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Formulation and Evaluation of Sustained Release Tablets of Chlorzoxazone

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Abstract

Chlorzoxazone is a centrally acting muscle relaxant used to treat muscle spasm and the resulting pain and discomfort which are having shorter half life (1.1hour) with the dose administration of 3-4 times a day. The aim of the study was to prepare and evaluate the Chlorzoxazone sustained release tablets in order to reduce the dose frequency and to improve the patient compliance. The tablets were prepared by direct compression method using synthetic polymers such as HPMC K15M (F1, F2 and F3), HPMC K100M (F4, F5 and F6) individually at different concentrations (45, 60, 75mg) and their combinations at 1:2 (F7) and 1:1 (F8) ratios. The tablets were evaluated for weight variation, hardness, friability, thickness, drug content uniformity and *in-vitro* drug release. All the formulations have passed in physical characterization as per the standard limits and found to be 147.7±1.2 mg in average weight, hardness ranges from 3.8±0.04 kg/cm^2 to 5.03±0.15 kg/cm^2, 1.99±0.05mm in thickness with the friability ranges from 0.2±0.01% to 0.5±0.04% and 90.06±0.9% to 105.1±0.5% in drug content. FT-IR studies, reveals that the drug was compatible with excipients. Based on the *in-vitro* drug release F3, F6 and F8 showed sustained release effect up to 8 hours (99.8%, 99% and 101%) having higher concentration high viscous polymer HPMC K100M. The $t_{50\%}$ and $t_{90\%}$ for F3 was 3.5 and 7.5 hours whereas for F6, F8 it was 4.0 and 7.5hours. The drug release pattern was followed by korsmeyer's-peppas model for F3 (0.9726), F6 (0.9952) and F8 (0.9856) respectively which depicts the diffusion mechanism.

Key Words: Chlorzoxazone, HPMC K15M, HPMC K100M, Sustained release.

INTRODUCTION

Sustained drug delivery systems are aimed to control the rate of drug release and to maintain desire drug level in the blood which is therapeutically effective for an extended period of time. Thus the reduction of both total dose of drug administered and the incidence of adverse side effects better patient compliance can be achieved [1, 2]. The most commonly used method for modulating the drug release is to include it in a matrix system [2]. Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules in slowly disintegrating or inert porous materials.

Chlorzoxazone (5-chloro-2,3-dihydro-1,3-benzoxazol-2-one) is a centrally acting muscle relaxant used to treat muscle spasm and the resulting pain and discomfort [3]. Chlorzoxazone may act by inhibiting calcium and potassium influx which would lead to neuronal inhibition and muscle relaxation. It is having a shorter half life (1.1hour) with the dose administration of 3-4 times a day leads to decreased patient compliance [3, 4]. In order to decrease the frequency of drug administration and for improving better patient compliance a sustained-release formulation of Chlorzoxazone is desirable.

Hydroxy Propyl Methyl Cellulose (HPMC) is the extensively used synthetic polymer derived from the cellulose. It is most widely used as the gel forming agent in the formulation of sustained release dosage form [7]. Its various grades have been used as release retarding agents and for different drugs [5, 6]. When it contacts with aqueous fluids were gets hydrated and to forms the viscous gel layer through which drug will be released by diffusion and/or by erosion of the matrix [6]. Hydroxy Propyl Methyl Cellulose are non-toxic nature, undergoes easy compression, having enough swelling properties and it can accommodate high levels of drug. The rate and extent of hydration of HPMC can influence the drug release from the dosage form through polymer swelling, drug dissolution, diffusion and matrix erosion. Based on different grades of HPMC and their optimum concentration in the formulation drug release rate can be modified [7, 8]. In the present work, the individual and combination effect of different grades of HPMC were studied in Chlorzoxazone.

MATERIALS AND METHODS

Chlorzoxazone was received as a gift sample from Orchid Chemicals and Pharmaceuticals Ltd, Chennai (India), Hydroxy Propyl Methyl Cellulose K15M, K100M, Lactose and Magnesium stearate were obtained from Loba Chemie Pvt Ltd., Mumbai. Talc was purchased from Micro fine chemicals, India.

PREPARATION OF CHLORZOXAZONE SR TABLETS [9]

Sustained release tablets each containing 150mg Chlorzoxazone were prepared by direct compression technique. The active ingredient and polymer HPMC K15M and HPMC K100M at various concentrations (45, 60, 75mg) were accurately weighed and passed through sieve no. 45. The content was mixed thoroughly in a mixer for 10 minutes. The lubricant and glidants were added to the above mixture and again mixed for 5 minutes. Then the mixture was directly compressed on a Rotary Tablet Machine (single punch, Inco) equipped with a 8 mm standard flat faced punch and die set. The effect of HPMC K15M and HPMC K100M were studied individually and their combination at 1:1 and 1:2 ratios were also observed. The compositions of different tablet formulations are shown in Table-1.

Table: 1 Composition of Chlorzoxazone SR Tablet formulations

INGREDIENTS (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Chlorzoxazone	10	10	10	10	10	10	10	10
HPMC K15M	45	60	75	----	----	----	30	60
HPMC K100M	----	----	----	45	60	75	60	60
Lactose	92	77	62	92	77	62	17	47
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight (mg)	150	150	150	150	150	150	150	150

Table: 2 Evaluation of Physical parameters of Matrix tablet.

Parameters	F1	F2	F3	F4	F5	F6	F7	F8
Weight variation (mg)	147.5±1.0	147±1.41	146.9±1.1	147.7±1.4	146.9±1.2	146.9±1.2	147.1±1.4	146.9±1.3
Friability (%)	0.5±0.04	0.4±0.02	0.4±0.15	0.5±0.06	0.3±0.05	0.2±0.01	0.3±0.06	0.28±0.01
Hardness (kg/cm^2)	3.8±0.04	4±0.1	4.2±0.1	3.9±0.1	4.4±0.15	4.8±0.1	4.5±0.05	5.03±0.15
Thickness (mm)	2.0±0.05	1.9±0.05	2.0±0.05	2.0±0.1	1.9±0.05	2.0±0.05	2.0±0.1	1.96±0.05
Diameter(mm)	8±0.01	8±0.03	8±0.01	8±0.02	8±0.05	8±0.01	8±0.02	8±0.01
Drug content (%)	98.42±0.7	104±0.5	90.6±0.9	105.1±0.5	102.5±0.6	96.3±0.6	98.4±0.5	93.8±0.7

***above values shows Mean ± S.D**

EVALUATION OF TABLETS

The compressed tablets were evaluated for physical parameters [10] such as weight uniformity, hardness, friability, drug content uniformity, *in vitro* release pattern and drug release mechanism.

Drug Content Uniformity

From each batch of prepared tablets, ten tablets were collected randomly and powdered in a mortar. From this powder equivalent to 10 mg of Chlorzoxazone was taken in a volumetric flask to this 5 ml of methanol was added and then the solution was subjected to sonication for about 10 min for complete solubilization of Chlorzoxazone and the solution was made up to the mark with methanol. The solution was filtered and further appropriate dilutions were made with phosphate buffer pH 7.4 and the drug content was estimated by measuring the absorbance at 280.5 nm by using UV-Visible spectrophotometer (Techcomp UV 2310) against phosphate buffer pH 7.4 blank.

Drug- Excipient Interaction Study [11]

By employing FT-IR spectroscopic technique, this type of interaction were studied which offers possibility of chemical interaction. In some cases drug – excipients interaction may occur in the formulation due to their intimate contact. FT-IR Spectrum of Chlorzoxazone, physical mixture and the formulation were obtained by KBr pellet method using Analytical FTIR Spectrometer model 2500 at a resolution of 4 cm^{-1}, from 4000 cm^{-1} to 300 cm^{-1}

In vitro dissolution studies [12]

The dissolution studies were performed in triplicate for all the batches in a USP XXIII dissolution test apparatus (Campbell electronics, DR-6) employing the paddle stirrer rotating at 75 rpm, 900 ml of phosphate buffer pH 7.4 as a dissolution medium at 37 ± 0.5ºC. 5 ml aliquots of dissolution medium was withdrawn at specified time intervals and the volume of the dissolution medium was maintained by adding the same volume of fresh pre warmed dissolution medium. The absorbance of the withdrawn samples was measured spectro photometrically at 280.5 nm**.**

Drug release kinetics [13]

To analyze the mechanism of drug release from the matrix tablets, the results of *in vitro* release data were plotted in various kinetic models like zero order, Higuchi model, Krosmeyer- peppas and Hixson crowell.

RESULTS AND DISCUSSION

Physical evaluation of Chlorzoxazone matrix tablets

After preparing the Chlorzoxazone matrix tablets all formulations were subjected to various physicochemical evaluation parameters such as weight variation, thickness, diameter, hardness, friability and drug content. The average percentage deviation of 20 tablets of each formulation was less than 5%. The thicknesses of the tablets were ranged from 1.9±0.05 to 2.0±0.1 mm and the diameter was 8 mm. The hardness and percentage friability for the tablets of all batches were ranged from 3.8±0.04 to 5.03±0.15 kg/cm^2 and 0.2±0.01% to 0.5±0.04% respectively. Drug content among different batches of tablets were ranged from 90.6±0.9% to 105.1±0.5%. Thus all the physical parameters of the matrices were practically within the limits which are shown in Table-2.

Compatability studies

The FT-IR spectra of physical mixture fig 2, 3 and formulation fig 4 were compared with the standard spectrum of Chlorzoxazone shown in fig 1. FT-IR spectrum of Chlorzoxazone was characterized by the absorption spectrum between 3100-3000 cm^{-1} (C-H stretching), for aromatic and alkene group (=C-H stretching), between 1600-1585 cm^{-1} (C-C stretching) may indicates for

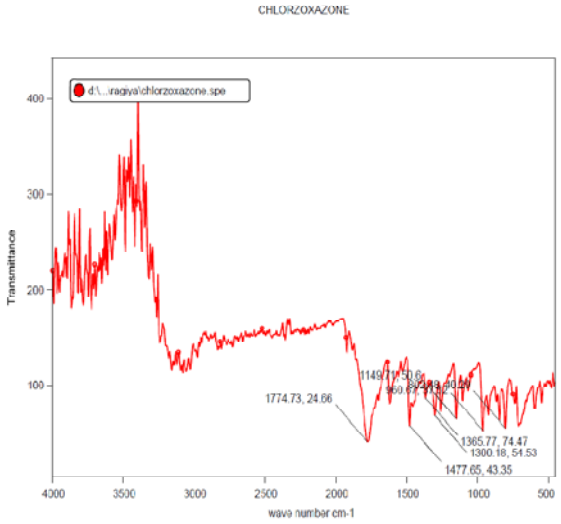

Fig. 1 FT-IR spectrum of Chlorzoxazone

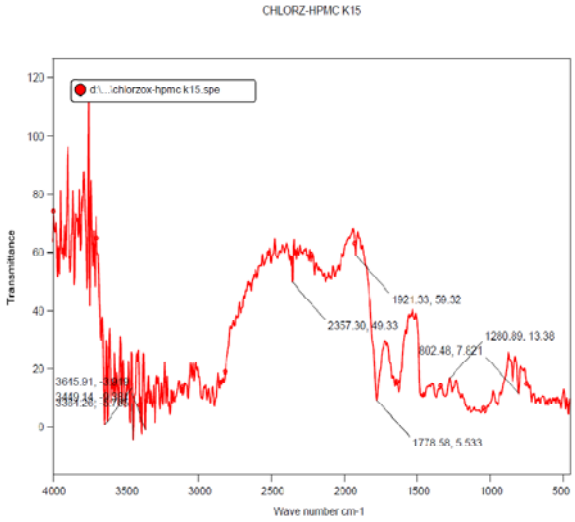

Fig. 2 FT-IR spectrum of physical mixture (Chlorzoxazone and HPMC K15M)

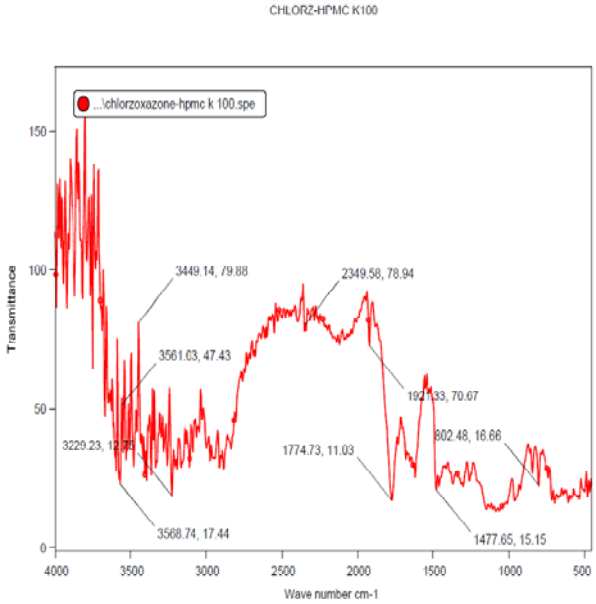

Fig. 3 FT-IR spectrum of physical mixture (Chlorzoxazone and HPMC K100M)

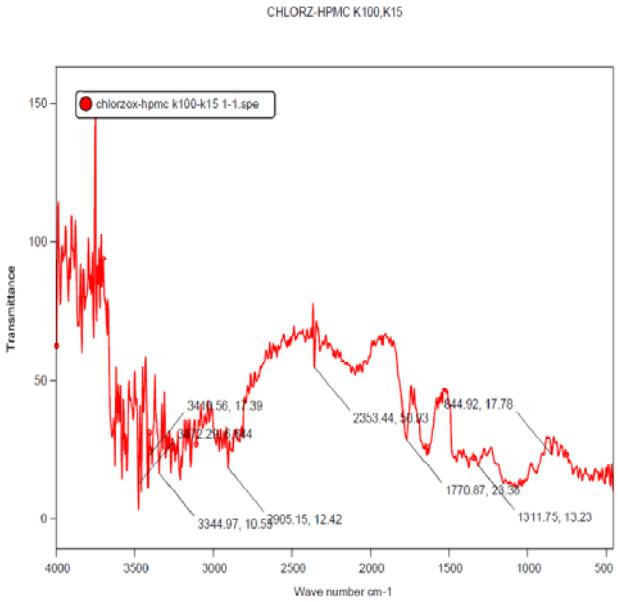

Fig. 4 FT-IR spectrum of F8 (HPMCK15M and HPMCK100M at 1:1 ratio)

aromatic ring. The wave number between 1000-650 cm^{-1} (=C-H bending) may depicts presence of alkene, from 3400-3250 cm^{-1} (N-H stretching) may represents amide group, between 1335-1250 cm^{-1} (C-N stretching) may indicates for aromatic amine and between 800-550 cm^{-1} may indicates for (C- Cl stretching) halide group, presence of carbonyl group may be observed at the spectrum (C=O stretching) in the range of 1665-1760 cm^{-1}. The FT-IR spectrum of physical mixture shows the above characteristic drug peaks with only negligible shift in wave number and hence it concludes that the Chlorzoxazone was compatible with the polymer.

***In - vitro* drug release study**

The results of dissolution studies for various formulations from F1 and F8 were shown in fig 5. The formulations F1 and F4 composed of 45 mg of polymer HPMC K15M and HPMC K100M showing 100% drug release within 3 hours. Formulations F2 and F5 containing 60 mg of polymer HPMC K15M and HPMC K100M, showing 100% release up to 6 hours where as formulation F3 and F6, having higher concentration 75mg of polymer HPMC K15M and HPMC K100M, exhibits sustained release for up to 8 hours. This result reveals that the drug release was retarded with proportional to polymer concentration where the amount of polymer influences the drug release. Further in order to prolong the release retarding effect an attempt was made where the polymers are used in the combination at 1:2 (F7) and 1:1 (F8) ratio of HPMC K15M and HPMC K100M where the high viscous polymer HPMC K100M may attributes positive effect at higher concentration. During *in vitro* drug release of the formulations F7 and F8 prepared in combination of HPMC K15M and HPMC K100M in the ratio of 1:1 showed sustained release effect for up to 8 hours but the same polymer 1:2 ratio showed

100% release within 6 hours and the results were made comparatively in fig 6. The higher viscosity grade polymers HPMC K15M and HPMC K100M both at individually were showing reduction in drug release rate for up to 8 hours which are found to be 99.8% (F3) and 99% (F6) but with respect to each time period (from 1 hour up to 8th hour) HPMC K100M were showing remarkable release retarding effect which can be found in $t_{50\%}$ and $t_{90\%}$ values were 3.5 and 7.5 hours for F3 where as for F6 and F8 it was 4.0 hour and 7.5 hours respectively which was depicted in Table-3. This effect was due to formation of high viscous gel layer around the tablet which could decrease the diffusion co-efficient of drug. Similar effect was also observed in 1:1 ratio (F7) also.

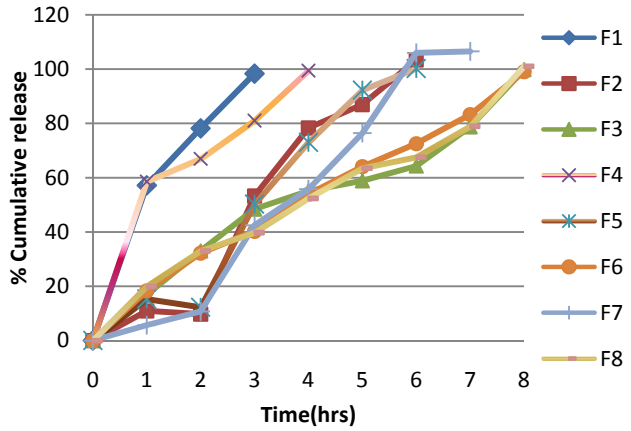

Fig. 5 *In vitro* release profile of Chlorzoxazone formulation from various batches (F1 to F8).

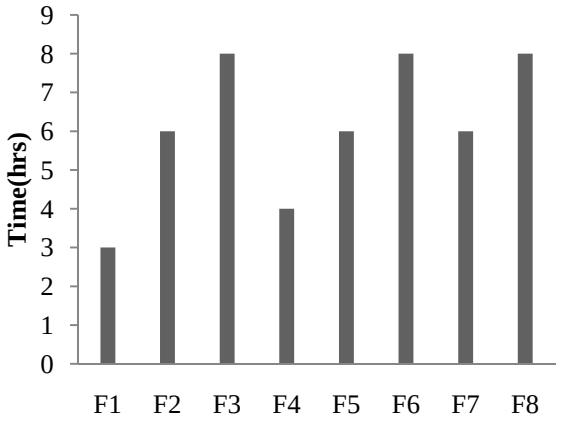

Fig. 6 Comparative percentage cumulative release of Chlorzoxazone formulation indicates the maximum time taken for the drug release.

Kinetic modeling of drug release

The release data was fitted to various mathematical models to evaluate the kinetics and the mechanism of drug release. The data was analyzed for the optimized formulations F3, F6 and F8 and the r^2 values are tabulated in Table-3. Among the models, zero order, Higuchi, Hixson-crowell and Krosmeyer peppas the above three formulation F3, F6 and F8 were best fitted in Krosmeyer-peppas and its r^2 values were found to be 0.9726 (F3), 0.9954 (F6) and 0.9856 (F8) which indicates diffusion is the mechanism of drug release.

Table: 3 Kinetics and $t_{50\%}$, $t_{90\%}$ data for the optimized formulations

MODEL	r^2 VALUE		
	F3	*F6*	*F8*
Zero order	0.9531	0.9954	0.9803
Higuchi	0.9419	0.9769	0.9525
Krosmeyer-peppas	0.9726	0.9954	0.9856
Hixson	0.7304	0.8551	0.7406
$t_{50\%}$	3.5	4.0	4.0
$t_{90\%}$	7.5	7.5	7.5

CONCLUSIONS

From the above study it may be concluded that at higher concentration of HPMC K15M and HPMC K100M at individually were exhibiting similar effect for retarding the release of Chlorzoxazone and by its combination at equal ratio produces higher drug release rate where as at high concentration of high viscous polymer shows moderate range in drug release rate. Thus the polymer concentrations were optimized for producing the oral SR tablets of Chlorzoxazone.

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REFERENCES

[1] Brahmankar, D.M., Sunil B, Jaiswal., *Biopharmaceutics and Pharmacokinetics*, 1995, 335-338.
[2] Shanmugam, S., Ramya Chakrahari., *Int. J. PharmTech Res*. 2011, 3, 526-527.
[3] Dong, D.L., Luan, Y., Feng, T.M., Fan, C.L., Yue, P., Yang, B.F., *Eur J Pharmacol*. 2006, 545, 161–166.
[4] Wan, J., Ernstgård, L., Song, B., Shoaf, S., *J Pharm Pharmacol*. 2006, 58, 51–61.
[5] Bravo, S.A., Lamas, M.C., Salomon, C.J., *Pharm Dev Tech*. 2004, 9, 75-83.
[6] Heng, P.W.S., Chan, L.W., Easterbrook, M.G., *J Control Release*. 2001, 76, 39-49.
[7] Mofizur Rahman, Md., Sumon, Roy., Sreedam Chandra Das., *J. Pharm. Sci. & Res*. 2011, 3 , 930-938 .
[8] Mofizur Rahman, Md., Sayeed Hasan., *Int J Pharm Biomed Res*. 2011, 2, 7-12.
[9] Akhtar Rasul., Muhammad Iqbal., Acta Poloniae Pharmaceutica-Drug Research. 2010, 67, 517-522.
[10] Lakade, S.H., Bhalekar, M.R., *Research J. Pharm. & Tech*. 2008, 1 (4), 410-413.
[11] Raghavendra Rao, N.G., Ashok Yadav., *Int J. Pharm & Res*. 2010, 2 (1), 34-42.
[12] Lakshmana Prabu, S., Shirwaikar, A.A., Shirwaikar A., *Ars Pharm*. 2009, 50 (1), 32- 42.
[13] Clement Jackson, Musiliu Adedokun., *Int J Pharm Pharm Sci*. 2011, 3 (5), 64-67.