International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.1, No.4, pp 1359-1367, Oct-Dec 2009

FORMULATION AND *IN-VITRO* EVALUATION OF SUSTAINED RELEASE DELIVERY OF DILTIAZEM HYDROCHLORIDE THROUGH WAX MATRICES

***Shende M. A.[1], Akare S. C[1]., Boorugu R[2] and Patil A. T[2]**
[1]B.K. College of pharmacy, Nagzira Road, Sakoli, Dist- Bhandara (M.S) India;
[2]Dept. of pharmaceutical Sciences, RTM Nagpur University, Nagpur, (M.S) India;

**E-mail:-mulchandshende@yahoo.com*

ABSRACT: The objective of this study was to design wax matrix tablets for oral sustained release of diltiazem hydrochloride and to investigate the sustained release behavior of the fabricated tablets. Matrices were prepared by melt granulation technique using carnauba wax as a release retardant. The FT-IR and DSC analysis indicated the stability and compatibility of drug with excipients. The formulation was optimized on the basis of acceptable tablet properties and *in-vitro* drug release. The resulting formulations produced monolithic tablets with optimum hardness, uniform thickness, consistent weight uniformity and low friability. The results of dissolution studies indicated that formulations F3 and F7 (45% of carnauba wax and 30 minute dispersion time) exhibited good drug release pattern to provide sufficient concentration for achieving satisfactory therapeutic value for extended period of time. The drug release from F3 formulation was sustained upto 16 hrs. The effect of filler and dispersion time on release profile of diltiazem hydrochloride was also studied. Tablet matrices containing dicalcium phosphate has given better release of the drug than other filler materials. Upon increasing dispersion time of drug-molten wax blending, the resulting matrices were found tobe more efficient for prolonged drug release. Fitting *in-vitro* drug release data from optimized matrix formulation to Higuchi model (Korsmeyer equation) indicated that diffusion could be mechanism of drug release. Matrix tablet F3 showed no change in physical appearance, drug content after storage 40^0C/ 75% RH for 9 months.
KEY WORDS: Carnauba wax, Diltiazem Hydrochloride (DHCL), Melt granulation, Sustained Release (SR), Wax matrix tablet.

INTRODUCTION

Chronic illness is said to account for billion of dollars in medical expenditure, which includes both, direct as well as indirect costs. Drug therapy is far more complex, comprehensive, challenging and requires long term therapy in chronically ill patients. Diltiazem hydrochloride (DHCL) is calcium channel blocker widely used for the treatment of chronic stable angina pectoris and for angina pectoris caused by coronary arterial spasm, systemic hypertension and many other cardiovascular disorders. DHCL is subjected to extensive and highly variable hepatic first pass metabolism following oral administration, with reported systemic bioavaibility of between 36 and 50 %.[1] As its biological half life is about 3.7 hour and eliminated rapidly, repeated daily administration are needed to maintain effective plasma levels that makes it suitable candidate to be delivered through oral route at controlled rate through out gastrointestinal tract. Sustained drug therapy of matrix type offers potential advantages, compared to conventional dosage forms, such as avoiding patient compliance problems, improving clinical efficacy, reducing fluctuations in blood and providing cost effectiveness[2]. As DHCL is highly water soluble drug, its formulation into sustained release (SR) products is rather difficult.

Hydrophobic wax matrix system is being widely used in oral sustained drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance. Natural waxes have been investigated for sustained release of highly water soluble drugs[3]. These materials are readily available and expected to be relatively inexpensive, biocompatible, biodegradable and ecofriendly. Carnauba wax, due to its ease and safety of application, drug embedding ability, and chemical inertness has also been used as rate retarding polymer and extensively studied by different investigators[4, 5]. In the present study, effort was

made to prepare DHCL matrix tablet using carnauba wax to enhance drug efficacy, reduce manufacturing cost and to provide an oral sustained release pharmaceutical preparation which releases the active drug gradually in the stomach or the intestinal tract after it is orally administered so that the active drug might be supplied in sufficient concentration for achieving satisfactory therapeutic value for extended period of time. Melt granulation method is a simple, efficient, less time and energy consuming process, no organic solvent or water required, since the molten polymer (wax) can function as thermal binder or retardant[6]. The previous studies reported the oral controlled release system of diltiazem hydrochloride in the form of matrix tablets; however, there is no report on natural carnauba wax matrix. Therefore, the objective of the present study was development and evaluation of matrix system of diltiazem hydrochloride using carnauba wax for sustained release. The effect of some formulations and process variables like concentration of wax, dispersion time and excipients on drug release was also investigated. Thus in order to develop a reproducible process these parameters should be optimized.

EXPERIMENTAL

Materials:

Diltiazem hydrochloride was received from Zim laboratories Pvt. Ltd, kalameshwar, Nagpur, India as a gift sample. Carnauba wax and microcrystalline cellulose was purchased from S.D. Fine chemicals Ltd. Mumbai, India. All other chemicals were used of analytical grade.

Preparation of Diltiazem Hydrochloride Matrix Tablets:

All the formulations were prepared according to the formulae given in table 1. Matrix tablets were prepared by melt granulation method. The specified amount of waxy material were taken in a beaker and melted by heating. Diltiazem hydrochloride and fillers was then dispersed in the melted wax with continuous stirring. The tablets weight (250 mg), diameter (9mm), Diltiazem hydrochloride concentration (36%w/w) and initial temperature (90-95°C) were kept constant throughout all formulations. Formulations F_1 to F_5 were formulated by dispersing the blend mixture of drug and excipients in molten wax for period of 30 min. However in formulations F_6, F_7 and F_8 the dispersion time was varied at 15, 30 and 45 min respectively, though the tablet composition was the same as F_3. This process temperature was lowered continuously to 40-45^{0}C. The hot mass was passed through # 16 sieves. The granules were lubricated and compressed at fixed compression force by single punch tabletting machine.

Fourier Transform Infra Red Spectroscopy (FT-IR):

The FT-IR spectra for pure drug, carnauba wax and mixture of drug-carnauba wax were recorded using potassium bromide disk method. Samples were prepared in potassium bromide disk by means of a hydrostatic press. Spectral measurements were obtained by powder diffuse reflectance on a FT-IR spectrophotometer (Shimadzu, 8033) in the wave number region 400-4000 cm^{-1} to find out drug-excipients interaction if any.

Differential Scanning Calorimetry (DSC):

All dynamic DSC studies were carried out on Du point thermal analyzer with 2010 DSC model. Colorimetric measurements were made with the help of an empty cell (high purity alpha alumina disc) as the reference. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10^{0}C/min.

Evaluation of granules:

Angle of repose of granules was determined by the funnel method. The diameter and height of the powder cone were measured and angle of repose was calculated using the equation Tan θ= h/r, where h and r are the height and radius of the powder cone. Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. LBD and TBD were calculated using the equations LBD = weight of the powder/volume of the packing; TBD = weight of the powder/tapped volume. The compressibility index of the granules was determined by Carr's index (Carr, 1965) using the equation, Carr's index = [(TBD-LBD) X 100)]/TBD[7].

Evaluation of tablets:

Thickness:

From randomly sampled tablets, thickness of 10 tablets were measured individually using vernier caliper.

Hardness:

Hardness of 10 tablets was measured individually using Monsanto hardness tester and mean ±SD was calculated.

Friability:

20 tablets were weighed and transferred into a Roche friabilator set for 100 revolutions. After completion of revolution dust was removed completely, weighed again and percent loss was calculated.

Weight variation:

20 tablets from each formulation were weighed using an electronic balance (Sartorius, 2434, Germany) and mean and relative standard deviations of the weight were determined based on an official method[8].

Evaluation of Diltiazem Hydrochloride content:

Twenty tablets were taken and powdered; powder equivalent to one tablet was taken and allowed to dissolve in 100 ml of water on a rotary shaker overnight. The suspension was centrifuged and supernatant liquid was collected and the absorbance was measured using UV-Visible Spectrophotometer at 240 nm[9].

In vitro drug release studies:

In-vitro drug release study of all the formulated tablets were carried out in USP dissolution apparatus II (paddle) at 37^{0}C ± 0.5^{0}C and 100 rpm in 900 ml distilled water without enzymes. At various intervals of time, samples were withdrawn and filtered through whatmann filter paper no.42. Fresh 5 ml of prewarmed dissolution medium was replaced into dissolution vessel after each sampling in order to maintain constant volume. The absorbance of each sample solutions were taken in UV-

Visible spectrophotometer at 240 nm using distilled water as a blank. The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (hours) curve as per procedure given in United State Pharmacopoeia, 2000.

Analysis of release data:

The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas (log cumulative percentage of drug released versus log time) equation models

Stability studies:

The optimized formulation was subjected to stability studies. The stability studies were carried out by storing matrices in aluminum foil and kept in glass bottle at 25^0C/ 60% RH, 30^0C/ 65% RH and 40^0C/ 75% RH for 90 days. These samples were collected on 15^{th}, 45^{th} and 90^{th} day and checked at regular intervals for changes in physical appearance and drug content was estimated spectrophotometrically at 240 nm.

RESULTS

Compatibility study of drug by FTIR and DSC

Determination of interaction between drug and polymer were performed using Fourier Transform Infrared spectroscopy and differential scanning colourimetry. The FT-IR spectrum of pure drug, carnauba wax and blend of carnauba wax with drug is shown in figure 1. FT-IR spectra of carnauba wax, C-H stretching vibration of saturated hydrocarbons are seen at about 3000 cm^{-1}, C-H bending at about 1470 $cm^{-1}$and 720 cm^{-1}, carbonyl C=O starching vibration in region of 1700 cm^{-1}. From the figure, it is clear that the characteristics peaks at 3282 cm^{-1} (O-H stretching), 1240 cm^{-1} (O-H bending) are seen in both pure Diltiazem hydrochloride and blend of carnauba wax with Diltiazem hydrochloride without any change in their position, indicating no chemical interaction between carnauba wax and Diltiazem hydrochloride. DSC studies were performed on pure drug; carnauba wax and blend of carnauba wax with drug have shown in figure 2. Thermograph of carnauba wax has large infinity sharp peak was observed at 83.1^OC followed by a small endothermic peak at 183^OC. A sharp endothermic was observed for Diltiazem hydrochloride at 213.17^OC. This melting endotherm was also observed for blend of drug with carnauba wax at 83^OC and 214^OC, indicating absence of drug to polymer interaction.

Evaluation of physical parameters of formulated powder blend

The preliminary study was conducted for formulated powder blend of different formulations. The formulated powder blends of different formulations (F1 to F7) were evaluated for angle of repose, true density, bulk density and compressibility index. The results of angle of repose and compressibility index are shown in Table 2. The results for angle of repose and compressibility index ranged from 26.35±0.08 to 32.80±0.07 and 12.55±0.08 to 21.97±0.10 respectively.

Evaluation of formulated tablets

The tablets of different formulation were evaluated for various parameters viz; hardness, friability, percentage weight variation and percentage drug content. The results of these parameters are given in table 2.

In-vitro release studies

The in vitro drug release profiles of DHCL from tablets containing carnauba wax in different proportion (F1, F2 &F3), effect of different diluents on dissolution profile (F4 &F5) and effect of dispersion time of carnauba wax with drug during melt granulation on release profile (F6 &F7) are shown in figure 3. To evaluate the drug release kinetics, formulations showing significantly slow release were chosen.

Stability studies

The stability study for the optimized formulation F_3 was performed to as certain whether the drug undergoes any changes or degradation during its shelf-life. The samples were checked for changes in physical appearance and drug content regular intervals to find out the effect of aging on formulation. The result is reported in table 4.

DISCUSSION

Evidence have shown in the recent years that waxy materials have the physical properties and behavior suitable to prepare gastro resistant, biocompatible to release embedded drug in the intestinal lumen[10]. From the FT-IR studies, the characteristic bands for important functional groups of pure drug, carnauba wax and drug-carnauba wax mixture were observed that characteristic bands of drug were not altered after successful dispersion without any change in their position indicating no chemical interaction between the drug and carnauba wax. A comparisons and interpretation of this region in our spectra agree with their conclusions[11, 12]. Also by DSC studies, absence of any new endothermic peak, disappearance of no shift of endothermic peak confirmed that there is no any interaction between drug and excipients and the drug is thermally stable[13].

Formulation of proper powder blend is the key factor in the production of tablet dosage form involving sustained release of drug from matrix type particle. The result of angle of repose (<30) indicated good flow properties of all the formulated powder blend except two formulations F1 and F6. The compressibility index values were recorded < 15 % of F3 and F 6, rest of the formulations were >15%, result in good to excellent flow properties and good compressibility index was obtained in one formulation(F3). Formulated powder blend, density and porosity are often interrelated properties and are likely to influence compressibility, dissolution profile and properties of tablets made from it. All these result indicate that the formulated powder blend processed satisfactory flow property and compressibility[14, 15]. The physical parameters of all tablet formulations showed

acceptable pharmacotechnical properties and complied with Pharmacopoeial specifications for weight variation, friability (less than 0.7%) and assay. Carnauba wax matrix tablets were found hardness values in the range of 4 to 4.5 kg/cm^2. The thickness and friability were found in the range of 2.30 to 3.20 mm and 0.06% to 0.45% respectively. The drug release from the matrix tablet is based on the porosity of tablets which is due to penetration of water into matrix system. The matrix tablets formulations F1, F2 and F3 containing 35%, 40% and 45% w/w of carnauba wax with Emcompress® (Dicalcium phosphate dehydrate) showed 95.09% , 95.14% and 83.49% drug released at the end of 10th, 11th and 13th hours respectively. It was found that the cumulative percentage drug release of the formulations F1 and F2 are faster than formulation F3 which showing the slowest release. Drug release was inversely proportional to the amount of rate retarding polymer present in the matrix system i.e. the rate and extent of drug release increases with decrease in total polymeric content of the matrix. Increasing dispersion time and carnauba wax concentration decreased initial burst release and retards further drug release from the matrix tablets. Carnauba wax is extremely hydrophobic in nature with lower wettability. Total release of drug from such matrix system is not possible since a certain fraction of dose is coated with impermeable wax. The dissolution profile of formulation containing microcrystalline cellulose and starch as a filler (F4 &F5) was differed significantly and unable to drug sustained up to 16th hours at the same concentration of carnauba wax. The difference in the release rate from different diluents can be attributed to many factors. Microcrystalline cellulose with larger particle size has higher porosity and starch made more hygroscopic caused a decrease in the toruosity of the diffusion path of drug as results, weakened the matrix integrity, more absorbed water when put into the aqueous dissolution media, thus forming channels which facilitated a faster drug release from inert matrix structure. The observed differences in the dissolution properties of the tablets were due to the differences in solubility, swellability and density of the filler excipients[16]. Being among the smallest particle size, hydrophobicity of dicalcium phosphate should have minimum porosity and maximum release retardation[17]. This result indicated hydrophobicity and hydrophilicity of fillers had significant effect on release profile. Since our formulation contain no channeling agents, formation of pores and cracks did not occur to facilitate drug release and the impervious hydrophobic matrix of carnauba wax decreased drug release. Thus it is concluded that dicalcium phosphate dehydrate acted as an inert filler to further drug release retard. The effect of dispersion time of blending of drug with carnauba wax during melt granulation on drug release from matrices were also observed that 30 minutes was an optimum dispersion time (F7) for sustained release of drug upto 16 hours. Formulations F_3 and F_7 were adequately follow USP dissolution limits. Different kinetic equations (zero-order, first-order and Higuchi's equation) were applied to interpret the release rate from matrix system. The best fit with higher correlation ($r^2 > 0.99455$) was found with the Higuchi's equation for the formulation indicating fickian diffusion as a primary mechanism for drug release follows Higuchi release kinetics. The rate of drug release was calculated from the slope of the Higuchi curve expressed as % drug released / hr$^{1/2}$. Such an increase in the polymer content results in a decrease in the drug release rate due to a decrease in the total porosity of the matrices[18]. Kinetic analysis of carnauba wax matrices yielded an aberrant value of release exponent (n) irrespective of physio-chemical nature of the drug and no clear inference could be made regarding the kinetics of drug release from such matrices. The mechanism of drug release from wax matrices has been a matter of controversy, since wax-systems tend to be crude and more heterogeneous than other classes of polymeric systems[19]. In some cases, it has been reported that the mechanism of release from wax matrices involves the leaching of drug by the eluting medium. Fluid enters through the cracks and pores of the matrix with diffusion of drug through the matrix being insignificant[20, 21]. Others have reported that release from a typical wax matrix is diffusion-controlled and is best described by Higuchi's t 1/2 model[22-25].

The selected formulation F3 was subjected to stability study as per ICH guidelines. There was no significant difference in the drug content before and after stability studies.

CONCLUSIONS

The study reveals that, the release of water soluble Diltiazem hydrochloride was sustained in concentration 45 % w/w of carnauba wax and 30 minute dispersion time for drug-excipients blend in order to retard the drug release up to 16 hrs. The mechanism of release was changed with concentration content of polymer, diluents and dispersion time in the matrix. From the present study it may concluded that Diltiazem hydrochloride can be formulated as sustained release drug delivery system with carnauba wax. The reproducibility and accuracy of formulation was required further in-vivo studies by comparing with marketed preparation.

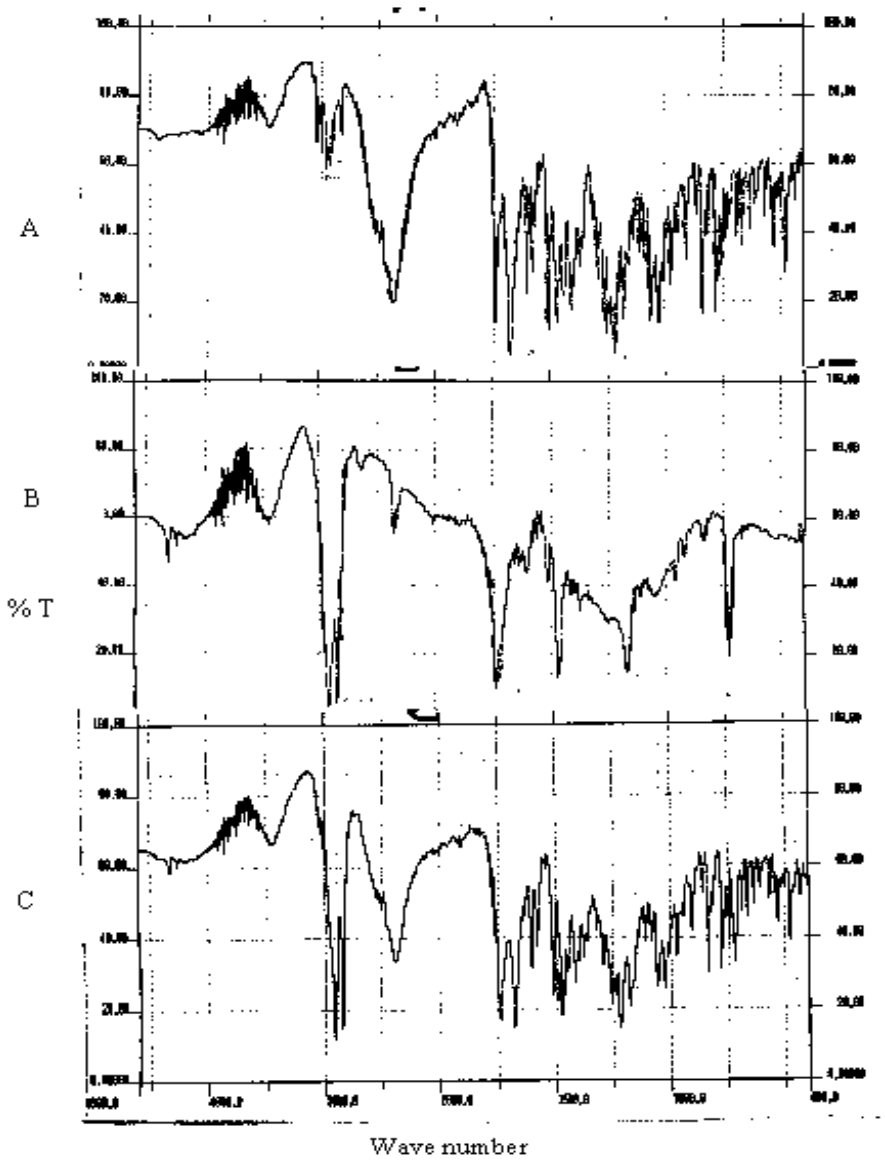

Figure 1: FTIR Spectral of pure Diltiazem hydrochloride (peak A), carnauba wax (peak B) and melt granules mixture (1:1) of Diltiazem hydrochloride and Carnauba wax (peak C)

Table 1: Percent Compositions of Carnauba wax matrix tablets of Diltiazem hydrochloride

Formulations		**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**
S.N	**Ingredients**	**Qt/tab (%)**	**Qt/tab (%)**	**Qt/tab (%)**	**Qt/tab (%)**	**Qt/tab (%)**	**Qt/tab (%)**	**Qt/tab (%)**	**Qt/tab (%)**
1	Diltiazem hydrochloride	36	36	36	36	36	36	36	36
2	Carnauba wax	35	40	45	45	45	45	45	45
3	Emcompress®	27	22	17	--	--	17	17	17
4	MCC	--	--	--	17	--	--	--	--
5	Starch	--	--	--	--	17	--	--	--
6	Talc	1	1	1	1	1	1	1	1
7	Magnesium stearate	1	1	1	1	1	1	1	1

Table 2: Properties of Matrix granules and Tablets

Formulation	Angle of repose ±S.D (n=3)	Compressibility index ±S.D (n=3)	Hardness (kg/cm^2) ±S.D (n=10)	Thickness (mm) ±S.D (n=10)	Friability (%)	Assay (%) ±S.D (n=3)
F_1	32.80±0.07	21.97±0.10	4.0±3.88	2.91±0.21	0.40	98.391±0.17
F_2	30.06±0.09	20.86 (0.11)	4.0±3.26	3.02±0.05	0.22	98.48±0.47
F_3	26.35±0.08	14.86±0.11	4.5±2.36	2.98±0.03	0.13	99.68±0.61
F_4	29.06±0.13	15.54±0.06	4.5±3.90	3.07±0.05	0.29	99.36±0.17
F_5	30.15±0.05	17.86±0.09	4.2±2.74	3.13±0.01	0.09	99.00±0.39
F_6	31.33±0.05	12.55±0.08	4.3±2.72	3.01±0.07	0.06	98.199±0.28
F_7	28.45±0.15	15.25±0.02	4.5±1.91	3.13±0.01	0.11	98.42±0.20
F_8	30.25±0.04	15.80±0.08	4.5±2.25	3.01±0.04	0.15	98.01±0.19

Table 3: *In- vitro* release kinetic values of Diltiazem hydrochloride from F3formulation

Models	**Correlation Coefficient (R)**	**Slope (n)**
Zero Order	0.9471	5.530
First Order	0.7062	0.084
Higuchi Square root	0.9949	0.4421
Peppas	0.9804	0.5670
Matrix	0.9843	0.5732
Hixon Crowell	0.8382	0.4875

Table 4: Stability study for drug content of Formulation F3

Stability condition	**Sampling (in days)**	**Drug content (%)**
25^0C/ 60% RH	15	98.46
	45	98.62
	90	98.18
30^0C/ 65% RH	15	98.42
	45	97.98
	90	98.57
40^0C/ 75% RH	15	98.66
	45	98.11
	90	97.90

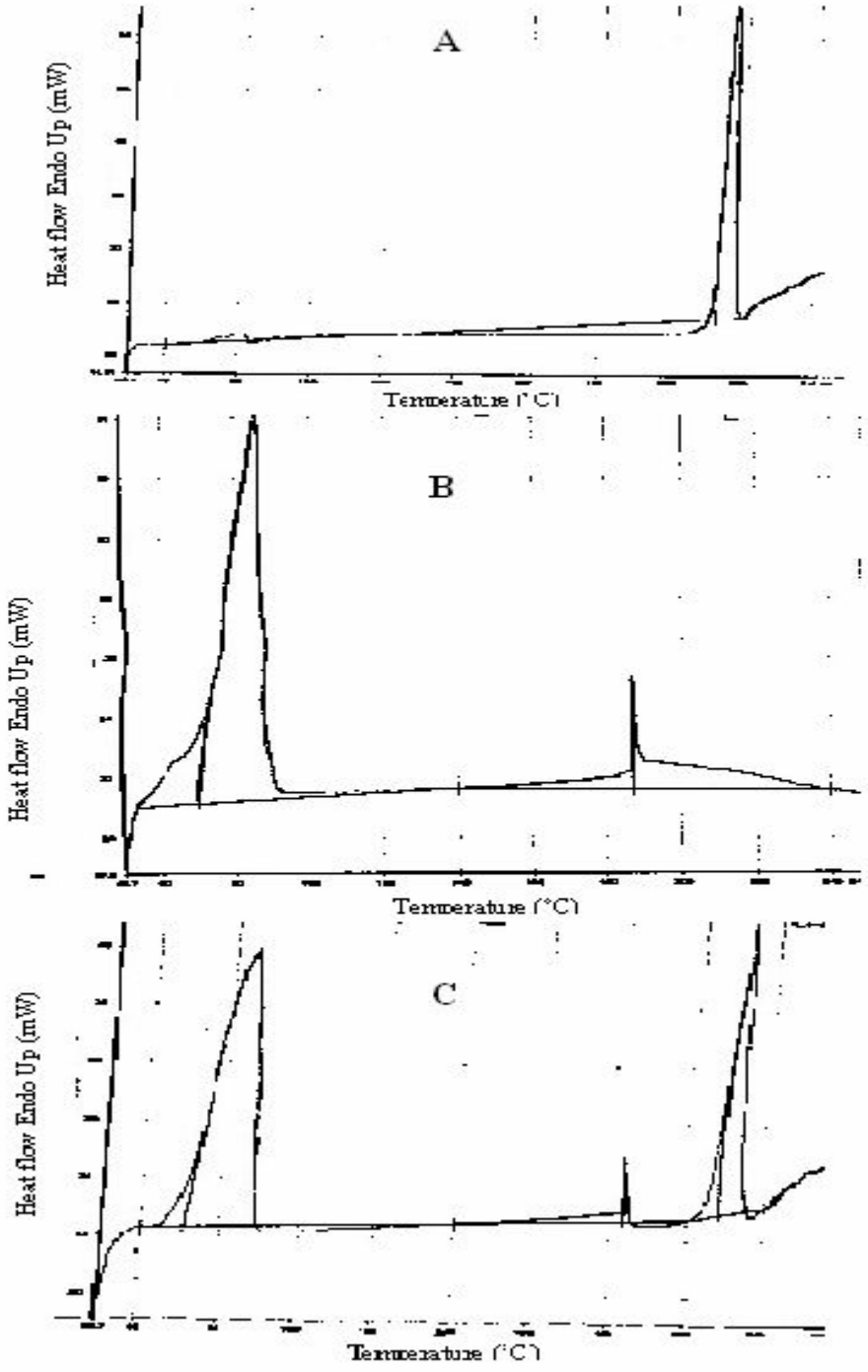

Figure 2: DSC Thermograms A) Pure Diltiazem Hydrochloride B) Pure Carnauba wax C) Melt granules (1:1) of Diltiazem hydrochloride and carnauba wax

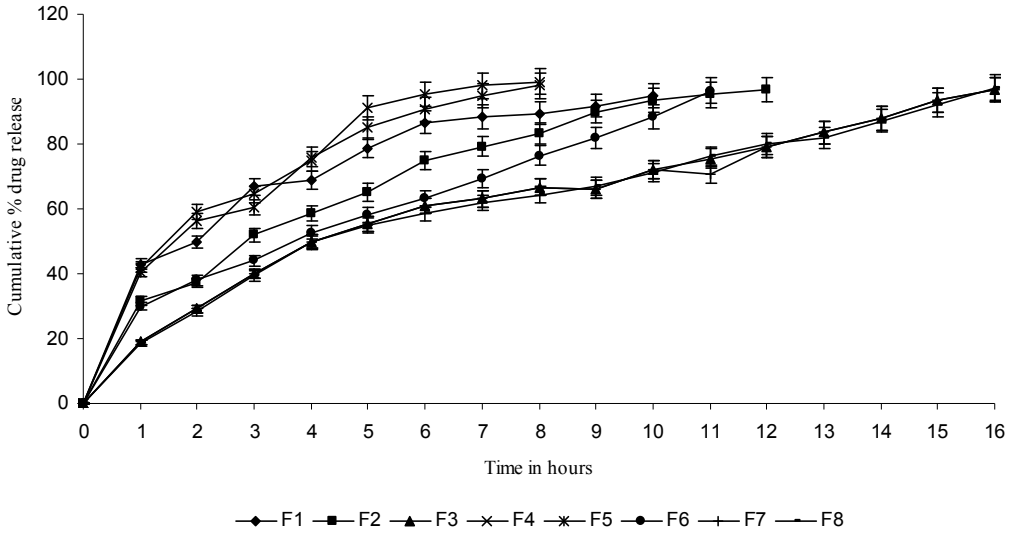

Figure 3: In vitro Drug Release profile from different formulations of CW matrix tablets

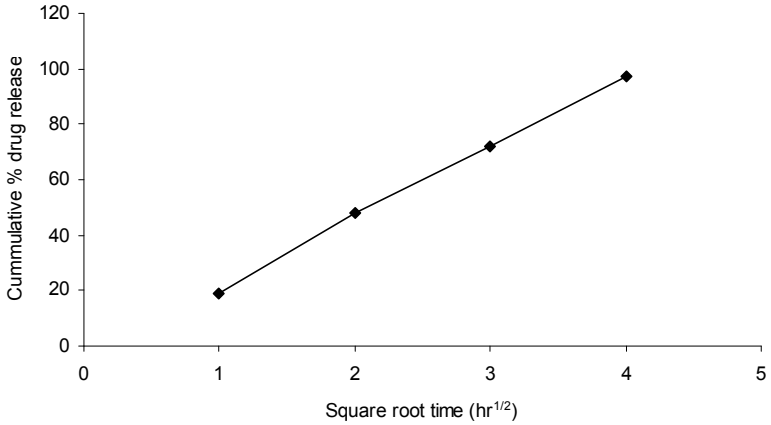

Figure 4: Higuchi square root plot

ACKNOWLDGEMENTS

Authors are thankful to management of B.K. College of pharmacy for providing financial assistance and Zim labs, Nagpur for gift sample.

REFERENCES

1. Murad F., Gilman A.G., Rall W.T., Nies M.A.and Taylor P. Good man and Gilman's Pharmacological basis of therapeutics 9th ed. New York: Mc Graw Hill Co., 1996.
2. Ravikumar M.N., Kumar N., Polymeric controlled drug delivery system; Perspective issues and opportunities, Drug Dev. Ind. Pharm., 2001, 27, 1-30.
3. EI- Shanawang S., Sustained release of Nitrofurantoin from Inert Wax Matrix, J. Contr. Rel., 1993, 26, 11-19.
4. Al-Shora H., Said S. and Hammad A.L., Sustained release from inert matrixes II. Effect of polyethylene glycols on theophylline release, Int J Pharm., 1980, 7, 77-82.
5. Goodhart F.W., McCoy M.A.and Ninger G.C., Release of a water-soluble drug from wax matrix time-release tablets, J Pharm Sci., 1974, 63, 1748-51.
6. Taggart C.M., Ganglely I.A. and Sick Mueller A., The Evaluation of Formulation and Processing Conditions of Melt granulation, Int. J. Pharm., 1984, 19, 139-48.
7. Shah D., Shah Y., Rampradhan M., Development and evaluation of controlled release Diltiazem hydrochloride microspheres using cross linked poly vinyl alcohol, Drug Dev. Ind. Pharm. New York, 1997, 23,567- 74.
8. Indian Pharmacopeia, Ministry of Health and family welfare, Government of India, The controller of publication, Delhi; 1996.vol.II: A82-84.
9. Manivannun R., Balsubramaniam A.,Premanand D.C., Sandeep G. and Rajkumar N., Formulation and in-vitro evaluation of mucoadhesive buccal

tablets of diltiazem hydrochloride, Research J. Pharm Tech., 2008,1(4), Oct- Dec, 478-480.
10. Schawartz J.B., Simonelli A.P. and Higuchi W.I., Drug release from wax matrices, Analysis of data with first order kinetics and with the diffusion controlled model, J. Pharm. Sci., 1968, 57, 274-77.
11. Skoog Doughes A., Holler James F. and Nieman Timothy A., Principles of instrumental analysis. 5th ed. United Kingdom: Thomson-Brooks Cole; 2005, p. 803-805.
12. Mills J.S. and White R., The organic chemistry of museum objects, Butterworth; 1987, 41-47.
13. Tipnis H.P. and Iyer E.K., Preformulation compatibility study between metoprolol and tablet excipients using differential scanning colourimetry, Ind J Pharm Sci.,1996, 58, 22-26.
14. Cooper J. and Gunn C., Tutorial pharmacy. 6th ed. Powder flow and compaction. In: Carter SJ. CBS publications and distributor. New Delhi, 1986, p. 211-233.
15. Patrick J.S., Martin's physical pharmacy and pharmaceutical sciences. 5th ed. (Indian ed.) London: Lippincott Williams and Wilkins; 2006, p. 533-560.
16. Selim Reza M.D., Quadir M.A. and Syed S.H., Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery, Pharm Pharmaceut. Sci., 2003, 6(2), 274-291.
17. Alvarez L.C., Gomez-Amoza J.L., Souto C. and Martinpacheco R., Effect of Microcrystalline Cellulose Grade and Process Variables on Pellets Prepared by Extrusion-Spheronization, Drug. Dev. Ind. Pharm., 2002, 28(2), 451-56.
18. Quadir M.A., Reza M.S. and Haider S.S., Effect of polyethylene glycols on release of Diclofenac sodium from directly compressed carnauba wax matrix tablets, J Bang Acad Sci., 2002, 26 (1), 1-8.
19. Akkuri A., Schroeder H.G., Deluca P.P., Sustained release from inert wax matrices II: Effect of surfactants on tripellenamine hydrochloride release, J Pharm Sci., 1978b, 67, 354-57.
20. Chwartz J.B., Simonelli A.P. and Higuchi W.I., Drug release from wax matrices I: Analysis of data with first order kinetics and with the diffusion controlled model, J Pharm Sci., 1968a, 57, 274-77.
21. Schwartz J.B., Simonelli A.P. and Higuchi W.I., Drug release from wax matrices II: Application of a mixture theory to the sulfanilamide-wax system, J Pharm Sci., 1968b, 57, 278-82.
22. Goodhart F, W., McCoy R, H. and Ninger F.C., Release of a water-soluble drug from a wax matrix timed-release tablet, J Pharm Sci., 1974, 63, 1748-51.
23. Parab P.V., Oh C.K. and Ritschel W.A., Sustained release from Precirol® (glycerol palmito-stearate) matrix: Effects of mannitol and hydroxypropyl methylcellulose on the release of theophylline, Drug Dev Ind Pharm., 1986, 12, 1309-27.
24. Peterlin A., Diffusion with discontinuous swelling. Type II diffusion in spherical particles, Polym Eng Sci., 1980, 20, 238-51.
25. Reza M.S., Quadir M.A. and Haider S.S., Development of theophylline sustained release dosage form based on kollidon SR, Pak J Pharm Sci., 2002, 15(1), 63-70.

*****