 6-hour formaldehyde cross-linked gelatin capsule sealed with an Ethyl Cellulose:HPMC K15M (2:1) hydrogel plug — achieved a precise 6-hour lag time followed by complete drug release (99.84%). The system demonstrated excellent stability over 3 months.

This pulsatile delivery system enables once-daily bedtime dosing, allowing Nabumetone plasma levels to peak in the early morning hours when arthritic symptoms are most intense. The approach reduces dosing frequency, improves patient compliance, and represents a viable platform for chronotherapeutic drug delivery in inflammatory disorders.

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