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FORMULATION AND CHARACTERIZATION OF SUSTAIN RELEASE TABLETS OF LABETALOL HYDROCHLORIDE

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Abstract

The present study aimed to formulate and evaluate sustained-release floating tablets of Labetalol hydrochloride, a non-selective β-blocker used in the management of hypertension, to improve gastric retention and achieve prolonged drug release. Preformulation studies confirmed the drug's physicochemical suitability, revealing it as a white to off-white, odorless crystalline powder with high solubility across multiple solvents and a melting point of 178–180°C. UV spectrophotometric analysis exhibited excellent linearity (10–50 µg/ml) at 295 nm with a correlation coefficient (R^2 = 0.999), while FTIR analysis confirmed the presence of characteristic functional groups without structural alteration. Tablets were prepared by direct compression using polymers such as Chitosan and Carbopol 940P, along with sodium bicarbonate as an effervescent agent. Pre- and post-compression evaluations indicated satisfactory flowability, mechanical strength, and uniformity, with all parameters within pharmacopeial limits. In-vitro buoyancy studies showed that formulation F8 achieved the shortest floating lag time (34 ± 4 sec) and remained buoyant for over 12 hours. The in-vitro drug release profile demonstrated sustained release up to 12 hours, with F8 exhibiting 98.12% cumulative drug release, attributed to the formation of a stable gel matrix. Kinetic modeling revealed that drug release followed first-order kinetics (R^2 = 0.9899) with a non-Fickian diffusion mechanism, as indicated by Higuchi (R^2 = 0.9147) and Korsmeyer–Peppas (R^2 = 0.9487) models. The optimized formulation (F8) demonstrated excellent buoyancy, prolonged gastric residence, and controlled drug release, ensuring better therapeutic efficacy and patient compliance. Thus, the developed floating matrix tablets of Labetalol hydrochloride present a promising approach for sustained antihypertensive therapy with improved bioavailability and reduced dosing frequency.

Introduction

Hypertension is one of the most prevalent cardiovascular disorders and represents a major global public health concern because of its strong association with cardiovascular morbidity and mortality (Lackland and Weber, 2015). Persistent elevation of blood pressure increases the risk of serious complications such as myocardial infarction, stroke, heart failure, renal dysfunction, and other vascular disorders. Effective and continuous control of blood pressure is therefore essential for reducing long-term complications and improving the quality of life of patients (Fuchs and Whelton, 2020). Pharmacological treatment of hypertension commonly involves drugs that act through different mechanisms to reduce cardiac output, vascular resistance, or both. However, conventional immediate-release dosage forms may require repeated

administration to maintain therapeutic drug concentrations, which can result in fluctuations in plasma drug levels and may adversely affect patient compliance (Redon and Carmena, 2024).

Labetalol hydrochloride is a synthetic antihypertensive agent possessing both selective α_1-adrenergic receptor blocking and non-selective β-adrenergic receptor blocking activities. By producing combined vasodilation and reduction in cardiac activity, labetalol hydrochloride decreases peripheral vascular resistance and blood pressure without producing a marked reflex increase in heart rate (Baker et al., 2026). It is widely used in the management of hypertension and has particular clinical importance in situations where rapid and effective blood pressure control is required. Despite its therapeutic usefulness, conventional oral administration of labetalol hydrochloride may require multiple doses during the day to maintain adequate therapeutic effects. Frequent dosing may contribute to variations in drug concentration and can negatively influence patient adherence to the prescribed treatment regimen (Elliott, 2006).

Sustained-release drug delivery systems have been developed to overcome several limitations associated with conventional dosage forms. A sustained-release tablet is designed to release the active pharmaceutical ingredient gradually over an extended period, thereby maintaining drug concentrations within the desired therapeutic range for a prolonged duration. Such systems can reduce the frequency of administration, minimize fluctuations in plasma drug concentration, improve therapeutic efficacy, and potentially reduce dose-related adverse effects. In addition, sustained-release formulations can improve patient convenience and compliance, particularly in the treatment of chronic diseases such as hypertension that require long-term medication (Manish and Abhay, 2012).

The development of a sustained-release formulation requires careful selection and optimization of pharmaceutical excipients capable of controlling drug release. Hydrophilic polymers such as hydroxypropyl methylcellulose, Carbopol, and other matrix-forming agents can form a hydrated gel layer around the tablet when exposed to gastrointestinal fluids. The resulting polymeric matrix can regulate drug diffusion and/or erosion, thereby providing prolonged drug release. Hydrophobic polymers and other release-retarding excipients may also be employed to modify

the release characteristics according to the desired therapeutic profile. The concentration and type of polymer, drug-to-polymer ratio, tablet hardness, and other formulation variables can substantially influence drug release behavior and the physicochemical characteristics of the final dosage form (Mori et al., 2024).

Labetalol hydrochloride is therefore a suitable candidate for investigation in a sustained-release tablet system with the objective of obtaining controlled and reproducible drug release over an extended period. A properly designed formulation may provide a more consistent pharmacological effect while reducing the need for frequent administration. During formulation development, tablets must be evaluated for important quality attributes including appearance, weight variation, thickness, hardness, friability, drug content uniformity, and in-vitro drug release (Barde et al., 2011).

The present research work is therefore aimed at the formulation and characterization of sustained-release tablets of labetalol hydrochloride using suitable release-retarding excipients. The study focuses on developing tablets with acceptable physicochemical properties and a controlled drug-release profile. Optimization of the formulation is expected to provide a sustained-release dosage form capable of maintaining prolonged drug release and potentially improving dosing convenience and patient compliance in the management of hypertension.

Material and Methods

Material

Labetalol hydrochloride was obtained as a gift sample from Cipla Ltd., Mumbai, India. Chitosan and Carbopol 940P were procured from Central Drug House (P) Ltd., New Delhi, India. Sodium bicarbonate, lactose, talc, magnesium stearate, and other excipients were obtained from Loba Chemie Pvt. Ltd., Mumbai, India. All other chemicals and reagents used were of analytical grade and were used as received. Distilled water was used throughout the formulation and evaluation studies.

Methods

Formulation of sustain release tablets of Labetalol hydrochloride

Sustained release tablets of Labetalol hydrochloride were prepared by direct compression method using varying polymer compositions. A total of nine formulations (F1 to F9) were developed, each containing 100 mg of Labetalol hydrochloride. The polymers used included Chitosan (30 mg in all batches) and Carbopol 940 P (used only

in F7, F8, and F9 at 20 mg), with Citric acid (5 mg) and Sodium bicarbonate (20 mg) added to each formulation as gas-generating agents to enhance floating properties.

All ingredients including the drug, polymers, and excipients were sieved through mesh #40 prior to mixing to ensure uniform particle size. The required quantity of each ingredient was accurately weighed as per the formulation design. The ingredients were then blended thoroughly in a mortar to obtain a uniform mixture (Gulkari *et al.,* 2016).

Table 1: Formulations of Labetalol hydrochloride sustain release tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Labetalol hydrochloride	100	100	100	100	100	100	100	100	100
Carbopol 940 P	-	-	-	-	-	-	20	20	20
Chitosan	30	30	30	30	30	30	30	30	30
Citric acid	5	5	5	5	5	5	5	5	5
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Lactose	80	80	80	80	80	80	60	60	60
Total Weight	250	250	250	250	250	250	250	250	250

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 formulas (Wasnik *et al.,* 2012).

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

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

Carr's index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula (Kadivar *et al.,* 2015):-

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

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

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

Hausner's ratio value <1.25 shows better flow properties

Evaluation of sustain release tablets

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 (Rahim *et al.,* 2015).

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined (Taghizadeh *et al.,* 2013). The tablets were crushed in a mortar and the powder equivalent to 10mg of drug was transferred to 10ml standard flask. 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 $\lambda_{max}$of 295 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 (Pawar *et al.,* 2013).

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 (Meka *et al.,* 2012).

Uniformity of weight

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

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.* The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid, pH 1.2 as per USP. 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). 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 Labetalol hydrochloride 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 (37°C) was supplanted each time with a similar amount of the sample and takes the absorbance at 295nm using UV/Visible spectroscopy.

Results and Discussion

The formulation composition of Labetalol hydrochloride sustained-release tablets is presented in Table 1. Nine formulations (F1–F9) were prepared using Labetalol hydrochloride as the active pharmaceutical ingredient. Chitosan, citric acid, sodium bicarbonate, magnesium stearate, talc, and lactose were incorporated as formulation excipients. Carbopol 940 P was introduced in formulations F7–F9 to further modify the drug-release characteristics. The total tablet weight was maintained at 250 mg for all formulations. The incorporation of chitosan and Carbopol 940 P was intended to provide

a suitable polymeric matrix for sustaining the release of Labetalol hydrochloride.

Pre-compression Properties

The pre-compression characteristics of the powder blends are presented in Table 2. The bulk density of the formulations ranged from 0.345 to 0.374 g/mL, while tapped density ranged from 0.463 to 0.496 g/mL. The compressibility index varied from 23.11 to 27.62%, and the Hausner ratio ranged from 1.301 to 1.382. These values indicated acceptable flow and packing characteristics of the powder blends, although some formulations exhibited moderate flowability. Formulation F3 showed the lowest compressibility index (23.11%) and Hausner ratio (1.301), indicating comparatively better flow characteristics. Overall, the pre-compression results suggested that the powder blends possessed adequate flow and compressibility for successful tablet compression.

Post-compression Properties

The post-compression evaluation of Labetalol hydrochloride tablets is presented in Table 3. The tablet thickness ranged from 3.2 to 3.6 mm, while hardness varied from 6.2 to 6.8 kg/cm². The tablet weight ranged from 245 to 255 mg, indicating satisfactory uniformity among the prepared formulations. Friability values ranged from 0.658 to 0.885%, indicating adequate mechanical strength of the tablets. The drug content ranged from 96.65 to 99.15%, demonstrating satisfactory drug distribution within the tablet matrix. All formulations exhibited a total floating duration of more than 12 h, confirming their prolonged floating behaviour. Among the formulations, F8 showed the highest drug content (99.15%) and satisfactory physical characteristics.

In-vitro Buoyancy Study

The in-vitro floating characteristics of the prepared Labetalol hydrochloride tablets are presented in Table 4. The floating lag time ranged from 34 ± 4 to 68 ± 6 seconds. Formulation F8 exhibited the shortest floating lag time of 34 ± 4 seconds, followed by F9 (45 ± 3 seconds) and F7 (48 ± 5 seconds). The progressively lower floating lag time observed in formulations containing Carbopol 940 P may be attributed to the polymeric matrix and its interaction with the gas-generating components. The presence of sodium bicarbonate and citric acid facilitated carbon dioxide generation upon contact with the dissolution medium, while the polymeric matrix helped retain the generated gas within the tablet structure. All formulations remained buoyant for more than 12 h, indicating satisfactory

gastroretentive floating characteristics. Based on its shortest floating lag time and satisfactory post-compression characteristics, F8 was selected as the optimized formulation for further drug-release evaluation.

In-vitro Drug Release Study of Optimized Formulation F8

The in-vitro drug-release profile of optimized formulation F8 is presented in Table 5. The formulation showed a sustained and controlled drug-release pattern throughout the 12-h study period. The cumulative drug release increased from 26.65% at 0.5 h to 56.65% at 2 h, followed by 79.98% at 4 h, 88.85% at 6 h, 95.45% at 8 h, and 98.12% at 12 h. The gradual release of Labetalol hydrochloride may be attributed to diffusion of the drug through the hydrated polymeric matrix formed by chitosan and Carbopol 940 P. The presence of the polymeric system provided resistance to rapid drug diffusion, thereby extending drug release over 12 h. The optimized F8 formulation therefore demonstrated desirable sustained-release behaviour along with prolonged gastric floating characteristics, indicating its potential as a gastroretentive sustained-release dosage form of Labetalol hydrochloride.

Table 2: Result of pre-compression properties

Formulation Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.345	0.465	25.81	1.348
F2	0.362	0.485	25.36	1.340
F3	0.356	0.463	23.11	1.301
F4	0.362	0.486	25.51	1.343
F5	0.374	0.495	24.44	1.324
F6	0.359	0.496	27.62	1.382
F7	0.365	0.487	25.05	1.334
F8	0.352	0.469	24.95	1.332
F9	0.361	0.482	25.10	1.335

Table 3: Results of post compression properties of Labetalol hydrochloride tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Thickness (mm)	3.3	3.4	3.6	3.5	3.2	3.4	3.6	3.5	3.4
Hardness (kg/cm²)	6.5	6.2	6.5	6.8	6.7	6.3	6.2	6.8	6.4

Weight variation (mg)	253	250	248	255	245	247	246	247	252
Friability (%)	0.705	0.658	0.745	0.885	0.658	0.763	0.745	0.685	0.772
Drug content (%)	96.65	98.12	97.75	96.65	97.25	97.65	98.12	99.15	97.56
Total floating duration (h)	>12	>12	>12	>12	>12	>12	>12	>12	>12

Table 4: Results of *in-vitro* buoyancy study of Labetalol hydrochloride tablets floating time

S. No.	Formulation Code	Floating lag times (sec)
1.	F1	68±6
2.	F2	63±9
3.	F3	60±5
4.	F4	59±4
5.	F5	55±3
6.	F6	52±6
7.	F7	48±5
8.	F8	34±4
9.	F9	45±3

Table 5: *In-vitro* drug release data for optimized formulation F8

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	26.65	1.426	73.35	1.865
1	1	0	32.25	1.509	67.75	1.831
1.5	1.225	0.176	48.98	1.690	51.02	1.708
2	1.414	0.301	56.65	1.753	43.35	1.637
3	1.732	0.477	66.95	1.826	33.05	1.519
4	2.000	0.602	79.98	1.903	20.02	1.301
6	2.449	0.778	88.85	1.949	11.15	1.047
8	2.828	0.903	95.45	1.980	4.55	0.658
12	3.464	1.079	98.12	1.992	1.88	0.274

Table 6: Regression analysis data of sustain release tablets

Batch	Zero Order	First Order	Higuchi	Peppas
	R^2	R^2	R^2	R^2
F8	0.7856	0.9899	0.9147	0.9487

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