RESEARCH ARTICLE

Formulation, *In-vitro* and *In-vivo* Evaluation of Chronology-based Mucoadhesive Drug Delivery System of an Antihypertensive Drug

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Received: 28th July, 2023; Revised: 03rd December 2023; Accepted: 12th February, 2024; Available Online: 25th March, 2024

ABSTRACT

Current research aimed to prepare and estimate chronology-based mucoadhesive PDDS of antihypertensive drug losartan potassium through formulation of fast-dissolving core tablet and incorporation of core tablet to polymer coating to formulate bioadhesive PDDS through direct compression system. The coating was done by using polymers ethyl cellulose and carbopol 934. Pre-compression and post-compression parameters, drug release, lag time and mucoadhesive examination was assessed for the formulation. The expected lag time for hypertension is 8 hours; hence, this lag time was achieved by using a bioadhesive pulsatile system. The optimized formulation showed 8 hours lag time with appropriate mucoadhesion for an equivalent period. Moreover, *in-vitro* as well as *in-vivo* mucoadhesion investigations reflected the positive outcomes. Consequently, the BPDDS was the finest preventative substitute for drugs with the highest absorption in the stomach and for drugs used to treat diseases related to circadian rhythm.

Keywords: Mucoadhesive drug delivery system, Losartan potassium, Lag time, Circadian rhythm, Bioadhesion, Drug release.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.1.14

How to cite this article: Janugade BU, Singla N. Formulation, *In-vitro* and *In-vivo* Evaluation of Chronology-based Mucoadhesive Drug Delivery System of an Antihypertensive Drug. International Journal of Drug Delivery Technology. 2024;14(1):94-101.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

In the recent era, the demand of novel drug delivery systems (NDDS) has been booming as more need in the pharmaceutical industry. This happened because of the invention of the latest NDDS technologies in pharmaceuticals. One of the approaches of NDDS is the controlled drug delivery system (CDDS). The CDDS is preferred because it achieves a constant drug concentration level in the body, leading to improved bioavailability of drug. However, variations in peak plasma levels and bioavailability are observed in oral dosage forms. This happens may be due to the gastric emptying rate of the stomach. As a result, the controlled release dosage forms (CRDF) approaches are not appropriate for a drug with a confined absorption range in the upper portion of the gastrointestinal tract. To conquer this drug, it should be developed in a suitable dosage form, which helps to prolong gastro-retention time (GRT) and also helps to enhance the absorption of the drug.[1-3]

The GRT of pharmaceutical dosage form is extended using gastroretentive dosage forms (GRDFs). The gastroretentive dosage forms can hold the drug inside the stomach. GRDFs helps to improve bioavailability and increase the gastro-retention of drugs. From various approaches of GRDF the bioadhesive drug delivery system (BDDS) shows more interest in developing the dosage form, as it adheres to the mucous membrane of the stomach, leading to gastro-retention for longer intervals of time to improve bioavailability.[4-6] PDDS is designed as a precautionary measure having advantages over conventional pharmaceutical formulations. It developed on account of the circadian rhythm of the body. PDDS represents the quick release of a particular quantity of drug in a less time interval directly later than a programmed off-release session, viz lags time, which depends on disease and is always greater than the gastrointestinal emptying time. But, just in case of drugs having maximum absorption in the stomach and if the drug is delivered in the small intestine or released after gastric emptying, then this leads into poor absorption of drug, which is a disadvantage of PDDS. Combinations of PDDS with BDDS can be preferable to subdue the same.[7,8] The floating PDDS (FPDDS) is another method to lengthen gastric emptying time. FPDDS formulation float over a gastric content but after gastric emptying, there is more probability that the formulation may entertain small intestine. This can be improved through BPDDS.[9,10]

The major goal of BPDD system is to achieve gastro-retention by adhering to the mucous membrane of the

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stomach using different types of bio-degradable polymer for bio-adhesion followed by pulsed drug release in the stomach. The pulsatile system releases medication at the proper time, at the accurate place of action and in exact quantity, which also beneficial compared to the common dosage form. In chrono-pharmacotherapy, the drug is delivered as per the circadian pattern of disease in therapy for diseases like hypertension, rheumatoid arthritis, and cardiovascular disease. The BPDDS has many advantages, like reduced dosing frequency, decreased side effects, and site-specific drug targeting like colon.[11] In this study, bio-adhesive PDDS of an antihypertensive drug of losartan potassium was prepared, which can be taken before bedtime (9 pm) and has the ability to release the drug later 8 hours of lag time.

MATERIALS AND METHODS

Materials

Losartan potassium was attained as a gift sample from Lupin Pharmaceutical Ltd, Palghar, Tarapur, India. Polyvinyl pyrrolidone, microcrystalline cellulose, cross povidone, ethyl cellulose, Carbopol 934 and magnesium stearate were gifted from Loba Chemicals, Mumbai, India. Each and every chemical utilized was of analytical grade.

Methods

Drug: Excipients compatibility study

- *Differential scanning calorimetry*

Differential scanning calorimetry (DSC) investigations were performed on discrete drugs, excipients, and their physical blends utilizing a Pyris 6 DSC instrument from Perkin Elmer in the Netherlands. Prior to analysis, the DSC system underwent calibration with pure indium. Samples weighing 3 to 5 mg were placed in aluminum pans, closed with a DSC sealer, and compared against empty reference pans. The investigation was conducted beneath a N_2 atmosphere flow rate at 20 mL min^{-1}, with a heating rate of 10°C min^{-1}, spanning a temperature range of 20 to 300°C.[11]

- *X-ray powder diffraction*

X-ray powder diffraction (XRD) examination was conducted using a Bruker X-RD-D8 Advance from Karlsruhe, Germany, to explore how dual and multi-combined blends of drugs and excipients affect the crystallinity of the drugs. The instrument featured a copper X-ray tube and a flat-plate specimen container. Specimens were exposed to X-ray beams with a wavelength of 1.54060 Å, generated at 40 kV and 40 mA. Examination was carried out for 25.5 minutes, scanning over a diffraction angle (2θ) range of 1.5 to 50° at a rate of 0.020°. XRD outlines of pure drugs, excipients, their physical mixtures are documented as well as analyzed.[12]

- *Preparation of core tablet (CT)*

Core tablet (CT) of losartan potassium with a dose 100 mg was formulated through a direct compression system using ingredients: polyvinyl pyrrolidone (7 mg), magnesium stearate (1-mg), cross povidone (varying 9/11/13/15/17 mg) and microcrystalline cellulose utilized as diluent with adjusting a tablet weight of 200 mg. All the ingredients were weighed and mixed well for about 15 minutes. In the formulation, crospovidone was used as a disintegrating agent, polyvinyl pyrrolidine was used as a binder, magnesium stearate was utilized as a lubricant, and MCC was used as a diluents. After mixing, powder was compressed into a tablet by using a rotatory tablet machine (Shakti Pharmatech Pvt. Ltd. Diameter 8 mm).[13-15]

Characterization

The losartan potassium spectrum was verified by using Fourier-transform infrared spectroscopy (FTIR) [Bruker, Germany (Alpha) Cary 630] and was also used to illustrate structural modification. A small quantity of sample, about 100 mg, were taken and then placed on FTIR platform and then spectra were recorded. The samples were analysed in the 4000 and 400 cm^{-1} regions.[16]

Pre-compression evaluation of granules

A quantity of powder weighed accurately and transferred to a 100 mL measuring cylinder. Then after transferring, the initial volume was noted as bulk volume. Tap volume (Vi) is taken up by powder after the tapping of powder for a definite interval of time by mechanical tapping of the container containing the sample using a graduated measuring cylinder. Then, tap density was computed using the following formula. Each analysis was performed for two times. The Carr's index (CI) and Hausner's ratio were computed utilizing bulk density (BD) and tap density (TD) values. The stationary funnel system was utilized to estimate the angle of repose of granules.[17-20]

Post-compression evaluation of tablets

The tablet thickness was determined using the vernier caliper, weight variation, hardness, and friability; disintegration time was performed per IP and USP. The dissolution study was accomplished by utilizing USP type II dissolution apparatus, 900 mL of 0.1N hydrochloric acid with 0.075% SLS as a medium at 37 ± 2°C and 100 rpm paddle speed.[14,15,21-23]

Preparation of bioadhesive pulsatile release tablet by direct compression technique

For the formulation dry coating was done using different concentration of ethyl cellulose and Carbopol 934. Polyvinyl pyrrolidine, magnesium stearate, and microcrystalline cellulose were also utilized to coat core tablets (Table 1). All ingredients were weighed and mixed manually to prepare the fined blend. The bioadhesive pulsatile release tablet (BPRT) was prepared using 13 mm die and punch set. Initially, 40% of final blend was added in the die, and core tablet was put on it. Then enduring 60% blend was added and tablet was compressed on KBR tablet press machine (Hi-labs Ltd E82664).[24,25]

Estimation of Various Tablet Properties of BPRT

The prepared press-coated tablet was assessed for weight variation, hardness, thickness, friability, etc., per official books.[14,15]

Table 1: Formulation of BPRT of losartan potassium

Ingredients (mg)	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*
Core tablet	200	200	200	200	200	200	200	200	200
MCC	228	180	132	188	140	92	148	100	52
Polyvinyl pyrrolidone	30	30	30	30	30	30	30	30	30
Ethyl cellulose	240	240	240	280	280	280	320	320	320
Carbopol	96	144	192	96	144	192	96	144	192
Magnesium stearate	6	6	6	6	6	6	6	6	6
Total weight (mg)	800	800	800	800	800	800	800	800	800

In-vitro mucoadhesion test

For the mucoadhesion test, the model was prepared using two pan balances. The two pans of a physical balance were taken out and replaced with beakers of the same weight. This entire setup was raised to fit a glass petri plate beneath left beaker, keeping a distance between the petri plate and left beaker of 0.5 cm. Before the mucoadhesion evaluation study, the chicken ileum was removed, cleaned, and equilibrated at 37ºC for 30 minutes in 0.1 N HCl medium. The ileum was tied tightly with thread to the mucus on the glass slide, which was then filled with 0.1N hydrochloric acid kept at 37ºC, so 0.1N HCl just reached the surface of the ileum membrane to keep it moist. This glass slide was placed beneath the left beaker and lowered down up to the petri plate of left beaker. The tablet was placed on the left beaker's base using two-way adhesive tape and the balance beam. The left beaker was then covered with a steady weight of 10 gm for the duration of 5 minutes, allowing the tablet to make complete contact with the ileum membrane. The mucoadhesive strength was then measured in terms of the weight (in gm) obligatory to remove the tablet from the membrane by adding weights to the right beaker. The time required to separate the tablet from the mucus membrane was recorded as an adhesion time.[26] Then a force of adhesion (N) was determined with the formula:

N = Mucoadhesive strength / 100 X 9.81 -------- (1)

In-vivo mucoadhesion test

Subsequent procedures of the Committee executed *in-vivo* mucoadhesion investigations for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) as well as the Institutional Animal Ethics Committee (IAEC) approved animal ethical protocol. For this study, male albino rabbits (2–2.5 kg) were utilized (n = 6) for *in-vivo* mucoadhesion analysis and positioned in polypropylene cages in a controlled room temperature (RT 22 ± 1°C and relative humidity (RH) of 60 to 70% in animal house. They were maintained with a standard pellet diet (Nutrivet Life Sciences) and water *ad libitum*. The rabbits were fed with 5% dextrose solution prior to feeding the optimized formulation using stomach tube (French Catheter No. 2). Immediately after this, the optimized formulation prepared with 25% barium sulfate and 75% API was administered orally to animals. The radiographic studies were performed by taking abdominal photographs using an X-ray machine at 2, 4, 8 and 12 hours intervals. The fluid level was maintained by giving 30 mL of 5% dextrose at each time interval.

In-vitro Dissolution Study of BPRT

Dissolution assessment was accomplished using USP type II dissolution apparatus, 900 mL of 0.1N hydrochloric acid with 0.075% SLS as a medium at 37 ± 2°C, 75 rpm. The sample was removed periodically and exchanged with fresh and clean dissolution medium by filtering through Whatman filter paper and then diluting it up to 10 mL using 0.1N hydrochloric acid. Then, samples were analysed via utilizing UV spectrophotometer.[25]

Stability Study

The optimized formulation was kept at a stability chamber at RT of 40°C and RH 75% for the duration of 45 days. Following a predetermined time period, the placed samples were assessed for weight variation, hardness, thickness, %drug release and drug content.[26]

RESULTS

Drug: Excipients Compatibility Study

DSC analysis

Figures 1-4 below display the DSC graph illustrating pure losartan potassium, excipient, and the mutual physical blend of constituents. The melting point for pure losartan potassium was found to be between 268 and 271°C, as per the literature. The early foremost thermal occurrence recorded in entirely specimens was an endothermic peak at 270.20°C. In contrast, the melting point with different excipients for example,

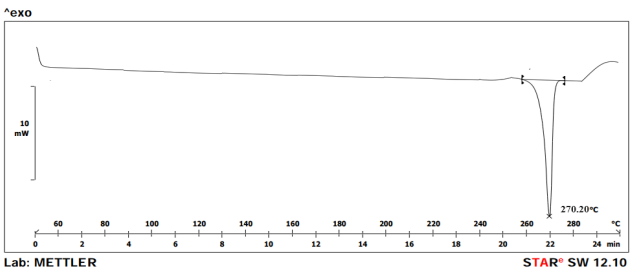

Figure 1: DSC spectra of losartan potassium

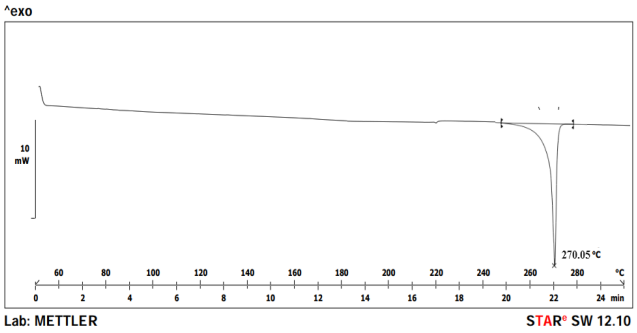

Figure 2: DSC spectra of drug and carbopol

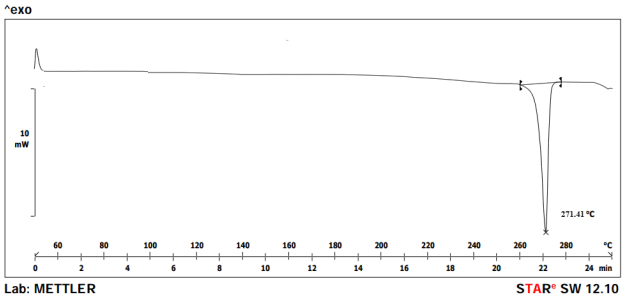

Figure 3: DSC spectra of drug with ethyl cellulose

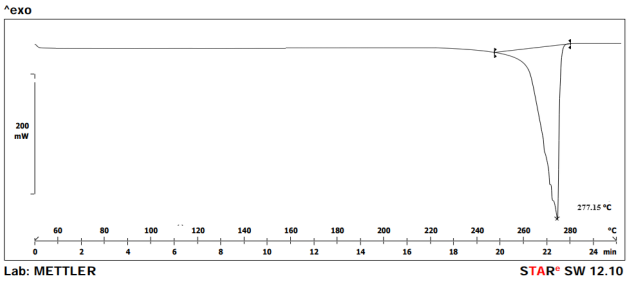

Figure 4: DSC spectra of physical mixture

Carbopol 934, ethyl cellulose and physical mixture was found to be 270.05, 271.41 and 277.14°C, which does not confirm any instability with the chosen polymer. So, the drug was said to be compatible.

XRD analysis

XRD was employed to examine the crystalline properties of the drug. The XRD was used to analyze the XRD patterns of excipients, drugs, and formulation. All XRD patterns were obtained at room temperature, covering a diffraction angle of 2θ ranging from 3° to 80°. The diffractogram of the pure drug exhibited several distinct sharp peaks, with the most prominent peaks falling between 7 and 28, confirming the crystalline nature of the drug. The characteristic peak for the drug was identified between 18° and 24° (2 Theta), while no peaks were observed for carbopol and ethyl cellulose, as depicted in Figures 5 and 6. In the case of physical mixtures with the drug, no peaks were detected, indicating that the drug was in an amorphous state.

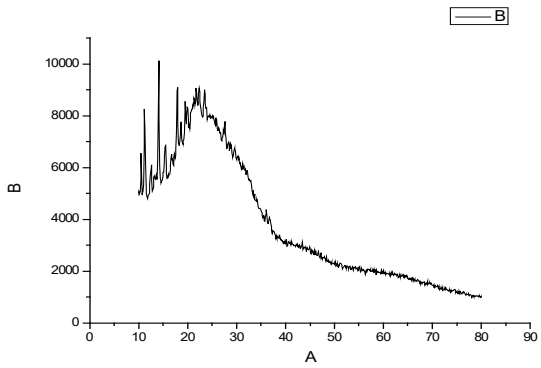

Figure 5: XRD diagram of losartan potassium

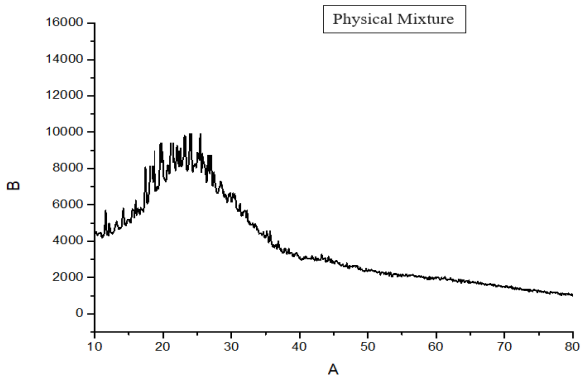

Figure 6: XRD diagram of losartan potassium physical mixture

Preparation of core tablet

Formulated core tablets were characterized and assessed for weight variation, hardness, friability, disintegration time and dissolution.

Characterization

FTIR spectra of pure losartan potassium, losartan potassium with Carbopol 934, losartan potassium with ethyl cellulose and drug with all excipients were shown in Figure 7. The spectrum of drug and excipients showed that major peaks of pure drug functional groups remained intact in the final mixture of the preparation. Hence it was concluded that the there was no major interface was observed between drug and excipients, indicating compatibility of drug and excipients.

Pre-compression evaluation of granules

The pre-compression evaluation parameters of final blend are BD, TD, Hausner's ratio and CI, as shown in Table 2. The result indicated that all the batches of formulations were suitable for the formulation of tablets by direct compression as it showed optimum flowability and compressibility.

Post-compression evaluation of tablets

Table 3 presents the values of post-compression parameters. Thickness, hardness, weight variation, %friability, disintegration time (DT) and drug content were well within the prescribed limit of official books.[14,15] *In-vitro* %drug release of all preparations of C1 to C5 were showed in Figure 8. For

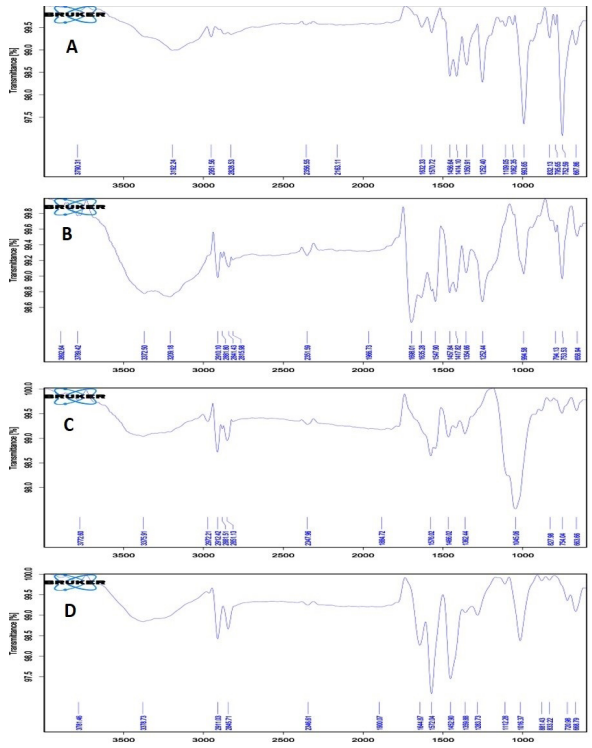

Figure 7: FTIR spectra of A. Pure losartan potassium, B. Drug with Carbopol 934, C. Drug with ethyl cellulose, D. Drug with all excipients

formulation, C5 98.10% of drug was released within 10 to 15 minutes so it was considered as burst release as accepted in the pulsatile drug delivery system. Batch C5 has shown all evaluation parameters comparatively better, so it was finalized as an optimized batch for further development of BPRT.

Preparation of BPRT by direct compression system

BPRT tablets were fabricated utilizing the direct compression technique and subjected to evaluation across various parameters.

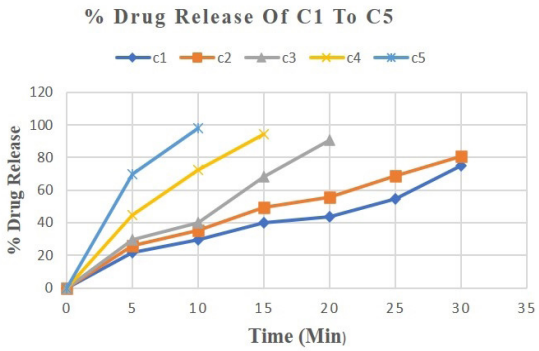

Figure 8: %drug release of C1 to C5

Evaluation of Various Tablet Properties of BPRT

The pre-compression evaluation parameters of the final blend are BD, TD; Hausner's ratio and CI as given in Table 4. The result indicated that all the batches of formulations were suitable for formulation of tablets by direct compression as it has optimum flowability and compressibility, and batch F5 was found to be optimized. The values of post-compression parameters and of the optimized batch (batch F5) are given in Table 5. Thickness, hardness, weight variation, %friability, disintegration time (DT) and drug content were well within the prescribed limit of official books.[14,15]

In-vitro mucoadhesion test

The results of adhesion time, mucoadhesive strength and force of adhesion of all formulations of F1 to F9 batches were as given in Table 5. Optimized batch F5 showed 9:15 hours of adhesion time, 30.25 gm of mucoadhesive strength and 2.96 N of adhesion force, which is sufficient for mucoadhesive tablet.

In-vivo mucoadhesion test

When X-ray images were captured at intervals of 2, 4, 8, and 12 hours, it was observed that the optimized formulation (batch F5) remained in the stomach of rabbits (Figure 9), thereby reflecting the mucoadhesive as well as bioadhesive properties.

Table 2: Pre-compression parameters of core tablet

Batch code	*BD (gm/cm^3)*	*TD (gm/cm^3)*	*Hausner's ratio*	*CI (%)*	*Angle of repose*
C1	0.35 ± 0.07	0.40 ± 0.08	1.14 ± 0.09	12.51 ± 0.10	29.01 ± 0.50
C2	0.39 ± 0.05	0.46 ± 0.11	1.17 ± 0.08	15.21 ± 1.19	28.19 ± 1.19
C3	0.37 ± 0.09	0.44 ± 0.06	1.18 ± 0.05	15.90 ± 1.10	21.15 ± 0.40
C4	0.38 ± 1.00	0.43 ± 1.07	1.13 ± 0.09	11.62 ± 0.20	26.15 ± 0.15
C5	0.41 ± 0.010	0.47 ± 0.01	1.14 ± 0.04	12.76 ± 0.30	26.9 ± 0.50

Table 3: Post-compression parameters of CT

Batch code	*Weight variation (mg)*	*Thickness (mm)*	*Hardness (Kg/cm^3)*	*Friability (%loss of weigh*	*DT (sec)*	*Drug content (%)*
C1	199 ± 0.13	3.11 ± 0.10	3.3 ± 013	0.52 ± 0.11	601.5 ± 0.90	97.50 ± 19
C2	200 ± 1.08	3.03 ± 0.05	3.5 ± 0.09	0.45 ± 0.34	510.9 ± 1.20	96.17 ± 0.65
C3	198 ± 0.06	3.07 ± 0.15	3.1 ± 0.19	0.58 ± 0.21	489.8 ± 0.90	98.10 ± 0.50
C4	202 ± 1.09	3.09 ± 0.09	3.9 ± 0.15	0.67 ± 0.32	350.2 ± 0.54	97.31 ± 0.75
C5	201.05 ± 0.2	3.06 ± 0.19	3.6 ± 0.19	0.44 ± 0.21	280.3 ± 0.60	98.15 ± 0.24

Table 4: Pre-compression parameters of BPRT

Batch code	*BD (gm/cm^3)*	*TD (gm/cm^3)*	*Hausner's ratio*	*CI (%)*	*Angle of repose (Θ)*
F1	0.52 ± 0.05	0.69 ± 0.01	1.32 ± 0.02	24.60 ± 0.9	27.01 ± 0.50
F2	0.51 ± 0.03	0.65 ± 0.04	1.27 ± 0.01	21.53 ± 1.2	28.19 ± 1.19
F3	0.55 ± 0.01	0.70 ± 0.01	1.27 ± 0.07	21.42 ± 0.8	29.15 ± 0.40
F4	0.50 ± 0.03	0.66 ± 0.06	1.32 ± 0.06	24.20 ± 0.5	26.15 ± 0.15
F5	0.57 ± 0.01	0.71 ± 0.02	1.24 ± 0.02	19.71 ± 1.1	26.90 ± 0.50
F6	0.53 ± 0.07	0.67 ± 0.09	1.26 ± 0.07	20.89 ± 0.9	28.17 ± 0.25
F7	0.55 ± 0.02	0.72 ± 0.03	1.30 ± 0.01	23.61 ± 1.1	27.51 ± 1.12
F8	0.56 ± 0.07	0.73 ± 0.01	1.30 ± 0.08	23.28 ± 1.3	28.52 ± 1.11
F9	0.57 ± 0.08	0.73 ± 0.03	1.28 ± 0.07	21.91 ± 1.9	29.39 ± 0.50

Table 5: Post-compression parameters of BPRT

Batch code	*Weight variation (mg)*	*Thickness (mm)*	*Hardness (kg/cm^3)*	*Friability (%)*	*Adhesion time (h)*	*Mucoadhesion strength (gm)*	*N*
F1	800 ± 1.2	7.06 ± 0.01	7.2 ± 0.01	0.62 ± 0.09	7:30	24.15	2.36
F2	801 ± 2.1	7.10 ± 0.06	7.3 ± 0.09	0.65 ± 0.07	8:10	29.30	2.87
F3	799 ± 1.9	7.08 ± 0.07	7.6 ± 0.12	0.61 ± 0.02	8:30	30.15	2.95
F4	800 ± 1.8	7.12 ± 0.09	7.4 ± 0.19	0.59 ± 0.01	7:50	25.30	2.48
F5	800 ± 1.5	7.06 ± 0.04	7.5 ± 0.19	0.54 ± 0.05	9:15	30.25	2.96
F6	798 ± 2.9	7.07 ± 0.05	7.6 ± 0.20	0.56 ± 0.04	9:45	32.15	3.15
F7	800 ± 1.1	7.09 ± 0.06	7.5 ± 0.09	0.55 ± 0.06	8:30	35.45	3.47
F8	801 ± 1.5	7.07 ± 0.09	7.6 ± 0.17	0.53 ± 0.12	8:45	36.10	3.54
F9	802 ± 2.1	7.15 ± 1.23	7.7 ± 0.01	0.52 ± 0.11	9:30	40.15	3.93

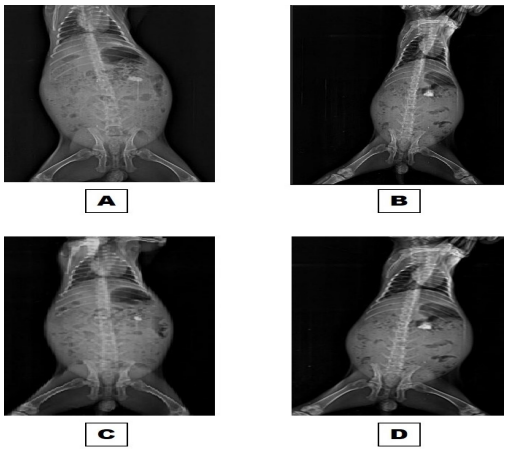

Figure 9: X-ray images A, B, C and D, taken at time intervals of 2, 4, 8 and 12 hours, respectively

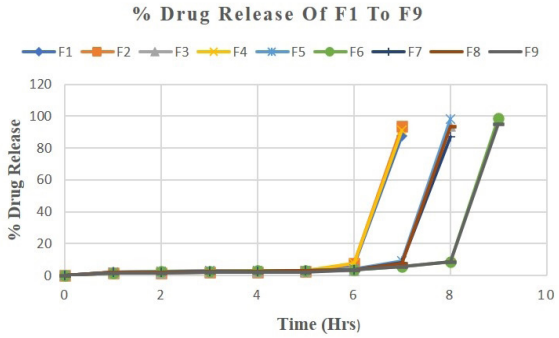

Figure 10: %drug release of F1 to F9

In-vitro Dissolution Study of BPRT

The preparations of bioadhesive pulsatile tablets of F1 to F9 showed distinct lag times and *in-vitro* %drug release of entirely preparations was showed in Figure 10. It has been observed that increased amount of polymers around tablets may have subsidized in the direction of the decreased drug releasing of losartan potassium caused by an increase in ethyl cellulose and Carbopol concentration. For formulation, F5 only 8.89% of drug was released up to at 8 hours and after that, 97.95% of drug was released for next hour so it was considered as burst release as accepted in pulsatile drug delivery. Also, F5 formulation showed the eight-hour desired lag time for hypertension as per the circadian rhythm.[25] A reduction in lag time was demonstrated when ethyl cellulose and Carbopol concentration rises.[26] It may be due to the reason of higher concentration of polymer decreases free water volume and increases the viscosity of the tablet coat, reasons decline in drug release.[27-33]

Stability Study

An optimized check-point batch (F5) was the subject of the stability investigation, which looked at a number of significant characteristics. The stability test results evidently show that the established pulsatile preparation was stable enough beneath accelerated and regulated circumstances. BPRT was determined to be stable under accelerated temperature settings

Table 6: Stability study of optimized batch (F5)

Time interval	*Weight variation (mg)*	*Hardness (kg/cm^3)*	*Thickness (mm)*	*Drug content (%)*	*% drug release*
0 days	800 ± 1.3	7.5 ± 0.15	7.06 ± 0.03	98.15 ± 0.50	97.95 ± 0.016
30 days	800 ± 1.4	7.6 ± 0.14	7.07 ± 0.06	97.10 ± 0.30	96.15 ± 0.027
60 days	800 ± 1.4	7.7 ± 0.19	7.09 ± 0.05	98.11 ± 0.20	96.55 ± 0.019
90 days	800 ± 1.5	7.7 ± 0.18	7.09 ± 0.07	98.11 ± 0.25	96.75 ± 0.019

since there was no appreciable change in physical appearance or other criteria such as weight variation, hardness, thickness, drug content and %drug release. After some intervals, the outcomes of several parameters studies are mentioned in Table 6.

DISCUSSION

The provided data presents a comprehensive evaluation of the development and characterization of BPRT containing losartan potassium. The study encompasses various analytical techniques and evaluation parameters to ensure the final product's compatibility, formulation optimization, and stability.

The initial investigation involved a compatibility study utilizing DSC, XRD, and FTIR methods. DSC thermograms revealed no significant shift in the melting point of losartan potassium when combined with different excipients, indicating compatibility. XRD patterns confirmed the crystalline nature of the drug, with no peaks observed in the physical blend, suggesting the drug was in an amorphous state, potentially enhancing dissolution properties. FTIR spectra further supported compatibility, showing that major peaks of functional groups in the pure drug remained intact in the final formulation.

Subsequent formulation development involved the preparation of core tablets and BPRT using direct compression methods. Pre-compression and post-compression evaluations ensured the suitability of preparations for tablet manufacturing, with optimized batches exhibiting desirable properties for example weight uniformity, hardness, friability, and drug content within specified limits.

The performance of BPRT formulations was evaluated through *in-vitro* and *in-vivo* examination. *In-vitro* dissolution examination revealed distinct lag times, with optimized formulations (e.g., batch F5) presenting a burst releasing of drug after the desired lag time of eight hours, aligning with the circadian rhythm for hypertension treatment. This delayed release pattern was attributed to the increased concentration of ethyl cellulose and Carbopol, which formed a barrier to drug release. Mucoadhesion tests confirmed the adhesive properties of the tablets, further supported by *in-vivo* retention studies in rabbits, demonstrating the tablets' bioadhesive characteristics.

Stability studies over a 90-day period under accelerated conditions showed that the optimized batch (F5) maintained physical integrity and met quality criteria, including weight variation, hardness and thickness, drug content, and drug release, indicating stability over time.

Overall, the data presented provides a comprehensive understanding of the formulation development, characterization, and stability assessment of BPRT containing losartan potassium. The optimized formulation demonstrates suitable properties for controlled release, offering potential benefits for hypertension management through pulsatile drug delivery systems.

CONCLUSION

The present research was about formulating and evaluating bioadhesive PDDS comprising losartan potassium as API for the management of hypertension. The research conducted successfully optimized the formulation of losartan potassium, with batch F5 demonstrating satisfactory outcomes, including a distinct lag time of 8 hours monitored through burst releasing and satisfactory mucoadhesion. Additionally, X-ray images taken at intervals of 2, 4, 8, and 12 hours revealed that the formulation remained in the stomach of rabbits. Consequently, this formulation shows promise for use in BPDDS of losartan potassium. This advancement could potentially improve patient compliance, reduce adverse effects, and optimize drug delivery to the intended site, thus representing a valuable contribution to future healthcare practices.

ACKNOWLEDGEMENT

The authors express gratitude to Lupin Pharmaceutical Limited, located in Palghar, Tarapur, India, for generously providing the losartan potassium drug as a gift sample.

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