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Formulation and evaluation of controlled release matrix tablet of diltiazem HCl by using HPMC and guar gum as polymeric matrix material.

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RESUMEN

Objetivos: En el presente trabajo se describe el desarrollo de comprimidos matriciales de clorhidrato de diltiazem.

Métodos: Se obtienen comprimidos matriciales mediante el uso de goma guar y HPMC. Se estudian distintas formulaciones en las que se cambia la composición de estos materiales matriciales como controladores de la cesión. Los comprimidos se prepararon por el método de granulación húmeda y se evaluaron uniformidad de contenido, índice de hinchamiento, estabilidad y velocidad de liberación.

Resultados: La capacidad de hinchamiento aumenta con el porcentaje utilizado de HPMC. Las formulaciones F7, F8 y F9 son las que muestran mejores características de liberación. Los estudios de estabilidad de la formulación seleccionada demuestran una buena resistencia a la rotura, capacidad de hinchamiento y control de la velocidad de disolución durante el estudio de estabilidad.

Conclusiones: Las formulaciones F7, F8 y F9 tienen unas buenas propiedades de control de liberación del fármaco durante al menos 8 horas. La cinética de liberación se pueden ajustar a un orden cero.

PALABRAS CLAVE: HPMC, goma guar, Diltiazem HCl, comprimidos matriciales, liberación controlada.

ABSTRACT

Aim: The present investigation concerns the development of controlled release matrix tablet of Diltiazem HCl.

Methods: Matrix tablet of Diltiazem HCl was formulated by using HPMC and Guar gum as a polymeric matrix forming materials in various concentrations (%w/w) to study their ability to retard the release. The tablets were prepared by wet granulation method and evaluated for physical properties, content uniformity, swelling index, stability and in-vitro drug release.

Results: Swelling was increased as the concentration and viscosity of HPMC increases. Tablets formulated using guar gum and HPMC alone were gave initial burst effect followed by controlled release for 8 hr. It was evident from the study that the formulationsF7,F8 &F9 have optimum swelling index and in vitro drug release up to 44% in 8hrs. The stability studies of optimized batch showed that there was no change in hardness, swelling index and in-vitro release up to 12 weeks.

Conclusions: The batches F7, F8 and F9 possessed the high potential to release the drug gradually for more than 8 hours. The zero-order release kinetic indicates concentration independent drug release ensuring that the formulated tablet showed promising result to be a sustained release formulation.

KEY WORDS: HPMC, Guar gum, Diltiazem HCl, controlled release, matrix tablets.

INTRODUCTION

Diltiazem HCl, an orally active calcium channel-blocking agent, is used in treatment of angina pectoris (variant & classical angina), hypertension and arrhythmias.[1,2] It is highly water soluble drug and is rapidly and almost completely (60-70%) absorbed from GIT, followed by oral administration, but undergoes extensive hepatic metabolism. The biological half-life of drug is 3.5 ± 1.2 h[3]. It is typically administered three or four times daily, in the form of conventional tablet. Thus frequently administration leads to constant change in blood concentration. To overcome the frequently administration and to minimize the peak to through oscillation of the blood concentration, control release formulation are developed. So, it has desired duration of action and localize the dosage form in a specific region and control the release rate of drug.[3]

Guar gum is natural gum and chemically; it is galactomannan polysaccharide. The gum consists of the pulverized endosperm of the seed of C. tetragonolobous. Guar Gum forms viscous colloidal dispersions when hydrated in cold water. It is used as a thickening agent for lotions and creams in concentration up to 2.5%, tablet binder (10%), emulsion stabilizer (1%). Chemically; HPMC is mixed alkyl-hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl groups. HPMC also forms viscous colloidal solution in cold water. It is used as a film former (2-10%), binder (2-5%). High viscosity grades are used to retard the release of water- soluble drugs. The present study aim to formulating controlled release matrix tablet of Diltiazem HCl, with the controlled release soluble matrix material (HPMC and Guar gum).[4]

MATERIAL AND METHODS

Materials

Diltiazem HCl was obtained as a gift sample from Sun pharmaceuticals Ltd, Baroda, India. HPMC K4M (Methocel®K4M) was obtained from Colorcon Asia Pvt. Ltd, Goa. Guar gum was obtained from the laser chemicals, Baroda. All other chemicals used were analytical grade and double distilled water used throughout the experiments.

Preparation of controlled release tablets of diltiazem

Controlled release tablets were prepared by wet granulation method. Hydroxypropyl methylcellulose, Guar gum was used as retardant material for preparation of tablets. Other excipients were dicalcium phosphate, magnesium stearate as a lubricant and talc as a glident. Distilled water was employed as a granulating fluid.

For preparation of controlled release tablets of Diltiazem, drug and polymer were weighed accurately, mixed thoroughly then other excipients were added and mixed by triturating.The resultant mixture was granulated by using distilled water and wetted mass pass through the 20 mesh sieve and retained on 40 mesh sieve. Then it was dried at 60°C for half an hour in an oven and processed to get 20:40 mesh granules. The dried 20:40 granules were mixed with glident(talc) and lubricant (Magnesium stearate). After mixing compressed into tablets using a Rotary tablet machine (Rimek Rotary tablet machine RSB-4 mini press) 12 mm die, and punches were used 400 mg is adjusted as a weight of each tablet and hardness between 3-5 kg/cm^2.[5,6] The composition of formulation is shown in (Table-1). These matrix tablets were evaluated for their physical properties (Table-2).

Evaluation of formulation:

Physical parameters:

Tablets were tested for hardness, friability, weight variation and drug content. Hardness of the tablets was tested using a Monsanto hardness tester and Friability of the tablets was determined in a Roche friabilator (Model EF2, Electrolab, Mumbai, India).[7]

Drug content:

The prepared tablets were analyzed for Diltiazem HCl contents. Tablets were crushed into fine powders and

Tabla 1. The composition of Diltiazem HCl controlled release matrix tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem HCl	120	120	120	120	120	120	120	120	120
Hydroxy propyl methyl cellulose	30	30	30	40	40	40	50	50	50
Guar gum	30	40	50	30	40	50	30	40	50
Di-Calcium Phosphate	211	201	191	201	191	181	191	181	171
Talc	6	6	6	6	6	6	6	6	6
Magnesium stearate	3	3	3	3	3	3	3	3	3
% of polymer to the total tablet weight	**15%**	**17.5%**	**20%**	**17.5%**	**20%**	**22.5%**	**20%**	**22.5%**	**25%**

F1 to F9 = Designed different batches according to different polymeric HPMC: Guar gum ratio

Tabla 2. Physical properties of diltiazem HCl controlled release matrix tablets

Formulation	Hardness (kg/cm²)	Friability (%)	Weight variation	Thickness (mm)	Drug content (%)
F1	3.58 ± 0.75	0.65	402.75 ± 8.44	5.027 ± 0.191	99.56
F2	4.02 ± 0.55	0.55	398.8 ± 6.92	5.037 ± 0.057	99.43
F3	3.96 ± 0.83	0.65	400.3 ± 6.98	5.103 ± 0.107	98.12
F4	3.68 ± 0.57	0.42	398.25 ± 8.03	4.913 ± 0.261	98.16
F5	3.76 ± 0.80	0.51	402.6 ± 6.36	4.930 ± 0.044	99.06
F6	4.20 ± 0.48	0.44	397.6 ± 6.58	4.973 ± 0.040	97.51
F7	3.95 ± 0.62	0.23	398.9 ± 5.75	4.833 ± 0.064	99.74
F8	3.80 ± 0.38	0.29	402.45 ± 5.86	5.003 ± 0.176	98.39
F9	4.20 ± 0.28	0.16	403.4 ± 6.58	4.948 ± 0.231	98.78

Each reading is an average of three determinations (Avg.± S.D)

Diltiazem HCl was extracted into water by shaking the crushed powder with water in a volumetric flask. The solution was filtered out and diluted with water and estimated in UV-Spectrophotometer (UV-1601, Shimadzu, Japan) at 235 nm after suitable dilution.[8]

Swelling index:

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of formulation F1 to F9 was studied. One tablet from each formulation was kept in a Petri dishcontaining pH 7.2 phosphate buffers. At the end of 1 hr, the tablet was withdrawn, kept on tissue paper and weighed. Then for 2 hr and every 2 hr, weights of the tablet were noted and the process was continued for 8hr.The % weight gain by the tablet was calculated by formula.[9]

$$S.I = \{(M_t - M_0) / M_0\} \times 100 \quad (1)$$

Where, S.I = Swelling index; M_t = weight of tablet at time't'; M_0 = weight of tablet at time t = 0

Swelling behavior of controlled release matrix tablets were represented in Figure 2.

In-vitro drug release studies:

A tablet was placed in USP XXIII paddle-type dissolution test apparatus (Model TDL-08, Electro lab, Mumbai, India) and immersed in 900ml of dissolution media phosphate buffer (pH 7.2), maintained at 37°C ± 0.5°C. Aliquot samples were withdrawn every hour up to a period of 8 hours. After each withdrawal, the withdrawn amount of dissolution media was replaced with buffer. The absorbance of the withdrawn samples, after appropriate dilution was measured at 237 nm against appropriate buffer blanks.[10, 11]

Stability study

Optimized batch of Diltiazen HCl tablets (Formulation F7 to F9) were kept for a short term stability study in high density polyethylene sealed cover at 40 ± 2 °C / 75 ± 5% RH as per ICH Guidelines. Samples were withdrawn for six and twelve weeks of storage and evaluated for appearance, drug content and *in vitro* dissolution.

Figure 1. Diltiazem HCl release profile from the matrix tablets of F1 to F9 batches

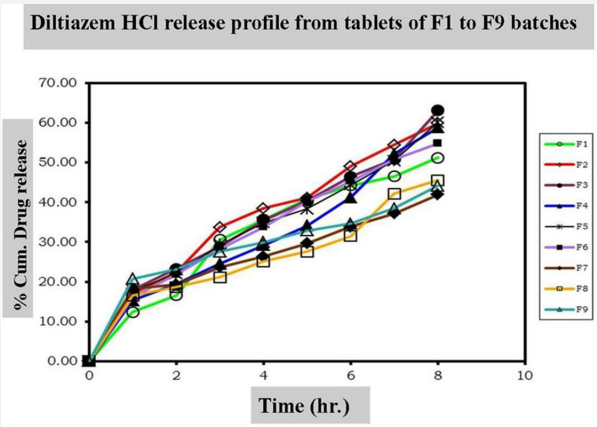
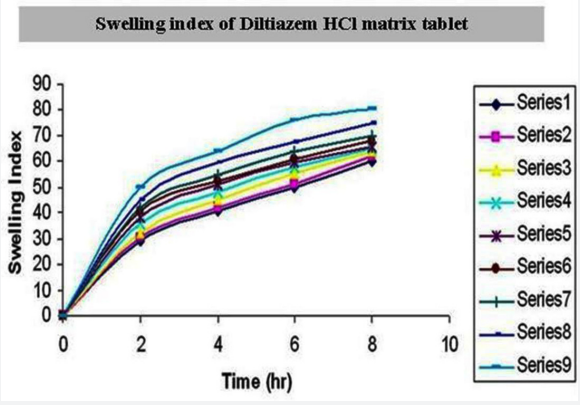


Figure 2. Swelling index of diltiazem HCl matrix tablet



RESULT AND DISCUSSION:

Controlled release matrix tablets were evaluated for its

Table 3. Comparison of r2 value of zero order Vs Higuchi's diffusion equation

Batch No	Zero order	Higuchi's diffusion
	r^2	r^2
F7	0.9944	0.9728
F8	0.970	0.935
F9	0.992	0.977

physical characteristics; the results are shown in Table 2. Hardness of the tablets was found in the range of 3.58 ± 0.75 to 4.20 ± 0.28 kg/cm^2. Percentage weight loss in the friability test was found to be 0.43% in all batches. Content uniformity of all the prepared batches is within the limit (Diltiazem 100 ± 3% of the labeled content). We can conclude that all the batches of tablets prepared were of good quality with regard to hardness, friability and drug content.

The matrix tablet was evaluated as a matrix forming material for oral controlled release tablets using Diltiazem HCl as a model drug. Matrix tablets, each containing 120mg of Diltiazem, were prepared using different matrix forming polymeric material (HPMC and Guar gum).

In-vitro swelling studies

The swelling index of controlled release matrix tablets for a period of 8hr was studied. The values obtained as shown in the Figure 2. It is evident that an increase in the amount of HPMC causes increase in swelling index. Among all the formulations F7, F8, and F9 showed the highest value of 69.8%, 74.9% and 80.5% respectively.

In-vitro release studies

The *In-vitro* release study showed satisfactory controlled release of Diltiazem from all medicated formula. The release of Diltiazem HCl from prepared formulations was analyzed by plotting cumulative % drug release verses time (hr) as shown in Figure 1.

Guar gum and HPMC are hydrophilic swellable polymer matrices; they are able to form a viscous gel layer; which controls the drug release via diffusion through the gel and erosion of the gel barrier. It was observed that as there was a reduction in the amount of the polymer to the half ensures faster release. This may be attributed due to the reduction of the strength of the gel layer, which enhances drug diffusion and water uptake through the matrix**.** It was concluded from the results that as there was increases in polymer concentration of HPMC the release of drug might be slower. This is also supported by Xu and Sunada who reported that HPMC content was predominant controlling factor.[1,2]

While using blends of polymers in different batches like Batch F7 (HPMC K4M 50 mg and Guar gum 30 mg), Batch F8 (HPMC K4M 50 mg and Guar gum 40 mg), and Batch F9 (HPMC K4M 50 mg and Guar gum 50 mg), the cumulative percentage (%) release of batch F7, F8 and F9 were found to be 41.91%, 45.55% and 44.13% in 8 hr, respectively.

Method of Bamba and Puisieusx was adopted to study model dependent kinetics of drug release for the most appropriate model. The dissolution data of all batches were fitted to zero-order and Higuchi.[13] The result is shown in Table 3. From all the formulations F7, F8 and F9 follows desired drug profile, i.e. near the zero order drug release.

Stability study

Stability studies of optimized formulations were analyzed for 12 weeks by evaluating its hardness, swelling index and release study. Table 4 indicates the stability study data of optimized formulations (F7, F8 and F9). It is seen that in all three batches, there is no any significance difference in hardness, swelling index and in-vitro release study till 12 week stability study. It reveals that all three formulations (F7, F8 and F9) are stable.

CONCLUSION:

Matrix tablets were prepared by wet granulation method using hydroxy propyl methyl cellulose (HPMC) and guar gum as a matrix forming materials in different proportion. Study indicates that HPMC and Guar gum (50:30, 50:40 and 50:50) ratio were found suitable for the

Table 4. Stability study of batch F7 to F9

Formulation	Parameter								
	Hardness(kg/cm^2)			Swelling index			Drug release (%)		
	F7	F8	F9	F7	F8	F9	F7	F8	F9
After 6 week	3.95 ± 0.62	3.80 ± 0.38	4.20 ± 0.28	69.63± 0.085	74.2 ± 0.023	80.5 ± 0.012	40.91	44.85	43.13
After 12 week	3.95 ± 0.89	3.80 ± 0.68	4.20 ± 0.80	69.85± 0.013	74.3 ± 0.015	80.75 ± 0.019	40.25	44.69	42.80

use as pharmaceutical excipients in the formulation and manufacturing of controlled release matrix tablets of Diltiazem HCl. The batches F7, F8 and F9 possessed the high potential to release the drug gradually for more than8 hours. It confirmed the fact that the formulated tablet showed promising result to be a sustained release formulation. It is evident from overall studies that hydroxy propyl methyl cellulose (HPMC) and guar gum possess potential for sustained release of Diltiazem HCl from the matrix tablet.

REFERENCES:

1. Rang HP, Dale MM. Pharmacology. 6th ed. Churchill Livingstone: Edinburgh. 1999. 829p.
2. Bhattacharya SK, Parantapa S, Arnabha R. Pharmacology. 2nd ed. Elsevier publication. 2003. 538p.
3. Parvez N, Ahuja A, Khar RK. Development and evaluation of muco-adhesive buccal tablets of lignocaine hydrochloride. Ind J Pharm Sci. 2002; 64(6):563-7.
4. Shenoy VR. Handbook of pharmaceutical chemistry. Mumbai: Multitech publishing co. 2000. 516 p.
5. Shirwaikar AA, Srinatha. Sustained Release Bi-Layered Tablets of diltiazem hydrochloride using insoluble matrix system. Ind J Pharm Sci. 2004; 66(4):433-7.
6. Lordi NG. Theory and practice of industrial Pharmacy. 3th ed. Mumbai: Varghese Publication House. 1991.759 p.
7. Lachman L, Lieberman HA, Kanig JL. The theory and practice of industrial pharmacy.3th ed. Mumbai: Varghese publishing house. 1987.678 p.
8. United States Pharmacopoeia XXVII-NF XXII. Asian edition; USP Convention Inc. 2004.1128 p.
9. Chitta SK, Anil B, Amarnath RB, Chandra SA. Development and in vitro evaluation of glibenclamide aloe barbadensis miller leaves mucilage controlled release matrix tablets. Int J Pharm Tech Res. 2008; 7(4):137-40.
10. Selvendran M. Formulation and evaluation of controlled release matrix tablet of ondansentron hydrochloride. The Indian Pharmacist. 2002; 1(5): 56-9.
11. Salomon CJ, Bravo SA, Lamas MA. In vitro studies of diclofenac sodium controlled release from bio-poymeric hydophillic matrices. J Pharm Sci. 2002;5:213-9.
12. Xu G, Sunada H. Influence of formulation change on drug release kinetics from HPMC matrix tablet. Chem Pharm Bull. 1995; 43(3):538-50.
13. Bamba M, Puisieusx F. Release mechanism in gel forming sustained release preparations. Int J Pharm. 1979; 2(5-6):307-15.