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FORMULATION AND EVALAUTION OF EPROSARTAN MESYLATE FLOATING TABLETS

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Abstract:

Eprosartan mesylate is angiotensin-II receptor antagonist used for the treatment of high blood pressure. The drug has poor bioavailability due to limited oral absorption and maximum absorption at proximal intestine. Direct compression method was selected for preparation of tablets and the drug is formulated with hydroxyl propyl methyl cellulose (HPMC) K15M, hydroxyl propyl methyl cellulose E15, Xanthan gum, Guar gum, Chitosan, Carbopol 940 P, Carbopol 934P etc. Eight formulations were made and evaluated for General appearance, Thickness, Hardness or Crushing strength Test, Friability Test, Estimation of drug content, In-vitro buoyancy studies and In-vitro drug release and the results obtained for the performed tests were found within the range of specified limits. Based on studies of floating lag time and entire floating time, uniformity of medication content, and in vitro dissolution, the preparation comprising karaya gum (F7) was chosen as the improved formulation because it had the smallest FLT of 1 sec, the longest TFT of 580 min, and the highest percentage of drug release at the termination of 600 min. It was subsequently given a release kinetics investigation, and the maximum correlation coefficient revealed t a zero-order non-fickian diffusion-controlled system. When the optimum preparation compared to FTIR results of pure drug, it was discovered that there was no drug-excipient interaction. Following stability investigations, it was discovered that the investigated post-compression parameters had not undergone any significant modifications. From the above findings, it was determined that Eprosartan mesilate floating tablets comprising karaya gum (F7) prolong the retaining of dosage form in stomach area for extended time and reduce drug variation in plasma concentration by regular treating of conventional immediate release dosage form.

Keywords: *Eprosartan mesylate HPMC K15M, HPMC E15, In-vitro buoyancy studies, In-vitro drug release.*

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INTRODUCTION:

Controlled release drug delivery systems that retain in the stomach for a long time have many advantages over sustained release formulations [1]. Such retention systems (GRDDS) are important for the drugs that are degraded in intestine or for drugs like antacids or certain enzymes that should act locally in the stomach. Gastric retention may increase solubility for the drugs which are poorly soluble in intestine due to alkaline pH before they are emptied, resulting in improved bioavailability [2]. These systems are also advantages in improving GIT absorption of a drug with narrow absorption windows as well as for controlling release of those drugs which are having site-specific absorption limitations. These systems are useful in case of those drugs which are best absorbed in stomach. Thus, the drug candidates having "absorption window" in a particular region of GI tract are difficult to be designed as oral Controlled release drug delivery system (CRDDS). This is because only the drug released in the region preceding the "window" and vicinity of "absorption window" is available for absorption [3,4].

Drug released from the Controlled release drug delivery systems after the "absorption window" has been crossed goes waste with no or negligible absorption occurring. This phenomenon drastically decreases the time available for drug absorption, after release of drug from CRDDS, thus jeopardizing the success of delivery system [5]. The CRDDS possessing the ability of being retained in the stomach are called gastro retentive drug delivery systems (GRDDS) and they can help in optimizing the oral controlled delivery of drug having "absorption window" by continuously releasing drug prior to absorption window, for prolonged period of time thus ensuring optimal bioavailability.

Floating drug delivery systems (FDDS) or hydrodynamically balanced systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. After the release of the drug, the residual system is emptied from the stomach [6,7].

Eprosartan mesylate is angiotensin-II receptor antagonist used for the treatment of high blood pressure. The drug has poor bioavailability due to limited oral absorption and maximum absorption at proximal intestine. Direct compression method was selected for preparation of tablets and the drug is formulated with hydroxyl propyl methyl cellulose (HPMC) K15M, hydroxyl propyl methyl cellulose E15, Xanthan gum, Guar gum, Chitosan, Carbopol 940 P, Carbopol 934P etc.

MATERIALS & METHODS:

Materials

Eprosartan mesylate was purchased from Hetero Drugs, Hyderabad. Carbopol 934P, 940 P was purchased from Yarrow Substances Ltd, Mumbai. HPMC E 15, K15 was purchased from Granules India Pvt Ltd, Hyderabad. Ethyl cellulose was purchased from Sigma Aldrich.

Methods

Drug excipient compatibility studies

FTIR analysis

The interaction between the medication molecule and the carrier in the solid state was evaluated using FTIR. An FTIR specto-photometer was used to record the IR spectra [8]. The moisture-free samples were glance over in the 4000-400 cm^{-1}.

Eprosartan mesilate floating tablets

By using the direct compression method, floating tablets were created [9,10]. Except for talc and magnesium stearate, the medication was combined with the remaining excipients after being weighed and separately passing through filter no. 60. Lastly, talc and magnesium stearate were added and well combined before being compacted into tablets in an eight-station tablet compression machine utilizing a flat round punch.

Table 1: Preparation of floating tablets of Eprosartan mesilate

Preparation Code (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Eprosartan mesilate	350	350	350	350	350	350	350	350
Carbopol 934P	80	-	-	-	-	-	-	-
HPMC E 15	-	80	-	-	-	-	-	-
Guar gum	-	-	80	-	-	-	-	-
Chitosan	-	-	-	80	-	-	-	-
Carbopol 940 P	-	-	-	-	80	-	-	-
Xanthan gum	-	-	-	-	-	80	-	-
Karaya gum	-	-	-	-	-	-	80	-
HPMC K15	-	-	-	-	-	-	-	80
$NaHCO_3$	25	25	25	25	25	25	25	25
Citric acid	10	10	10	10	10	10	10	10
MCC	20	20	20	20	20	20	20	20
Talc	10	10	10	10	10	10	10	10
Magnesiumstearate	5	5	5	5	5	5	5	5
Entire weight (mg)	500	500	500	500	500	500	500	500

Characterization of floating tablets:

Pre-Compression parameters:

Bulk density:

A 100 ml measure was occupied with a precisely weighed amount of powder mixture without being compacted. The powder was gently levelled deprived of compressing, and the bulk volume that had not yet settled, or Vo, was noted [11].

pb = M / Vo

where pb, M, and Vo stand for the respective quantities of bulk density, sample weight, and bulk volume of powder.

Tapped density:

The sample used to determine bulk density was tapped in a 100 ml measuring cylinder 500 times at until the variance among the subsequent measurements was <2%.

By means of the equation ptap = M / Vf,

where ptap, M, and Vf stand for the tapped density, sample weight, and powder tapped volume, correspondingly.

Compressibility index:

The compressibility index, reflects the variations among the bulk and tapped densities for poor flowing ingredients since there are often stronger interparticle connections and a better disparity amid the two [12].

Carr's Index is equal to 100(ptap - pb) / ptap,

where pb and ptap are the respective values for bulk density and tapped density.

Hausner's ratio:

The relationship between tapped density and bulk density is used to calculate Hausner's ratio. The flow property will be better the lower the Hausner's ratio value.

Hausner's Ratio = ptap / pb,

Post-Compression parameters:

General appearance:

The size, shape, surface roughness, physical defects every tablet from every formulation were examined [13].

Thickness:

Using a vernier calliper, the width of the tablets from each lot was measured.

Hardness test:

The "Monsanto Hardness Tester" is the device used to gauge tablet hardness. Using a Monsanto tablet hardness tester, the hardness of six tablets from each batch was assessed [14].

Friability test:

The Roche friabilator, which subjects the tablets to the joint effects of abrasion and shock by employing a plastic compartment that circles at 25 rpm and drops the drugs a distance of six inches with each revolution.

$$\text{Percentage loss} = \frac{\text{Initial mass} - \text{Final mass}}{\text{Initial mass}} x\ 100$$

Weight variation test:
Each batch of twenty tablets was randomly chosen, and the average weight was computed. After that, each tablet was weighed individually, the results of which were compared to the average weight, and the weight variation was articulated as a percentage deviation [15].

Drug content:
Tablets were crushed in mortar and pestle and converted to powder. Add buffer, collect the supernatant liquid. Eprosartan mesilate was detected in the eluents at a wavelength of 233 nm [16].

Determination of swelling index:
Its pH value of 1.2 was established in simulated stomach fluid at room temperature. Over a 24 hr period, the tablet's enlarged weight was calculated [17]. A percentage was used to express the swelling index (SI)

$$SI = \frac{\text{Final mass of tablet} - \text{Initial mass of tablet}}{\text{Initial mass of tablet}} x\ 100$$

***In vitro* buoyancy studies:**
In order to conduct this test, arbitrarily selected tablets from each preparation were placed in a beaker with 100 ml of simulated stomach fluid pH 1.2, kept at 37 ºC. Floating lag time (FLT) and Total floating time (TFT) were assessed [18].

***In vitro* dissolution studies:**
With the help of the USP Dissolution Testing Apparatus II (Paddle type), the drug release rate from floating tablets was calculated. 900 cc of simulated stomach fluid pH 1.2, 37 ±0.5ºC, and 50 rpm were used in the dissolving test. For 10 hours, an aliquot of the sample was taken out of the dissolution equipment at predetermined intervals and replaced with new dissolution medium [19]. Whatman Filter Paper No. 41 was used to filter the samples. These solutions' 233 nm absorbance was measured. A calculation resulting from a standard arc was used to calculate the cumulative percentage of medication release. Eprosartan mesilate floating tablets were used to repeat the process, and absorbance was recorded at 233 nm.

***In vitro* drug release kinetics:**
Drug release data was analysed in command to pinpoint the precise mechanism of medicine release from the tablets. The goodness of fit test was cast-off to determine the selection criteria for the best model.
Zero order calculation
% drug released = kt
First order calculation
Log % unreleased = kt/2.303
where k is constant and t is time

Korsmeyer – Peppas equation

$$M_t / M_\infty = kt^n$$

where M_t / M_∞ signifies the portion of medicine release at time t and n is the diffusion coefficient.
or

Log medication released = log k + n log t
where n is releasing exponent
Higuchi equation
% drug released = $kt^{0.5}$

Stability studies
Finest floating tablets of were packaged and loaded for three months at accelerated settings like 40°C, 2°C, 75%, and 5% RH [20]. The effectiveness of various post-compression settings was assessed during the initial stage and once a month after that.

RESULT & DISCUSSION:

Drug excipient Compatibility study by FTIR analysis

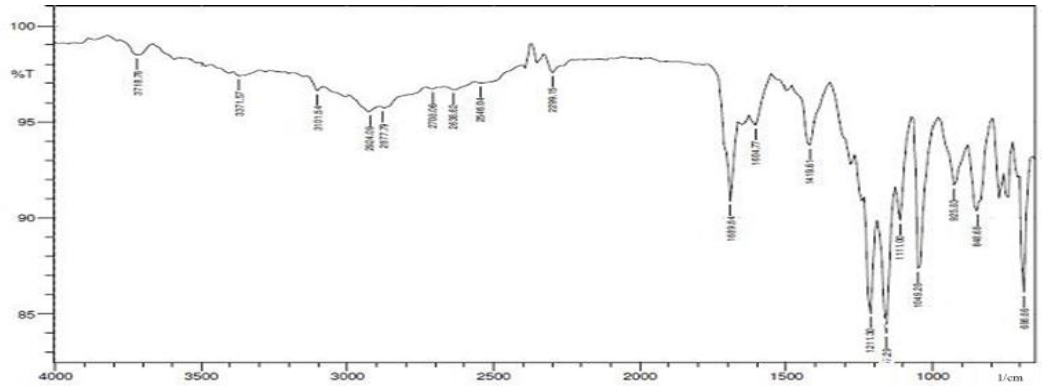

Fig. 1: FTIR spectra of Eprosartan mesilate

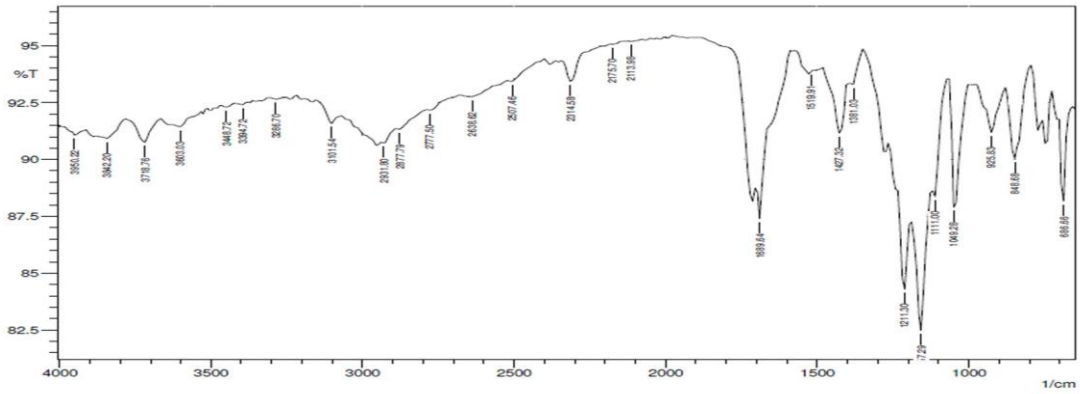

Fig. 2: FTIR spectrum of best preparation of Eprosartan mesylate

The NH stretching peak appeared at 3371 cm-1, the aromatic CH peak at 3101 cm-1, the -COOH peak at 2924 cm-1, the C=C aromatic peak at 1639 cm-1, the S=O peak at 1111 cm-1, and the C-N vibration peak at 1049 cm-1. From the findings, it was concluded that there was no chemical contact amid the medicine and excipients in the best preparation of eprosartan mesilate when compared with spectra of uncontaminated medicine.

Table 2: Assessment of floating tablets of Eprosartan mesilate

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Friability	Weight variation	FLT (sec)	TFT (min)	Drug content (%)
F 1	2.88±0.010	4.88±0.08	0.30	0.508±0.006	1	265	90.98
F 2	2.96 ± 0.16	4.58±0.08	0.38	0.502±0.006	1	335	89.0
F 3	2.78±0.005	4.65±0.20	0.30	0.488±0.004	1	320	91.00
F 4	3.01±0.006	4.88±0.08	0.08	0.504±0.18	1	255	87.88
F 5	2.98±0.004	4.88±0.32	0.18	0.488±0.008	1	320	88.90
F 6	2.88±0.006	4.90±0.09	0.28	0.488±0.004	1	385	89.92
F 7	2.7±0.005	4.8±0.2	0.29	0.488±0.006	1	575	92.20
F 8	2.78±0.005	4.88±0.08	0.30	0.488±0.18	1	445	90.12

Table 3: *In vitro* dissolution data for floating tablets

Time(min)	% Medication released							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	16.54	17.14	15.29	18.28	11.61	11.24	2.58	4.72
10	28.24	28.91	21.67	22.32	24.19	24.91	7.48	10.96
30	36.32	36.27	31.28	34.17	35.29	35.64	13.27	21.24
60	48.65	41.78	47.35	59.41	48.61	46.14	25..60	32.62
90	56.87	49.45	56.27	71.56	54.73	58.91	32.69	41.24
120	65.62	58.27	68.62	78.81	60.81	62.27	41.09	51.33
180	71.36	65.34	72.41	84.67	72.14	75.69	48.33	59.71
240	84.27	78.54	85.21	90.65	84.27	81.42	55.24	67.36
300	92.68	84.82	92.32	--	91.84	88.13	64.54	72.96
360	--	89.65	--	--	--	92.54	72.57	80.02
420	--	--	--	--	--	--	79.68	86.27
480	--	--	--	--	--	--	84.48	94.68
540	--	--	--	--	--	--	89.76	--
570	--	--	--	--	--	--	93.24	--
600	--	--	--	--	--	--	98.47	--

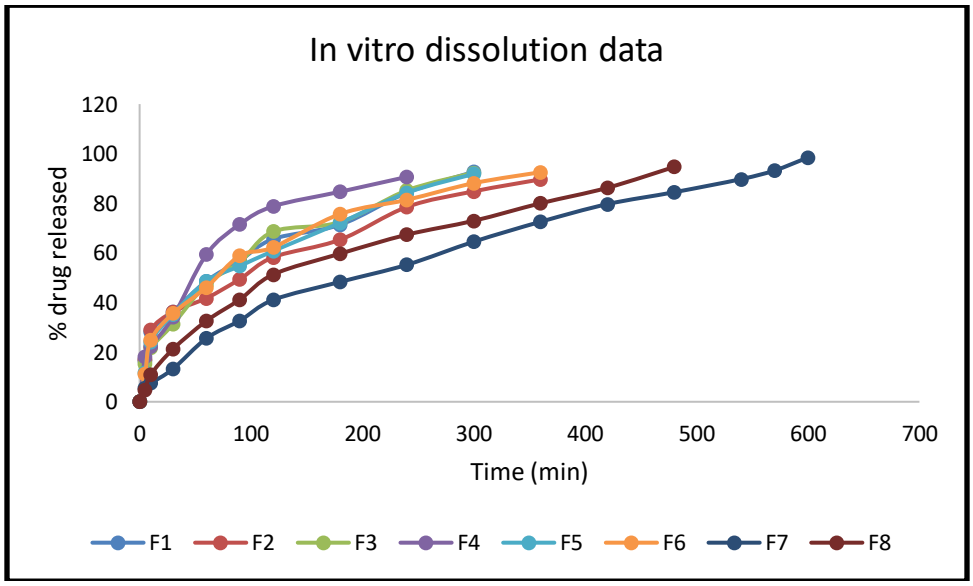

Fig. 3*: In vitro* dissolution outline for floating tablet of Eprosartan mesylate

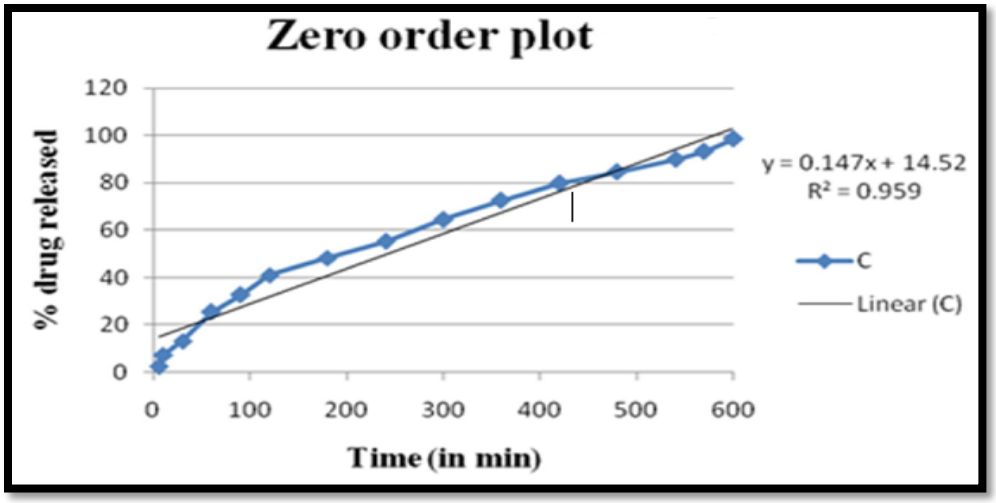

Fig. 4: Zero order design of F7

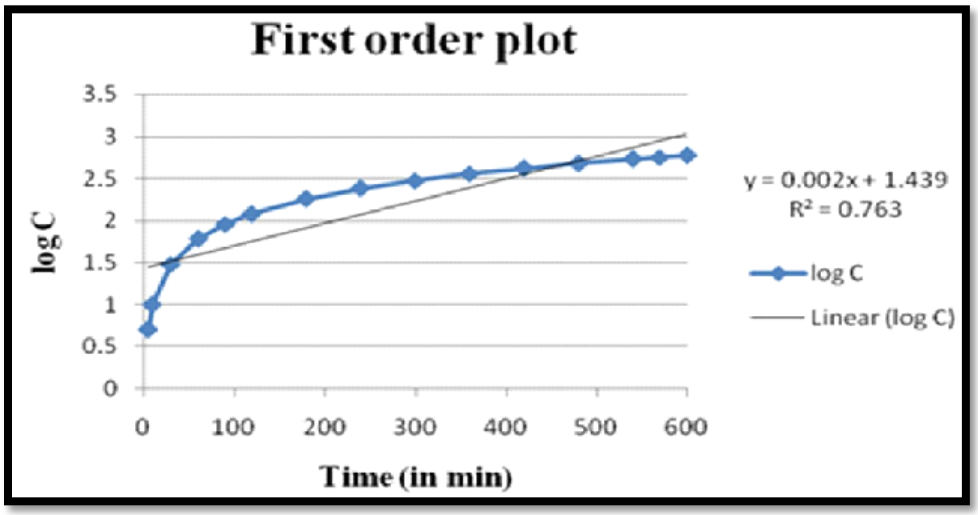

Fig. 5: First order plot of F7

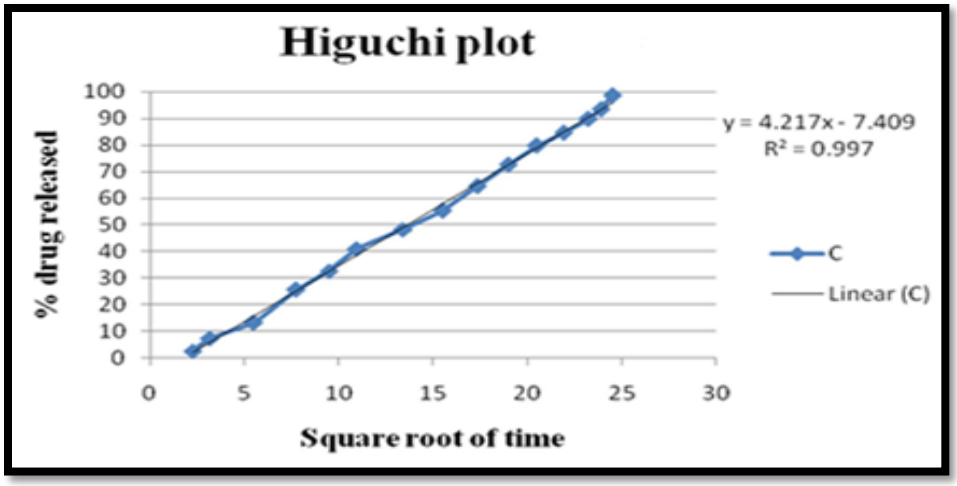

Fig. 6: Higuchi plot for of F7

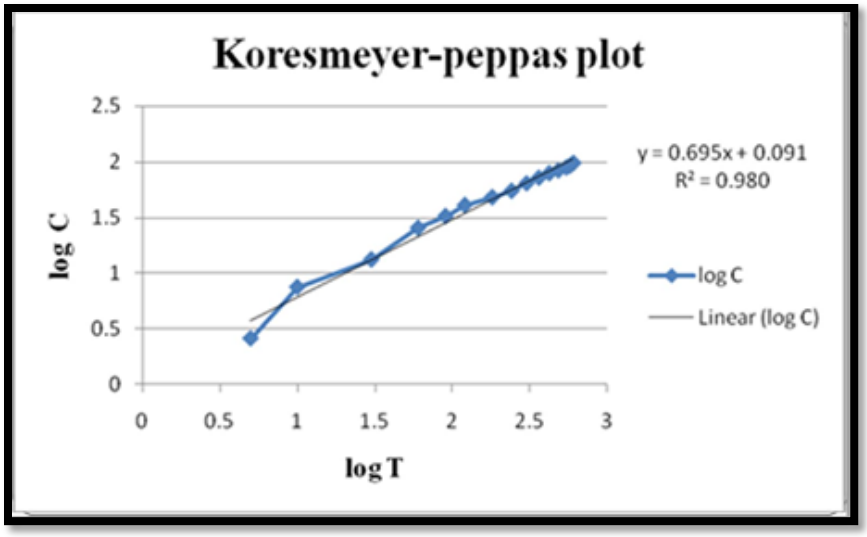

Fig. 7: Koresmeyer peppas plot of F7

According to the findings, all of the tablets had decent aesthetics and were not cracked; their thickness ranged from 2.78 to 3 mm. These tablets ranged in hardness from 4.70 to 4.94 kg/cm2, in friability from 0.16 to 0.45% w/w, and in weight fluctuation from 5%w/w. The overall floating period ranged from 260 to 580 minutes for all formulations, with a floating lag time of 1 second.
All of the formulations had drug concentrations between 86.32 and 93.14%. Compared to other formulations, the preparation containing karaya gum (F7) drifted for a longer period of time in simulated stomach fluid pH 1.2, according to the findings of the in vitro dissolution investigations shown in table 15. This is because karaya gum has the highest swelling index, which encourages the development of porous gel more than other polymers. In vitro dissolution studies demonstrated sustained drug release from floating tablets for 600 min. This finding was additional supported by the release kinetics, which shadows zero order non-fickian diffusion.

Stability studies

When stability investigations on the optimized preparation E7 were conducted, they showed that the parameters did not significantly alter.

Table 4: Stability studies facts for finest floating tablet of Eprosartan mesylate

Constraints	Original	Afterward 3 months
Hardness (kg/cm^2)	5.18	5.28
Friability (%)	0.36	0.34
FLT (sec)	1	1
TFT (min)	575	580
Medicine content (%)	92.80	92.30

CONCLUSION:

It had become a challenging experience and effort for a formulator to develop and innovate a drug with maximum bioavailability. In the present study the focus of research is in the treatment of Hypertension, which is one of the most prevalent cardiovascular diseases in the world, affecting a big proportion of the adult and old age population. Eprosartan mesylate is angiotensin-II receptor antagonist used for the treatment of high blood pressure. The drug has poor bioavailability due to limited oral absorption and maximum absorption at proximal intestine. This warrants and offers the use of Gastro Retentive Drug Delivery System (GRDDS) for sustained release formulation in order to achieve prolonged action and to improve patient compliance. In the current study, an effort was ended to formulate a floating tablet individually using a direct compression method. Based on studies of floating lag time and entire floating time, uniformity of medication content, and in vitro dissolution, the preparation comprising karaya gum (F7) was chosen as the improved formulation because it had the smallest FLT of 1 sec, the longest TFT of 580 min, and the highest percentage of drug release at the termination of 600 min. It was subsequently given a release kinetics investigation, and the maximum correlation coefficient revealed t a zero-order non-fickian diffusion-controlled system. When the optimum preparation compared to FTIR results of pure medicine, it was discovered that there was no drug-excipient interaction. Following stability investigations, it was discovered that the investigated post-compression parameters had not undergone any significant modifications.

From the above findings, it was determined that Eprosartan mesilate floating tablets comprising karaya gum (F7) prolong the retaining of dosage form in stomach area for extended time and reduce drug variation in plasma concentration by regular treating of conventional immediate release dosage form.

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