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Research Article

Development and Evaluation of Gastro Retentive Controlled Release Dosage Form of Chlordiazepoxide

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ABSTRACT

The aim of present study was to develop and evaluate gastro retentive controlled release dosage form - Hydrodynamically balanced system of Chlordiazepoxide by using Hydroxy Propyl Methyl Cellulose K 4 M and Xanthum gum to avoid accumulation of metabolites of Chlordiazepoxide and to reduce dosing frequency. Tablets were prepared successfully by wet granulation method by using PVP K30 as binding agent and HPMC K4M, Xanthum gum as retarding polymer. Optimization of formulation was done by using 3^2 full factorial design where independent variables are X1 (concentration of HPMC K4M) and X2 (concentration of Xanthum gum).The prepared blend of tablet were evaluated for pre-compression parameters like bulk density, tapped density, carr's index, hausner' ratio, in vitro drug release, % swelling index and stability study. The prepared blend has good flow property and compressibility.Due to combination of HPMC K4M and Xanthum gum polymers tablets maintain its matrix integrity and show good prolonged release in controlled manner. Swelling index was in range from 33 to 75 %. *In vitro* drug release of tablet was carried in 0.1N HCL up to 18 hrs. and its show 95-98 % drug release. Use of Xanthum gum control the initial burst drug release effect of matrix tablet and HPMC is rapidly swelling hydrophilic polymer which form highly viscous gel barrier which control the drug release from system.

Keywords: Chlordiazepoxide, gastro retentive, hydrodynamically balanced drug delivery system, controlled release, HPMC K4M, Xanthum gum.

INTRODUCTION

Anxiety is a feeling of fear, uneasiness, and worry, usually generalized and unfocused as an overreaction to a situation that is only subjectively seen as menacing. Anxiety disorders are the most common of mental disorders. They can cause such distress that it interferes with your ability to lead a normal life. This type of disorders are a serious mental illness. It is caused by dysfunction of one or more neurotransmitters and their receptors. Low levels of GABA, a neurotransmitter that reduces activity in the central nervous system, contribute to anxiety. A number of anxiolytics produced their effect by modulating the GABA receptors[1]. Chlordiazepoxide is benzodiazepine BCS II class of drug which is widely used as anxiolytic and sedative. Chlordiazepoxide binds to GABA receptor and potentiate the effect inhibitory neuronal activity of GABA receptor. It has also been used in the symptomatic treatment of alcohol withdrawal. Oral Chlordiazepoxide is rapidly and completely absorbed well absorbed, peak plasma concentrations appear 30 min after dosing. The drug is biotransformed into a succession of pharmacologically active products: desmethyl Chlordiazepoxide, demoxepam, desmethyldiazepam, and oxazepam. Chlordiazepoxide binds to stereospecific benzodiazepine (BZD) binding sites on GABA (A) receptor complexes at several sites within the central nervous system, including the limbic system and reticular formation. This results in an increased binding of the inhibitory neurotransmitter GABA to the GABA (A) receptor. BZDs, therefore, enhance GABA-mediated chloride influx through GABA receptor channels, causing membrane hyperpolarization. The net neuro-inhibitory effects result in the observed sedative, hypnotic, anxiolytic, and muscle relaxant properties[2, 3].

Chlordiazepoxide is mostly absorb from the upper gastro intestinal tract and stomach. Multiple dose therapy leads to accumulation of parent compound and active metabolites which leads to excessive sedation, respiratory depression and muscle weakness. Chlordiazepoxide

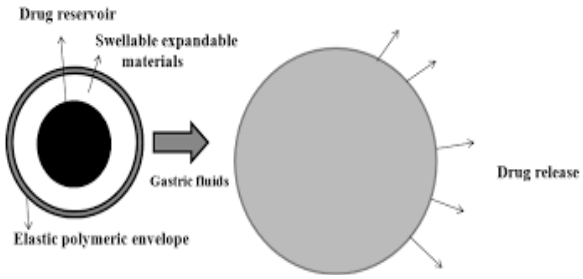

Figure 1: Hydrodynamically Balanced System Mechanism (HBS) [6]

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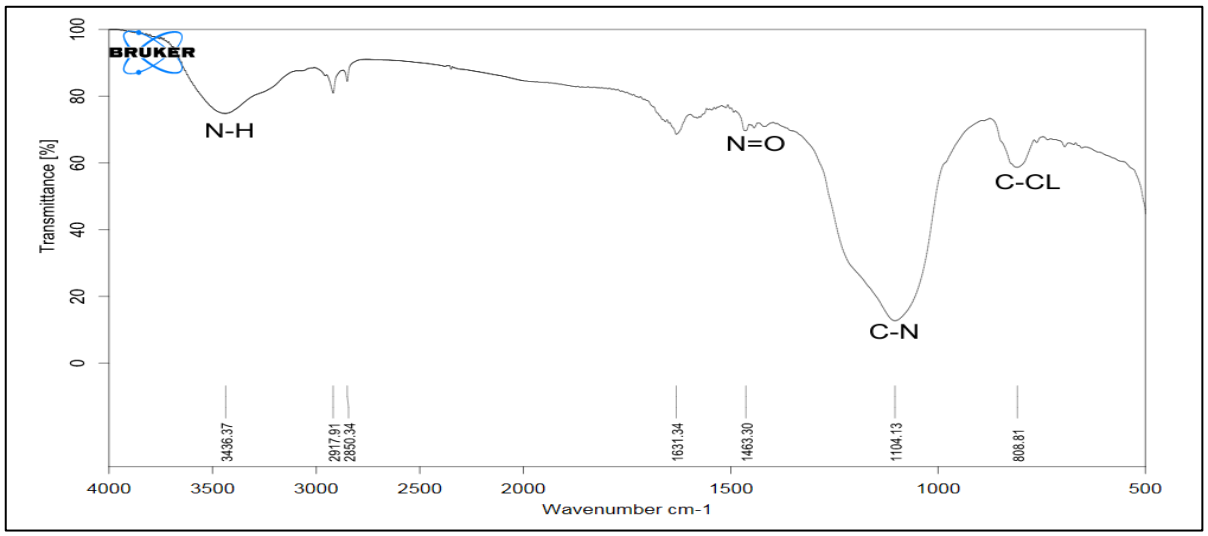

Figure 2: FTIR Spectra of Chlordiazepoxide.

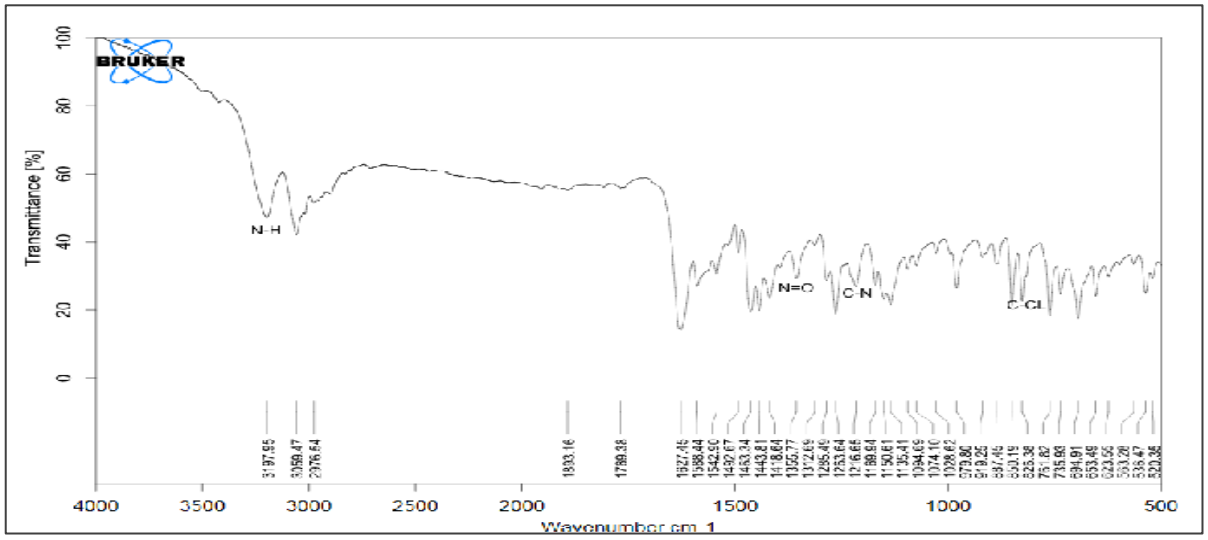

Figure 3: FTIR Spectra of Chlordiazepoxide and Excipients.

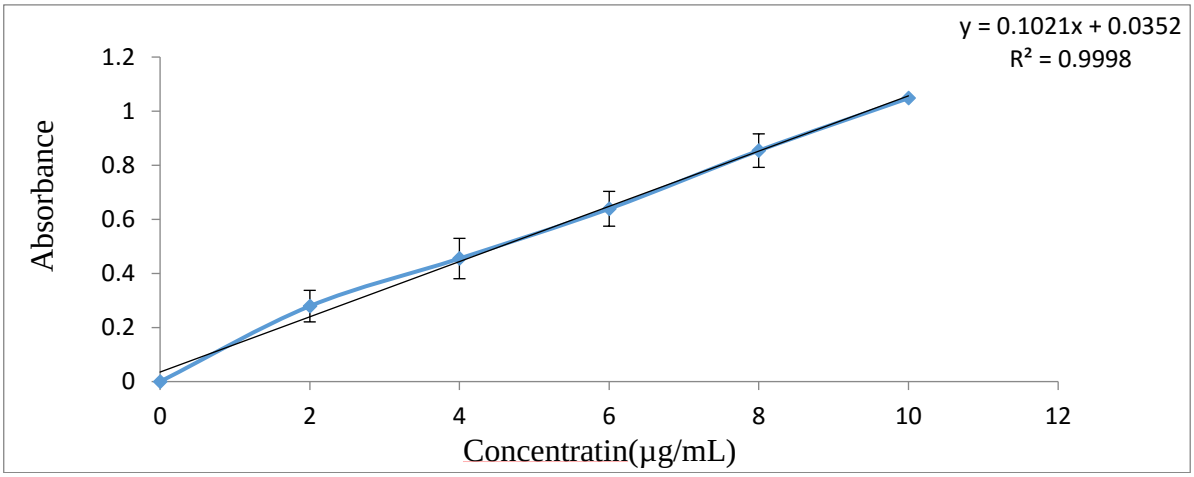

Figure 4: Calibration Curve of Chlordiazepoxide in 0.1 N HCL at 245 nm.

conventional dosage from have more dosing frequency which may cause plasma peak fluctuation.

Therefore, Chlordiazepoxide if given through gastro retentive system in controlled release manner it reduced accumulation of drug, reduced drug side effect by

Table 2: Calibration Curve of Chlordiazepoxide in 0.1 N HCL.

Sr. No.	Concentration(µg/ml)	Mean Absorbance (±) SD
1	2	0.279±0.00368
2	4	0.455±0.0583
3	6	0.639±0.07466
4	8	0.854±0.06431
5	10	1.048±0.0618

(Where n=3, Mean ± SD)

maintaining plasma blood level, also increases patient compliance. Oral controlled release (CR) dosage forms (DFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation[4].

Gastro retentive drug delivery system **(**GRDDS) remains in the stomach for several hours by passing the gastric transit. These dosage forms can float in the stomach and releases and absorption of the drug in a controlled manner for prolonged periods of time. The different type and concentration of the polymer were used that swells, will control the drug release rate.

Hence GRDDS improves their bioavailability, therapeutic efficiency and possible reduction of the dose and many pharmacokinetic advantages like, maintenance of therapeutic levels, reduction of dose size, improvement of the drug solubility that is less soluble in high PH environment.

Swelling System

These are a type of non-floating gastro retentive drug delivery system which when enters to stomach, swells (due to presence of swell able polymers) to an extent that cannot pass through the pyloric sphincter leading to its retention in the stomach.

Hydrodynamically balanced systems are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. To remain in the stomach for a prolonged period of time. The dosage form must have a bulk density of less than 1.

Hydrodymamically balance system (HBS) contains drug with gel forming hydrocolloids meant to remain buoyant

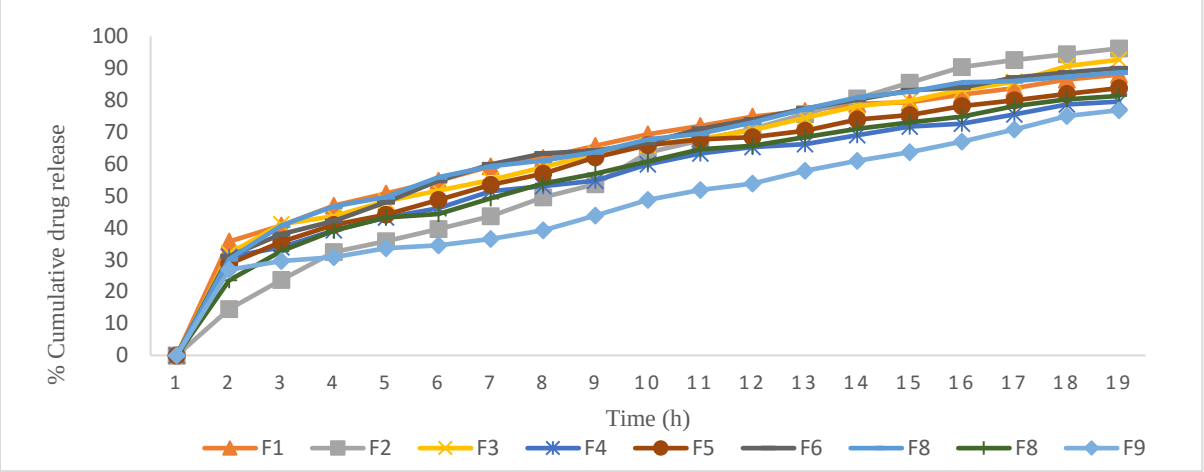

Figure 5: % Cumulative Drug Release of Preliminary Trial Batches of F1-F9, % Swelling Index of 3^2 Full Factorial Design Batches F1-F9.

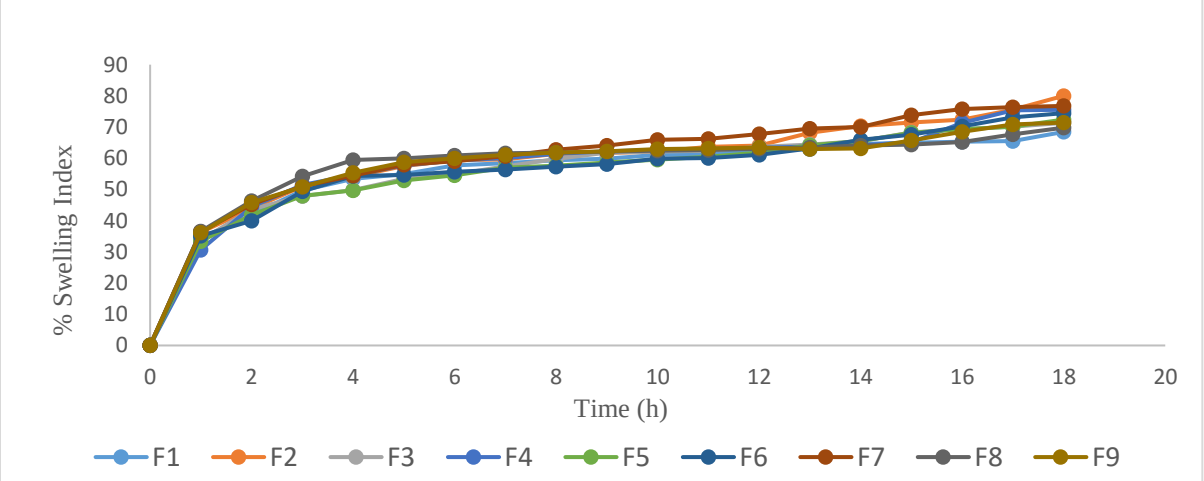

Figure 6: % Swelling Index of Preliminary Trial Batches of F1-F9.

Table 1: Composition of 3^2 Full Factorial Design Batches F1-F9.

Sr No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Chlordiazepoxide	40	40	40	40	40	40	40	40	40
2	MCC (Avicel 102)	330.5	300.5	360.5	300.5	240.5	330.5	270.5	270.5	300.5
3	HPMC K4M	120	150	120	180	180	150	150	180	120
6	Xanthum Gum	90	90	60	60	120	60	120	90	120
7	PVP K30	15	15	15	15	15	15	15	15	15
8	Colloidal Silicon Dioxide	3	3	3	3	3	3	3	3	3
9	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
10	Total weight (mg)	600	600	600	600	600	600	600	600	600

Table 3: Pre-compression Observation of Preliminary Trial Batches F1-F9.

Batch No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Hausner Ratio
F1	0.271 ± 0.005	0.313 ± 0.0043	14.81 ± 0.0201	1.15 ± 0.0023
F2	0.263 ± 0.0021	0.315 ± 0.0020	13.33 ± 0.0321	1.15 ± 0.0056
F3	0.255 ± 0.0032	0.296 ± 0.0036	13.79 ± 0.0021	1.16 ± 0.0071
F4	0.274 ± 0.0087	0.319 ± 0.0065	12.90 ± 0.0042	1.14 ± 0.00063
F5	0.544 ± 0.0085	0.642 ± 0.0082	15.09 ±0.0031	1.18 ± 0.0097
F6	0.498 ± 0.0053	0.561 ± 0.0031	15.56 ± 0.0102	1.14 ± 0.0109
F7	0.486 ±0.0076	0.554 ± 0.0029	12.7 ± 0.0305	1.15 ± 0.0023
F8	0.384 ± 0.0053	0.422 ± 0.0083	13.20 ± 2.304	1.14 ± 0.096
F9	0.380 ± 0.0074	0.440 ± 0.109	13.61 ± 1.487	1.14 ± 0.0119

Table 4: Post Compression Parameters of Preliminary Trial Batches F1-F9

Batch No.	Weight Variation(mg)	Hardness (Kp)	Thickness (mm)	% Friability
F1	600.10±0.004	7.63±0.16	4.62±0.004	0.83 ± 0.016
F2	600.07±0.005	7.3±0.08	4.34±0.02	0.91±0.012
F3	602.14±0.05	7.6±0.08	4.44±0.016	0.86±0.012
F4	603.30±0.17	7.7±0.08	4.52±0.02	0.95±0.20
F5	599.72±0.45	7.66±0.09	4.57±0.004	0.886±0.024
F6	603.55±0.09	7.56±0.12	4.46±0.004	0.93±0.024
F7	600.33±0.10	7.86±0.12	4.64±0.01	0.86±0.016
F8	601.54±0.0054	7.64±0.012	4.62±0.052	0.891±0.006
F9	600.98±0.062	7.42±0.24	4.36±0.08	0.854±0.002

on stomach contents. These systems incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. E.g. HEC, HPMC, NaCMC, Polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy[5].

MATERIALS AND METHODS

Materials

Chlordiazepoxide was obtained from Sun Pharmaceutical Industry Ltd. Vadodara. Microcrystalline cellulose (Avicel ph 102) was obtained from FMC Biopolymer, Bangalore, India. Polyvinylpyrollidone K30 was obtained from Colorcon Pharma, Verna and Goa. HPMC and Xanthum gum were obtained from DFE Pharma, Cuddlier, India. Talc was obtained from Luzenac Pharma, Mumbai, India. Magnesium stearate was obtained from Petergreven Pharma, Muenster Eifel, Germany.

Method

Preparation of gastro retentive controlled release tablet

Different Chlordiazepoxide controlled release tablet were prepared by Wet granulation technique. Firstly, Chlordiazepoxide pure drug, HPMC K4M, MCC (Avicel pH102), xanthum gum weighed accurately and shifted through 40# mesh. Magnesium stearate and colloidal silicone oxide weighed accurately and shifted through 60# mesh. Wet granulation was done in Rapid Mixing Granulator (RMG). In RMG, Chlordiazepoxide pure drug, HPMC K4M, MCC (ph 102), xanthum gum were mixed and then the RMG was operated at a high speed. Then prepared solution of PVP K30 in isopropyl alcohol sufficiently was added in blend. Then lastly for two minutes the RMG operated on slow speed to form granules. The prepared granules were dried at 60ºC for 20min and then it was sifted through sieve # 20. In extra granulation step Magnesium stearate (Diluent) and colloidal silicone oxide was accurately weighed and

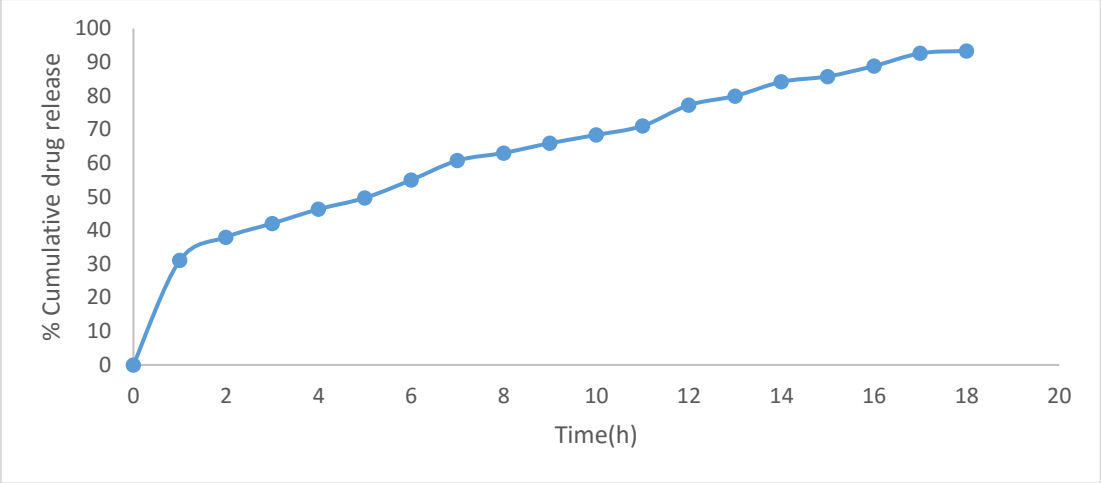

Figure 7: % Cumulative Drug Release of Optimized Batch F2.

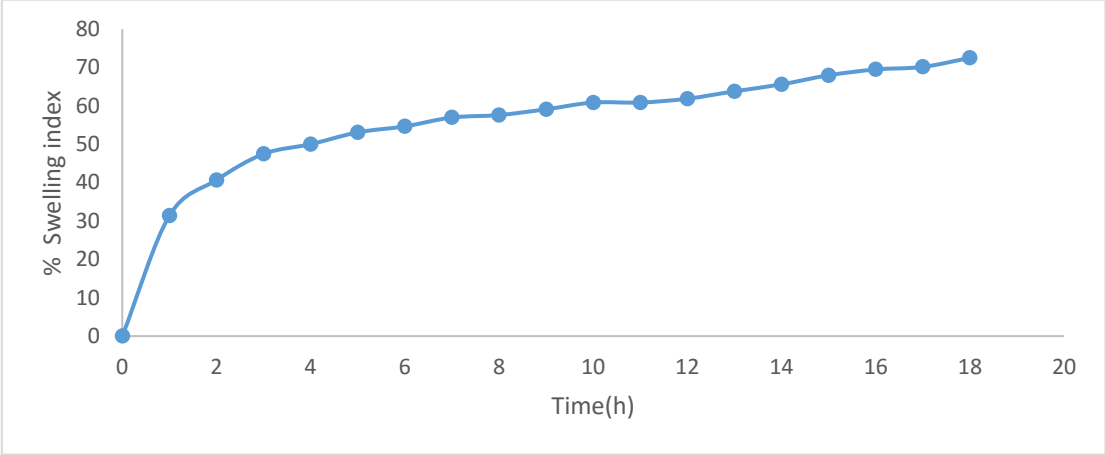

Figure 8: % Swelling Index of Optimized Batch F2.

shifted through 60 # mesh and mix for 10min. In final Mixing step, in Blender firstly dried granules of above mixture was added then lubricating agent magnesium stearate and colloidal silicone oxide was mixed for 5 minutes. Finally, these granules are ready for compression. Then these granules are compressed by using 12mm punch[7]. The Composition of 3^2 Full Factorial Design Batches F1-F9 shown in table no. 1.1

Pre-compression Parameters of Blend of Gastro Retentive Controlled Release Chlordiazepoxide Tablet:

Carr's Index Compressibility Index[8,9]

The carr's index compressibility index was calculated from the bulk and tapped density value by following equation.

$$Carr's\ Index = \frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density} X\ 100$$

Hausner Ratio[8,9]

The hausner ratio was calculated from the following equation:

$$Hausner\ Ratio = \frac{Tapped\ Density}{Bulk\ Density}$$

Bulk Density[8, 9]

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape and the tendency of the particles to adhere to one another. [49,50]

Method

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of accurately weighed powder (bulk) from each formula, previously shaken to break any agglomerates formed was introduced into a 25ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 sec interval. The taping was continued until no further change in volume was noted.

$$Bulk\ Density = \frac{Weight\ of\ the\ Powder}{Volume\ of\ Powder}$$

$$Tapped\ Density = \frac{Weight\ Powder}{Volume\ of\ Tapped\ Powder}$$

Post Compression of Gastro Retentive Controlled Release Chlordiazepoxide Tablet

Hardness[8,9]

To avoid damage due to mechanical shocks of handling in manufacture, packaging and shipping tablets required physical strength or hardness. Tablet hardness tester was used to measure tablet hardness. Its unit is Kp. For that randomly selected from all formulation batches and from

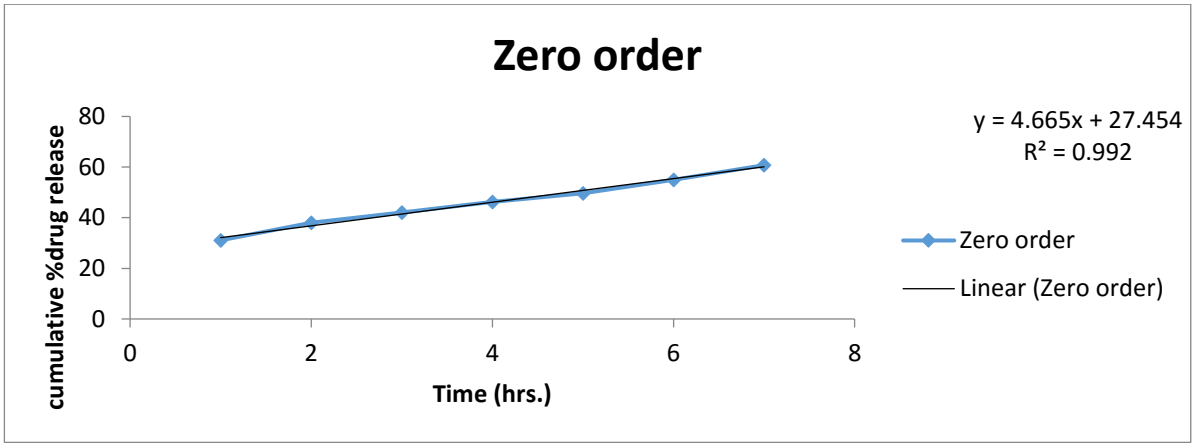

Figure 9: Zero OrderModel of Optimized Batch No.F2.

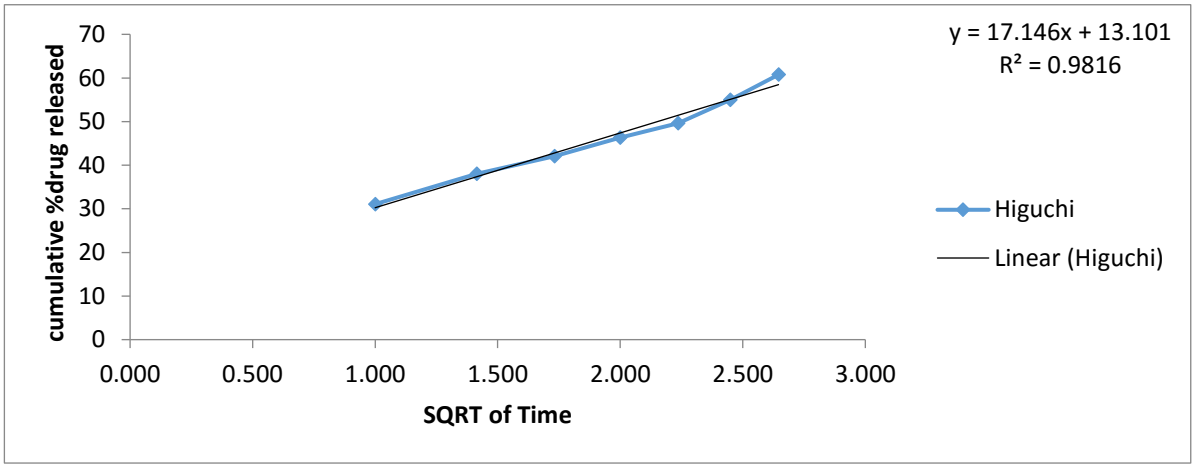

Figure 10: Higuchi Model of Optimized Batch No.F2.

that an average and standard deviation values were calculated.

% Friability Test[8,9]

It was performed to check damage occur during mechanical shock or attrition. Roche friabilator was mainly used for to detect tablet friability. Its unit is percentage (%). Ten tablets were initially weighed (W0) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by –

%F = 100 (1-W0/W)

% Friability of tablets less than 1% are considered acceptable.

Determination Weight Uniformity [8,9]

To determine tablet weight uniformity, 30 tablet were sampled and accurately weighed using an electronic analytical balance. The results were expressed as mean Values of 30 determinations. The coefficient of variation was calculated using the Formula:

Coefficient of variation (%) =

Standard deviation / Mean × 100

% Swelling Index Determination[10]

Gastro retentive tablet was weighed individually (designated as W1) and placed separately in glass beaker containing 200 ml of 0.1N HCL and incubated at 37ºC ± 1ºC. At regular 1h time intervals until 24 h, the tablet was removed from beaker, and the excess surface liquid was removed carefully using the filter paper. The swollen tablet was then re-weighed (W2) and swelling index (SI) was calculated using the following formula11.

% Swelling Index = (W2 – W1)/W1*100

In Vitro Drug Release Studies[10,11]

In vitro drug release studies were carried in USP type II apparatus at 50 rpm maintained at 37 ± 5°C. Tablets were placed into the dissolution medium of 900 ml 0.1 N HCL. The 10 ml of aliquots was withdrawn from the dissolution vessel at specific time intervals and replaced with equivalent volume of fresh medium 0.1 N HCL. Collected dissolution samples were filtered using Whatmann filter (Grade I) paper and then, used for determination of released drug concentrations by using a UV-VIS spectrophotometer

Stability Study[10]

A stability study of optimized batch were performed according to ICH (International Conference on Harmonization) guidelines the stability chamber were placed at 40 ± 2˚C, and relative humidity 75% ± 5%. Samples were evaluated at 0, 15 and 30 days interval. The physical stability of tablet were observed periodically by evaluating appearance, hardness, % swelling index and *in-vitro* release study.

RESULT AND DISCUSSION

Table 5: Stability Study Data for Optimized Batch F2.

Sr. No.	Parameters	Storage Periods (Days) at 40 ± 2 °C Temperature and 75 ± 5 % Relative Humidity		
		At 0 day	At 15 days	At 30 days
1	Appearance	Light yellow crystalline powder	Light yellow crystalline powder	Light yellow crystalline powder
2	Hardness	7.2±0.148	7.3±0.162	7.2±0.089
3	Swelling index (%)	71 ± 1.914	70± 1.002	72 ± 1.015
4	In-vitro drug dissolution Up to 18 hrs.	93 ± 2.714	92 ± 2.152	91 ± 1.967

Preformulation Study

Fourier Transforms Infrared Spectroscopy (FTIR)

FTIR spectra for drug alone and with excipients were taken using a FTIR spectrophotometer with KBr pellets for the identification of the drug and excipients and to study drug-excipients compatibility. FTIR spectra of Chlordiazepoxide are shown in Figure.2 and 3.The peaks in FTIR spectra of drug with the other excipients were nearly similar to the peaks of pure drug present in the FTIR spectra of pure drug.Therefore, these results showed that the drug was compatible with excipients and neither drug decomposition nor drug-excipients and excipients-excipients interactions occurred in the formulation.

Analytical Method

Standard curves of Chlordiazepoxide in 0.1 N HCL were 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 0.9998

Pre-compression Evaluations of 3^2 Full Factorial Design Batches F1-F9

The pre compression parameters of blend were evaluated according to USP. The result of pre compression parameters were shown in Table 3. Pre-compression evaluation of 3^2 full factorial design batches revealed that all the 9 batches had good flow properties.

Post-compression Evaluations of 3^2 Full Factorial Design Batches F1-F9

The results of weight variation, thickness, hardness, friability of all the prepared core tablets are shown in table 4. These results show that all the prepared tablet formula agree with the requirements of USP.

The results of all the parameters revealed that prepared Tablet had sufficient mechanical strength. Post compression parameters like weight variation and friability were in range of British pharmacopeia. The weight of all the 9 batches Tablets are ranges from 599.72 ± 0.45 to 601.54 ± 0.0054. it revealed that method selected for the preparation of Tablet is suitable and reproducible.

% Cumulative Drug Release of 3^2 Full Factorial Design Batches F1-F9

The result of % Cumulative drug release of all the 3^2 full factorial design batches F1-F9 revealed that, the batch F2 had shown highest % cumulative drug release 99.23±0.35 up to 18 hrs. in a controlled manner. All batches having HPMC K4M and Xanthum gum which are highly swellable polymers and gave prolonged drug release up to 18 hrs. Obtained result revealed that with increasing concentration of HPMC K4M and xanthum the% cumulative drug release of the optimized batch was decreased due to increase in viscoelasticity of matrix of prepared Tablet.

The result of % swelling index revealed that batch F2 had highest % swelling index. It happened due to the higher concentration of hydrophilic and swellable polymers. The results of % swelling index of batch F2 was 77.72 ± 0.96 up to 18 hrs. This results revealed that with increasing concentration of HPMC K4M and xanthum the % swelling index of the optimized batch was increased. It occurs because of hydrophilic nature and higher swelling property of both the polymers.

Release Kinetic of Optimized Batch F2

The final selected optimized batch was subjected to different kinetic models to study the different mechanism of drug release from matrix tablet.

Regression coefficient 0.992 of zero order suggested that drug release from the matrix tablet follows zero order and from the tablet drug was release continuously in a controlled manner up to 18 hrs. Thus, the selected batch F2 followed zero order. Drug release mechanism occur first by swelling of polymer matrix and then drug was diffuse out from the matrix, followed by erosion of gel layer, therefore its follow Higuchi model also[12].

Stability Study Data for Optimized Batch F2

CONCLUSION

In this research work gastro retentive controlled release Chlordiazepoxide tablet were prepared and evaluated with an objective to achieve controlled release of drug to reduced dosing frequency and to avoid accumulation of active metabolites, reduced side effects, so that the formulation can be successfully and effectively used in anxiety disorders.

In preformulation study, FTIR show that there is no drug-excipients and excipient-excipient interactions occurred in the formulation. Analytical method was performed by UV Spectrophotometer and regression co-efficient (R^2) was found to be near to one and which showed linear relationship between absorbance and concentration.

The preliminary trial batches was performed for selection of the polymer and its concentration. From the result of preliminary trial batches HPMC K4M and Xanthum gum were selected for the formulation of tablet and it believed that polymeric matrix of these polymers gave prolonged release in controlled manner and also maintain the integrity of matrix table. So that concentration of HPMC K4M and Xanthum gum were selected for optimization of formulation.

Experimental design was developed using software Design Expert 9 for optimization of independent variables (HPMC K4M and Xanthum gum). Different concentration of HPMC K4M and Xanthum gum containing batches F1-F9 were prepared and evaluated. Gastro retentive controlled release Chlordiazepoxide tablet developed with 142.84 mg HPMC K4M and 79.84 mg Xanthum gum concentration which showed % Cumulative drug release 93.35 ± 0.432 % Swelling index 72.48 ± 0.981 for 18 hrs. Optimized batch showed good matrix integrity and exposed for stability study. Stability study results revealed that batch F2 was stable for one month.

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