INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

FORMULATION DEVELOPMENT AND EVALUATION OF DILTIAZEM HYDROCHLORIDE SUSTAINED RELEASE MATRIX TABLET.

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ARTICLE INFO

Article history
Received 08/03/2017
Available online
10/04/2017

Keywords
Hypertension,
Sustained Drug Delivery,
Matrix,
Kollidon,
Factorial Design.

ABSTRACT

The aim of the current study was to design sustained release tablet of Diltiazem hydrochloride and to optimize the drug release profile and dissolution time using response surface methodology. Diltiazem hydrochloride is an antihypertensive drug, a benzothiazepine derivative with vasodilating action. It is prescribed for the treatment of hypertension and other cardiovascular disorder. Antihypertensive should continue for several months. Diltiazem hydrochloride has half-life of 3-4.5 hours. So its chronic use necessitates the sustained release formulation to reduce dose and dosing frequency. A 32 full factorial design (2 factors at 3 levels each) was employed to systematically optimize the drug release profile. Kollidon SR and HPMC K100 were taken as the independent variables. The % drug release at 4 hr and % drug release at 24 hr were dependent variables .Tablets were prepared by direct compression and evaluated for Hardness, Friability, Percent drug content and In-vitro drug release pattern. Both the polymers had significant effect on the drug release and of the tablets. All the formulation release the drug for more than 24 hours. The optimized formulation F6 having Kollidon SR 135mg and HPMC K100 105mg showed maximum release of 98.70 % drug release for 24 hr. Most of the formulation followed Higuchi Model.so sustained release tablet of diltiazem HCl was formed which provide drug release for 24 Hrs.

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*Please cite this article in press as **D V Derle** et al. Formulation Development and Evaluation of Diltiazem Hydrochloride Sustained Release Matrix Tablet.. Indo American Journal of Pharmaceutical Research.2017:7(03).*

INTRODUCTION

Main objective of the study is to desing sustained release matrix tablet of diltiazem HCl. Over the past decades the treatment of acute and chronic illness has been accomplished by many conventional drug delivery systems such as tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories. These conventional drug delivery systems are still the primary pharmaceutical products commonly seen today in prescription. Oral route is the most commonly employed route of drug administration. Although different route of drug administration are used for the delivery of drugs, oral route remain the preferred route. Even for sustained release systems the oral route of administration has been investigated the most because of flexibility in dosage forms design that the oral route offers.[14]

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges. Also in these types of systems, for achieving and maintaining concentration of drug within the therapeutic range, frequent dosing is required which result into see-saw pattern of the drug levels.**[**15**]**

To overcome these problems sustained release systems were introduced three decades ago. Sustained release, sustained action, prolonged release, controlled release, extended action, timed release, depot and repository dosage forms are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[16] The term "controlled release" has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rate over long period of time.

The basic goal of drug therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non-to2xic for an extended period of time. To achieve better therapeutic action various types of drug delivery systems are available, out of which sustained release systems are gaining much importance because of their wide advantages over others like ease of administration, convenience and non-invasiveness.[13] The vast majority of traditional dosage forms can be described as dump systems which deliver their active substances in a first order fashion, that is, release occurs at rates that are highest initially and then decline steadily thereafter. Clinically this peak and valley pattern results in a time dependent mix therapy.[20] Drug side effects tend to predominate at the high peak concentration in blood, whereas, an inadequate therapeutic effect may prevail at the valley level. Use of controlled release systems provides an excellent tool to achieve precise control of rate standpoint, but also at a particular site.

Aside from the biological benefits incurred from the prolong and predictable drug levels sustained release system can allow for significant reduction in frequency of drug administration and better patient compliance, more predominantly on chronic ailments such as high blood pressure, arthritic, asthma and diabetes.[20]

Diltiazem is non dihydropyrimidine calcium channel blocker used in treatment of angina pectoris, Hypertension and some types of arrhythmia it relaxes smooth muscles in wall of arteries, allow blood to flow more easily and lowers blood pressure Diltiazem hydrochloride (DTZ) is a calcium channel blocker that is widely prescribed for the treatment of hypertension and angina. It is highly water soluble and almost completely absorbed. However, its bioavailability is 30 to 40 % owing to first pass metabolism, and it has an elimination half-life of 3.5 h.[32]

Therefore, DTZ requires multiple daily drug dosage in order to maintain adequate plasma concentrations, and is thus a suitable model candidate for sustained drug delivery .The present study investigates Kollidon SR with HPMC K100 as a suitable, natural, low-cost matrix material for the formulation of sustained release tablets.[29] Modulation of DTZ release from its matrix tablet using Kollidon SR with HPMC K100 as well as release mechanism were also assessed.

MATERIAL AND MEHTOD

Materials

Diltiazem hydrochloride was obtained as gift sample from Holden Laboratories, Sinner. Kollidon SR and HPMC K100 was obtained as gift sample from Alkem Laboratories Ltd., Mumbai. Other materials used were of Analytical grade and were purchased from Modern Scientifics, Nasik.

Preliminary trial batches

Composition of preliminary trials batches for sustained release formulation is shown in Table 5. In all the formulations dose of Diltiazem HCl 90 mg was taken. Diltiazem HCl matrix tablets were prepared by direct compression method. The excipients used were Kollidon SR and HPMC K100 (matrix forming material), Micro crystalline cellulose (MCC) PH102 (filler), Talc (glidant) and Magnesium stearate (lubricating agent).

Direct compression technique:

Diltiazem HCl, Kollidon SR, HPMC K100 and MCC were mixed properly. The powder blends were lubricated using Magnesium stearate and Talc was added finally. Tablets were prepared using 10-station rotary compression machine. The prepared tablets were evaluated for hardness and *in vitro* drug release.Composition of preliminary trials batch for sustained release formulation is shown in Table 1. Kollidon SR and HPMC K100 were used as sustained release polymer.

Table 1: Composition of preliminary trial batches.

Ingredients (mg) / batch	P1	P2	P3	P4
Diltiazem HCl	90	90	90	90
Kollidon SR	90	135	180	180
HPMC K100	90	110	90	110
MCC 102	120	65	30	10
Mg. Stearate	5	5	5	5
Talc	5	5	5	5
Total	400	400	400	400

Factorial design:

Based on the results obtained with preliminary formulations, 32 randomized full factorial design was applied in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combination. The independent variables selected for the present study was Kollidon SR (X1), HPMC K100 (X2). The translation of coded values for 32 factorial experimental designs is shown in Table 02.

The levels of independent variables had been selected from the preliminary batches and the literature envisaged.[22]
Dependent (response) variables evaluated include:
Y1 = % of drug release in 4th Hrs (Q4)
Y2 = % of drug release in 24th Hrs (Q24)

Formulation of Diltiazem HCl SR matrix tablets

Table 2 Translation of coded values for 32 factorial experimental designs.

Sr. No	Coded Value	Level	Experimental Actual Value	
			X1	X2
1	-1	Low	90	75
2	0	Intermediate	135	90
3	+1	High	180	105

Table 3: Formulation of 32Factorial Design Batches.

Ingredients (mg) / batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem HCl	90	90	90	90	90	90	90	90	90
Kollidon SR	90	90	90	135	135	135	180	180	180
HPMC K100	75	90	105	75	90	105	75	90	105
MCC 102	135	120	105	90	75	60	45	30	15
Mg. Stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total	400	400	400	400	400	400	400	400	400

Evaluation of powder flow properties of factorial batches[5-13]

The quality of tablet depends upon the quality of powder from which it is prepared. Therefore, it is quite necessary to evaluate the powder and see whether it is of required quality or not. The powder of factorial batches were evaluated for Bulk density, Tapped density, Carr' index (compressibility), Angle of repose and Hausner's ratio.

Bulk density

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined. The bulk density (ρb) was calculated using following formula:

Bulk Density = M / Vb

Tapped density

The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tapping). The minimum volume (Vt) occupied in the cylinder and weight of the blend was measured. The tapped density (ρt) was calculated using following formula,

Tapped Density = M / Vt

Carr's index

The Carr's index is expression that shows the compressibility of the powder. It is calculated by using the formula,

Carr's Index = [(Tapped Density – Bulk Density) / Tapped Density] x 100

The Carr's index is frequently used as flowability characteristic. The Carr's index of 5 -15%is considered as excellent and acceptable upto 21% while the index greater than 23% indicates poor flow.

Hausner's ratio

The Hausner's ratio (H) is an indication of flowability of the powder. It is calculated by the formula,

$$H = \frac{\rho_t}{\rho_b}$$

A Hausner ratio less than 1.25 indicates good flow and greater than 1.25 is considered to be an indication of poor flowability.

Angle of repose

It is a maximum angle possible between the surface of pile and the horizontal plane. The lesser the angle of repose, more is the free flowing powder and vice-versa. The angle of repose for the powder of each formulation was determined by the funnel method. The fixed amount (8 g) of powder mass was allowed to flow out of the funnel orifice fixed at a height of 2.5 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of the powder from the funnel mouth forms a pile of powder at the surface; it was continued until the pile touches the stem tip of the funnel. The base of the pile was marked and the radius of the powder cone (r) and height of the pile (h) was measured. Angle of repose was then calculated with the use of the following formula:

tan θ = h/r

i.e. θ = tan-1(h/r)

h = height of pile r = radius of the pile base

Preparation of Tablets:

The direct compression method was utilized for the preparation of tablets. The drug Diltiazem HCl, Kollidon SR, HPMC K100 and MCC PH102 were mixed thoroughly in mortar and pestle for 5 min. The blends of the prepared powder were lubricated with Magnesium stearate and mixed with Talc. The tablets were compressed using 10 mm punches at on multiple punches 10 station tablet machine. The formulae of all factorial batches of Diltiazem HCl SR Matrix tablet are shown in the Table 08.

Evaluation of Diltiazem HCl (SR) matrix tablets[5-13]

Appearance and thickness :

The thickness of tablet as a dimensional variable was evaluated. The tablet thickness was controlled within ±5% of average value. The colour, odour and any other flaws like chips, cracks, surface texture, etc. are other important morphological characteristics were observed.The thickness of tablet was measured in mm using micrometre screw gauge and diameter defined by die used in the preparation of tablets

Hardness

Tablet hardness is defined as force required to crushing the tablet in diametric compression test. The hardness was measured with Pfizer hardness tester. The tablets were placed diametrically between two plungers and the lower plunger is kept in contact of tablet to read as zero. The upper plunger is forced against a spring by turning the screw until tablet fractures.

Weight variation test

Twenty tablets were taken and weighed and average weight of the tablet was determined. The tablets were weighed individually and the weight variation was determined.

USP limit for weight variation:

Table 4: Allowable limit for weight variation USP.

Average Weight of Tablets (mg)	Maximum Percentage Difference Allowed
130 or less	10
130-324	7.5
More than 324	5

IP limits for weight variation:

Table 5: Allowable limit for weight variation IP.

Average Weight of Tablets (mg)	Maximum Percentage Difference Allowed
80 or less	10
80 – 250	7.5
More than 250	5

PD = (W avg wt.) - (W individual wt.)/(W avg wt.)× 100

Where,
PD = Percentage deviation.
W avg wt. = Average weight of tablet.
W individual wt. = Individual weight of tablet.

Friability

Twenty tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which revolves at 25 rpm for 4 min. dropping the tablets through a distance of 6 inch with each revolution. This process was repeated for all formulations and the percentage friability was calculated.
The % Friability was then calculated by,

% Friability = Winitial – Wfinal / Winitial × 100

Drug content[33]

Randomly selected 20 tablet from each batch was crushed in a mortar and pestle. The crushed powder equivalent to 30 mg of Diltiazem HCl was taken and dissolved in 30 ml of buffer pH 6.8 (1000µg). Then filtered through Whattman filter paper No.42. The concentration of Diltiazem HCl was determined by measuring the absorbance at 237nm.(UV-2450 SHIMADZU).

***In vitro* drug release study[23]**

The drug release rate from Diltiazem HCl SR matrix tablets was determined using USP apparatus type II (lab India, India). The dissolution test was performed using 900 ml of 0.1N HCl for first 2 Hrs and then buffer pH 6.8 for remaining 22 Hrs at 37 0.5C and 100 rpm. A sample (10 ml) was withdrawn at a specific interval and replaced with fresh dissolution medium of same quantity. The samples were filtered through a Whatman filter paper. Absorbance of the solutions was measured at 237 nm by UV-Visible Spectrophotometer (UV-2450 SHIMADZU).The drug release and drug release kinetics was calculated.

Kinetics analysis of drug release:
In order to investigate the mode of release from the tablets the release data were analysed with the following mathematical models:

Zero-order kinetic:

Q0 = Qt + k0t

Where, Qt is amount of drug release at time t
K0 is zero order release rate constant.
Q0 is amount of drug present initially at t = 0

First-order kinetic:

ln (100 – Q) = lnQ0 – k1t

Where, Q = amount of drug release at time t
Q0 = amount of drug present initially
K1 = first order release rate constant

Higuchi equation

Q = kH t1/2

Where, Q = amount of drug release at time t
KH = Higuchi dissolution constant

Korsmeyer-Peppas model:

Q =kP tn

Where, Kp is a constant incorporating the structural and geometric characteristics of the drug dosage form.
n is the release exponent indicative of the mechanism of release.

This equation was further simplified and proposed by Ritger and Peppas, Mt/M= Ktn Where, Mt is the drug released at time t, M is the amount of drug released at infinite time K is a kinetic constant, and n is the diffusional exponent. The value of n indicates the drug release mechanism. For a slab the value n = 0.5 indicates Fickian diffusion and values of n between 0.5 and 1.0 or n = 1.0 indicate non- Fickian mechanism. In case of a cylinder n = 0.45 instead of 0.5, and 0.89 instead of 1.0. This model is used to analyse the release from polymeric dosage forms, when the release mechanism is not well known or when there is a possibility of more than one type of release phenomenon involved.

Table 6: Interpretation of diffusional release mechanism from polymeric films.

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.5 < n > 1.0	Anomalous transport(non-Fickian)
1.0	Case-II transport
Higher than 1.0	Super Case-II transport

RESULT AND DISCUSSION

The release profile of preliminary formulations (P1 to P4) given in Table 20. Formulation P1 to P4 drug release studied for 24 Hrs. The burst release may be due to high water solubility of drug was observed in P1 batch due to less conc. of polymer. The problem was overcome by increasing the conc. of polymers kollidon SR, HPMC K100. Batch P2 shows drug release upto 95.61% in 24 Hrs. But batches P3, P4 shows less drug release due to higher conc.of polymers. So batch P2 is selected for further study.

Preliminary trial batches

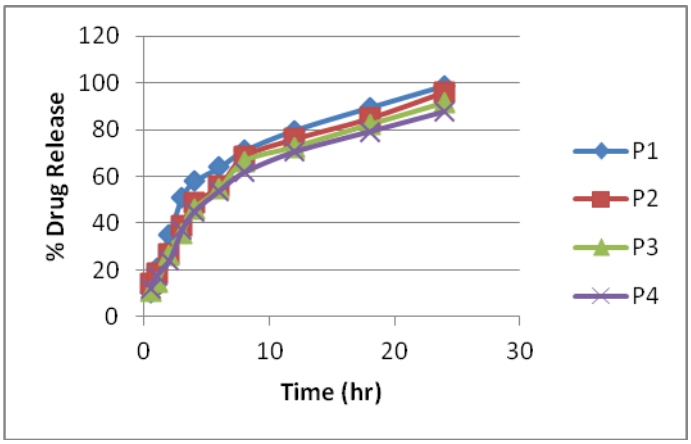

Figure 1: % Drug release of Preliminary Batches.

Evaluation of flow properties of powder blends of factorial batches

The characterization of flow properties of powder blends is important in tablet compression. The powder blends with good flow properties gives uniform die fill and consequently it gives the uniform tablet weight.

Bulk density

The bulk density of powder is important parameter in the compressibility of the powder. The bulk density was between 0.451 to 0.480 gm / cm3.

Tapped density

The tapped density of powder is important parameters in the compressibility of the powder. The tapped density was found to be 0.545 to 0.582 gm/cm3.

Carr's index

The Carr's index is indicator of compressibility. The value below 21 % shows good to passable compressibility. It was found to be 11.92 to 19.41 % indicating good to passable compressibility.

Hausner's ratio

The Hausner ratio is another parameter indicating the flow properties. The value of ratio below 1.25 indicates good flow while above 1.25 indicates the poor flow It was found to be 1.13 to 1.24 indicating goodt flowability.

Angle of repose

The angle of repose can be correlated with type of flow of powder. The angle of repose 20 to 30º indicates the good flow while the angle of repose more 30º indicates poor flow properties and angle of repose below 20º indicates excellent flow properties.The angle of repose was found to be within the range of 24.12º to 28.94º indicating good.

Table 7: Powder Flow properties of factorial batches.

Batch	Bulk Density* (gm/cm3)	Tapped Density* (gm/cm3)	Carr's Index* (%)	Hausner's Ratio*	Angle of Repose* (0)
F1	0.463± 0.004	0.561± 0.19	17.14± 1.10	1.21± 0.09	27.15± 1.23
F2	0.454± 0.007	0.557± 0.09	18.49±1.13	1.22± 0.04	28.57± 1.05
F3	0.451±0.006	0.552±0.05	18.29± 1.09	1.22± 0.10	28.41± 1.25
F4	0.476± 0.003	0.550± 0.07	13.45± 1.32	1.15± 0.048	24.63± 1.08
F5	0.459± 0.007	0.557± 0.012	17.59± 1.20	1.21± 0.043	26.72± 1.15
F6	0.471± 0.003	0.564± 0.022	16.48± 1.20	1.19± 0.012	26.43± 1.30
F7	0.480± 0.008	0.545± 0.015	11.92± 1.24	1.13± 0.094	24.12± 1.20
F8	0.465± 0.001	0.553± 0.022	15.91± 1.52	1.18± 0.060	25.56± 1.09
F9	0.469± 0.006	0.582± 0.030	19.41± 1.30	1.24± 0.041	28.94± 1.30

All values are mean±SD,* =3.

Evaluation of Diltiazem HCl Sustained release matrix tablets :

The tablets from the factorial batches were evaluated for different evaluation parameters of tablets.as shown in table 7

Appearance

The tablets from all factorial batches were white, circular. The surface texture was smooth. The thickness of tablets of factorial batches was 3.14 to 3.23 mm and it was found to be within limit of deviation from average value (not more than 5%).

Weight variation

For tablet weighing 325 mg or more, not more than two tablets differ from the average weight by 5% deviation. The percent deviation in weight variation from average value for all formulation of factorial design batches were within limit (Table 24). The weight variation within limits indicates uniformity in tablet compression and consequently content of drug in a unit.

Hardness

The hardness is important characteristics to be evaluated for handling and transportation properties of the tablets. The hardness of tablets was found to be 6.2 to 7.5Kg/cm2 which indicate good handling and transportation characteristics.

Friability

The friability of tablets was less than 1% which indicates good handling and transportation characteristics

Drug content

The drug content of the nine formulations was found to be between 97.63 to 100.12 % (i.e. variation of ±2.5%). The value ensures good uniformity of the drug content in the tablet.

Thus all the physical parameters of the compressed matrices were found to be practically within control.

***In vitro* drug release studies**

Formulation containing combination of Kollidon SR and HPMC K100 retarded the drug release upto 24 Hrs but showed 40 to 45% drug release in first 4 Hrs in initial batches which were not appropriate. This burst release may be due to high water solubility of drug and more time required for wetting of tablet. From the release pattern of formulations containing Kollidon SR with HPMC K100 it could be concluded that.

Table 8: Evaluation of Diltiazem HCl SR matrix tablets.

Batch	Appearanc	Weight variation* mg ± SD	Hardness (Kg/cm2) ±SD	Friability# %	Thickness (mm) ±SD	Drug content (%mg) ±SD
F1	White, circular	400±0.76	7.1±0.71	0.59±0.05	3.32±0.13	98.45±0.14
F2	White, circular	400±0.68	6.9±0.70	0.63±0.02	3.37±0.22	98.13± 1.11
F3	White, circular	400±1.01	7.3±0.21	0.68±0.07	3.33±0.05	99.09±0.45
F4	White, circular	400±0.54	6.5±0.55	0.49±0.04	3.32±0.11	99.31±0.79
F5	White, circular	400±0.59	6.4±0.12	0.51±0.05	3.25±0.16	99.57±0.49
F6	White, circular	400±1.35	6.2±0.6	0.54±0.02	3.34±0.15	98.90± 0.49
F7	White, circular	400±0.32	7.0±0.20	0.43±0.07	3.31±0.22	99.98±0.83
F8	White, circular	400±1.80	7.1±0.53	0.67±0.01	3.35±0.16	100.12± 0.36
F9	White, circular	400±1.95	7.5±0.51	0.69±0.02	3.39±0.09	97.63± 0.52

The combination of these polymers worked well and the initial burst was controlled as well as the release of the drug was better in the initial 4 Hrs. Kollidon SR a reported gelling agent as well as sustained / controlled release agent decreased initial burst release. The 32 factorial designed batches were formulated and *in vitro* drug release was studied. The formulations F1, F4 and F6 comprising of Kollidon SR 90 mg, 135 mg, 135 mg resp. and HPMC K100 75 mg, 75 mg, 105 mg resp. showed improved drug release upto 24 Hrs. and minimum burst release with more than 80% release in 24 Hrs. Hence formulation with comparatively lower polymer concentration F6 was selected as optimized formulation.

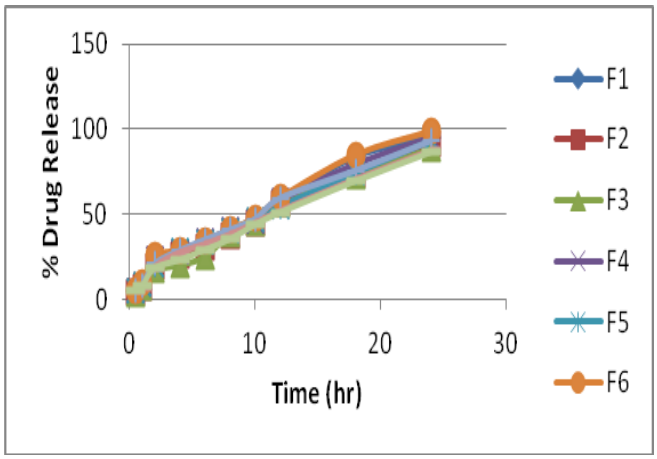

Figure 2: Percent cumulative drug release of formulation F1 to F9.

Table 9: Model fitting data of SR matrix tablet of Diltiazem HCl of F1 to F9.

formulation	Zero order	First order	higuchi	Korsmeyer peppas	Hixon crowell
F1	0.904	0.659	0.984	0.972	0.990
F2	0.983	0.735	0.977	0.978	0.982
F3	0.981	0.749	0.973	0.983	0.988
F4	0.977	0.724	0.972	0.971	0.965
F5	0.962	0.731	0.981	0.984	0.970
F6	0.977	0.721	0.985	0.979	0.985
F7	**0.976**	0.731	0.965	0.968	0.945
F8	0.976	0.724	0.984	0.982	0.978
F9	0.990	0.790	0.960	0.982	0.978

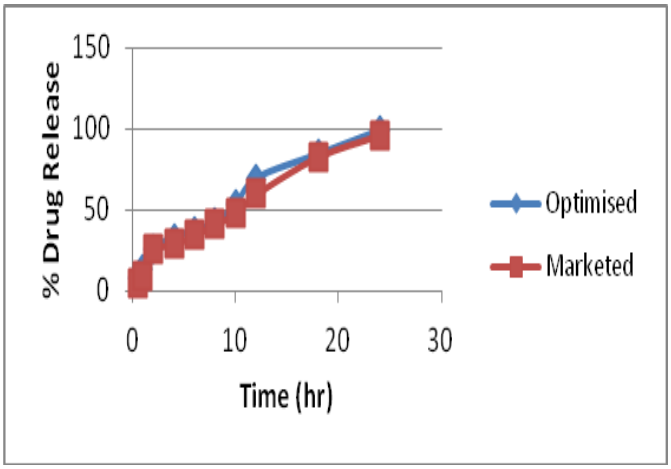

Figure 3: Percent cumulative drug release of formulation F1 to F9.

CONCLUSION

The polymer selected for the sustaining the release i.e. Kollidon SR, HPMC K100 are compatible with the Diltiazem HCl. The oral sustained release drug delivery system of Diltiazem HCl provides the drug release for 24 Hrs in a sustained manner to achieve the desired therapeutic profile with maximum drug utilization, improve patient compliance.Release pattern of formulations containing Kollidon SR with HPMC K100 it could be concluded that, the combination of these polymers worked well and the initial burst was controlled as well as the release of the drug was better in the initial 4 Hrs. Kollidon SR a reported gelling agent as well as sustained / controlled release agent decreased initial burst release.

ACKNOWLEDGMENTS

The authors wish to thank toMVP's collage of pharmacy,nasik & respected guide Dr. Deeliprao V. Derle, Prof. and Principal, MVPS, College Of Pharmacy, Gangapur Road, Nashik, for his valuable support, inspiration and encouragement through project work.also thanks to Holden Laboratory ,Sinner for drug sample&Alkem Laboratories for providing HPMC & Kollodion SR.Author has no conflict of interest.

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