WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 3, 1036-1047. Research Article ISSN 2277– 7105

# FORMULATION AND EVALUATION OF GASTRO RETENTIVE CONTROLLED RELEASE TABLETS OF CHLORDIAZEPOXIDE

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Article Received on
02 Jan. 2019,

Revised on 22 Jan. 2019,
Accepted on 13 Feb. 2019

DOI: 10.20959/wjpr20193-14334

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## ABSTRACT

The aim of present study was to develop and evaluate gastro retentive controlled release tablets - 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. The prepared blend of tablet was evaluated for pre-compression parameters like bulk density, tapped density, carr's index, hausner's 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, 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.[1] They can cause such distress that it interferes with

your ability to lead a normal life. This type of disorders is 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 receptors1. Chlordiazepoxide is benzodiazepine BCS II class of drug which is widely used as anxiolytic and sedative. Chlordiazepoxide binds to GABA receptor and potentiates 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 absorbed 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 conventional dosage form has 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 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.

**Hydro dynamically 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 one. Hydrodymamically balance system (HBS) contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents.[5] These systems incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids. E.g. HEC, HPMC, sodium CMC, 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.

## MATERIALS AND METHODS

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. Magnesium stearate was obtained from Luzenac Pharma, Mumbai, India.

**Standard Calibration Curve**

10 mg of Chlordiazepoxide was weighed and dissolved in 10 ml 0.1 N HCL, to give a solution of 1000 µg/ml concentration. From this solution 1 ml was taken and diluted to 10ml using 0.1 N HCL to produce a stock solution of 100 µg/ml. From this stock solution different concentrations were prepared. The absorbance of these solutions was measured at 245 nm by UV spectrophotometer.[6] The standard curve for chlordiazepoxide is shown in the figure-1.

**Table 1: Standard Curve 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 |

**Preparation of gastro retentive controlled release tablet**

Different Chlordiazepoxide controlled release tablet were prepared by Wet granulation method. Initially, Chlordiazepoxide pure drug, HPMC K4M, MCC (Avicel pH102), xanthum gum weighed accurately and shifted through sieve 40. Magnesium stearate and colloidal silicone oxide weighed accurately and shifted through sieve 60.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.[7,8] The prepared granules were dried at 60ºC for 20 min in hot air oven and then it was sifted through sieve 20. In extra granulation step Magnesium stearate (Diluent) and colloidal silicone oxide was accurately weighed and shifted through sieve 60 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 compressed by using tablet compression machine.

**Table 2: Formulation Development of Ibuprofen floating tablets.**

| S. 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 | 330 | 300 | 360 | 300 | 240 | 330 | 270 | 270 | 300 |
| 3 | HPMC K4 M | 120 | 150 | 120 | 180 | 180 | 150 | 150 | 180 | 120 |
| 4 | Xanthum gum | 90 | 90 | 60 | 60 | 120 | 60 | 120 | 90 | 120 |
| 5 | PVP K30 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| 6 | Colloidal silica | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 7 | Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 8 | Total | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 |

**Pre-compression Parameters**

**1. Angle of Repose:** It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane.[9, 10] It was determined by the following equation.

$$\text{Tan } \theta = h/r$$

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

**2. Carr's Index:** The carr's index compressibility index was calculated from the bulk and tapped density value by following equation.[11, 12]

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

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

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

**4. Bulk Density:** 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. 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 and the initial volume was observed.[14] It is given by the equation as

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

**5. Tapped density:** Weighed quantity of tablet blend was introduced into a graduated cylinder. Volume occupied by the drug was noted down. Then cylinder was subjected to 100, 200 and 300 taps in tap density apparatus.[15] According to USP, tapped density was given by

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

**Table-3: Specifications for flow properties.**

| Flow Character | Carr's index (%) | Hausner's ratio | Angle of repose |
|---|---|---|---|
| Excellent | <10 | 1.00-1.11 | 25-30 |
| Good | 11-15 | 1.12-1.18 | 31-35 |
| Fair (aid not needed) | 16-20 | 1.19-1.25 | 36-40 |
| Passable (may hang up) | 21-25 | 1.26-1.34 | 41-45 |
| Poor (must agitate/vibrate) | 26-31 | 1.35-1.45 | 46-55 |
| Very poor | 32-37 | 1.46-1.59 | 56-65 |
| Very, very poor | >38 | >1.60 | >66 |

**Table 4: Pre-compression Parameters of Chlordiazepoxide tablets.**

| Batch code | Angle of Repose | Carr's Index (%) | Hausner's Ratio | Bulk Density(gm/ml) | Tapped density(gm/ml) |
|---|---|---|---|---|---|
| F1 | 21.3 | 14.82 | 1.14 | 0.27 | 0.31 |
| F2 | 23.6 | 13.65 | 1.13 | 0.26 | 0.32 |
| F3 | 26.5 | 13.51 | 1.15 | 0.25 | 0.29 |
| F4 | 28.7 | 12.68 | 1.16 | 0.27 | 0.31 |
| F5 | 27.9 | 15.23 | 1.13 | 0.54 | 0.64 |
| F6 | 24.4 | 15.38 | 1.15 | 0.49 | 0.56 |
| F7 | 23.5 | 12.58 | 1.17 | 0.48 | 0.55 |
| F8 | 21.8 | 13.29 | 1.15 | 0.38 | 0.42 |
| F9 | 27.2 | 13.94 | 1.16 | 0.37 | 0.44 |

**Post Compression parameters**

**1. Weight variation test**

Twenty Chlordiazepoxide tablets were weighed individually, average weight was calculated and individual tablet weights were compared to the average weight. The tablets met the USP test if no more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit.[16]

**2. Hardness test**

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in $kg/cm^2$. Six tablets were randomly picked from each formulation and the mean values were calculated.[17]

**3. Friability**

A friability test was conducted on Chlordiazepoxide tablets using a Roche friabilator. Twenty tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The tablets were initially weighed and transferred into friabilator.[18,19] The drum was rotated at 25 rpm for 4 minutes after which the tablets were removed. Any loose dust was removed from the tablets as before and the tablets were weighed again. The percentage friability was then calculated by

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

**4. Swelling Index Determination**

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 one

hour time intervals until 24 hours, the tablet was removed from beaker, and the excess surface liquid was removed carefully using the filter paper.[20] The swollen tablet was then re-weighed (W2) and swelling index (SI) was calculated using the following formula.

**% Swelling Index = (W2 – W1)/W1 x 100**

**5. In Vitro Drug Release Studies**

*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 spectrophotometer.[21,22]

**6. Stability Study**

A stability study of optimized batch was performed according to ICH (International Conference on Harmonization) guidelines the stability chamber was placed at 40°C, and relative humidity 75%. Samples were evaluated at 0, 15 and 30 days interval.[23] The physical stability of tablet was observed periodically by evaluating appearance, hardness, % swelling index and *in-vitro* release study.

**RESULTS AND DISCUSSION**

The pre compression parameters of blend were evaluated according to USP. The result of pre compression parameters were shown in Table-4. Pre-compression evaluation revealed that all the nine batches had good flow properties. The results of weight variation, thickness, hardness, friability of all the prepared core tablets are shown in table-5. 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 nine batches Tablets are ranges from 599.8 to 601.5. It revealed that method selected for the preparation of Tablet is suitable and reproducible. The result of percent Cumulative drug release of all the batches F1-F9 revealed that, the batch F2 had shown highest % cumulative drug release 96.23% up to 17 hrs in a controlled manner shown in the figure-2. All batches having HPMC K4M and Xanthum gum which are highly swellable polymers and gave prolonged drug release up to 17 hrs. Obtained result revealed that with increasing concentration of HPMC K4M and xanthum the percent cumulative drug

release of the optimized batch was decreased due to increase in visco elasticity of matrix of prepared Tablet. The result of % swelling index revealed that batch F2 had highest percent of swelling index. It happened due to the higher concentration of hydrophilic and swellable polymers up to 17 hrs. These 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.

**Table 5: Post-compression Parameters of Chlordiazepoxide tablets.**

| Batch code | Average weight(mg) | Hardness(kg/cm$^2$) | Friability (%) | Swelling index (%) | Lag time(sec) |
|---|---|---|---|---|---|
| F1 | 600.1 | 7.6 | 0.83 | 70.15 | 105 |
| F2 | 600.3 | 7.2 | 0.91 | 71.25 | 240 |
| F3 | 602.4 | 7.3 | 0.86 | 69.13 | 255 |
| F4 | 603.1 | 7.8 | 0.95 | 68.25 | 245 |
| F5 | 599.8 | 7.5 | 0.88 | 67.16 | 248 |
| F6 | 603.4 | 7.3 | 0.93 | 65.19 | 238 |
| F7 | 600.4 | 7.1 | 0.86 | 67.25 | 254 |
| F8 | 601.5 | 7.9 | 0.89 | 63.29 | 261 |
| F9 | 600.9 | 7.2 | 0.85 | 69.26 | 239 |

**Table-6: Cumulative Percentage Drug Release of Chlordiazepoxide tablets.**

| Time(hrs) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 6.53 | 6.62 | 6.32 | 6.45 | 6.26 | 6.52 | 6.12 | 6.23 | 6.43 |
| 3 | 30.51 | 32.54 | 29.51 | 28.36 | 34.21 | 32.61 | 33.29 | 32.15 | 28.54 |
| 5 | 45.32 | 46.21 | 43.64 | 40.61 | 44.69 | 43.25 | 41.96 | 41.25 | 36.19 |
| 7 | 60.11 | 61.52 | 58.29 | 55.68 | 59.34 | 58.24 | 62.64 | 59.21 | 41.27 |
| 9 | 68.32 | 69.28 | 66.32 | 60.47 | 65.24 | 64.27 | 72.52 | 64.28 | 55.36 |
| 11 | 74.83 | 75.23 | 72.68 | 64.21 | 72.68 | 72.59 | 77.84 | 70.19 | 62.15 |
| 13 | 81.29 | 84.54 | 79.64 | 72.92 | 79.56 | 80.26 | 81.42 | 72.51 | 68.59 |
| 15 | 87.54 | 92.62 | 81.53 | 78.21 | 84.91 | 86.29 | 87.59 | 78.54 | 73.48 |
| 17 | 91.52 | 96.23 | 86.57 | 86.25 | 92.64 | 91.54 | 90.21 | 84.24 | 79.62 |

**Table 7: Stability data of optimized formulation F2 at 40$^0$C and 75%RH.**

| S. No | Parameters | At 0 days | At 15 days | At 30 days |
|---|---|---|---|---|
| 1 | Appearance | Light yellow crystalline powder | Light yellow crystalline powder | Light yellow crystalline powder |
| 2 | Hardness (Kg/cm) | 7.2 | 7.3 | 7.2 |
| 3 | Swelling index (%) | 71.25 | 71.59 | 71.21 |
| 4 | In vitro drug release (%) | 96.23 | 95.28 | 95.14 |

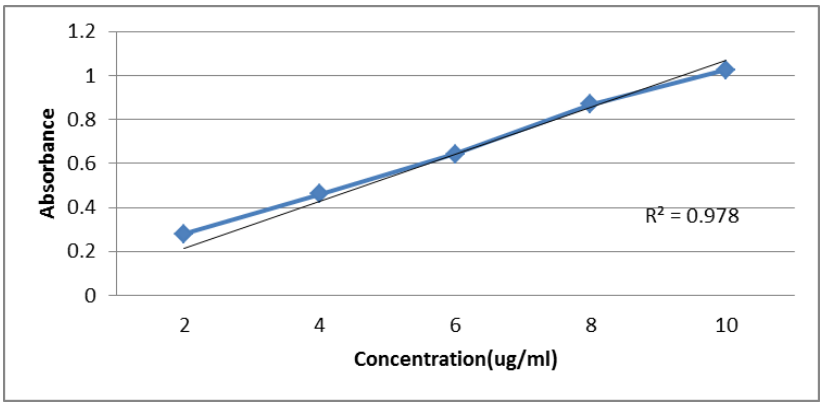


**Fig: 1- Standard graph of chlordiazepoxide.**

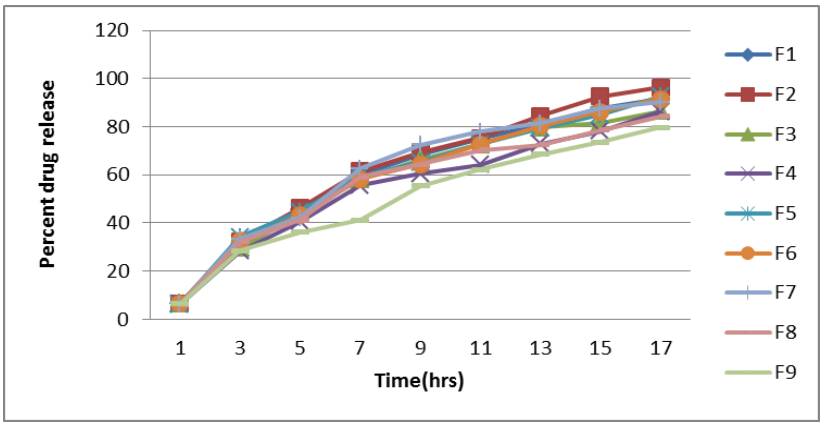


**Fig: 2- Cumulative drug release of Chlordiazepoxide tablets (F1 to F9).**

## 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. Analytical method was performed by UV Spectrophotometer and regression co-efficient (R2) was found to be near to one and which showed linear relationship between absorbance and concentration. The preliminary trial batches were 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. Different concentration of HPMC K4M and Xanthum gum containing batches F1-F9 were prepared and evaluated. Optimized batch (F2) showed good matrix integrity and exposed for stability study.

**ACKNOWLEDGEMENT**

The author was Thankful to Dr. K. S. Murali Krishna, Principal, MLR Institute of Pharmacy for his kind support and encouragement.

**CONFLICT OF INTEREST**

No conflict of interest was associated with this work.

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