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FORMULATION AND CHARACTERIZATION OF OSMOTIC DRUG DELIVERY SYSTEM OF LABETALOL AS ANTIHYPERTENSIVE AGENT

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ABSTRACT

The present research work focuses on the formulation and characterization of an osmotic drug delivery system of labetalol as an antihypertensive agent for the effective management of hypertension. Labetalol is a combined alpha- and beta-adrenergic receptor blocker that reduces peripheral vascular resistance and heart rate, thereby helping to lower blood pressure. Conventional oral dosage forms may require repeated administration and can produce fluctuations in plasma drug concentrations, depending on the dosage regimen and individual patient response. Therefore, the development of a controlled-release drug delivery system may offer advantages in regulating drug release, maintaining therapeutic drug concentrations, and improving patient compliance. Osmotic drug delivery systems are promising controlled-release technologies that utilize osmotic pressure to regulate the release of a drug through a semipermeable membrane. The present study aims to develop a suitable osmotic tablet formulation of labetalol using appropriate pharmaceutical excipients, including osmotic agents, release-controlling membrane materials, diluents, binders, and other necessary formulation ingredients. The formulation development process will involve the selection of suitable excipients, optimization of formulation variables, and preparation of tablets using an appropriate manufacturing technique. The prepared formulations will be evaluated for relevant pre-compression parameters, where applicable, and post-compression characteristics such as appearance, thickness, diameter, hardness, friability, weight variation, drug content uniformity, and in-vitro drug release. Dissolution studies will be conducted under suitable experimental conditions to investigate the influence of formulation composition and membrane characteristics on the drug-release profile. Overall, the study is intended to investigate the potential of osmotic drug delivery technology for controlling the release of labetalol and developing a suitable oral dosage form for hypertension management. The actual performance and therapeutic benefits of the developed system will be established through experimental evaluation and, where necessary, appropriate pharmacokinetic and clinical studies.

KEYWORDS: Osmotic drug delivery system, controlled release, antihypertensive agent, hypertension, Labetalol.

INTRODUCTION

Conventional oral dosage forms, such as immediate-release tablets, are widely used because they are convenient, economical, and generally easy to administer. However, depending on the drug's pharmacokinetic properties and prescribed dosing schedule, conventional formulations may produce fluctuations in plasma drug concentrations. These fluctuations can influence the duration of therapeutic action and may necessitate repeated administration to maintain adequate drug exposure. Frequent dosing can also reduce patient adherence, particularly in individuals requiring long-term treatment for chronic diseases such as hypertension. These limitations have encouraged pharmaceutical researchers to develop modified-release formulations capable of controlling the rate and duration of drug release. Controlled-release dosage forms aim to provide a more predictable drug-release profile and improve the convenience of treatment.[1]

Osmotic drug delivery systems are advanced pharmaceutical formulations that utilize osmotic pressure to control the release of a drug. These systems generally consist of a drug-containing core surrounded by a semipermeable membrane. Water from the surrounding gastrointestinal fluids enters the dosage form through the membrane, creating osmotic pressure within the system. This pressure promotes the movement of dissolved drug through a delivery orifice or another appropriately designed release pathway. The rate of drug release depends on factors such as membrane permeability, membrane thickness, osmotic pressure difference, drug solubility, and the design of the dosage form. By optimizing these variables, the formulation can be designed to achieve a predetermined drug-release profile.[2]

The mechanism of osmotic drug delivery begins when the administered dosage form comes into contact with gastrointestinal fluids. Water penetrates the semipermeable membrane because of the osmotic pressure difference between the formulation core and the external environment. The incoming water dissolves the drug and, where applicable, the incorporated osmotic agent. The resulting internal pressure facilitates the controlled expulsion of the drug solution or suspension through a delivery orifice. In elementary osmotic pump systems, the release rate can approach a constant rate under suitable conditions. However, the actual release profile depends on the drug's physicochemical properties and the formulation design. Proper optimization of the membrane and core composition is therefore essential for achieving the desired performance.[3]

The performance of an osmotic drug delivery system depends on the selection and proportion of its formulation components. The drug-containing core consists of the active pharmaceutical ingredient and suitable excipients. Osmotic agents, such as sodium chloride or other appropriate osmogens, may be incorporated to generate the required osmotic pressure. A semipermeable membrane, prepared using a suitable polymer, regulates water entry into the tablet. Plasticizers may be added when necessary to improve membrane flexibility and processing characteristics. Additional excipients, including diluents, binders, and lubricants, may be required to facilitate tablet manufacturing and maintain acceptable physical properties. The delivery orifice, when used, must also be appropriately designed to support reproducible drug release. The selection of these components should be based on compatibility studies and experimental optimization.[4]

Osmotic drug delivery systems offer several potential advantages over conventional oral formulations. Their drug-release mechanism is primarily governed by osmotic pressure and membrane characteristics, which can provide more predictable release under suitable formulation conditions. These systems may reduce the influence of certain physiological variables on drug release compared with some conventional controlled-release technologies. Other potential benefits include prolonged drug delivery, reduced dosing frequency, improved treatment convenience, and better control over the release profile. Nevertheless, the suitability of an osmotic system depends on the drug's solubility, dose, stability, and ability to be formulated into an appropriate delivery device. These factors must be considered during formulation development.[5]

2. METHODOLOGY

Formulation of core tablets using wet granulation method

All the formulations are prepared by wet granulation method. A core tablets were prepared by wet granulation method. Ingredients were weighed accurately and shifted through # 40 mesh. Accurately weighed MCC, HPMC EV5 and sodium chloride osmogen mix with drug mixed in cage blender for 10 min at 20 rpm again passed through # 40 mesh sieve. To make the binder solution, IPA was used to dissolve precisely weighed PVP K-30. Using a ready-made binder solution, the blend was granulated.

The granules were dried in a tray dryer at 65 °C until their LOD ranged from 2% to 3% by weight. Dried granules were fed through an oscillating granulator with a mesh size of 20. Magnesium stearate and talc were accurately weighed and passing through # 60 mesh. Magnesium stearate and talc were used to lubricate the a for mentioned blend in a cage blender for 3 minutes at 20 rpm. The granules were compressed after being tested for pre compression settings. Compression was carried out. Wet granulation is used because, as opposed to compaction, an adhesive is used to bind the powders together to form the granules. Tensile strength and capillary pressure are primarily responsible for the development and strength of the initial granules, and the liquid plays a crucial role in the granulation process by creating liquid bridges between the particles.[6,7]

Table 1: Formulation Composition of Experimental Batches.

Ingredients	**Formulation code**								
Quantity (mg)	**LC1**	**LC2**	**LC3**	**LC4**	**LC5**	**LC6**	**LC7**	**LC8**	**LC9**
Labetalol	50	50	50	50	50	50	50	50	50
Sodium Chloride	10	10	10	20	20	20	30	30	30
HPMC EV5	50	75	100	50	75	100	50	75	100
PVP K- 30	15	15	15	15	15	15	15	15	15
MCC	150	125	100	140	115	90	130	105	80
Magnesium Stearate	2	2	2	2	2	2	2	2	2

Talc	3	3	3	3	3	3	3	3	3
Total Weight (mg)	280	280	280	280	280	280	280	280	280

Coating of core tablets

Spray coating was used to apply coating solution to the core tablet. Cellulose acetate was dissolved in acetone to create the coating solution, which was then well agitated to dissolve the polymer. 1% weight-to-volume PEG 400 and sorbitol were added to this solution. According to the composition, four test coating solutions were made. The coating solutions were stirred properly and stored in closed container.[8-10]

Table 2: Composition of Coating Solutions.

Ingredients	C1	C2	C3	C4
Cellulose acetate (mg)	25	30	25	30
PEG 400 (mg)	10	10	10	10
Sorbitol (% w/v)	0.5	0.5	1	1
Acetone (ml)	100	100	100	100
Amaranth 3%	q.s	q.s	q.s	q.s

Evaluation Parameters

i) Weight Uniformity

Twenty tablets were weighed individually and average weight was determined. The individual tablet weight was compared with average tablet weight.[11]

ii) Thickness and Diameter

Tablet was selected at random from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement. Tablet thickness should be controlled within a ± 0.5% variation of standard value.[12,13]

iii) Hardness and Friability

Tablet was selected at random from individual formulations and hardness was measured using Monsanto hardness tester. Friability of core tablets was carried out on a Roche Friabilator for 20 accurately weighed tablets. Friability of the tablets should be less than 1%.[14,15]

iv) Content Uniformity

The content uniformity test was performed to determine the uniformity of the amount of active pharmaceutical ingredient present in individual tablets. Ten tablets were randomly selected from the prepared batch, and each tablet was weighed individually. Each tablet was finely powdered separately, and a quantity of powder equivalent to the required amount of drug was accurately weighed and transferred into a suitable volumetric flask. A suitable solvent or dissolution medium was added, and the mixture was shaken or sonicated sufficiently to extract the drug completely. The volume was then made up to the mark with the same solvent. The solution was filtered, if necessary, to remove insoluble excipients, and the appropriate dilution was prepared with the selected solvent. The absorbance of each individual tablet solution was measured using a suitable UV–Visible spectrophotometric method against an appropriate blank. The amount of Labetalol present in each tablet was calculated from the calibration curve, and the results were expressed as the percentage of the labeled drug content. The individual values were compared to evaluate the uniformity of drug content among the tablets.[16,17]

In-vitro Drug Release Studies

The release rate of drug from osmotic tablets was determined using the Dissolution Apparatus II (paddle method). The experiment was carried out in 750 mL of 0.1 N HCl for two hours, and then the solution was dissolved at a pH of 6.8 (adjusted by adding 250 mL of 0.2 M trisodium phosphate). A 5 mL aliquot was taken and 5 mL of fresh medium was reintroduced to maintain the original volume at regular intervals. Drug was detected using UV spectrophotometric method in aliquots after 2 hours of dissolution in 0.1M HCl and dissolution in phosphate buffer pH 6.8 upto 24 hrs.[18-20]

3. RESULT

Evaluation parameters of osmotic tablet

Table 3: Evaluation of post compression parameters of batches.

Batch Code	Average Weight(mg)	Hardness ($kg/cm^{2)}$	Diameter (mm)	Thickness (mm)	Friability (%)	Drug Content(%)
LC1	280.11±1.2	6.66±0.17	6.481 ± 0.03	3.61±0.02	0.21±0.022	99.23±0.04
LC2	280.21±1.6	6.43±0.19	6.465 ±0.02	3.60±0.02	0.14±0.022	99.42±0.05
LC3	279.54±1.7	6.89±0.13	6.473 ± 0.03	3.61±0.02	0.12±0.04	99.41±0.05
LC4	280.47±1.8	5.89±0.17	6.511 ± 0.01	3.61±0.04	0.29±0.046	99.40±0.04
LC5	280.53±1.3	6.17±0.16	6.482 ± 0.04	3.61±0.03	0.16±0.023	98.61±0.03
LC6	279.0±1.42	6.75±0.18	6.479 ± 0.02	3.63±0.02	0.17±0.04	98.86±0.05
LC7	280.04±1.2	5.84±0.18	6.491 ± 0.05	3.59±0.01	0.11±0.04	99.97±0.03
LC8	280.35±1.1	6.91±0.12	6.50 ± 0.01	3.61±0.01	0.18±0.047	99.12±0.04
LC9	279.62±1.3	6.84±0.11	6.51 ± 0.12	3.60±0.03	0.17±0.063	98.81±0.06

Weight variation of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value. The average weight of the batches found to be within the limit given in the

Indian Pharmacopeia. All of the tablets had a friability rate of less than 1%.

Evaluation of coated tablet formulation

Formulations were coated with four coating solutions to check the quality of film, uniformity of coating and film thickness.

Table 4: Optimization of coating solution.

Parameter	C1	C2	C3	C4
Physical Appearance	Thin and non-uniform coating	Uniform and smooth coating surface	Thin and non-uniform coating	Uniform coating and smooth coating surface
Film thickness	0.31	0.58	0.29	0.59
Weight variation	0.43	0.41	0.44	0.42

Based on the findings of the trial batches prepared with varying concentration of cellulose acetate and sorbitol, composition of C2 batch was optimized for further coating of tablets.

Table 5: Evaluation of Coated tablet.

Formulation	Average Weight (mg)	Thickness of coated tablet	Thickness of film(mm)
LC1	286.95±1.35	4.19±0.01	0.58
LC2	286.60±1.09	4.20±0.01	0.60
LC3	285.95±1.21	4.20±0.02	0.59
LC4	286.60±1.15	4.21±0.01	0.60
LC5	285.05±1.17	4.20±0.01	0.59
LC6	286.10±1.47	4.20±0.02	0.59
LC7	286.01±1.08	4.21±0.01	0.58
LC8	287.63±1.03	4.20±0.02	0.59
LC9	286.31±1.12	4.14±0.012	0.61

In-vitro drug release of batches

Table 6: In-vitro dissolution data (cumulative percent release).

Time hrs.	LC1	LC2	LC3	LC4	LC5	LC6	LC7	LC8	LC9
1	2.1	2.1	1.9	2.4	2.4	2.3	2.6	2.5	2.4
2	7.7	7.8	7.2	8.8	8.5	7.8	9.1	9.6	9.3
3	17.05	17.02	17.25	21.19	20.18	19.11	22.52	21.58	20.58
4	26.25	26.4	24.55	30.96	28.85	26.93	32.79	30.88	29.88
6	34.5	33.2	32.98	39.27	36.57	34.09	42.81	39.12	37.12
8	45.06	44.6	43.79	53.8	50.95	48.52	56.96	53.66	50.52
12	58.89	66.38	54.35	67.66	64.12	61.15	70.83	66.03	63.15
18	70.18	68.18	65.5	81.29	77.52	74.90	84.15	80.02	78.90
24	80.87	77.80	75.27	94.24	89.95	87.11	99.02	91.79	90.12

It was observed that as the concentration of osmogen was increase the drug release also increase. From the results of in vitro drug release, formulation LC7 containing 30mg of osmogen (Sodium chloride) showed maximum drug release over the period of 24 h.

4. CONCLUSION

The prepared formulations are intended to be evaluated for their physical and pharmaceutical properties, including appearance, thickness, hardness, friability, weight variation, and drug content uniformity. In-vitro dissolution studies will help determine the rate and extent of labetalol release and identify the influence of formulation variables on the release pattern. Mathematical kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, may be applied to interpret the drug-release mechanism. Based on these evaluations, the optimized formulation can be selected according to its pharmaceutical quality, reproducibility, and ability to provide the desired controlled-release profile. In conclusion, the formulation and characterization of an osmotic drug delivery system of labetalol may provide a useful pharmaceutical approach for investigating controlled drug release in the management of hypertension. A successfully optimized formulation could potentially improve dosing convenience and provide more consistent drug delivery compared with an appropriate conventional formulation. However, these advantages must be confirmed through experimental results, and any improvement in therapeutic effectiveness, patient compliance, or safety requires further pharmacokinetic and clinical evaluation. Overall, the study may contribute to the development of an

alternative oral drug delivery strategy for labetalol, subject to successful formulation optimization, in-vitro characterization, stability assessment, and subsequent evaluation of its clinical suitability.

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