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FORMULATION AND CHARACTERIZATION OF ORAL CONTROLLED RELEASE TABLET FOR ANTI- HYPERTENSIVE DRUG USING NATURAL POLYMERS

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ABSTRACT

The present study focuses on the development and evaluation of oral controlled release floating tablets of Losartan potassium using natural polymers to enhance therapeutic efficacy and patient compliance in the management of hypertension. Controlled drug delivery systems are designed to release drugs at a predetermined rate by maintaining a constant drug level in the body, thereby reducing dosing frequency and minimizing side effects. Losartan, a selective angiotensin II receptor antagonist, has a short half-life and poor bioavailability due to extensive first-pass metabolism, making it an ideal candidate for gastroretentive drug delivery systems (GRDDS). In this formulation study, various natural polymers such as xanthan gum, guar gum, and chitosan were used to prepare floating matrix tablets using the direct compression method. The prepared formulations were evaluated for pre-compression parameters (bulk density, compressibility index, Hausner's ratio), post-compression parameters (hardness, friability, weight variation, thickness, and drug content), buoyancy characteristics, and *in-vitro* drug release profiles. Among the nine formulations (F1–F9), formulation F6 showed the most desirable characteristics, including short floating lag time (40±5 sec), prolonged total floating duration (>12 h), and sustained drug release (99.05% over 12 hours). Drug release kinetics of the optimized formulation followed first-order and Peppas models, indicating a combination of diffusion and polymer erosion mechanisms. These findings demonstrate that natural polymers can be successfully utilized to develop an effective gastroretentive controlled release system for Losartan, thereby improving its therapeutic potential and patient adherence.

Keywords: Losartan Potassium, Controlled Release Tablets, Natural Polymers, Floating Drug Delivery System, Gastroretention; Buoyancy Study, Drug Release Kinetics, Hypertension, Matrix Tablets; Swelling Polymers.

INTRODUCTION

Hypertension, often referred to as the "silent killer," is one of the most common chronic health conditions globally, significantly contributing to the burden of cardiovascular diseases (CVDs) such as stroke, myocardial infarction, heart failure, and chronic kidney disease (WHO, 2021). Effective long-term management of hypertension is essential to reduce morbidity and mortality. Among the various classes of antihypertensive agents, Angiotensin II Receptor Blockers (ARBs) have gained widespread clinical acceptance due to their efficacy and tolerability profile. One of the most frequently prescribed ARBs is Losartan potassium.

Losartan is a selective, competitive antagonist of the angiotensin II type 1 (AT1) receptor, which plays a crucial role in regulating vascular tone and sodium-water homeostasis. By inhibiting angiotensin II at the AT1 receptor, Losartan leads to vasodilation, reduced aldosterone secretion, decreased sodium reabsorption, and ultimately, lower blood pressure (Burnier, 2001; Oparil *et al.*, 1996). It also provides renal protective effects, making it especially beneficial for patients with type 2 diabetes and proteinuria (Brenner *et al.,* 2001).

Although Losartan is effective in managing hypertension, it suffers from a relatively short biological half-life of approximately 2 hours. Its active metabolite, EXP3174, has a longer half-life (6–9 hours) and is responsible for much of the drug's antihypertensive activity. Nevertheless, once or twice daily dosing is often required to maintain consistent plasma drug levels (Sweetman, 2009). Such frequent dosing can negatively impact patient adherence, particularly in populations with polypharmacy regimens.

To overcome these challenges, controlled-release (CR) drug delivery systems are being developed to ensure prolonged therapeutic action, reduce dosing frequency, and improve patient compliance. Controlled release formulations maintain steady-state plasma concentrations of the drug, minimize peaks and troughs in drug levels, and reduce the potential for side effects associated with high plasma concentrations (Chien, 1992).

Among the different excipients used in CR formulations, natural polymers are attracting increased attention due to their biocompatibility, biodegradability, low toxicity, economic feasibility, and regulatory acceptance. Natural polymers such as gellan gum, xanthan gum, chitosan, pectin, guar gum, and tragacanth gum possess functional properties like swelling, mucoadhesion, and gel formation that can be harnessed to develop sustained or controlled drug release matrices (Patel *et al.,* 2012; Singh *et al.,* 2015).

In the context of gastroretentive drug delivery systems (GRDDS), which aim to prolong gastric residence time, these polymers can also enhance the absorption of drugs like Losartan, which exhibit site-specific absorption in the upper gastrointestinal tract (Deshpande *et al.,* 1996). For example, swelling polymers such as xanthan gum or gellan gum form a gel matrix in gastric fluid, controlling drug release while preventing premature transit through the pylorus.

The development of Losartan-controlled release tablets using natural polymers thus represents a promising approach to improving the therapeutic efficacy and patient adherence in the management of hypertension. This review focuses on the formulation strategies, role of natural polymers, and evaluation of controlled-release oral dosage forms of Losartan for enhanced therapeutic performance.

MATERIALS AND METHODS

Materials

The materials used for the formulation and evaluation of Losartan oral controlled release tablets included Losartan Potassium (gift sample from Pharmaceutical company), Xanthan gum (HiMedia, Mumbai), Guar gum (Loba Chemie, Mumbai), and Chitosan (Sigma-Aldrich, Bangalore) as natural polymers. Sodium bicarbonate and citric acid (S.D. Fine Chemicals, Mumbai) were used as gas-generating agents. Other excipients such

as lactose monohydrate (Qualikems, Vadodara), talc (CDH, New Delhi), and magnesium stearate (Loba Chemie, Mumbai) were also used. Analytical grade 0.1 N HCl (Merck) and freshly prepared distilled water were utilized for in-vitro studies. All reagents and chemicals were of analytical or pharmaceutical grade.

Methods

Method for preparation of oral controlled release tablets of Losartan

Direct compression was taken after to manufacture the gas generating floating tablets of Losartan (Basavaraja *et al.,* 2015). Nine different formulations (F1, F2, F3, F4, F5, F6, F7, F8, and F9) were set up by direct compression. 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. Optimization of formulation using amount of excipient used like Guar gum, Xanthan gum and Carbopol 940 P.

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 (Bharadwaj *et al.,* 2000).

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

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

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:-

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

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 (Pundir *et al.,* 2015).

Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined (Basak *et al.,* 2006). 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 λ_{max} of 233 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 (Varshosaz *et al.,* 2006).

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 (Venkataramudu *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±0.5°C and rpm of 75. One prepared Losartan 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 233nm using UV/Visible spectroscopy.

RESULTS AND DISCUSSION

The development of oral controlled release floating tablets of Losartan aimed to enhance gastric retention, sustain drug release, and improve patient compliance by using natural polymers. Various pre-compression and post-compression evaluations were conducted, and the results are discussed below.

The flow properties of powder blends, as indicated in Table 2, revealed acceptable values for bulk density (0.325–0.385 g/ml) and tapped density (0.436–0.496 g/ml) across all formulations (F1–F9). The Carr's compressibility index ranged between 22.38% to 29.22%**,** which is within the acceptable limit for good flow. The Hausner ratio varied from 1.288 to 1.413**,** suggesting fair to good flowability, suitable for direct compression methods. F3 and F4 formulations showed relatively better flow properties, which might be due to an optimal balance between drug and polymer content.

As shown in Table 3, the tablet thickness was uniform across all batches, ranging from 3.15 to 3.36 mm**.** The hardness was found between 6.1 to 6.8 kg/cm²**,** which reflects sufficient mechanical strength of the tablets to withstand handling. The weight variation was within pharmacopeial limits, indicating uniformity in the die-fill during tableting. The friability was below 1% for all formulations, indicating good mechanical integrity. Drug content ranged from 96.96% to 99.12%**,** confirming uniform drug distribution within the tablets. Notably, all formulations floated

for more than 12 hours**,** confirming the robustness of the floating system.

Table 4 indicates that all tablets exhibited short floating lag times**,** ranging between 40 to 63 seconds, which is desirable for quick floatation and gastric retention. The fastest floating was seen with F6 (40±5 sec), possibly due to optimal polymer concentration and better gas entrapment. Longer lag times in F7 and F8 could be attributed to denser polymer matrices or higher viscosity formulations.

The drug release profile shown in Table 5 demonstrates that formulations released Losartan over extended periods, showing potential for controlled release. F1 to F5 released over 85–98% drug within 3–4 hours**,** indicating relatively faster release. F6 emerged as the optimized formulation, showing a sustained drug release up to 12 hours, achieving 99.05% cumulative release. This sustained release can be attributed to the swelling and gel-forming nature of polymers like xanthan gum and chitosan used in its matrix.

The extended release from F6 supports its application in controlled release therapy. F8 and F9 also showed prolonged release but had higher initial bursts, which may not be ideal for controlled delivery.

From regression analysis data (Table 6), F6 followed first-order kinetics **(**R^2 = 0.9743**),** suggesting that drug release rate depends on the concentration remaining in the dosage form. The Higuchi model (R^2 = 0.9202) indicates diffusion-controlled release, and Peppas model (R^2 = 0.9534) confirms anomalous (non-Fickian) diffusion, i.e., a combination of both drug diffusion and matrix erosion. This kinetic behavior is ideal for a controlled release system.

Table 1: Various formulations of oral controlled release tablets of Losartan

Excipients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Losartan	50	50	50	50	50	50	50	50	50
Guar gum	100	120	140	-	-	-	50	60	70
Xanthan gum	-	-	-	100	120	140	50	60	70
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
$NaHCO_3$	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	110	90	130	110	90	110	90	70
Total Weight	350	350	350	350	350	350	350	350	350

Table 2: Result of pre-compression properties of Losartan

Formulation Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.341	0.458	25.55	1.343
F2	0.356	0.485	26.60	1.362
F3	0.385	0.496	22.38	1.288
F4	0.365	0.475	23.16	1.301
F5	0.345	0.463	25.49	1.342
F6	0.325	0.436	25.46	1.342
F7	0.328	0.436	24.77	1.329
F8	0.327	0.462	29.22	1.413
F9	0.356	0.475	25.05	1.334

Table 3: Results of post compression properties of oral controlled release tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3	Total floating duration (h)
F1	3.24±0.15	6.1±0.2	355±5	0.785±0.023	98.25±0.15	>12
F2	3.15±0.22	6.2±0.3	348±6	0.668±0.045	98.36±0.32	>12
F3	3.22±0.35	6.3±0.2	350±4	0.589±0.065	98.45±0.25	>12
F4	3.18±0.12	6.5±0.1	356±5	0.745±0.015	98.36±0.63	>12
F5	3.16±0.18	6.5±0.5	343±8	0.698±0.036	98.65±0.25	>12
F6	3.22±0.32	6.3±0.6	350±6	0.775±0.025	99.12±0.41	>12
F7	3.25±0.36	6.8±0.1	356±5	0.865±0.033	97.12±0.32	>12
F8	3.36±0.15	6.4±0.4	345±7	0.732±0.026	96.96±0.15	>12
F9	3.25±0.18	6.5±0.6	353±5	0.765±0.015	98.85±0.65	>12

Table 4: Results of *in-vitro* buoyancy study of Losartan oral controlled release floating time

S. No.	Formulation Code	Floating lag times (sec)
1.	F1	58±5
2.	F2	55±6
3.	F3	53±4
4.	F4	59±3
5.	F5	52±6
6.	F6	40±5
7.	F7	63±4
8.	F8	60±7
9.	F9	54±3

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

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	42.25	38.85	36.65	32.25	30.25	26.65	30.25	29.98	28.85
1	56.65	52.23	48.85	45.65	43.32	35.56	38.85	35.65	36.65
1.5	69.98	65.45	59.98	63.32	59.98	46.65	49.98	46.65	46.65
2	86.65	79.98	66.65	81.15	76.65	59.98	62.25	53.32	55.45
3	98.95	86.65	72.23	92.23	88.85	68.87	73.32	68.98	62.25
4	-	98.85	86.65	98.44	93.32	79.98	89.98	74.45	73.32
6	-	-	99.05	-	98.85	84.45	96.65	88.98	89.98
8	-	-	-	-	-	92.25	-	98.85	99.45
12	-	-	-	-	-	99.05	-	-	-

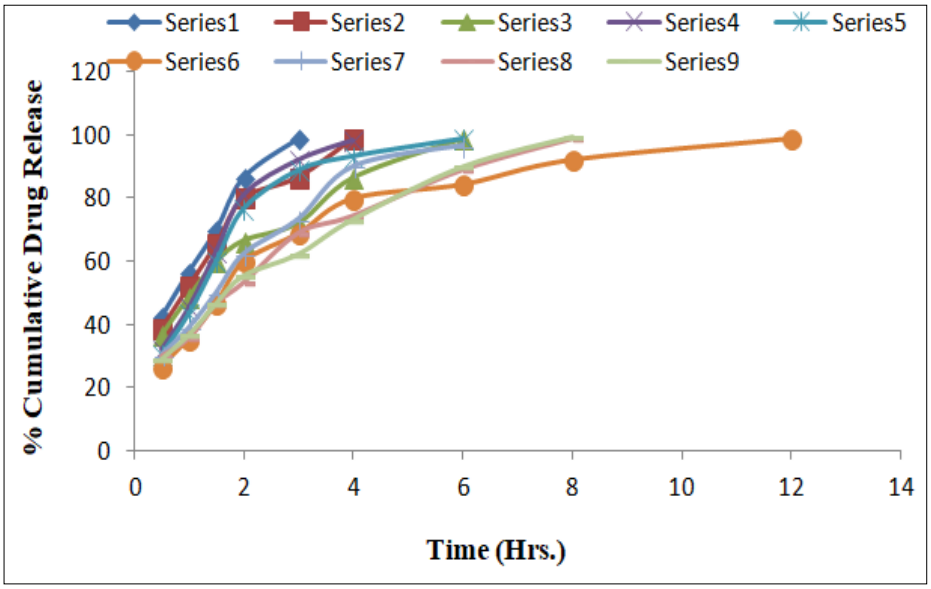

Figure 1: *In-vitro* drug release study of GRF tablets

Table 6: Regression analysis data

Batch	Zero Order	First Order	Higuchi	Peppas
	R^2	R^2	R^2	R^2
F6	0.7941	0.9743	0.9202	0.9534

CONCLUSION

Formulation F6 emerged as the most promising batch based on its excellent pre- and post-compression characteristics, rapid buoyancy, extended floating time, and desirable drug release profile. The study successfully demonstrates that a gas-generating, matrix-based floating tablet of Losartan can be effectively formulated to provide sustained drug release, improved gastric retention, and enhanced therapeutic efficacy, making it a viable option for the treatment of hypertension through oral controlled drug delivery.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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