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Research Article

DESIGN AND CHARACTERIZATION OF CHLORZOXAZONE FLOATING BIOADHESIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Objective: The objective of the work is to formulate chlorzoxazone floating bioadhesive tablets which will significantly improve the bioavailability of drugs under the condition of prolonged use of drugs and reduce the total dosage of administered drug and reduce the side effect.

Methods: Floating bioadhesive tablet was prepared by direct compression of polymer such as HPMCK4M and Carbopol934p in combination.

Result: After analysis of different evaluation parameter and drug release, F9 batch was selected as promising formulation for delivery of chlorzoxazone floating bioadhesive tablets with 92.1% drug release at 12th h.

Conclusion: It was observed that the combination of polymers in 22.5% (HPMCK4M) and 12.5% (Carbopol 934p) give the best drug release and sustain the drug release for 12 h. Among the other batches, F9 batch was selected as an optimized batch because the pre- and post-compression parameters results are satisfactory.

Keywords: Chlorzoxazone, Floating bioadhesive tablets, HPMCK4M, Carbopol 934p, Direct compression.

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INTRODUCTION

The design of oral modified release dosage form is intended to optimize a therapeutic regimen by providing controlled delivery of drug over the entire dosing interval. Among the various routes of administration oral intake have long been the most convenient and commonly employed route. There are many ways to intend modified release dosage forms for oral administration and one of them is floating bioadhesive tablets [1].

FBDS is a gastro-retentive dosage form, which can prolong the gastric residence time to produce an acceptable drug bioavailability. Floating bioadhesive drug delivery system (FBDDS) is suitable for drugs with an absorption window in the stomach or the upper small intestine, for drugs which act locally in the stomach and for drugs that are poorly soluble or unstable in the intestinal fluid FBDDS or hydro-dynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Based on the mechanism of buoyancy, two distinctly different technologies, i.e., non-effervescent and effervescent systems, have been used in the development of FBDDS.

The effervescent system uses matrices prepared with swellable polymers and effervescent components, for example, sodium bicarbonate and citric acid or stearic acid. In non-effervescent FBDDS, the drug mixes with a gel-forming hydrocolloid, which swells in contact with gastric fluid after oral administration to maintain a relatively stable shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy on these dosage forms [2].

Chlorzoxazone (structure shown in Fig. 1), (2-hydroxy-5-chlorobenzoxazole) is a Class-II drug low solubility, high permeability, a centrally acting central muscle relaxant with sedative properties. It is claimed to inhibit muscle spasm by exerting an effect primarily at the level of the spinal cord and subcortical areas of the brain [3].

MATERIALS AND METHODS

Chlorzoxazone was a procured from Yarochem, Mumbai. HPMCK4M were procured from Chemdyes Corporation, Gujarat. Carbopol 934p were procured from Research Lab-Fine Chem. Industries, Mumbai. Lactose, Sodium Bicarbonate, Magnesium stearate was procured from Thomas Baker Pvt. Ltd, Mumbai. All reagents used were of analytical grade.

METHODS

Drug excipient compatibility studies

Fourier-transform infrared (FT-IR) spectrum matching approach was used for detection of any possible chemical interaction between the chlorzoxazone and polymers. IR spectroscopy was conducted using a FTIR spectrophotometer (Jasco FT-IR 410), and the spectrum was recorded in the wavelength region of 4000–400/cm. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressed into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path, and the spectrum was obtained. Samples were prepared for chlorzoxazone, polymers such as Carbopol 934, HPMCK4M and physical mixture of drug with polymers. The spectra obtained were compared and interpreted for the functional group peaks [4].

Preformulation studies

Ultraviolet (UV)-spectrum of drug chlorzoxazone

The solution of chlorzoxazone in 0.1N HCL screened in the range of 200–400 nm.

Melting point

The melting point of the drug was determined using packing a capillary method.

Physical properties of drug powder

The drug chlorzoxazone undergoes through various tests to know its physical properties.

Table 1: Composition floating bioadhesive tablet of chlorzoxazone prepared by direct compression

Ingredient	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Chlorzoxazone	300	300	300	300	300	300	300	300	300
HPMC K4M	87.5	87.5	87.5	100	100	100	112.5	112.5	112.5
Carbopol 934p	20	25	30	20	25	30	20	25	30
Sodium bicarbonate	50	50	50	50	50	50	50	50	50
Mg. St.	5	5	5	5	5	5	5	5	5
Lactose	37.5	32.5	27.5	25	20	15	12.5	7.5	2.5
Total	500	500	500	500	500	500	500	500	500

Construction of calibration curve

The calibration curve for chlorzoxazone was determined in 0.1N HCl pH 1.2 in UV spectrophotometer in Fig. 2.

The flow properties of granules were characterized in terms of angle of repose, Carr's index, Compressibility index, and Hausner's ratio. The bulk density and tapped density were determined, and from this data, Carr's index and Hausner's ratio were calculated [5].

Formulation of floating bioadhesive tablet of chlorzoxazone

Floating bioadhesive drug delivery of chlorzoxazone was prepared by direct compression method. The composition of formulations is shown in Table 1. All the powders were passed through a 60 mesh sieve. The required quantity of drug, polymers mixture and diluents were mixed. The powder blend was lubricated with magnesium stearate and compressed using (11.6 mm diameter punches) multiple punch rotary tablet machine. In total, 9 formulations containing different amounts of HPMCK4M and Carbopol934p combination were prepared.

Characterization of matrix tablets

Thickness

Selected randomly 5 tablets from each batch were used for thickness determination. The thickness of each tablet was measured in mm using a digital Vernier Caliper their values were reported in millimeters. The mean and standard deviation was calculated and reported.

Weight variation test

A total of 20 tablets were selected randomly from each batch and individually weighed using an electronic balance. The average weight was calculated. The percentage deviation from average weight was reported.

Hardness

The hardness of five tablets which randomly selected from each batch was measured using Monsanto hardness tester and expressed in kg/cm^2.

Friability

Five tablets were randomly selected from each batch and accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablet re-weighed and percentage loss was determined. Friability of tablets was performed using Roche Friabilator.

Drug content analysis

Five tablets were weighed individually, and the average was calculated and grounded in a mortar with a pestle to get a fine powder. An amount equivalent to 300 mg of the drug was extracted with 100 ml of 0.1 N HCl. The drug content was determined by UV spectrophotometer at a wavelength 282 nm, and the percentage drug content was calculated.

Swelling index

The swelling of the mucoadhesive polymer is an important factor affecting adhesion. To carry out the study, a tablet was weighed and placed in a Petri dish containing 5 ml of 0.1N HCL buffer pH 1.2 in 5 hrs at regular interval of time (1, 2, 3, 4, and 5) the tablet was taken care by using filter paper. The swelling index was calculated using the following formula,

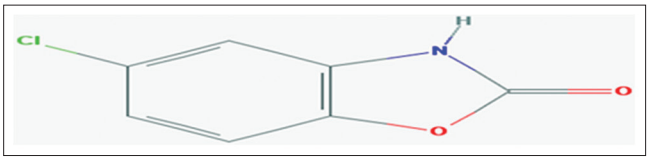

Fig. 1: Chlorzoxazone drug structure

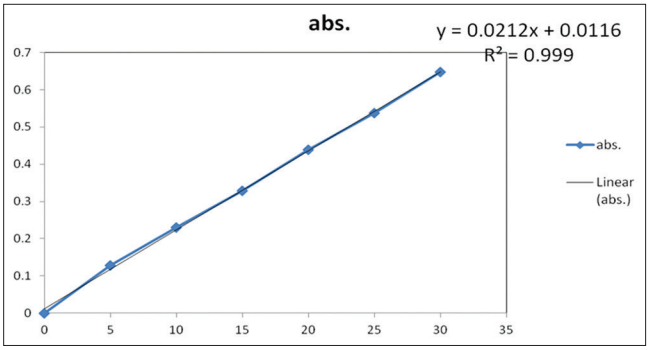

Fig. 2: Calibration curve of chlorzoxazone

Swelling index = $w_t - w_0 / w_0 \times 100$

Mucoadhesive strength measurement [6-9]

The mucoadhesive strength of the tablet was measured on the modified physical balance apparatus consists of a modified double beam physical balance in which the right and left pan has been replaced by lighter pans. The left side of the balance was made 5 g heavier than the right side by placing a 5 g weight on left side pan. Another Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in a beaker, which was then placed below the left-hand set of the balance.

The goat gastric mucosa was used as the model membrane, and pH 1.2 was used as the moistening fluid. The goat gastric mucosa was kept in Tyrode solution at 37°C for 2 h. The underlying mucous membrane was separated and washed thoroughly with a pH 1.2 solutions. It was then tied to a Teflon-coated glass slide, and this slide was fixed over the protrusion in the Teflon block using a thread. The block was then kept in a beaker containing pH 1.2 buffer solutions at the level that just touches the membrane. By keeping a 5 g weight on the right pan, the two sides of the balance were made equal. The beaker with the Teflon block was kept below the left hand set up of the balances. The tablets of each batch were struck on to the lower side of the left-hand side pan. The 5 g weight from the right pan was then removed. This lowered the left pan along with the tablet over the membrane with a weight of 5 g. This was kept undisturbed for 5 min. Then, the weight on the right-hand side was slowly added in an increment of 0.5 g till the tablet just separated from the membrane surface. The excess weight on the right pan, i.e., total weight −5 g was taken as a measure of the mucoadhesive strength.

From the mucoadhesive strength, the force of adhesion was calculated using the following formula:

$$Force\ of\ adhesion(N) = \frac{Bioadhesive\ strength}{100} \times 9.81$$

***In vitro* buoyancy study [10]**

The in vitro buoyancy was determined by measuring floating lag time and duration of buoyancy. The tablets were placed in a 100 ml beaker containing 100 ml of 0.1 N HCl. The time required for the tablet to rise to the surface and float was taken at the floating lag time. The time for which tablets kept floating was termed as "buoyancy time" of the tablets which were determined for all the formulations.

***In vitro* drug release study**

In vitro, drug release studies were performed using the USP dissolution apparatus Type-II. The drug release profile was studied in 900 ml of 0.1N HCl buffer of pH 1.2 at 37±0.2°C. The rotational speed of the paddle was 50 RPM. Aliquots of 5 ml of dissolution medium were withdrawn at specific time intervals, filtered and replaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed after appropriate dilution by a UV spectrophotometer (Shimadzu UV 1800) at 282 NM, and drug release was determined from the standard curve.

Statistical analysis

To evaluate the contribution of each factor with different levels on responses, two-way analysis of variance (ANOVA) was performed using GraphPad Prism 7.04 Software.

RESULTS AND DISCUSSION

Drug excipient compatibility studies

The results showed that the principle IR peak of pure drug, its physical mixture with polymer was almost similar, signifying no interaction between drug and polymer during formulation of tablets.

UV-spectrum of drug chlorzoxazone

The solution of chlorzoxazone in 0.1N HCL was found to exhibit maximum absorption (λ_{max}) at 282 nm after scanning in the range of 200–400 nm. As shown in Fig. 3.

Physical properties of drug powder

The drug chlorzoxazone undergoes through various tests to know its physical properties Table 2.

Preformulation studies of powders

The prepared powders were characterized for angle of repose, bulk density, tapped density, Hausner's factor, Carr's index, and compressibility index and the values were reported in Table 3. The angle of repose of the different batches of powders was determined as per the method mentioned earlier, and the results ranged between 20.005° and 24.38°. The powder with the angle of repose <20° indicates excellent flow properties. The bulk densities of powder were ranged between 0.25 g/cm^3 and 0.33 g/cm^3. The low bulk density is due to the presence of more fines in the powder. Tapped density ranged between 0.303 g/cm^3 and 0.4 g/cm^3.

Evaluation of bioadhesive floating tablet

Weight variation, thickness, hardness, friability, and drug content analysis

The results were represented in Table 4. The diameters of prepared tablets were ranged from 11.98 to 12.003. The weights of prepared tablets were ranging from 488.1±24.40 to 494.2±24.71. The thickness of prepared tablets ranged from 4.08 to 4.48. It was also observed that increasing the polymer concentration resulted in a slight decrease in the thickness of tablet formulations. These results indicate that the polymers may have high binding properties. Hardness of tablet ranged from 5.16 to 7.34 kg/cm^2. For all formulation, friability ranged from 0.0 to 0.7% it indicating that friability is within the prescribed limit of 1%. The drug content (%) of floating bioadhesive tablet from each formulation was found to be uniform and ranged from 93.99 to 96.98%.

Table 2: Physical properties of drug powder

Sr. No	Test	Result
1	Bulk density (g/ml)	0.433
2	Tap density (g/ml)	0.534
3	Carr's compressibility	19%
4	Hausner's ratio	1.23
5	Angle of repose	30°
	Flow properties	Passable

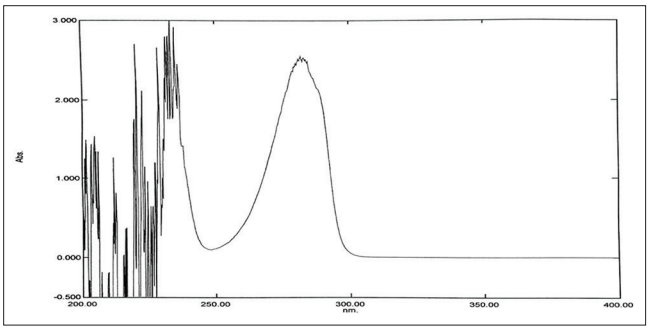

Fig. 3: Ultraviolet spectrum of chlorzoxazone

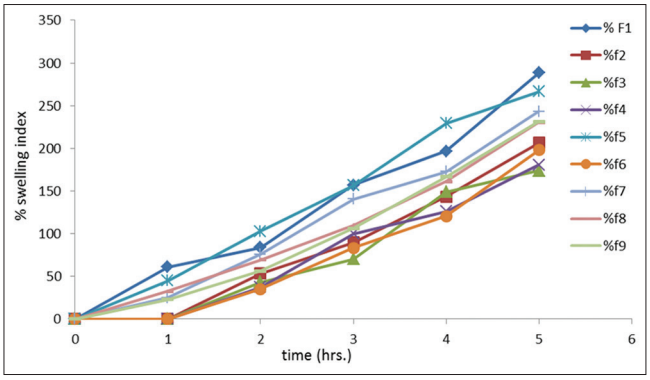

Fig. 4: Swelling index studies of floating bioadhesive tablets

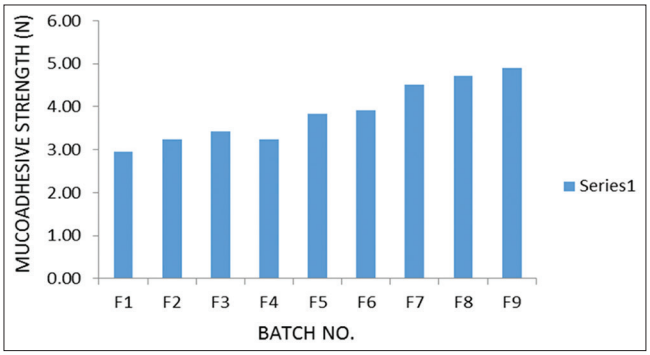

Fig. 5: Bioadhesive strength of a tablet

Swelling studies

Swelling index profile of all formulations is shown in Table 5 and Fig. 4. Swelling index of all formulations is varies between 230.61 and 288.36%. Swelling of the matrix, this is indicated by the transition of the polymer from the glassy to the rubbery state. It is an important parameter in determining the release characteristics of the matrix system. As swelling process proceeds, the gel layer gradually becomes thicker, and therefore the drug concentration gradient along the diffusional path length is decreased results in the slow drug release.

Table 3: Pre-compression parameter of blend

Batches	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio	Carr's index (%)	Angle of repose (degree)
F1	0.33	0.4	16.66	1.21	18	20.005
F2	0.303	0.384	21.21	1.267	22	23.85
F3	0.277	0.344	19.44	1.515	20	21.55
F4	0.294	0.344	14.70	1.12	14.6	21.31
F5	0.25	0.33	25	1.32	25	21.75
F6	0.25	0.312	20	1.248	19.9	21.44
F7	0.25	0.303	17.5	1.212	17.5	22.04
F8	0.263	0.303	13.5	1.152	13.3	24.38
F9	0.277	0.33	16.66	1.19	17	21.75

Table 4: Tablet evaluation

Formulation code	Diameter* (mm)	Thickness* (mm)	Hardness* (kg/cm^2)	Friability (%)	% Weight variation^	% drug content*
F1	11.98±0.005	4.18±0.036	5.16±0.288	0	492.4±24.62	93.99±0.00
F2	11.99±0.005	4.08±0.011	5.33±0.288	0.7	493.5±24.67	94.86±0.375
F3	11.99±0.005	4.32±0.034	5.5±0.00	0.5	491.8±24.59	96.56±0.640
F4	12.003±0.005	4.40±0.02	6±0.00	0.6	493.9±24.69	96.56±0.640
F5	12.003±0.005	4.48±0.011	6.16±0.288	0	493.2±24.66	95.07±0.375
F6	12±0.017	4.48±0.015	6.16±0.288	0.6	489.6±24.48	95.93±0.00
F7	11.99±0.005	4.33±0.02	7±0.00	0.5	493.6±24.68	96.76±0.393
F8	11.98±0.01	4.3±0.026	7.16±0.288	0.7	488.1±24.40	96.77±0.416
F9	11.99±0.02	4.32±0.01	7.34±0.288	0	494.2±24.71	96.98±0.393

*All values expressed in mean±SD, n=3, ^all value expressed in mean±SD, n=10. SD: Standard deviation

Table 5: Swelling index studies of floating bioadhesive tablets

Time	%F1	%F2	%F3	%F4	%F5	%F6	%F7	%F8	%F9
0	0	0	0	0	0	0	0	0	0
1	61.22	53.60	43.15	37.37	44.92	35.41	25.25	32.65	22.91
2	83.67	89.69	70.12	100.00	102.89	83.33	75.75	69.38	56.25
3	157.14	143.29	148.96	126.26	156.72	120.83	140.40	110.20	106.25
4	196.93	206.59	173.85	180.80	229.19	197.91	172.72	161.22	166.67
5	288.36	283.50	263.07	261.61	266.45	264.58	243.43	230.61	231.25

Table 6: Bioadhesive strength of a tablet

Batch no.	Bioadhesive strength (g)	Bioadhesion force (N)
F1	30	2.94
F2	33	3.24
F3	35	3.43
F4	33	3.24
F5	39	3.83
F6	40	3.92
F7	46	4.51
F8	48	4.71
F9	50	4.91

Table 7: Floating lag time

Batch no.	Floating lag time (s)	Total floating time (h)
F1	10±0.5	>12
F2	11±0.5	>12
F3	13±0.5	>12
F4	12±1.5	>12
F5	24±2	>12
F6	27±1.15	>12
F7	22±4.6	>12
F8	17±1.15	>12
F9	22±2	>12

Measurement of bioadhesion force

The mucoadhesive strength of the tablet was dependent on the property of the bioadhesive polymers, which on hydration adhere to the mucosal surface and also on the concentration of polymer used. Bioadhesive force values ranged from 2.94 to 4.91. Results were represented in Table 6 and Fig. 5.

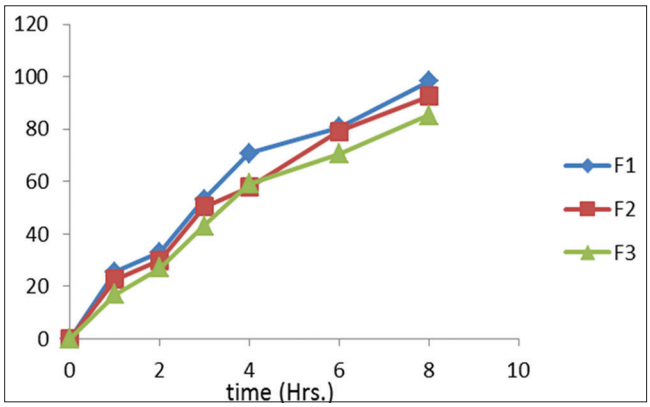

Fig. 6: *In vitro* drug release profile of batches (F1-F3)

In vitro buoyancy study

Floating lag time of all nine batches shown in Table 7.

In vitro dissolution studies

All the nine formulations were subjected to *in vitro* dissolution studies using a USP Type-II dissolution test apparatus. The dissolution medium

Table 8: *In vitro* dissolution study of tablets

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	25.33±0.05	22.52±0.01	16.61±0.17	15.57±0.27	8.32±0.10	6.66±0.32	6.63±0.29	6.6±0.27	3.86±0.14
2	32.72±0.15	30.07±0.09	27.10±0.04	21.33±0.21	21.32±0.21	18.36±0.21	16.55±0.40	14.26±0.26	9.48±0.31
3	53.14±0.15	50.03±0.23	43.23±0.29	47.32±0.22	32.66±0.18	35.61±0.09	29.69±0.24	35.6±0.08	24.42±0.22
4	70.70±0.17	57.52±0.36	59.31±0.40	57.47±0.33	55.98±0.16	53.35±0.38	50.38±0.36	41.51±0.35	37.38±0.36
6	80.48±0.23	79.76±0.55	70.21±0.23	73.15±0.15	67.20±0.23	64.24±0.24	58.32±0.42	58.31±0.41	55.32±0.42
8	98.21±0.04	92.62±0.42	85.16±0.06	83.37±0.29	73.65±0.47	73.75±0.35	74.51±0.34	71.54±0.40	67.4±0.20
10	-	-	-	88.51±0.12	83.18±0.45	82.52±0.11	82.41±0.26	78.38±0.29	83.57±0.11
12	-	-	-	-	-	-	87.41±0.26	88.53±0.12	92.1±0.77

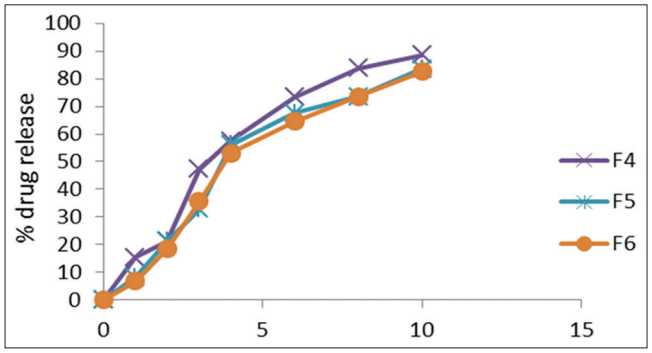

Fig. 7: *In vitro* drug release profile of batches (F4-F6)

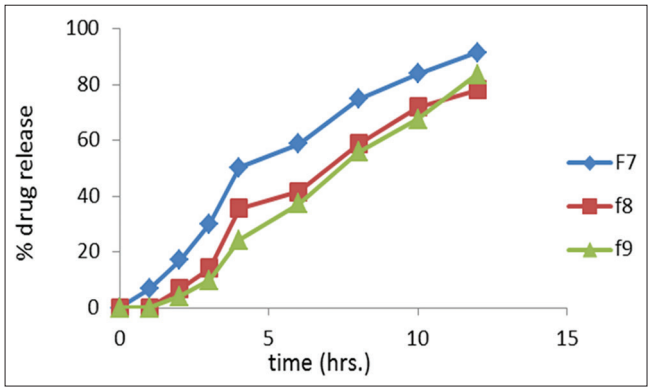

Fig 8: *In vitro* drug release profile of batches (F7-F9)

1.2 pH buffer was used to study the drug release. The samples were withdrawn at different intervals of time and analyzed at 282 NM using a UV spectrophotometer. The cumulative percentage drug release was calculated. The data obtained from *in vitro* release for formulations prepared by direct compression technique are tabulated in Table 8.

In vitro dissolution studies of nine batches that the batch F1, F2, and F3 tablets completely disintegrated at 8 h (Fig. 6) and batch F4, F5, and F6 completely disintegrated at 10 h, so these batches were rejected (Fig. 7). Among the other batches, F7, F8, and F9 batches were completely disintegrated at 12 h (Fig. 8).

CONCLUSION

Floating mucoadhesive tablet of chlorzoxazone was prepared by direct compression method using a polymer such as HPMC K4M, Carbopol 934p, and other excipients. All pre- and post-compression study was done in all nine batches of the tablet. *In vitro* dissolution studies of nine batches concluded that the batch F1, F2, and F3 tablets completely disintegrated at 8 h and batch F4, F5, and F6 completely disintegrated at 10 h, so these batches were rejected. Among the other batches, F9 batch was selected as an optimized batch because the pre- and post-compression parameters results are satisfactory. The F9 batch showed that the best result as the percent cumulative drug release of F9 is 91.22% at 12 h.

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AUTHORS CONTRIBUTION

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Mr. Manish Kumar Pal collected the data, analyzed the data, all the laboratory work performed, wrote the introduction, discussion and the material and method part. Dr. Ganesh Deshmukh proof-read the whole manuscript as well as helps in designing and conducting the study.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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