International Journal of Pharmaceutical Research and Development (IJPRD)
Platform for Pharmaceutical Researches & Ideas
www.ijprd.com

DESIGN DEVELOPMENT AND EVALUATION OF DILTIAZEM HYDROCHLORIDE SUSTAINED RELEASE TABLET

R.Gowri[1]*,
N.Narayanan[1], A.Maheswaran[1], P.Vijayalakshmi[1], M. Rekha[1]

[1]Dept of Pharmaceutics, Jaya College of Pharmacy, Thiruninravur, Chennai, Tamil Nadu, India.

ABSTRACT

This work aims at the investigating use of Diltiazem hydrochloride as sustained release tablets which could release the drug for 12 h with predetermined rate. Matrix tablets are prepared by wet granulation method. Four batches of tablets were prepared (F1-F4) by using various polymer concentrations and granulation technique on the release of Diltiazem hydrochloride was studied. The influence of polymer concentration and granulation technique on the release of Diltiazem hydrochloride was studied. The formulated tablets were characterized by different physical parameters like hardness, friability, weight variation etc. The dissolution results showed that F4 showed prominent by reduced rate of release. F4 with higher hardness of 6.48 kg/cm^2 slowed the drug release pattern in the dissolution study. Model fitting analysis for formulation F4 fitted in zero order and follows Higuchi kinetics indicates good swelling and gel formation property of Carbopol, supporting the drug release followed both diffusion and erosion mechanism. The physical parameters of all formulated tablets were within the acceptable limits. The effects of storage on in vitro release and physiochemical parameters of successful batch were studied and were found to be in acceptable limits. Thus Diltiazem hydrochloride is a promising candidate for the development of oral sustained release drug delivery system.

Correspondence to Author

R.GOWRI

Dept of Pharmaceutics, Jaya College of Pharmacy, Thiruninravur, Chennai, Tamil Nadu, India.

Email: gowripharmajaya@gmail.com

KEYWORDS : *sustained release, Diltiazem hydrochloride, Carbopol.*

INTRODUCTION

Novel techniques of drug delivery aims to control the drug delivery rate, the duration of therapeutic activity sustained, targeting the drug delivery to a tissue [1]. Sustained release dosage form retards the release of therapeutic agents in such a manner that in the systemic circulation its appearance is delayed by exhibiting the plasma profile in sustained duration of action[2]. Better patient compliance and reduction in frequency of intakes attracted sustained release dosage form superior than other dosage form[3-4]. Diltiazem hydrochloride

is an extensively used cardiovascular drug for the treatment of angina, hypertension and atrial flutter[5-6]. It has a short biological half life and undergoes high hepatic first pass metabolism causing gastrointestinal discomfort[7]. In the present study attempt has been made to formulate Diltiazem hydrochloride as a sustained release tablet to reduce the disadvantage produced by other drug delivery system[8].

MATERIALS AND METHODS

Diltiazem hydrochloride was obtained as a gift sample from Torrent Pharmaceuticals, Ltd, Gujarat, India. Hydroxy propyl methyl cellulose K4M, Hydroxy propyl methyl cellulose K100, Carbopol 971, Microcrystalline cellulose (Avicel PH 101) a gift sample from S.D.Fine Chemicals, Mumbai. All other chemicals and reagents were obtained from commercial sources and were of Analytical grade.

Drug – Excipent compatibility studies

IR Spectra of mixture of drugs, drugs and polymer and the formulation were obtained using Thermo Nicolet FT (IR-200). Thermal analysis was performed on the mixture of drugs and selected formulations using a Mettler Tcll TA processor differential scanning calorimeter to establish the compatibility of ingredients.

Preparation of SR matrix Diltiazem Hydrochloride tablets

Sustained release tablets of Diltiazem hydrochloride was prepared by wet granulation technique (formulation F1-F4). Using drug and different polymer ratios viz., 1:0.6, 1:0.8, 1.1, 1:1.2. Microcrystalline cellulose solution was used as diluent, magnesium stearate and talc were incorporated as lubricant. Diltiazem hydrochloride, Avicel PH 101 and all ingredients were screened through sieve no: 100, weighed and blended. The granulating fluid was PVP-K30 in isopropyl alcohol. The wet coherent mass was passed through sieve no: 16. The obtained granules were dried in hot air oven for one hour. The dried granules were lubricated with magnesium stearate. The lubricated granulates were compressed using 10 station rotary tablet press (Rimek, Ahmedabad, India) with 8 mm flat faced punches. The results has been shown in Table: 1

Table 1: *Composition of Diltiazem hydrochloride sustained release tablet*

Ingredients (mg)	Formulation code			
	F1	F2	F3	F4
Diltiazem hydrochloride	90	90	90	90
HPMC K4M	54	-	-	-
HPMC K100	-	72	-	-
HPC- HF	-	-	90	-
Carbopol	-	-	-	108
Avicel PH 101	47	-	-	-
Magnesium stearate	02	02	02	02
$PVPK_{30}$	07	07	07	07
Total weight	200	200	200	200
Drug gum: ratio	1:0.6	1:0.8	1:1	1:1.2

Evaluation of granules

The granules were evaluated for angle of repose[9], bulk density[10] and compressibility index[11] using USP tapped density tester. The angle of repose was measured by a reposograph whereby cone formed on the base of reposograph was examined to observe the zone, which indicates flowability of granules. Loose bulk density (LBD) and tapped bulk density (TBD) were measured using formula,

LBD= weight of powder/volume of the packing.

TBD=weight of powder/ tapped volume of the packing.

Compressibility index of the granules was determined by using the formula,

CI (%) = [(Total Bulk Density-Loose Bulk Density)/Total Bulk Density]*100.

Table 2: *Preformulation studies of granules*

Formulation code	Angle of repose(h/r)	Loose Bulk density g/ml	Tapped bulk density g/ml	Compressibility Index
F1	28^{o}	0.665±0.03	0.533±0.04	18.75±0.02
F2	25^{o}	0.672±0.04	0.540±0.03	18.59±0.04
F3	26^{o}	0.682±0.03	0.554±0.02	18.99±0.03
F4	24^{o}	0.612±0.02	0.579±0.03	18.57±0.04

All the values are Mean ± S.D n=5

Evaluation of tablets

The thickness and diameter was measured using a digital slide caliper, Mitutioyo, Japan. Weight variation test was conducted as per specifications. Hardness test was performed using Monsanto hardness tester[12]. Friability test was determined using friability testing apparatus, Mumbai[13].

Diltiazem hydrochloride calibration curve

Calibration curve of Diltiazem hydrochloride was prepared by using phosphate buffer 5.8 in the concentration range of 1-15 µg/ml. The drug was analyzed spectrophotometrically (UV 1601 Shimadzu, Japan) at 236 nm.

Drug content

5 tablets from each formulation were chosen randomly to 90 mg of Diltiazem hydrochloride was extracted with 100 ml phosphate buffer pH 5.8. Aliquot from subsequent filtered solution was further diluted in phosphate buffer pH 5.8. Theoretical concentration was same as that of standard concentration. The resulting solutions were analyzed using UV Spectrophotometer[14].

Table 3: *Physical properties of diltiazem hydrochloride SR tablets*

Tablet formulation	Drug content (%)	Hardness(K g/Cm^2)	Friability (%)w/w	Thickness (mm)	*In vitro* drug release
F1	93±0.24	5.40±0.52	0.18	3.2	84.32
F2	92±0.3	5.35±0.19	0.21	3.2	88.28
F3	94±.35	6.40±0.71	0.16	3.2	92.54
F4	97±0.72	6.50±0.86	0.30	3.3	96.97
M1	98±0.86	6.85±0.18	0.54	3.5	98.34

***In vitro* drug release studies**

In vitro drug release studies were carried out using tablets dissolution test apparatus USPXXII at 100 rpm. The dissolution medium consisted of 5.8 phosphate buffer. Aliquot of 10ml were withdrawn at predetermined time intervals and equivalent amount of fresh dissolution fluid equilibrated at same temperature was replaced. Aliquot were withdrawn and the fluid analyzed by measuring the absorbance at 236nm. *In vitro* dissolution study was also carried out with marketed sustained release product (MSR) for comparative analysis.[15-16]

Fig 1: *In vitro dissolution profile of different formulations of Diltiazem hydrochloride*

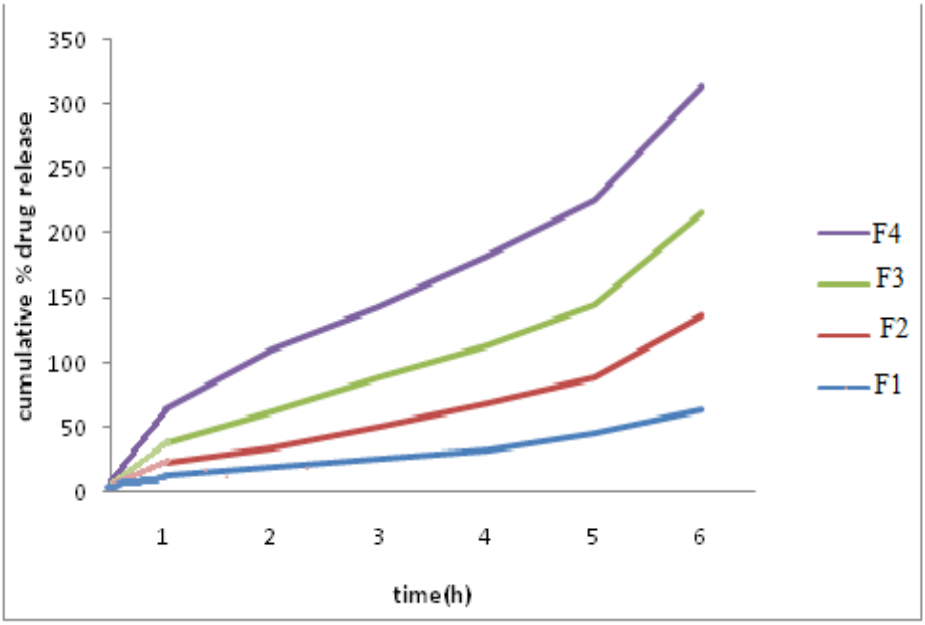
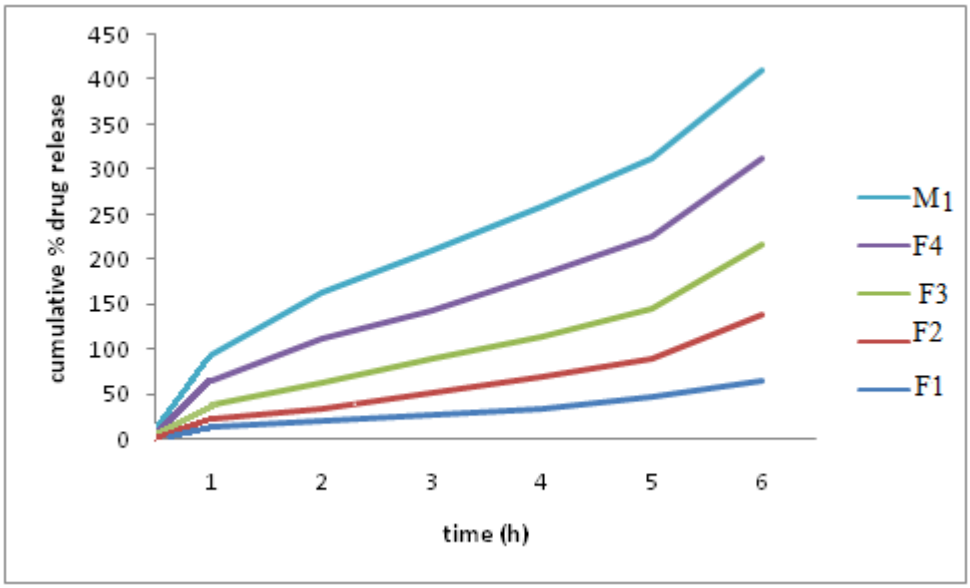


Fig2 : *Comparative dissolution study of optimized formulation F4 and Marketed formulation M1*



Study of release kinetics

The *in vitro* drug release profile were plotted to zero order equation *($Q=K_o t$)*, first order equation *($In\ (100-Q) = In\ Q-K_1 t$),* Higuchi equation*($Q=Kt^{1/2}$)*, Korsmeyar and peparequation *($Q=K_p t^n$)*, where Q is the percent of drug release at time t and $K_o$and K_t are the co-efficient of the equation. K_p is constant incorporating structural and geometrical characteristics of the release exponent indicative mechanism of release. All these models were used to analyse the drug release mode from tablets.[18-19]

Stability studies

Stability study was carried out to study the effects of temperature and relative humidity (RH) on optimized formulation (F4) by keeping (0-4^{o}C) 100 ml, temperature (29^{o}C) and at 45^{o}C in air tight high density polyethylene bottles for three months at RH 76±4%. Physical evaluation and *in vitro* release were carried out.[20-2]

Table 4:*Physical properties of Diltiazem hydrochloride SR tablets (F4) after stability study at 0-4^{o}C, 29^{o}C and 45^{o}C.*

Formulation	Drug Content (%)	Hardness (Kg/Cm^2)	Friability (%)
After 1 month	100.80	6.60±0.43	0.36
2 months	100.82	6.48±0.18	0.34
3 months	100.66	6.35±0.54	0.32

Table 5: *Correlation co-efficient according to different kinetics*

Formulation	Kinetic model			
	Zero order	First order	Highuchi square ratio	Kosemeyerpeppa
F1	0.9925	0.8967	0.9825	0.9393
F2	0.9856	0.9926	0.9816	0.9386
F3	0.9875	0.9651	0.9629	0.9498
F4	0.9896	0.9752	0.9784	0.9582

RESULTS AND DISCUSSION

The present investigation was undertaken to design formulate and evaluate Diltiazem hydrochloride sustained release tablet for sustained release dosage form and compared with the marketed products. FT-IR and DSC study indicates good compatibility with polymer and excipients.Formulated SR tablets meets the pharmacopoeial requirement for uniformity of weight. The data shown in table 3, viz. Hardness, % Friability and Thickness were found to be well within the acceptable limits as per I.P.

The granules of different formulation were evaluated for angle of repose, LBD, TBD and compressibility index. The angle of repose of various batches was less than 30^{o} indicating good flow property. The results of LBD, TBD and compressibility index are mentioned in Table 2. The result of compressibility index lies between 11.57±0.04 and 12.99±0.03 which is below 15% indicating excellent flow properties.Diltiazem hydrochloride release from all tablets was found to be slow and extended over longer period of time. It was observed that increase in polymer concentration did not alter the thickness of the tablet significantly. F1 failed to release beyond 64%. F4 was selected as optimized formulation on the basis of results of *in vitro* dissolution studies, as it gave good sustained actionof 96.97%. The marketed sustained release product (MSR) showed release of 98.34 at the end of 12 hours, which is well comparable to F4.

Similarity factor of F2 were calculated andwere compare to formulation F3 with marketed available SR tablets F2 value. 53.083 showed similarities of dissolution profiles with that of marketed formulation.

Upon model fitting analysis for F4, fitted in zero order and Higuchi kinetics with R values as 0.9951 and 0.9969 indicating that there was no erosion of matrix. (Table 5)

The examination of scanning electron microscopy (SEM) and photographic results of formation F4 indicated, drug in tablet form have smooth plain, porous less sectioned surface after swelling. This proves good swelling formulation property of Carbopol and uniformity mixing of all ingredients. It was evident that drug release were retarded with increase in the polymer content. The drug release followed first order kinetics and Higuchi model, thus indicating that there was no erosion of the matrix and tablet maintains its surface area and shape. The results of stability studies conducted on F4 revealed no change in physical appearance, hardness, drug content and dissolution profile whereas IR spectrum obtained exhibits no incompatibility. Hence formulations were found to be stable at tested temperature. Stability studies reveal that good stability of formulation without any physical and chemical degradation.

From the above results it can be concluded that formulation F4 has achieved the objectives of prolonged drug release, patient convenience, cost effectiveness as a combined dosage form and appears to be assured further by conducting bioavailability studies in human volunteers and long term stability testing.

CONCLUSION

Emerging pharmaceutical industry in recent era opts for sustained drug delivery system encompassing quality with swifter therapeutic effect. Sustained release tablet makes glorious impact in the market despite the advancement made in other drug delivery system making beneficial means of an administration enhancing patient compliance. The developed Diltiazem hydrochloride sustained release tablet will maintain better plasma levels.

REFERENCES

1. Y.W. Chien; 'Novel Drug Delivery System': Fundamentals, Developmental Concepts and Biomedical Assessments'. Dekker, New York (1982).
2. Y.W. Chien; 'Rate- Control drug delivery systems': Control release vs sustained release. Medical Progress Through Technology, 15:21-46 (1989)
3. Toti US, .*J Control Release*. 95:567, 2004.
4. R.Colombo, P.S.Bettini, N.A.Peppas, Snellable'Matrixes for controlled drug delivery': gel-layer behavior, Mechanisms and Optimal Performance, Pharm. Sci. Technol. Today. 3(2000) 198-204.
5. David A. Williams, 'Foye's Principles of Medicinal Chemistry', 5th edition, 557.
6. F.W.Merkus, 'Controlled and Rate-controlled drug delivery'; principal characteristics, possibilities and limitations, In Strukyer-Boudies, H.A. (eds), Rate-Controlled Drug Administration and Action CRC press, Boca Raton, FL, USA, (1986) 15-47.
7. H P Rang, M M Dale, J M Ritter, R J Flower; 'Rang and Dale's Pharmacology', 5th edition, 296.
8. Beckert, T.E., Lehmman, K., Schmidt, P.C., Compression of enteric coated pellets to disintegrating tablets, *Int. J. Pharm*., 1996, 143, 13-23.
9. Cooper J. and Gunn C: 'Powder flow and compaction. In. Carter SJ, eds. 'Tutorial Pharmacy', CBS publishers and distributors, New Delhi, 1986, 211-233.
10. Shah D., Shah Y. and Rampradhan M: Development and evaluation of controlled release diltiazem hydrochloride micro particulate using cross linked polyvinyl alcohol, *Drug DevInd Pharm*. 1997, 23(6), 567-574.
11. Aulton M. E and Wells T. I. Pharmaceutics: 'The Science of Dosage Form Design Churchill Living Stone', London, England, 1988, 247-248.
12. Lachman L., LibermanH.A.Kanig J.L. eds: 'The Theory and Practice of IndustrialPharmacy' , Lea and Febiger, Philadelphia, PA, 1987, 317-318.
13. *Pharmacopoeia of India,* Controller of Publication, Ministry of Health and Family Welfare, Government of India, New Delhi, 1996,735.
14. *Pharmacopoeia of India* 1996, vol(I) , 257.
15. The United States Pharmacopoeia , The United States Pharmacopoeia Convention, Rockville, MD, 2000, 1942.
16. Higuchi J:'Mechanism of Sustained Action Medication': Theoretical analysis of rate of solid drug dispersed in solid matrices *J Pharm Sci*. 1963, 52(12), 1145-1149.
17. Remington, 'The Science and Practice of Pharmacy', 20thedition, vol-1 1995. IST publication.
18. Libermann HA, Lachman L, Schwartz JB, 'Pharmaceutical Dosage Forms': Tablets 2ndEdition Vol: 1, 274-278(1990).
19. Koresmeyer R.W., Gurny R. Doelker E., Buri.P. andPeppas N.A.: Mechanism of solute release from porous hydrophilic polymer. *Int J Pharm.* 1983, 15,25-35.
20. R.Nagaraja and Rajesh Kaza, Formulation and Evaluation of Bilayer Sustained Release Tablets of Salbutamol and Theophylline: *Int J Pharm*

SciAnd Nano Techn. Vol 2; issue 3 Oct – Dec 2009.

21. Gilberts, Banker,' Modern Pharmaceuticals', 2nd edition ,1990, 647-649.

*****