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FORMULATION AND CHARACTERIZATION OF FLOATING SUSTAINED RELEASE TABLETS OF NEFOPAM HYDROCHLORIDE

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ABSTRACT

The present study was aimed at formulating and evaluating floating sustained release tablets of **Nefopam Hydrochloride** to prolong gastric residence time and achieve controlled drug release, thereby improving therapeutic efficacy and patient compliance. Nine formulations (F1–F9) were prepared using varying concentrations of **hydrophilic polymers** such as **HPMC K15M** and **Carbopol 934**, along with **sodium bicarbonate** as a gas-generating agent. Pre-compression and post-compression evaluations were conducted to assess powder flow, hardness, friability, drug content, and floating properties. In-vitro buoyancy and drug release studies were performed using USP dissolution apparatus. The release data were fitted to various kinetic models to determine the mechanism of drug release. All formulations showed acceptable pre-compression properties with good flowability. Post-compression results confirmed uniform weight, acceptable hardness (6.3–6.8 kg/cm^2), low friability (<1%), and high drug content (96.45%–99.25%). All tablets exhibited **floating lag times below 65 seconds** and **total floating durations exceeding 12 hours.** Among the formulations, **F7** showed optimal performance with a cumulative drug release of **99.01% at 12 hours,** and followed **first-order release kinetics** (R^2 = 0.9665), indicating a **concentration-dependent release mechanism.** The Peppas model (R^2 = 0.9332) suggested **anomalous transport** as the drug release mechanism. The optimized formulation (F7) successfully achieved sustained drug release and prolonged gastric retention, making it a promising candidate for once-daily oral therapy of Nefopam Hydrochloride.

Keywords: Nefopam Hydrochloride, Floating tablets, Sustained release, Gastroretentive drug delivery, In-vitro release, Kinetic modeling

Introduction

Oral drug delivery remains the most preferred and convenient route of administration, especially for chronic therapies. However, drugs with a narrow absorption window, short half-life, or poor gastric stability often face challenges in conventional dosage forms due to variable gastrointestinal transit times and limited bioavailability. To overcome such limitations, gastroretentive drug delivery systems (GRDDS), particularly floating drug delivery systems (FDDS), have gained significant attention. These systems are designed to remain buoyant in the stomach for prolonged periods, thereby enhancing gastric residence time and improving drug absorption in the upper gastrointestinal tract [1,2].

Nefopam hydrochloride is a centrally acting non-opioid analgesic used for the treatment of moderate to severe pain. It possesses a short elimination half-life (3–5 hours), necessitating frequent dosing, which may lead to reduced patient compliance [3]. Moreover, nefopam is primarily absorbed from the upper gastrointestinal tract, making it a suitable candidate for gastroretentive formulations [4]. Sustained release formulations can help maintain steady plasma concentrations, reduce dosing frequency, and minimize side effects.

Floating sustained release tablets offer a practical approach by combining low-density polymers and gas-generating agents to enable buoyancy and sustained drug release. Polymers such as hydroxypropyl methylcellulose (HPMC), carbopol, and ethyl cellulose are commonly used to modulate the release of the drug over an extended period [5,6]. The selection and optimization of these excipients are crucial in achieving desired floating lag time, total floating time, and controlled drug release profiles.

In the present study, floating sustained release tablets of nefopam hydrochloride were formulated and evaluated with the objective of prolonging gastric retention, sustaining drug release, and improving overall therapeutic efficacy.

Materials and Methods

Material

The materials used in this study included Nefopam Hydrochloride (gift sample from a reputed pharmaceutical company) as the active drug. HPMC K15M (Colorcon Asia Pvt.

Ltd., Goa) and Carbopol 934 (Lubrizol, USA) were used as sustained release polymers. Sodium bicarbonate and citric acid (S.D. Fine Chemicals, Mumbai) acted as gas-generating agents to achieve buoyancy. PVP K30 (Loba Chemie, Mumbai) was used as a binder, while talc and magnesium stearate (Loba Chemie) served as glidant and lubricant, respectively. Lactose monohydrate (Mylan Laboratories Ltd., Hyderabad) was used as a diluent, and distilled water was used as the processing solvent. All chemicals and excipients were of analytical or pharmaceutical grade.

Methods

Method for preparation of sustained release tablets of Nefopam HCl

Direct compression was taken after to manufacture the gas generating floating tablets of Nefopam HCl. Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, and F9) were set up by direct compression (7). Every one of the polymers chose, drug and excipients were gone through strainer no. 40 preceding utilizing into plan. The sum and proportion of drug and polymers were weighed according to given in table no. 1 and all the definition were utilized for encourage assessments parameters.

7.1.1 Optimization of sustained release tablets of Nefopam HCl

Optimization of formulation carried out on the basis of OVAT (One variable at time) using amount of excipient used like Excipients.

Table 1: Preparation of sustained release tablets of Nefopam HCl

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nefopam HCl	30	30	30	30	30	30	30	30	30
Carbopol 940 P	-	-	-	-	-	-	20	20	-
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Lactose	130	130	130	130	130	130	110	110	130
Total Weight	200	200	200	200	200	200	200	200	200

Evaluation of precompression parameter

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formula:

$$\text{LBD (Loose Bulk Density)} = \frac{\text{Mass of powder}}{\text{Volume of Packing}}$$

$$\text{TBD (Tapped Bulk Density)} = \frac{\text{Mass of powder}}{\text{Tapped Volume of Packing}}$$

Carr's Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\text{Carr's Index} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \text{X } 100$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation (8):-

$$\text{Housner's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose Bulk density}}$$

Hausner's ratio value <1.25 shows better flow properties

Evaluation of tablets

All the tablets were evaluated for following various parameters which includes;

General Appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated (9).

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask (10). The powder was dissolved in 5 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and for drug content by UV spectrophotometer at λ_{max} of 264 nm using of 0.1 N HCl as blank.

Hardness

For each formulation, the hardness of five tablets was resolved utilizing the Monsanto hardness tester (11).

Friability

The friability of a sample of 10 tablets was estimated utilizing a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated (12).

Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated (13).

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method. The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid, pH 1.2 as per USP (14). The time necessary for the tablet to increase to the outside and float was determined as floating lag time.

Dissolution rate studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type) (15). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of 37±0.5ºC and rpm of 75. One prepared Nefopam HCl tablet was set in every container of dissolution apparatus. The mechanical

assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 10 hours using 10ml pipette. The new disintegration medium (37ºC) was supplanted each time with a similar amount of the sample and takes the absorbance at 264nm using UV/Visible spectroscopy.

Results and Discussion

The present study aimed to formulate and evaluate floating sustained release tablets of Nefopam Hydrochloride using various polymeric matrices to ensure prolonged gastric retention and controlled drug release.

The pre-compression parameters (Table 2) including bulk density, tapped density, Carr's index, and Hausner ratio indicated good flow properties of the powder blend for all formulations. The compressibility index ranged between 23.81% (F5) to 30.31% (F1), while Hausner's ratio values ranged from 1.313 to 1.435, suggesting acceptable to good flow behavior, essential for uniform die filling during tableting.

The results of post-compression parameters (Table 3) confirmed uniform tablet quality across formulations. The tablet thickness ranged between 3.15 mm and 3.25 mm, and hardness was found to be within 6.3–6.8 kg/cm^2, ensuring adequate mechanical strength. The weight variation, friability (<1%), and drug content (ranging from 96.45% to 99.25%) were within pharmacopeial limits, indicating good content uniformity and resistance to abrasion. Notably, all formulations showed total floating duration greater than 12 hours, confirming effective gastro-retention.

As shown in Table 4, the floating lag time varied among the formulations, with F7 showing the shortest lag time (35±6 sec). This indicates rapid buoyancy, likely due to the optimized polymer and gas-generating agent ratio. The prolonged floating duration (>12 hours) across all batches signifies successful formation of a low-density matrix.

The in-vitro release profiles (Table 5) revealed controlled and extended drug release over 12 hours. Among all formulations, F7 exhibited a sustained release pattern, with 99.01% cumulative drug release at 12 hours, and a well-maintained release rate throughout the study duration. Other formulations (e.g., F1, F2, F4) showed rapid drug release within 4–6 hours, which may not meet the desired sustained release criteria.

The drug release data of the optimized batch F7 was subjected to kinetic modeling (Tables 6 & 7) to understand the mechanism of release. The highest correlation coefficient (R^2 = 0.9665) was obtained for the First Order model, suggesting that the drug release is concentration-dependent. The Peppas model (R^2 = 0.9332) further indicated that the release followed anomalous (non-Fickian) transport, i.e., a combination of diffusion and polymer relaxation/erosion mechanisms. The Higuchi model (R^2 = 0.9079) supported diffusion as a major mechanism.

Formulation F7 demonstrated superior pre- and post-compression characteristics, the fastest onset of buoyancy, prolonged gastric retention, and a desirable sustained release profile for up to 12 hours. The release kinetics and mechanisms confirm that F7 is an effective floating sustained release tablet of Nefopam Hydrochloride, potentially enhancing patient compliance and therapeutic efficacy.

Table 2: Result of pre-compression properties of Nefopam HCl

Formulation Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.315	0.452	30.31	1.435
F2	0.342	0.468	26.92	1.368
F3	0.336	0.459	26.80	1.366
F4	0.327	0.448	27.01	1.370
F5	0.336	0.441	23.81	1.313
F6	0.325	0.438	25.80	1.348
F7	0.308	0.419	26.49	1.360
F8	0.312	0.425	26.59	1.362
F9	0.328	0.436	24.77	1.329

Table 3: Results of post compression properties of sustain release tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3	Total floating duration (h)
F1	3.18	6.4	205	0.775	98.74	>12
F2	3.15	6.5	203	0.685	97.15	>12
F3	3.16	6.3	202	0.732	98.65	>12
F4	3.18	6.8	206	0.715	98.12	>12
F5	3.22	6.5	198	0.795	97.85	>12
F6	3.25	6.8	200	0.885	96.45	>12
F7	3.19	6.7	202	0.798	99.25	>12
F8	3.22	6.4	195	0.763	98.15	>12
F9	3.17	6.5	199	0.669	97.22	>12

Table 4: Results of *in-vitro* buoyancy study of sustain release Floating time

S. No.	Formulation Code	Floating lag times (sec)
1.	F1	55±4
2.	F2	48±8
3.	F3	45±5
4.	F4	63±4
5.	F5	58±3
6.	F6	53±5
7.	F7	35±6
8.	F8	49±7
9.	F9	55±4

Table 5: *In-vitro* drug release study of FGR tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	39.85	36.65	34.45	34.41	30.45	28.85	20.25	17.74	14.65
1	58.85	48.85	46.65	46.65	43.32	43.32	35.45	34.65	30.65
1.5	72.25	63.32	58.85	69.95	59.98	55.48	43.36	40.25	40.47
2	89.98	79.98	71.12	79.91	76.65	68.74	57.74	52.21	49.98
3	98.25	86.65	78.85	88.97	84.45	78.95	68.88	60.36	58.85
4	-	98.25	89.98	98.58	98.85	86.65	79.98	68.98	68.87
6	-	-	99.05	-	99.25	97.74	85.66	78.88	78.84
8	-	-	-	-	-	98.11	90.25	86.65	83.32
12	-	-	-	-	-	-	99.01	90.25	85.45

Table 6: *In-vitro* drug release data for optimized formulation F7

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	20.25	1.349	77.68	1.890
1	1	0	35.45	1.565	63.25	1.801
1.5	1.225	0.176	43.36	1.647	55.68	1.746
2	1.414	0.301	57.74	1.753	43.35	1.637
3	1.732	0.477	68.88	1.817	34.44	1.537
4	2	0.602	79.98	1.897	21.11	1.324
6	2.449	0.778	85.66	1.920	16.77	1.225
8	2.828	0.903	90.25	1.954	10.02	1.001
12	3.464	1.079	99.01	1.999	0.26	-0.585

Table 7: Regression analysis data of sustain release Tablets

Batch	Zero Order	First Order	Higuchi	Peppas
	R^2	R^2	R^2	R^2
F7	0.7744	0.9665	0.9079	0.9332

Conclusion

The present study successfully formulated and evaluated floating sustained release tablets of Nefopam Hydrochloride using hydrophilic polymers such as HPMC K15M and Carbopol 934, along with suitable gas-generating agents. All formulations exhibited acceptable pre- and post-compression characteristics, good buoyancy, and prolonged floating time exceeding 12 hours. Among the nine formulations, F7 was identified as the optimized batch based on its short floating lag time, sustained drug release (99.01% over 12 hours), and favorable release kinetics following first-order and Peppas models, indicating a concentration-dependent and anomalous drug release mechanism. Thus, the developed formulation offers a promising gastroretentive drug delivery system for Nefopam Hydrochloride, potentially improving patient compliance and therapeutic efficacy in pain management.

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