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Research Article

Asian Journal of Chemical and Pharmaceutical Research
www.pharmaresearchlibrary.com/ajcpr
AJCPR, 2013: Vol.1(1): 1-12

Formulation and Evaluation of Sustained Release Matrix Tablet of a Model Drug

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Available Online: **24 November 2013**

Abstract

The purpose of this work was to prepare oral sustained release matrix tablet of highly water soluble drug and to evaluate the effect of concentration of lipophilic binderand effect of type of lipophilic binder and effect of release enhancers such as lactose. Based on Preformulation studies the concentrations of the hydrophobic polymers to be used in the formulation were optimized. The compatibility between the pure drug and excipients used in design of the formulations were confirmed by IR studies. Diltiazem hydrochloride tablets were prepared by melt granulation technique using hydrophobic polymers namely Stearic acid and Stearyl alcohol to formulate six different formulations. The tablets were then evaluated for their hardness, thickness, friability, weight variation, drug content and In-vitro dissolution studies. Drug release is inversely proportion to the level of rate retarding polymers present in matrix system i.e extent of drug release decrease with increase in wax content of the matrix. In-vitro drug release profile of formulation F2 resembles with that of marketed formulation hence considered as satisfactory formulation. Stearic acid was found to be a good retardant science it forms thin coating on surface of drug particle. Drug release increases with increase in concentration of release enhancers such as lactose. Optimized formulation F2 was subjected to accelerated stability study was found to be stable.
Keywords: Melt granulation, sustained release, Diltiazem hydrochloride, Stearic acid and Stearyl alcohol

Introduction

Sustained- release dosage form is defined as any drug or dosage form modification that prolongs the therapeutic activity of the drug.(1) In market there are many antihypertensive drugs even in sustained release tablets to be taken once daily. Thus, sustained drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects.(2) But melt granulation is new technique for making sustained release tablet which involves the use of a substance, which melts at relatively low temperature. This substance can be added in the molten form over the substrate or in the solid form, which is then heated above its melting point.(3) In this melt granulation, substance itself acts as a liquid binding agents. Moreover, in melt granulation the drying granulation the drying step is not necessary, thus process is less consuming in terms of time and energy compared to other methods.(4, 5) Different lipophilic binders such as stearic acid, stearic alcohol, glyceryl monostearate and hydrogenated castor oil were tried by melt granulation technique.(6-9)

Diltiazem hydrochloride (DHCL) is a Calcium channel blocker which is used as anti-anginal and Class IV anti-arrhythmic drug. It is a drug of choice for stable and unstable angina pectoris, myocardial infarction, coronary artery spasm, cardiac arrhythmia, PSVT and hypertension.(10, 11) It is well absorbed from the gastro-intestinal tract and undergoes presystemic metabolism with about 45-55% of the drug reaching to the systemic circulation. Its biological half-life is 3-4.5 hrs with the usual dose of 30-90 mg thrice daily. Because of high frequency of administration and short biological half-life, Diltiazem HCl was considered as a model drug for designing sustained release formulation.(12) Also it has melting point of 214-218 °C hence can be used for melt granulation technique.(13). In present work an attempt has been made to develop sustained release tablets of diltiazem hydrochloride by melt granulation technique by using different concentrations of lipophilic matrix forming polymers. Hydrophobic polymers namely Stearic acid and Hydrogenated Stearyl alcohol were used to formulate six different formulations. Other excipients used were of directly compressible grade. Aerosil used as a glidant. Lactose

used as a diluent in the formulation.(14) Sustained release tablets were formulated using melt granulation technique. The tablets were then evaluated for their shapes, color, thickness, friability, weight variation, drug content and In-vitro dissolution studies.

Experimental

Materials

Diltiazem hydrochloride was received from Themis Pharmaceuticals Limited, Mumbai, India as a gift sample. Stearic acid and stearyl alcohol was purchased from Wockhardt research centre, Aurangabad, India. Aerosil and all other chemicals were used of analytical grade.

Instruments used

Tablet Punching machine, Dissolution test apparatus (Electro lab.), UV-visible Spectrophotometer (Shimadzu 1700), Roche Friability Tester (Lab Hosp), Hardness rester (Monsanto) used for this study.

Preparation of Matrices by Melt Granulation

The meltable binder Stearic acid and Stearyl alcohol were respectively melted in porcelain dish on a water bath maintained at constant temperature as per their melting points. Diltiazem HCl was gradually added to the molten wax with continuous stirring. The molten mixture was allowed to cool and solidified at room temperature. The drug was present in its solid form within the molten mass. The solidified mass was pulverized in mortar and sieved through a 16 # screen. The ratio of drug: binder was varied like 1:1,1:2,1:3 for both the binders as shown in table no. 1. The tablets were prepared as per optimized formulation and evaluations were carried out.

Characterization of granules

Particle Size Distribution[15]

The particle size distribution of granules was evaluated by sieve analysis using a vibrating shaker using six standard sieves in the range of 250-1000 µm. The fraction was collected and weight.

Infrared Spectroscopy[16]

Fourier transform-infrared (FTIR) spectra of drug, meltable binders and granules were obtained on FTIR (Agilent Cary 630 ATR). The spectra were scanned over the wave number range from 4000-600 cm^{-1}.

Evaluation of granules

The granules were also evaluated for angle of repose, bulk density, compressibility index and Hausner's ratio to check the flowability. The results are shown in table no.2.

Loose bulk Density[17]

Bulk Density = Mass of the powder/ Bulk volume

Tapped bulk density[17]

Tapped density = Mass of the granular powder/ Tapped volume of granules

Angle of repose[18]

$\Theta = \tan^{-1} h/r$

Compressibility Index[19]

Carr's index = (Tapped density– Bulk density/Tapped density) X 100

Hausner's ratio[19]

Hausner's Ratio = Tapped denisity / Bulk denisity

Preparation of tablets

The granules passed through 16 # sieve were mixed with lactose and compressed in to a tablet with 10 mm deep concave punch using single punch tablet machine (Cemach Co. Pvt,Mumbai, Lt). Different concentration of Diltiazem HCL and meltable binders, and lactose were mixed in a mortar for 10 minutes then aerosol was mixed in it. Those physical mixtures were compressed into deep concave tablets by direct compression method. Formulation corresponding to two different meltable binders were studied. Tablet formulation shown in table no 1.

Evaluation of tablets

Weight variation Test [20, 21]

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Adventure OHAUS) and the test was performed according to the official method.

Thickness [21]

Thickness and diameter of tablets was determined using calibrated Vernier caliper. Five tablets from each batch were used, and their average values calculated.

Friability [21]

For each formulation, the friability of 20 tablets was determined using the Roche friabilator (Lab Hosp.). This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed 20 tablets was placed in Roche friabilator, which was then operated for 100 revolutions for 4 minutes. The tablets were then dusted and reweighed.

Hardness [21, 22]

For each formulation, the hardness of 6 tablets was determined using calibrated Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm2.

Drug content[23]

Five tablets were weighed individually, and these tablets were crushed in mortar. Drug equivalent to 10 mg of powder was taken, to this 10 ml of distilled water was added. The mixture was heated to melt (as per melting point of meltable binders) and allowed to cool to room temperature. The lipid was solidified and drug solution was filtered through Whatmann No.1 paper. The absorbance was measured at 237 nm after suitable dilution. The drug content was determined. According to USP Extended release Diltiazem HCl tablet contains NLT 90% and NMT 110% Diltiazem HCl.

In- Vitro Drug Release Studies of Formulated Tablets[24]

In-vitro drug release studies of Diltiazem HCl matrix tablets were carried out using six station USP type II Dissolution Testing Apparatus (8 vessel assembly, Paddle type) at 100 rpm. The dissolution medium consisted of 900 ml of 1.2 pH buffer (0.1 N HCl) for first 2 hours. Then 900ml of pH 7.4 phosphate buffer for remaining period of study. Temperature was maintained at 37±0.5^{0}C. Aliquots of 5ml were withdrawn at predetermined time intervals & an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots were filtered through wattman filter paper, suitably diluted using each dissolution media (1.2 pH buffer and phosphate buffer pH 7.4) and analyzed spectrophotometrically at 237nm. Also the in vitro drug release study for the marketed tablets (Dilgard XR 90 mg) was conducted. The results are shown in table no.5, 6 and figure no.5, 6.

A. Effect of Concentration of Lipophilic Binders

To study the effect of concentration of different lipophilic binders, in-vitro drug release of different formulation (F1-F6) was compared with each other.

B. Effect of Type of Lipophilic Binder

In order to study effect of type of lipophilic binder tablets were prepared by taking drug: wax concentration of 1:1 i.e concentration of all lipophilic binders was kept constant and in-vitro release profile were compared with each other.

C. Effect of Release enhancers such as Lactose

Effect of release enhancers such as lactose was studied on formulation F1-F3 by taking different concentration of Lactose i.e. 215mg, 125mg and 35mg and in-vitro release profile were studied.

Kinetic Modelling [25]

To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted in to, Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected. The results are shown in table 8 and 9.

Stability Study[26]

In the present study, stability studies were carried out on optimized formulation i.e (F2). The tablets were stored at temp 40^{0}C & RH 75 % for duration one month (30 days). After 30 days, each sample was withdrawn and tested for different tests such as thickness, hardness, drug content and in-vitro drug release studies. The results were shown in table 10, 11 and figure 8.

Results and Discussion

Table 1: Tablet Formulation

Formulation code	Diltiazem HCl	Stearic Acid	Stearyl Alcohol	Lactose	Aerosil	Total Weight
F1	90	90	-	215	5	400
F2	90	180	-	125	5	400
F3	90	270	-	35	5	400
F4	90	-	90	215	5	400
F5	90	-	180	125	5	400
F6	90	-	270	35	5	400

Characterization of granules

Particle Size Distribution Table 2 shows the particle size distribution of Diltiazem HCL granules prepared by using lipophilic binder in different concentrations. The amount of fine power (size < 250 µm) and the amount big lumps (size > 1000 µm) were low. The main fraction was 250-1000 µm and maximum percentage of granules was present

in this range. Results also showed that concentration of meltable binder increase particle size also increases. Particle size distribution is shown in Figure 1, 2.

Table 2: Particle size distribution of melt granules

Formulation	% particle size (microns)		
	<250	250-1000	>1000
F1	36	61	3
F2	25	73	2
F3	18	77	5
F4	17	79	4
F5	32	66	2
F6	27	69	4

Infrared Spectroscopy

The IR spectrum of granules of formulation F1 and F4 prepared by melt granulation were studied. Spectrum of prepared granules were compared with that of pure drug IR spectra and were found to show no significant change in the appearance of characteristic peaks of pure drug spectra. This indicates that the drug is compatible with the meltable binders. The spectra are shown in Figure 3 and 4.

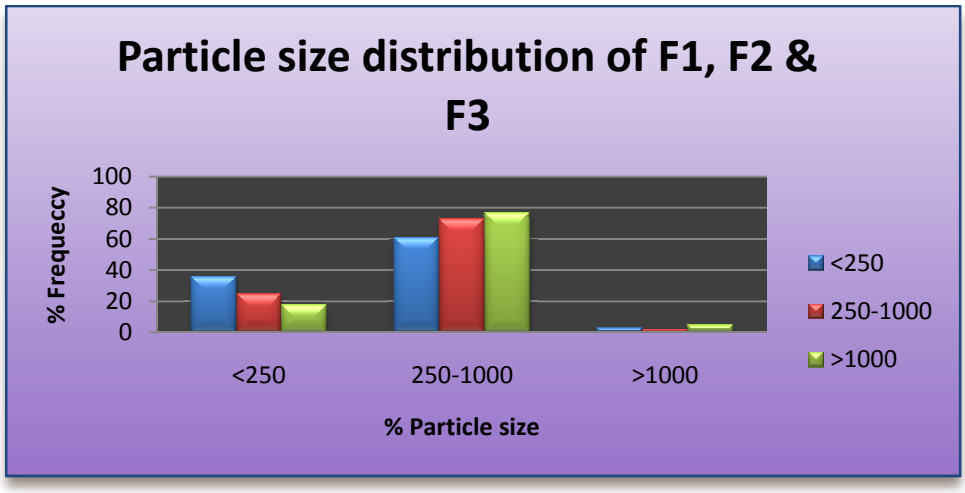

Figure.1: Particle size distribution of formulation F1, F2 and F3

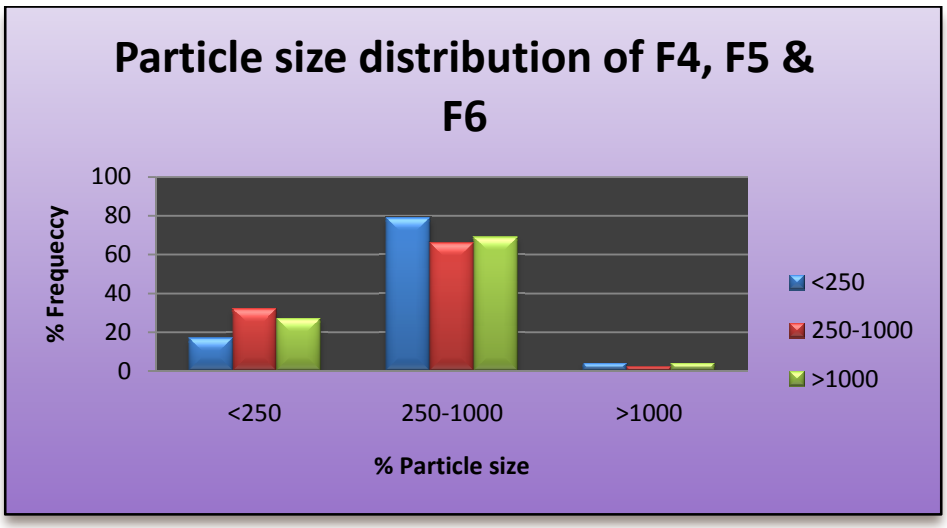

Figure 2: Particle size distribution of formulation F4, F5 and F6

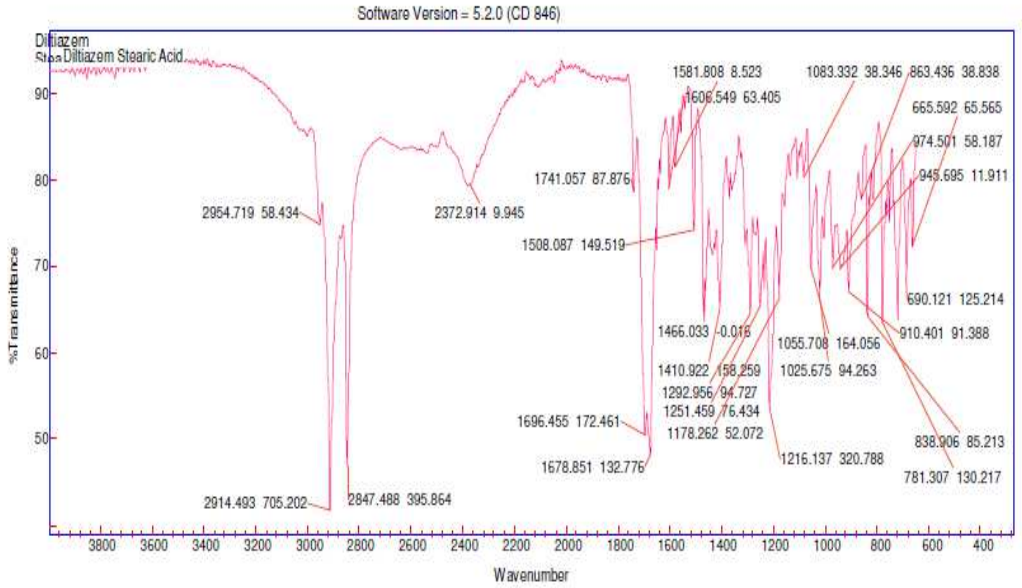

Figure.3: IR Spectra of Diltiazem HCl with Stearic acid

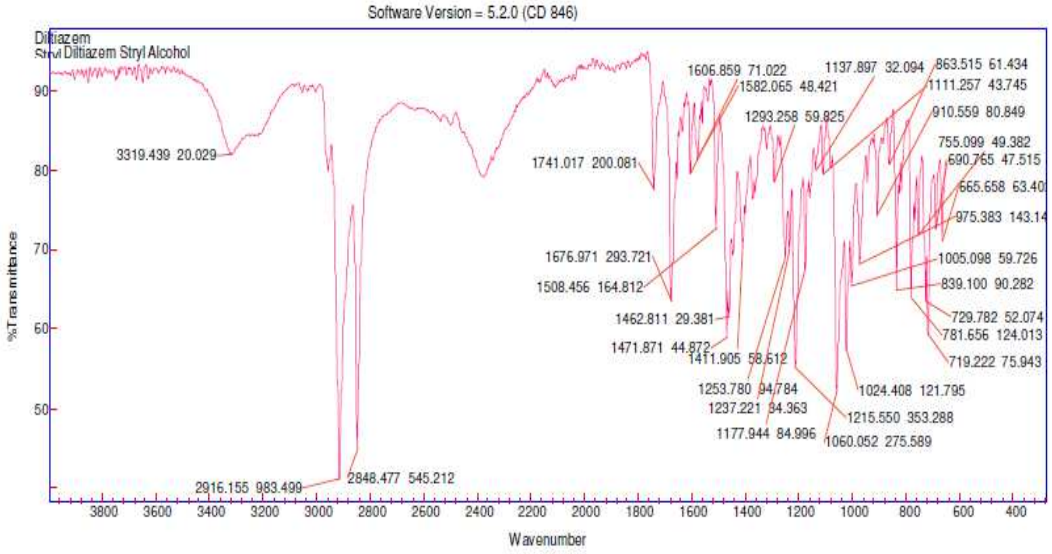

Figure 4: IR Spectra of Diltiazem HCl with Stearyl alcohol

Evaluation of granules

All the formulation granules were evaluated for pre-compression parameters such as Angle of the repose, Loose Bulk Density, Tapped Bulk Density, Carr's Index and Hausner's Ratio and results obtained are shown in the table 3 below.

Table 3: Evaluation of lubricated granules

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose	Carr's index (%)	Hauser ratio
F1	0.443	0.508	29.05^0	12.69	1.145
F2	0.488	0.522	28.39^0	7.89	1.069
F3	0.466	0.528	27.66^0	11.76	1.133
F4	0.469	0.506	28.99^0	8.41	1.077
F5	0.455	0.495	28.50^0	8.68	1.089
F6	0.434	0.498	26.57^0	11.35	1.148

The results of angle of repose of all the formulations were found to be in range of $27^0$66'to $29^0$05', indicating good flow property and this was further supported by lower compressibility index values. The loose bulk density and tapped bulk density values for all the formulation varied in range of 0.434 g/cm^3 to 0.488 g/cm^3 and 0.495 g/cm^3 to 0.528 g/cm^3 respectively. The values obtained lies within the acceptable range. The percent compressibility for all formulation lies within the range of 7.89 % to 12.69 % and Hausner's ratio was found to be in a range of 1.077 to 1.148, indicates acceptable flow property.

Evaluation of tablets

Tablets of all formulations (F1 to F6) were evaluated for different parameters such as thickness, hardness, weight variation, drug content and friability and results shown in Table 4. Hardness values of the formulation ranged from 4.43 to 6.91 kg/cm^2, which indicate good strength of tablet. Friability values of all the formulation were less than 1%, indicating good strength of tablet. The average percent deviation of all tablets was found to be within the limit (394.7 -401.8 mg) and hence all formulation passes the weight variation test. The thickness of tablets ranged from 5.24mm to 5.39mm. All formulations showed uniform thickness. The drug content was found to be uniform among all formulation and ranged from 94.89% to 99.33%.

Table 4: Evaluation of tablet parameters

Formulation code	Thickness (mm)	Hardness (kg/cm^3)	Friability (%)	Weight Variation (mg)	Drug Content (%)
F1	5.39	4.43	0.41	397.1	99.07
F2	5.30	5.83	0.35	394.7	97.56
F3	5.27	6.15	0.25	398.2	98.11
F4	5.29	5.15	0.34	399.3	94.89
F5	5.24	5.75	0.26	401.8	98.66
F6	5.27	6.91	0.22	400.6	99.33

In- Vitro Drug Release Studies

The in-vitro drug release characteristics were studied in pH 1.2 buffer (0.1 N HCl) for first two hours and in phosphate buffer pH 7.4 for next 10 hours under sink condition using USP dissolution apparatus type II. Uniform matrices of Diltiazem HCL with lipophilic binders such as Stearic acid and Stearyl alcohol were obtained. In present investigation granules with drug and different concentrations of lipophilic binders were studied to examine the effect of increasing amount of matrix former on the release rate Diltiazem HCL. Effect of type of lipophilic binder was also studied by making tablets with same concentration of both lipophilic binders (drug: wax is 1:1) and release profile was compared. Effect of release enhancers such as lactose was studied on formulation F1-F3 by taking different concentration of Lactose i.e. 215mg, 125mg and 35mg and in-vitro release profile were studied. Release profile of all formulations was compared with marketed SR tablet.

Effect of Concentration of Lipophilic Binders

Table 5: In-vitro dissolution data of F1, F2, F3 & Marketed formulation

Time in Hours	% Cumulative drug release			Marketed
	F1	F2	F3	M
1	23.58	20.18	18.14	21.52
2	31.24	29.11	26.72	26.42
3	42.42	35.14	37.13	36.89
4	50.48	41.46	40.67	40.75
5	57.28	47.52	45.59	48.03
6	68.23	54.59	52.94	57.54
7	76.41	63.04	58.09	62.99
8	85.99	70.31	63.06	71.35
9	90.89	75.74	69.27	78.63
10	92.38	84.28	73.41	85.62

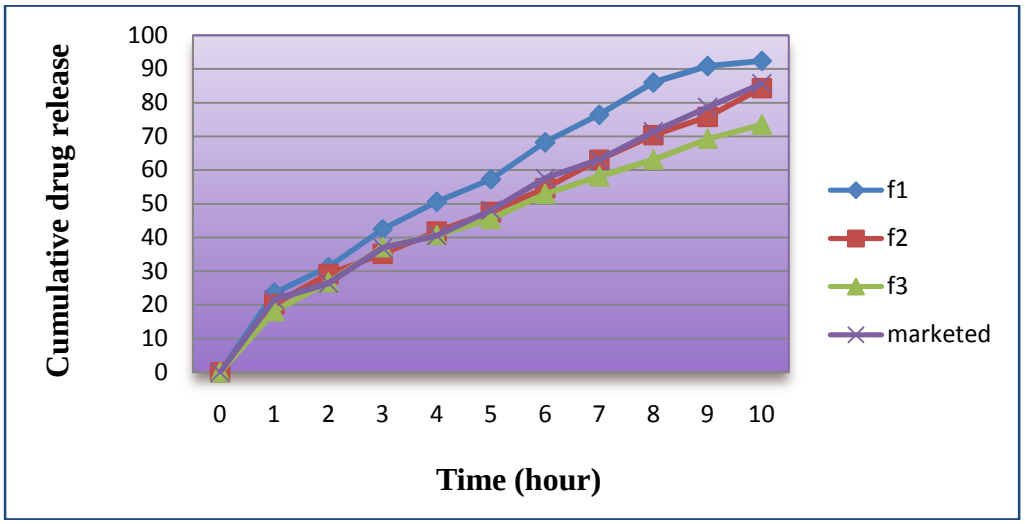

Figure 5: In-Vitro Dissolution Profile of Formulation F1, F2, F3& Marketed Formulation

Table 6: In-vitro dissolution data of F4, F5, F6 & Marketed formulation

Time in Hours	% Cumulative drug release			Marketed
	F4	F5	F6	M
1	27.21	19.86	19.03	21.51
2	39.23	23.77	24.72	26.42
3	45.07	36.08	39.23	36.89
4	51.23	42.36	41.35	40.75
5	58.83	46.36	45.91	48.03
6	69.04	52.57	50.74	57.54
7	75.64	55.64	54.13	62.99
8	86.33	65.93	61.42	71.35
9	91.67	72.72	66.39	78.63
10	94.30	81.08	70.85	85.62

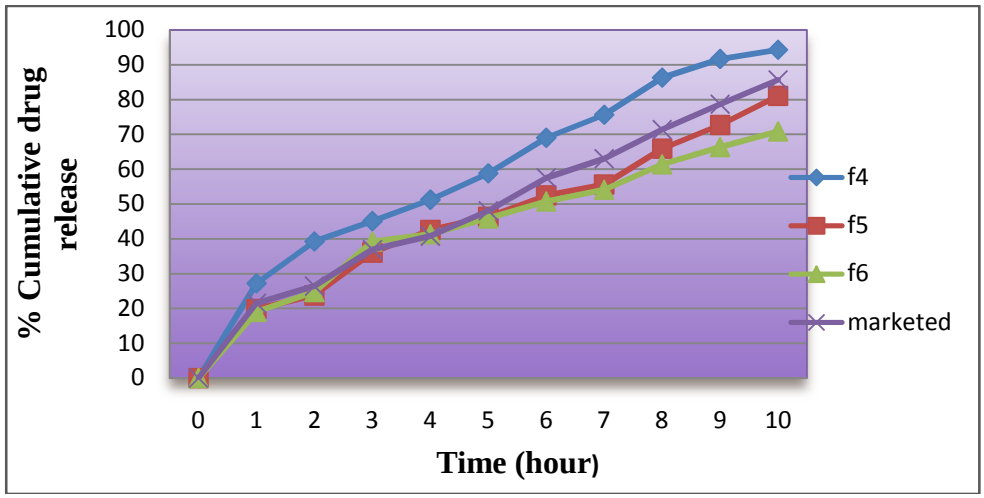

Figure 6: In-Vitro Dissolution Profile of Formulation F4, F5, F6& Marketed Formulation

The drug release profiles for tablet made from melt granulation are shown in Figure 5 and 6. In preliminary studies it was observed that at lower concentration of meltable binder the matrices were disintegrated during dissolution test. Disintegration properties of these matrices were depends on content of matrix forming agent. Hence different ratios of drug: lipophilic binders were designed to prepare matrices and drug release retardation.Increasing the ratio of drug: lipophilic binders resulted in decreasing release of drug.In the similar way, significantly faster release was obtained from matrices containing lower percentage of lipophilic binder. The effect of meltable binder content on the release characteristics was found to be irrespective of their chemical nature. Among all the formulations F3 and F6 shows maximum drug release retardation because of high concentration i.e. 73.41 and 70.85 respectively.

From Figure 5 and 6 it can be observed that for all the matrices drug release is inversely proportional to level of rate retarding matrix former present in the matrix system i.e. the rate and extent of drug release decrease with increase in total lipid content of matrix.

Diltiazem HCL release was found to occur by different mechanisms such as matrix integrity, diffusion or erosion depending on lipid binder used.

The drug release revealed that formulation F1, F2 and F3(DLT: S.A) showed 23.58 %, 20.18 %, and 18.14 % of Diltiazem HCL within first hour and 92.38 %, 84.28 % and 73.41 at the end of 10 hour respectively. This finding may be attributed to fast dissolution of drug on the surface.

The result of dissolution studies were found as F4, F5 and F6(DLT: S.AL) showed 27.21 %, 19.86 %, and 19.03 % of Diltiazem HCL within first hour and 94.30 %, 81.08 % and 70.85 at the end of 10 hour respectively.

Release profile of marketed formulation when compared with all formulations, it was found that release profile of F2 formulation resembles with marketed formulation i.e. 84.28 % (F2) and 85.62 % (M) after 10 hours.

From the above observations the drug release retardation from tablets was found to be in the following order.

F6 > F3

F6 > F3

Effect of Type of Lipophilic Binder

In order to study effect of type of lipophilic binder tablets were prepared by taking drug: wax concentration of 1:1 i.e concentration of all lipophilic binders was kept constant and in-vitro release profile was compared with each other. From Table 5 and Table 6 it was found that Dltiazem: Stearic acid (1:1) showed maximum retardation of drug release i.e. 92.38 % (F1) than that of Dltiazem: Stearyl alcohol (1:1) which is 94.30 %. This may be attributed to high lipophilicity, high melting point (69ºc) and granules with particle size from 500-1200 µm of stearyl alcohol. It has been reported that decrease in drug release may be attributed to the slower penetration of dissolution medium in matrices due to waxy mature.

Stearic acid was found to be a good retardant science it forms thin coating on surface of drug particle. The slow release of drug could be due to the formation of uniform coating on individual drug particles by hydrophobic polymer during melt granulation.

The melting point, HLB value, lipophilicity, and matrix integrity are the important factors determining drug release properties from lipidic matrices prepared by melt granulation.

Hence from the above results it was found that the decreasing order of retardation of drug release is as follows:

Stearic Acid > Stearyl Alcohol

Effect of Release enhancers such as Lactose

Effect of release enhancers such as lactose was studied on formulation F1-F3 by taking different concentration of Lactose i.e. 215mg, 125mg and 35mg and in-vitro release profile were studied.

Table 7: In-vitro dissolution data of formulation containing different proportions of lactose as release enhancers

Time in Hours	% Cumulative drug release		
	215 mg	125 mg	35 mg
1	23.58	20.18	18.14
2	31.24	29.11	26.72
3	42.42	35.14	37.13
4	50.48	41.46	40.67
5	57.28	47.52	45.59
6	68.23	54.59	52.94
7	76.41	63.04	58.09
8	85.99	70.31	63.06
9	90.89	75.74	69.27
10	92.38	84.28	73.41

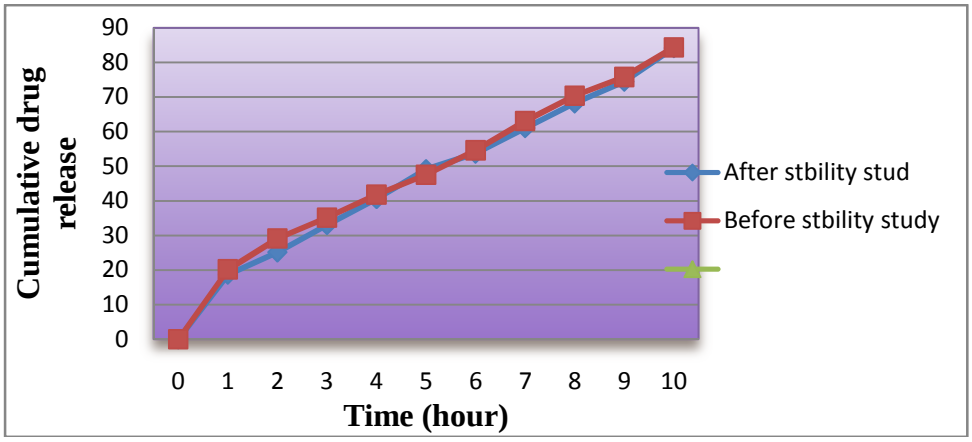

Figure 7: Dissolution profile of formulation F1, F2 and F3 containing different proportions of lactose as release enhancers

The effect of release enhancers such as lactose at different concentration on drug release was studied. The control of these factors can be successfully used to modulate the release rate from matrices. The Figure 7 shows the effect of lactose on the release of drug. It can been seen from the graph that increasing amount of lactose in the matrix resulted in significant increase in the release of Diltiazem HCL.It was due to rapid solubility of lactose and tendency to form pores in the matrix which allow the dissolution medium to penetrate the matrix and dissolve the drug.

Release kinetics

Table 8: Kinetic data of Diltiazem HCl matrix tablets

Formulation Code	Zero Order (R^2)	First order (R^2)	Matrix Model (R^2)	Korsemeyer-peppas Model (R^2)	Hixson Crowell Model (R^2)
Marketed SR tablet	0.9276	0.9734	0.9481	0.9862	0.9664
F1	0.9217	0.9835	0.9867	0.9767	0.9690
F2	0.9685	0.9993	0.9894	0.9638	0.9842
F3	0.9257	0.9372	0.9688	0.9879	0.9865
F4	0.9653	0.9428	0.9842	0.9462	0.9994
F5	0.9565	0.9851	0.9467	0.9904	0.9639
F6	0.9629	0.9124	0.9871	0.9796	0.9278

Table 9: Model fitting for sustained release tablet of Diltiazem HCL

Formulation code	n	k	r^2	Best fit Model
Marketed	0.8037	12.4519	0.9862	Peppas
F1	0.8361	12.5117	0.9867	Matrix
F2	0.7859	10.8169	0.9894	First order
F3	0.8277	13.6834	0.9879	Peppas
F4	0.7945	11.0989	0.9994	Hixson-Crowell
F5	0.8446	11.6545	0.9904	Peppas
F6	0.8285	13.5947	0.9871	Matrix

From table 9, it was observed that the best fitting linear parameter for formulation F1 and F6 was that of Higuchi Matrix model. This indicates that the drug release is controlled by diffusion of drug through the pores. Formulation F2 was best fitted in first order, which represents ideal release profile in order to achieve prolonged pharmacological

action. Formulation F4 was best fitted in Hixson-Crowell model. Formulation F3, F5 and marketed formulation were best fitted in Korsmeyer-Peppas model. This indicates that the release mechanism is not known or more than one type of release phenomenon could be involved.

Accelerated stability study

The stability studies were carried out on optimized formulation i.e. F2. The formulation was stored at 40 ± 2^0C/75 ± 5 % RH for one month (30 days). After 30 days, samples were withdrawn and retested for thickness, hardness, drug content and in-vitro drug release studies. The results are shown in Table 10 and Table 11.

Table 10: Parameters studied on F2 formulation before and after stability study

Parameters	Before stability study	After stability study
Thickness (mm)	5.30	5.28
Hardness (Kg/cm^2)	5.83	5.50
Drug content (%)	97.56	95.87

Table 11: In-vitrodissolution study of F2 formulation before and after stability study

Time (hrs)	% Cumulative drug release	
	Before Stability Study	After Stability Study
0	00.00	00.00
1	20.18	18.67
2	29.11	25.11
3	35.14	33.03
4	41.46	40.53
5	47.52	49.09
6	54.59	53.67
7	63.04	61.04
8	70.31	68.17
9	75.74	74.43
10	84.28	84.11

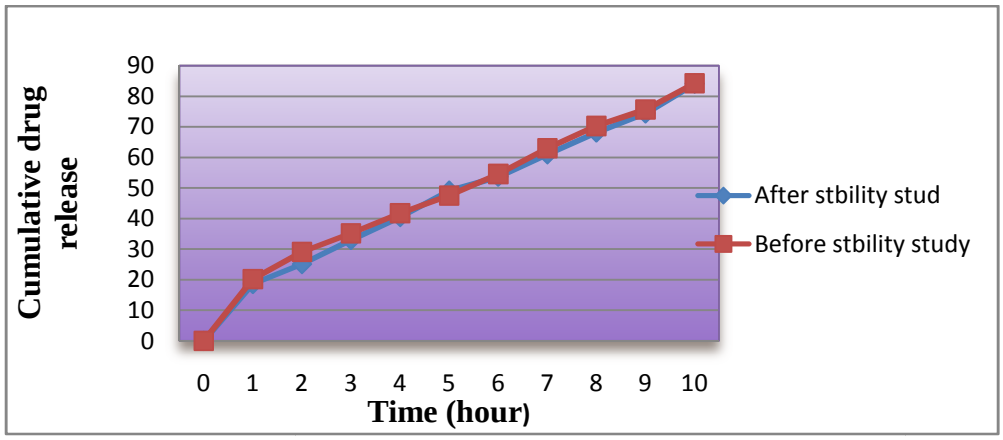

Figure 8: Dissolution profile of formulation F2 before and after stability study

Table 10 showed that there were no considerable changes in thickness, hardness and drug content of F2 formulation before and after accelerated stability study. Also Table 11 and Figure 8 showed that there was hardly any difference between dissolution profile of F2 formulation before and after stability study. Hence matrix tablet prepared were found to be stable.

Summary and Conclusion

Sustained release drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing the medicament over an extended period of time. Such systems extend the duration time of drug therapy, reduce side-effects and increase the safety and patient compliance by reducing frequency of dosing.

Melt granulation offers several advantages compared to conventional wet and dry granulation since the liquid addition and subsequent drying step are omitted. Moreover, it is also a good alternative to the use of solvents, in terms of cost and safety, when granulating water sensitive materials. IR spectrum study reveals that there is no interaction between physical mixture of drug and polymers. From the results of the above mentioned study, it can be concluded that, Lilipophilic binders (Stearic acid and Stearyl alcohol) are appropriate waxy materials that can be utilized as matrix forming agent to sustaine the release of Diltiazem HCL. Drug release is inversely proportion to the level of rate retarding polymers present in matrix system i.e extent of drug release decrease with increase in wax content of the matrix. In-vitro drug release profile of formulation F2 resembles with that of marketed formulation hence considered as satisfactory formulation. Stearic acid was found to be a good retardant science it forms thin coating on surface of drug particle. The slow release of drug could be due to the formation of uniform coating on individual drug particles by hydrophobic polymer during melt granulation. Drug release from matrix is primarily controlled by diffusion process. This process seems to be governed by amount of hydrophobic polymer. Higher the amount of hydrophobic polymer tends to show diffusion controlled release of drug. The release kinetics model for matrices prepared by melt granulation showed the correction factor (R^2) for the best statistical lines revealed that first order model was better applicable to release data. Drug release increases with increase in concentration of release enhancers such as lactose.It was due to rapid solubility of lactose and tendency to form pores in the matrix which allow the dissolution medium to penetrate the matrix and dissolve the drug. Optimized formulation F2 was subjected to accelerated stability study.The data obtained from stability studies indicate that there is no much change in the release profile of tablets. Hence prepared tablets of F2 formulation is stable.

Acknowledgment

The authors wish to thanks Themis Pharmaceuticals Limited, Mumbai, India for sparing gift sample of Diltiazem hydrochloride for research work.

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