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FORMULATION AND EVALUATION OF CONTROLLED RELEASE GASTRORETENTIVE FLOATING TABLET OF CHLORDIAZEPOXIDE

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ABSTRACT

Gastro-retentive drug delivery system (GRDDS) may be used to increase gastric retention time coupled with drug release for extended period of time to reduce more dosing frequency which may leads to plasma peak fluctuation. Chlordiazepoxide is a long-acting benzodiazepine having anxiolytic, sedative & hypnotic activity. But, its multiple dose therapy leads to accumulation of parent compound and active metabolites causing various side effects. Chlordiazepoxide as GRDDS will reduce drug accumulation and side effects by maintaining plasma blood level. Formulations were prepared by direct compression method using HPMC and Ethyl cellulose as rate controlling polymers and were evaluated for thickness, diameter, weight variation, hardness, and friability along-with buoyancy studies and in vitro drug release study. The precompression & postcompression parameters were found within the acceptable limits. I*n vitro* dissolution studies of all the formulations showed controlled release of drug over a period of 12hrs. Among all the twelve formulations, F12 was selected as a best formulation which had the better retardant effect (67.1% in 12 hours) & floating lag time of 70 sec. A floating drug delivery system using a suitable composition of HPMC K15M and ethyl cellulose could give the desired dissolution profile for formulating the controlled release tablets of Chlordiazepoxide.

KEYWORDS: Chlordiazepoxide, Benzodiazepine, Anxiolytic, Gastro-retentive, HPMC.

INTRODUCTION

Controlled Drug Delivery System (prolonged release) implies the predictability and reproducibility to control drug release in the body with low and less frequent dosing. Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages like ease of administration, patient compliance and flexibility in formulation.[4]

The most preferable approach for oral controlled drug delivery is **Gastro-Retentive Drug Delivery Systems** (GRDDS), in which the dosage form remains in stomach for prolonged period & increases Gastric Residence Time (GRT). GRDDS can be defined as a system which retains in the stomach for a sufficient period of time and thus releasing the active moiety in a controlled manner. Over the last two decades, numbers of approaches for GRDDS have been designed to prolong GRT(As shown in Figure-1). It improves bioavailability, therapeutic efficacy, reduction of dose & drug waste, and many pharmacokinetic advantages like maintenance of therapeutic levels, dose size reduction and improvement of the drug solubility which is less soluble in high PH environment and thus improves solubility of drug. It is used for local drug delivery to the stomach and proximal small intestine**. Floating drug delivery systems** (FDDS) have a bulk density less than the density of gastric fluids and so remain buoyant in the stomach without any effect on gastric emptying rate for a prolonged period of time.[5]

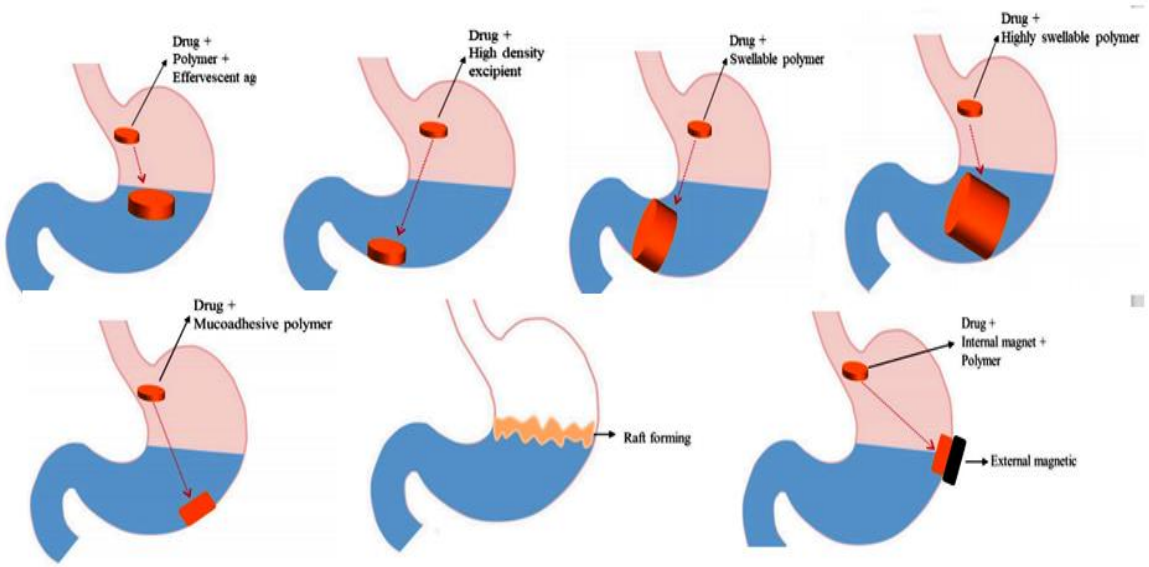

Figure-1: Approaches for GRDDS[10]: (1) Low density systems and (2) High density systems (3) Expandable systems (4) Superporous hydrogel systems (5) Mucoadhesive systems (6) Raft forming systems (7) Magnetic systems.

Anxiety is mental health disorder which is characterized by feelings of anxiety or fear, worry that are strong enough to interfere with individual's daily activities. It is caused by dysfunction of neurotransmitters and their receptors. Decreased levels of GABA, a neurotransmitter that reduces activity in the central nervous system, contributing to anxiety.[1] **Chlordiazepoxide** is a long-acting benzodiazepine with anxiolytic, sedative & hypnotic activity and also used in symptomatic treatment of alcohol withdrawal. It increases inhibitory effect of GABA by binding to the benzodiazepine site at GABA receptor-chloride ionophore complex in CNS. This causes an increased binding of the inhibitory neurotransmitter GABA at the GABA (A) receptor. BZDs, therefore, enhances GABA-mediated chloride influx through GABA receptor channels & causing membrane hyperpolarization. The net neuro-inhibitory effects results in the observed anxiolytic, sedative, hypnotic and muscle relaxant properties.[2]

Oral Chlordiazepoxide is rapidly and completely well absorbed, peak plasma concentrations appear 30 min after dosing. The drug is metabolized into a succession of pharmacologically active compounds: desmethyl Chlordiazepoxide, desmethyldiazepam, demoxepam, and oxazepam. Chlordiazepoxide is mostly absorbed from the upper part of gastro intestinal tract and stomach. Its multiple dose therapy leads to accumulation of parent compound and active metabolites which leads to various side effects like excessive sedation, respiratory depression and muscle weakness.[3] Chlordiazepoxide conventional dosage form has more dosage frequency that may cause plasma peak fluctuation. Therefore, Chlordiazepoxide if given as gastro retentive system in controlled release manner it reduces accumulation of drug, reduced drug side effect by maintaining plasma blood level and increases patient compliance.

RATIONAL: Rational for this Research iis shown in Figure - 1 Given below.

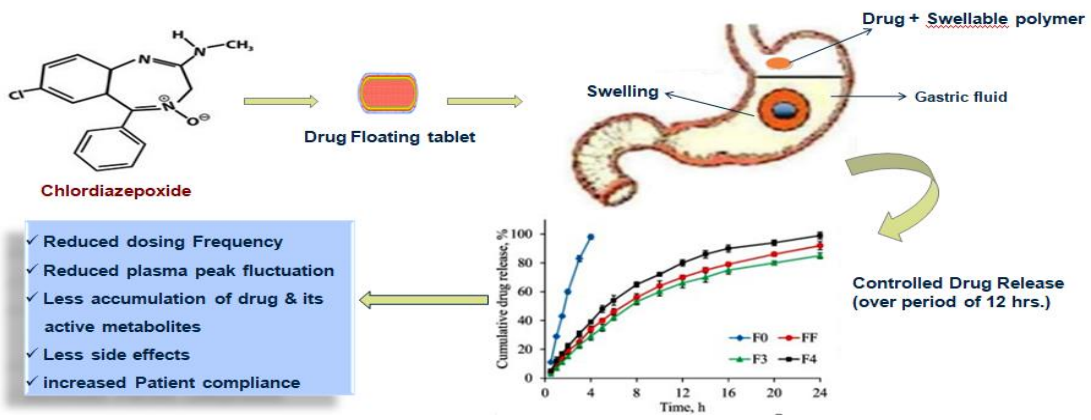

Figure 2: Rational behind research.

MATERIALS AND METHODS

Materials: Chlordiazepoxide was obtained from Salvavidas Pharmaceutical Pvt. Ltd, Gujarat. HPMC K4M & HPMC K15M was obtained from Merck india ltd. Mumbai. Ethyl Cellulose was obtained from S.D. Fine Chem Limited, Mumbai. Magnesium stearate, Lactose, and Talc were obtained from LobaChemie Pvt. Ltd, Mumbai, India.

Method for formulation of floating tablet

Floating tablets containing Chlordiazepoxide were prepared by direct compression technique using varying concentrations of different grades of polymer HPMC (HPMC K4 M and HPMC K15 M) and Ethyl cellulose. All the ingredients were accurately weighed as quantity given in Table -1 and passed through different mesh sieves accordingly. Then, except Magnesium stearate and talc all other ingredients were mixed uniformly in mortar after sufficient mixing of drug as well as other components. Magnesium stearate and talc was added, as lubricant, and further mixed for additional 2-3 minutes. The blend was characterized for different physical parameters such as bulk density, Tapped density, Angle of repose, Hausners ratio and Carr's index. The tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation. Tablets were compressed at 350 mg weight on tablet punching machine with 12-mm punches.

Table 1: Formulation of Gastroretentive floating tablets of Chlordiazepoxide.

	Ingredients Quantity For 1 Tablet (Mg)							
Formulation Code	**Chlordiazepoxide**	**HPMC K4M**	**HPMC K15M**	**Ethyl Cellulose**	**Lactose**	**Mg. Stearate**	**Talc**	**Total wt (mg)**
F1	50	40	-	-	257	1.5	1.5	350
F2	50	80	-	-	217	1.5	1.5	350
F3	50	120	-	-	177	1.5	1.5	350
F4	50	-	40	-	257	1.5	1.5	350
F5	50	-	80	-	217	1.5	1.5	350
F6	50	-	120	-	177	1.5	1.5	350
F7	50	120	-	40	137	1.5	1.5	350
F8	50	120	-	80	97	1.5	1.5	350
F9	50	120	-	120	57	1.5	1.5	350
F10	50	-	120	40	137	1.5	1.5	350
F11	50	-	120	80	97	1.5	1.5	350
F12	50	-	120	120	57	1.5	1.5	350

EVALUATION PARAMETERS

A). Pre-compression Parameters of Blend of Controlled Release Gastro Retentive Chlordiazepoxide Tablet.

1. **Angle of Repose:** It is defined as maximum angle that can be obtained between the free standing of powder pile and horizontal plane.[8] It was determined by using following equation.

Tan θ = h/r

Where, θ = Angle of repose, h = powder pile, r =Radius of the powder cone.

2. **Bulk Density:** Bulk density is defined as mass of a powder divided by bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere one another. A quantity of accurately weighed bulk powder from each formula, previously shaken to break any agglomerates formed and transferred into a 25ml measuring cylinder and initial volume was observed.[6] It is calculated by the equation as

$$\text{Bulk density} = \frac{\text{Mass of the powder}}{\text{Bulk volume of powder}}$$

3. Tapped density: Weighed quantity of tablet blend was transfered into a graduated cylinder. Volume occupied by the powder mixture was noted down. Then measuring cylinder was subjected to 100, 200 and 300 taps in tap density apparatus.[15] According to USP, tapped density was calculated by formula as

$$\text{Tapped density} = \frac{\text{Mass of the powder}}{\text{Tapped volume of powder}}$$

4. Carr's Index: The carr's index or compressibility index was calculated from the bulk and tapped density value by using following equation.[7]

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

5. Hausner's Ratio: It is measure of frictional resistance of tablet blend. The ideal range of Hausner's Ratio should be 1.2-1.5. It was determined by ratio of tapped density and bulk density.[13]

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

B). Post Compression Parameters of Controlled Release Gastro Retentive Chlordiazepoxide Tablet

i). General appearance: The formulated tablets are evaluated for general appearance Like color, odour, shape etc.

ii). Tablet Dimension: Determination of thickness and diameter for tablets are carried out using digital vernier caliper. Three tablets are measured from each batch and results are expressed in millimeter (mm).

iii) Weight variation test Twenty tablets are selected randomly, individually weighed in a single pan electronic balance and the average weight is calculated. The uniformity of weight is determined in accordance to I.P. specification. As per IP not more than two of individual weights should deviate from average weight by more than 5% and none deviate more than twice that Percentage.[8]

iv). Hardness test: Tablet requires a certain amount of strength/hardness and resistance to friability to withstand mechanical shocks of handling in manufacturing, packing and shipping. Monsanto hardness tester is commonly used to measure the hardness of tablet.[13] Three tablets from each batch are taken for hardness test and results are expressed in Kg/cm^2.

v). Friability test: This test is done in Roche friabilator apparatus where the tablets are subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that rotates at 25 rpm for dropping the tablets from a distance of six inches with each revolution. Pre weighed samples of 20 tablets are placed in friabilator, and operated for 100 revolutions. Tablets are then redusted and reweighed. Compressed tablets which loss less than 0.5 - 1.0% of their weight are generally considered to be acceptable.[9] The percentage friability is calculated by using following formula.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

vi). Drug content uniformity: Collectively Ten tablets are weighed and taken in a mortar and crushed uniformly to make powder form. A quantity of powder weighing equivalent to 40mg of drug is taken into 100ml volumetric flask and 0.1 N HCL is added. The solution is filtered by membrane filter (0.45µm) and 10 ml of filtrate is taken in 100 ml volumetric flask and made up to final volume with 0.1 N HCL.[18] Then its absorbance is measured at 245nm wavelength using UV Visible spectrometer. The amount of drug present in one tablet is calculated by using standard graph of Chlordiazepoxide.

%Purity = Absorbance of unknown (Au)/Absorbance of standard (As)*10C,

vii). In vitro floating lag time[20]: The in vitro buoyancy was determined by floating lag time (FLT). The tablet was placed in a 250 ml beaker containing 0.1N HCl acid buffer. The media was kept stable in stagnant condition and the temperature was maintained at 37^0 C. The time required for the tablet to rise onto the surface and float was determined as floating lag time.

viii). In vitro floating duration time: The floating capacity of tablets was determined by using USP Dissolution apparatus II containing 900ml of simulated gastric fluid. The time interval between introduction of tablet into the dissolution media and its buoyancy to the dissolution medium was measured as buoyancy lag time/ Total floating time(TFT) and for which time tablet constantly floats onto the surface of media was observed visually and taken as floating duration time.[15]

ix). In vitro drug release studies: Dissolution study of formulated floating tablets of Chlordiazepoxide is carried out by using USP Type II (paddle) dissolution test apparatus for 12 hrs.

METHOD

900 ml of 0.1N HCL acid buffer was filled in dissolution vessel and temperature of the medium is set to 37°C ± 0.5°C. One tablet of different batches is placed in each dissolution Apparatus and rotational speed of paddle was set at 50 rpm. 5ml of sample is withdrawn at every one hour for up to 12 hours and same volume of fresh medium is replaced immediately. The withdrawn sample is then diluted to 10ml in volumetric flask with acid buffer and filtered through 0.45µ membrane filter.[22] The resultant samples are analyzed for Concentration at 245nm using UV-Visible spectrophotometer.

RESULT AND DISCUSSION

Analytical method was performed by UV Spectrophotometer. Standard curves of Chlordiazepoxide in 0.1 N HCL was analyzed in the range of 2-10µg/ml. The selected range of Chlordiazepoxide was found to be linear. Regression coefficients at 245 nm were found to be 0.978. Standard curve data is given in Table - 2 and Standard curve for Chlordiazepoxide in Figure – 2 given below.

Table 2: Standard Curve data of Chlordiazepoxide.

S. No	Concentration (µg/ml)	Absorbance
1	2	0.281
2	4	0.462
3	6	0.643

4	8	0.869
5	10	1.025

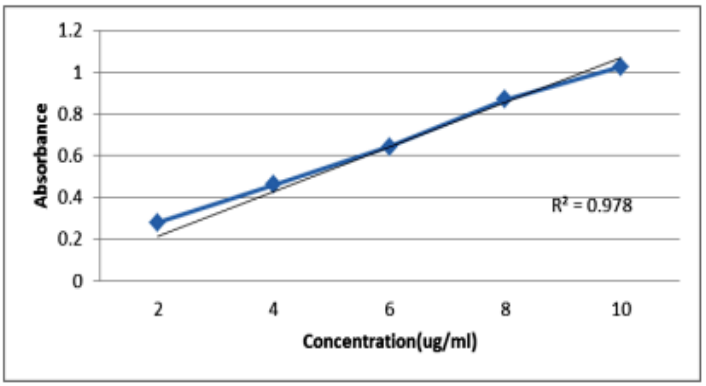

Figure 3: Standard Curve of Chlordiazepoxide in 0.1 N HCL.

The pre compression parameters of blend were evaluated. The result of pre compression evaluation parameters were shown in Table - 3. All these results indicate that the powder blend of all the formulations possessed satisfactory flow properties.

The results of post compression parameters weight variation, thickness, hardness, friability of all the prepared tablets are shown in table -4. These results show that all the prepared tablet formulations agree with the requirements of USP. Results of all the parameters revealed that prepared Tablets had sufficient mechanical strength. Post compression parameters like weight variation and friability were in range of Indian pharmacopeia. The weight of all the twelve batches Tablets are ranges from 349 to 352. It revealed that method selected for the preparation of Tablet is suitable and reproducible. Floating lag time was <3 min. The *in vitro* dissolution studies of all the twelve formulations showed controlled release of the drug over a period of 12hrs. The overall drug release retarded in the following order.

HPMC K15M & EC > HPMC K4M & EC > HPMC K15M > HPMC K4M

Obtained result revealed that with increasing concentration of HPMC percent cumulative drug release of the optimized batch was decreased due to increase in viscosity of matrix of prepared Tablet. The combination of Hydrophilic and hydrophobic polymer, which restricts Penetration of dissolution medium inside the matrix, also restricts the formation of gel layer around the matrix. So that, the drug release from the hydrophobic matrix tablets decreased as compared to the hydrophilic polymers alone.

Among all the twelve formulations, F12 was selected as a best formulation which had the better retardant effect (67.1% in 12 hours) & floating lag time of 50 sec. A decrease in release of the drug was observed on increasing polymer ratio.

Table 3: Precompressional Evaluation data for Powder Blend.

Formulation code	Angle of repose(degree)	BD (gm /ml)	TD (gm/ml)	Carr's index (%)	Hausner's ratio (%)
F1	24.12	0.317	0.367	14.65	1.08
F2	23.07	0.327	0.389	15.21	1.09
F3	26.04	0.337	0.381	13.63	1.11
F4	25.01	0.347	0.391	16.52	1.19
F5	22.97	0.296	0.320	13.12	1.16
F6	25.71	0.260	0.336	15.27	1.15
F7	24.16	0.266	0.372	14.56	1.16
F8	21.11	0.307	0.332	13.41	1.17
F9	26.16	0.312	0.356	16.31	1.18
F10	26.04	0.347	0.381	13.63	1.11
F11	25.01	0.296	0.391	16.52	1.19
F12	22.97	0.260	0.320	13.12	1.16

Table 4: Postcompressional Evaluation data of Floating Tablets.

Batch No.	Tablet Thickness (mm)	Weight Variation (mg)	Hardness kg/cm ^{2}	Drug Content (%)	Friability (%)	Lag Time (sec)	Total Floating Time
F1	3.52	350	4.0	98.78	0.44	65	>12
F2	3.53	350	4.1	97.6	0.45	68	>12
F3	3.55	352	4.06	96.6	0.36	70	>12
F4	3.53	352	4.02	93.3	0.51	80	>12
F5	3.51	351	4	86.6	0.52	73	>12
F6	3.52	350	4.3	99.9	0.27	70	>12
F7	3.56	351	4.0	98.1	0.37	62	>12
F8	3.55	349	4.3	101	0.38	55	>12
F9	3.51	349	4.0	99.3	0.42	45	>12
F10	3.59	349	4.2	99.3	0.45	65	>12
F11	3.53	352	4.2	97.37	0.45	55	>12
F12	3.58	351	4.1	97.5	0.43	50	>12

In Vitro Drug Release Study

Data for In Vitro Drug Release study of various formulations with different concentration and combinations of polymers are shown in table 5 to 8 along with their respective curves (Figure - 4 to 7).

Table - 5: Cumulative % drug release of formulations with HPMC K4M.

S. No	Time (hrs)	F1	F2	F3
1	0	0	0	0
2	1	21.22	19.97	18.50
3	2	33.13	29.13	26.70
4	4	50.56	47.00	40.36
5	6	73.18	64.46	62.83
6	8	99.91	73.61	75.07
7	12	-	99.33	92.88

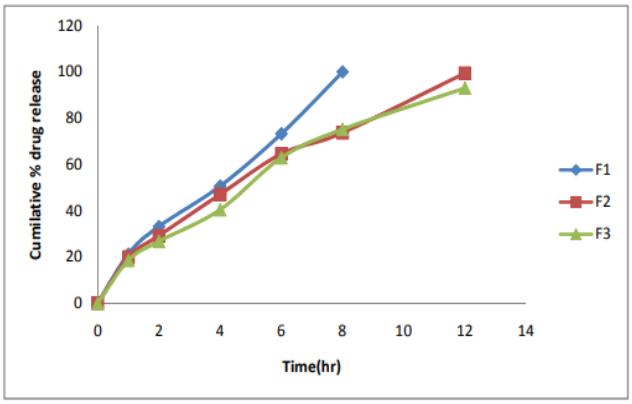

Figure – 4: % Cumulative Drug Release of Batch F1, F2, F3.

Table - 6: Cumulative % drug release of formulations with HPMC K15M.

S. No	Time (hrs)	F4	F5	F6
1	0	0	0	0
2	1	17.98	15.17	14.83
3	2	29.98	24.41	20.57
4	4	47.55	41.41	36.70
5	6	63.52	55.66	50.41
6	8	76.57	69.32	61.12
7	12	95.84	85.33	1

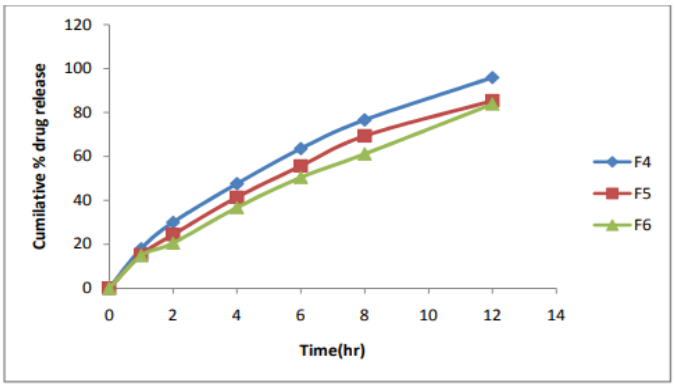

Figure 5: % Cumulative Drug Release of Batch F4, F5, F6.

Table - 7: Cumulative % drug release of formulations with HPMC K4M & Ethyl Cellulose.

S. No	Time (hrs)	F7	F8	F9
1	0	0	0	0
2	1	11.99	10.10	9.29
3	2	23.71	15.17	14.89
4	4	40.68	29.87	23.71
5	6	57.02	47.52	44.52
6	8	72.97	60.95	57.72
7	12	90.47	78.21	70.54

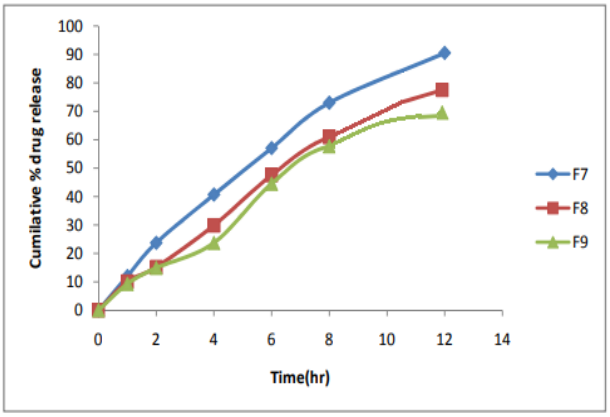

Figure – 6: % Cumulative Drug Release of Batch F7, F8, F9.

Table 8: Cumulative % drug release of formulations with HPMC K15M & Ethyl Cellulose.

S.No	Time (hrs)	F10	F11	F12
1	0	0	0	0
2	1	15.20	10.94	12.69
3	2	24.43	16.79	21.26
4	4	33.11	24.29	33.08
5	6	46.56	34.07	44.13
6	8	58.53	47.18	55.57
7	12	80.36	75.86	67.1

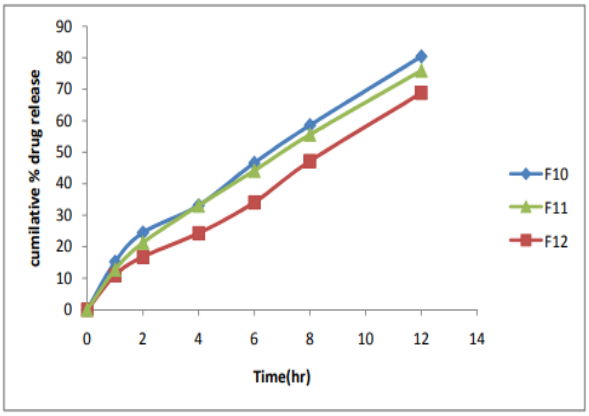

Figure – 7: % Cumulative Drug Release of Batch F10, F11, F1.

CONCLUSION

A floating drug delivery system is a promising approach to achieve in vitro buoyancy and extended drug release. The results of the present study clearly indicate that by selecting a suitable composition of HPMC K15M and Ethyl cellulose, the desired dissolution profile could be achieved. Hence combination of both hydrophilic and hydrophobic polymers successfully employed for formulating the controlled release floating tablets of Chlordiazepoxide.

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