International Journal for Pharmaceutical Research Scholars (IJPRS)

V-4, I-2, 2015 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Formulation and Evaluation of Extended Release Tablets of Diltiazem HCl

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Manuscript No: IJPRS/V4/I2/00073, Received On: 25/04/2015, Accepted On: 30/04/2015

ABSTRACT

The objective of the present research study is to formulate and evaluate extended tablets containing Diltiazem HCl to have better patient compliance and reduce side effects. The extended release tablets of Diltiazem HCl was prepared by direct Compression method using polymers like HPMC K4M, HPMC K15M, HPMC K100M, Glyceryl behanate, Glyceryl palmitostearate and Ethyl Cellulose in different concentrations. Formulated tablets were characterized for different parameters like hardness, thickness, weight variation, Friability, Disintegration time, % Cumulative drug release etc. A 3^2 factorial design was employed to study the effect of Glyceryl Dibehanate & Glyceryl Palmosterate in tablets. From the formulated factorial batches, F6 batch containing 15% Glyceryl Dibehanate and 15% Glyceryl Palmosterate showed the % CDR of 94.43 %. The tablets of Diltiazem HCl was formulated to give extended release effect using various polymers. From the results obtained, it was found that concentration of polymer played important role in achieving desired % CDR of the formulated tablets. Hence the optimum concentration of Glyceryl behanate & Glyceryl palmitostearate were required to formulate extended release tablets. The application of experimental design was helpful in obtaining optimum formulation with less number of experiments. From the results obtained, it was concluded that the optimized formulation containing Glyceryl Dibehanate and Glyceryl Palmosterate shows better release with extended drug release properties. Hence Glyceryl Dibehanate is a potential polymer for formulation of extended release tablets.

KEYWORDS

Extended release tablets, Diltiazem HCl, Hypertension

INTRODUCTION

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. Some drugs also possess solubility problems. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels as shown in Figure 1.

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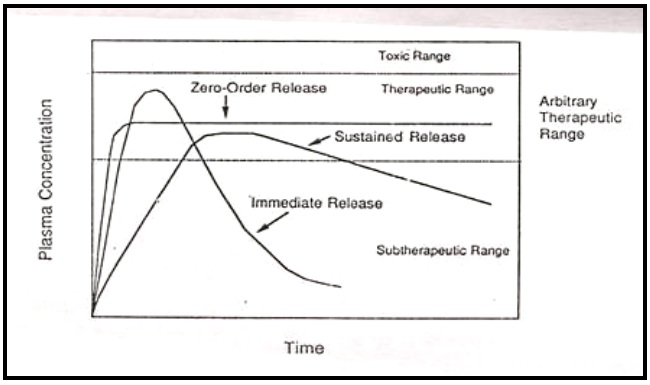

Figure 1: Drug level verses time profile showing differences between zero order, controlled release, first order sustained release and release from conventional tablet

To overcome these problems, controlled drug delivery systems were introduced three decades ago. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity, and improved patient convenience. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies.

Simple definition of sustained release drug system is "any drug or dosage form modification that prolongs the therapeutic activity of the drug"

Ideally a sustained release oral dosage form is designed to release rapidly some pre-determined fraction of the total dose in to GI tract. This fraction (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then release at a constant rate. The rate of the drug absorption from the entire maintenance dose into the body should equal to the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required.

The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. Thus, the release commences as soon as the dosage form is administered as in the case of conventional dosage forms. Controlled drug delivery is delivery of drug at a rate or at a location determined by needs of body or disease state over a specified period of time.

Ideally two main objectives exist for these systems: Spatial delivery, which is related to the control over the location of drug release. Temporal drug delivery, in which the drug is delivered over an extended period of time during treatment.

Why API as Extended Release Antihypertensive?

API Compete with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart. Beta(1)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure.

API is commercially available as conventional tablets and capsules which require two or three times a day dosing. Fast acting dosage forms leads to patient noncompliance and fluctuation in plasma concentration. To overcome this extended release dosage form is better choice. It is desirable in the therapeutic and prophylactic treatment of diseases to provide the drug in extended release form.

Extended release dosage forms can increase patient compliance due to reduction in frequency of dosing. They may also reduce the severity and frequency of side effects as they typically maintain substantially constant plasma levels. Hence the current research work is carried out to develop pharmaceutical equivalent extended release dosage form in comparison with innovator product.

The most commonly used method of modulating the drug release is to include it in a matrix system. Diffusion controlled polymeric matrix devices have been widely used as drug delivery systems owing to their flexibility to obtain a desirable drug release profile, less chance of dose dumping, cost effectiveness and broad regulatory acceptance. The controlled drug-delivery systems are useful to increase the retention time of the drug-delivery systems for more than conventional dosage forms.

MATERIALS AND METHODS

Diltiazem HCl was received as gift sample from Centurian Laboratories, Vadodara (India) and Glyceryl Palmostearate, Glyceryl Behanate obtained from Gatefosse Gmbh (Weil am Rhein Germany). All other reagents and chemicals used were of analytical grade.

Drug and Excipients Compatibility Study by FTIR spectroscopy

FTIR spectroscopy was mainly done for the identification of drug compound and also for the determination of whether any reaction occur between drug and polymer mixer. For that all the ingredients used in the formulation were mixed properly and then FTIR was carried out. From the graph of FTIR, we can decide identify the

drug by its characteristic peak at particular wave number.

Preparation of Extended Release Tablets

The respective powders (drug, polymers and excipients) will passed through 60# sieve separately and collected. The ingredients will be weighed and mixed in geometrical order. Required quantity of powder blend will be compressed using tablet punching machine.

Table 1: Composition of Formulation Batches F1 to F9

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem HCl	90	90	90	90	90	90	90	90	90
HPMC K4M	80	-	-	120	-	-	160	-	-
HPMC K15M	-	80	-	-	120	-	-	160	-
HPMC K100M	-	-	80	-	-	120	-	-	160
Dicalcium Phosphate	198	198	198	158	158	158	118	118	118
Talc	4	4	4	4	4	4	4	4	4
Magnesium Stearate	8	8	8	8	8	8	8	8	8
PVP K30	20	20	20	20	20	20	20	20	20
Total (mg/tablet)	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

Table 2: Composition of Formulation Batches F10 to F18

Ingredients (mg)	F10	F11	F12	F13	F14	F15	F16	F17	F18
Diltiazem HCl	90	90	90	90	90	90	90	90	90
Glyceryl Palmostearate	80	120	160	-	-	-	-	-	-
Glyceryl Behanate	-	-	-	80	120	160	-	-	-
Ethyl Cellulose	-	-	-	-	-	-	40	80	120
Dicalcium Phosphate	198	158	118	198	158	118	238	198	158
Talc	4	4	4	4	4	4	4	4	4
Magnesium Stearate	8	8	8	8	8	8	8	8	8
PVP K30	20	20	20	20	20	20	20	20	20
Total (mg/tablet)	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

Evaluation Parameters

Pre-compression Evaluations

A. Bulk Density

It is a measure used to describe a packing of particles or granules. An accurately weighed quantity of powder, which was previously passed through sieve # 18 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density is calculated by following formula.

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk Volume}}$$

B. Tapped Density

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (Va) and again tapped for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb is consider as final tapped volume. The tapped density is calculated by the following formula.

$$\text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped Volume}}$$

C. Angle of Repose

Angle of repose is the tan inverse of angle between height of pile of powder and the radius of the base of conical pile.

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

Where, h = height and r = radius

Values for angle of repose less than or equal to 30 degrees suggest a free flowing material and angles greater than or equal to 40 degrees suggest a poorly flowing material. Hopper flow rate measurement is also a method for measuring flow ability.

D. Compressibility Index (CI)

Compressibility is indirectly related to the relative flow rate, cohesiveness and particle Size distribution of the powder. Powders with compressibility values lesser than about 20% have been found to exhibit good flow properties. Tapped (ρ2) and Apparent (ρ1) Bulk density measurements can be used to estimate the compressibility of a material.

$$Carr's\ Index = \frac{tapped\ density - bulk\ density}{tapped\ density} X\ 100$$

E. Hausner's Ratio

It is the ratio of bulk volume to tapped volume or tapped density to bulk density. Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculation by the following formula.

$$Hausner's\ ratio = \frac{tapped\ density}{bulk\ density}$$

Value < 1.25 indicate good flow (=20% Carr's index)

While > 1.50 indicate poor flow (=35% Carr's index)

Between 1.25 and 1.5, adding glidant will improve flow. The index of carr is a one point determination and does not reflect the ease or speed with which consolidation occur. Indeed some materials have high index suggesting poor flow but may consolidate rapidly, which is essential for uniform filling on tablet machines when the power flows at nearly equal to bulk density in to the die and consolidates to approaching tapped density prior to compression.

Post-compression Evaluations

A. Weight Variation Test

To study weight variation twenty tablets of the formulation were weighed using a Mettler Toledo electronic balance and the test was performed according to the official method.

B. Hardness

The hardness of five tablets was determined using the Dr. Schleunizer type hardness tester and the average values were calculated.

C. Thickness

The Thickness and Diameter of the tables was determined by using Digital vernier calipers. Five tablets were used, and average values were calculated.

D. Friability

The friability of twenty tablets was measured by Roche friabilator for 4min at 25rpm for 100 revolutions. Accurately weigh twenty tablets placed into Roche friabilator for 100 revolutions than dedust the tablets and weigh.

$$F = \frac{Winitial - Wfinal}{Winitial} X\ 100$$

E. Assay

Twenty randomly chosen tablets from each formulation were thinly powdered in a mortar and a portion of the resulting powder equal to the weight of the respective tablet was solubilized in 0.1 N HCl to make a solution of 9 mg of diltiazem HCl per ml. Several aliquots were then filtered using a sintered glass filter and assayed spectrophotometrically at 237 nm. Each measurement was carried out in triplicate and the results averaged. A blank solution containing all the components, except for the drug, was also prepared. Corresponding concentrations were calculated from the standard curve. No other assay method was considered necessary, since no interference was observed at 237 nm.

F. In–vitro Drug Release Study

Dissolution Parameter

Medium: 0.1N HCl for 2 hours and then pH 6.8 Phosphate buffer till 24 hours

Volume: 900ml

Apparatus: USP – apparatus II (paddle type)

RPM: 50 rpm

Time point: 0.5 1, 2, 3, 4, 6, 8, 12, 16, 20, 24 hrs.

Temperature: 37°C ± 0.5°C

Kinetic Data Analysis

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order Eq. (1) describes the systems where drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3).

$$C = k_o t \quad (1)$$

Where, k_0 is zero-order rate constant expressed in units of concentration/time and t is time.

$$LogC = LogC_0 - kt/2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$Q = Kt^{1/2} \quad (3)$$

Where, K is the constant reflecting the design variables of the system.

The following plots were made: *cumulative % drug release vs. time* (zero order kinetic models); *log cumulative of % drug remaining vs. time* (first order kinetic model); *cumulative % drug release vs. square root of time* (higuchi model) and *log cumulative % drug release vs. log time* (korsmeyer model).

RESULTS AND DISCUSSION

Drug-Excipient Compatibility Study

Drug and Excipients compatibility study was performed by using FT-IR spectrophotometer. It would be concluded that, the drug is compatible with all the excipients used in the formulation.

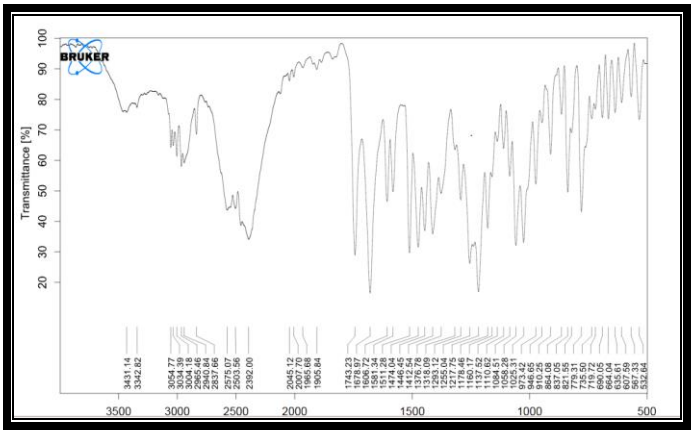

Figure 2: Fourier Transfer Infrared spectroscopy of Diltiazem HCl

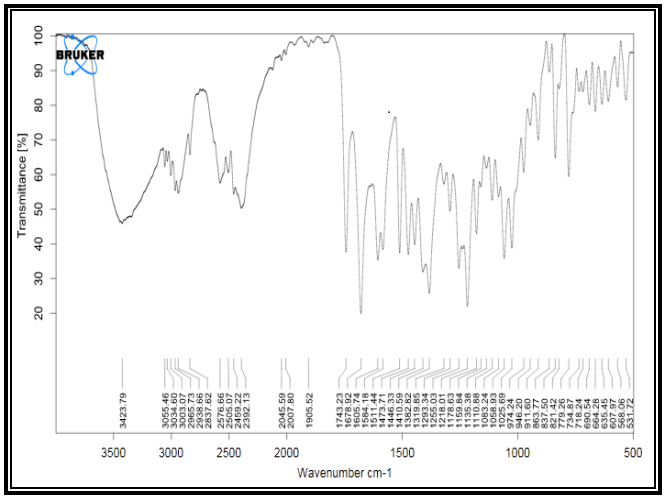

Figure 3: FTIR Spectroscopy of Diltiazem HCl+ HPMC K4 M

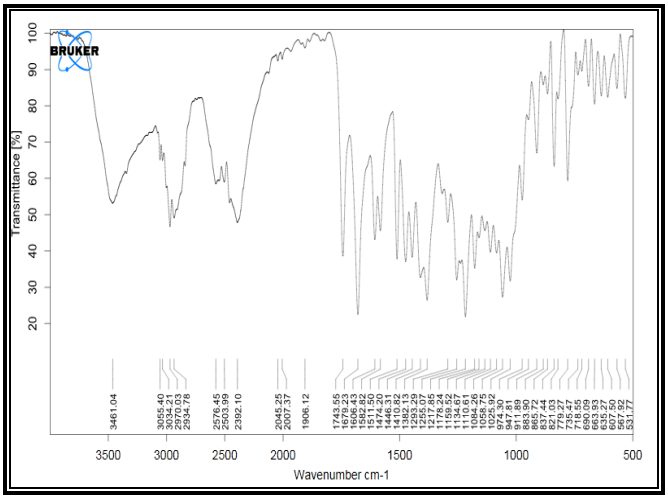

Figure 6: FTIR Spectroscopy of Diltiazem HCl + Ethyl Cellulose

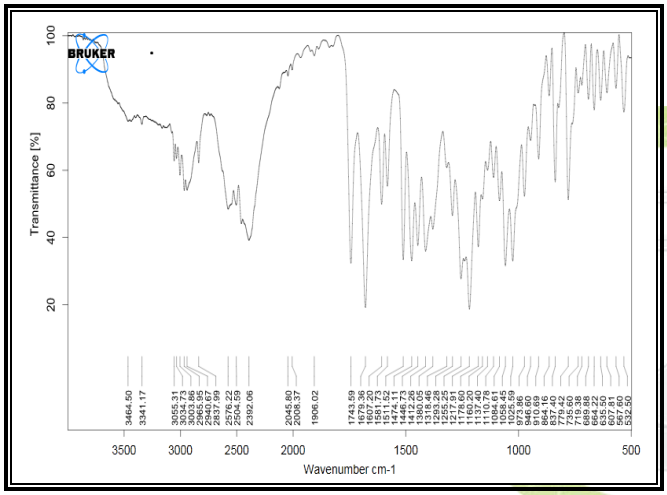

Figure 4: FTIR Spectroscopy of Diltiazem HCl + HPMC K15 M

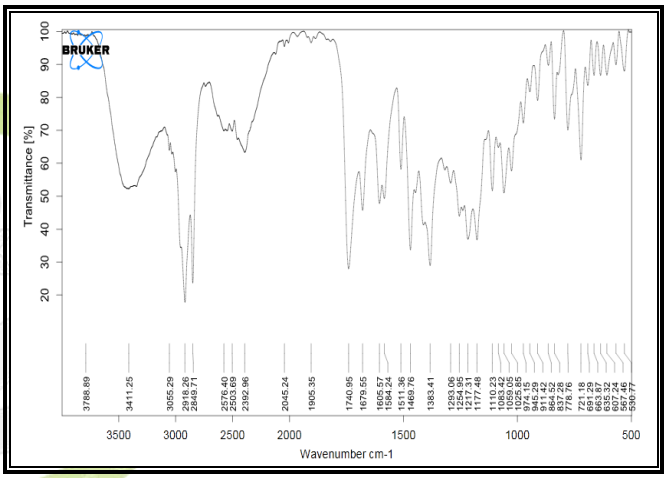

Figure 7: FTIR Spectroscopy of Diltiazem HCl+ Glyceryl behanate (Compritol 888 ATO)

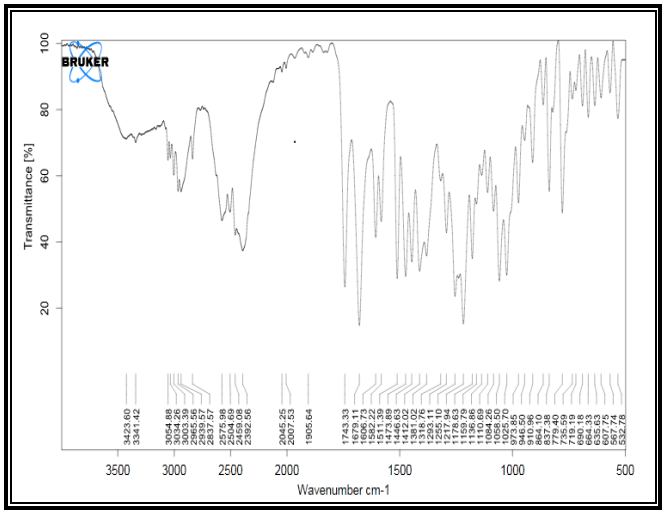

Figure 5: FTIR Spectroscopy of Diltiazem HCl + HPMC K100 M

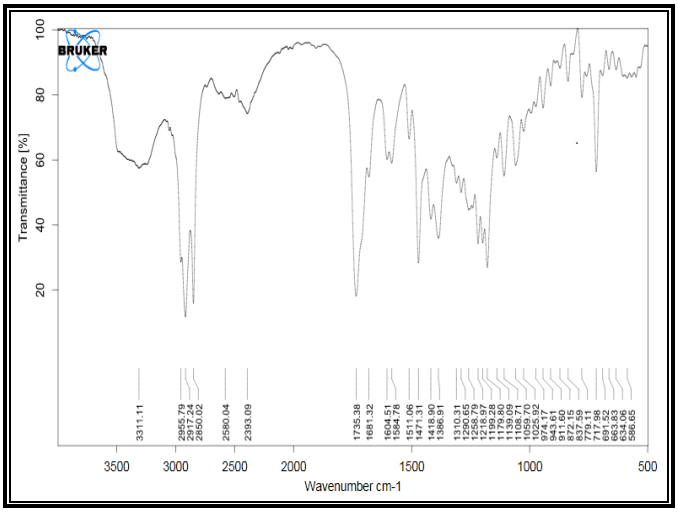

Figure 8: FTIR Spectroscopy of Diltiazem HCl + Glyceryl palmostearate (Precirol ATO 5)

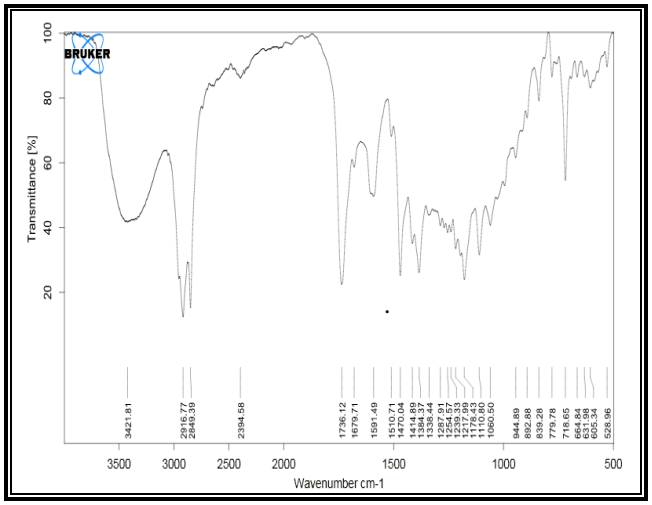

Figure 9: FTIR Spectroscopy of Diltiazem HCl+ All Polymers

Evaluation Parameters

Pre-compression Evaluations for Batches F1 to F18

The powder blend of formulation batches of API were evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio. The results of angle of repose and compressibility index ranged from 9.09 to17.5 and 29.45 to 31.27 respectively. The results of Hausner's ratio ranged from 1.13 to 1.21. The results of angle of repose (<30) indicate good flow properties of the powder. This was further supported by lower compressibility index values. Generally, compressibility index values up to 15% results in good to excellent flow properties.

Table 3: Result of evaluation of powder blend of Formulation batches F1 to F 18

Batches	Bulk Density gm/cm^3 (±%S.D) (n=3)	Tapped density gm/cm^3 (±%S.D) (n=3)	Angle of repose (Θ^o) (±%S.D) (n=3)	Hausner's ratio (±%S.D) (n=3)	Carr's Index (±% S.D) (n=3)
F1	0.29± 0.01	0.33± 0.04	12.1± 1.04	1.13± 0.020	31.27± 2.4
F2	0.30± 0.02	0.33± 0.04	16.1±0.36	1.11± 0.015	30.49± 2.4
F3	0.33± 0.04	0.4± 0.08	17.5± 1.30	1.21± 0.090	31.27± 2.4
F4	0.33± 0.04	0.4± 0.08	17.5± 1.30	1.21± 0.090	30.72± 1.5
F5	0.29± 0.01	0.33± 0.06	12.1± 1.04	1.13± 0.020	29.45± 1.7
F6	0.30± 0.02	0.33± 0.06	16.1±0.36	1.11± 0.015	28.12± 2.4
F7	0.33± 0.04	0.4± 0.030	17.5± 1.30	1.21± 0.090	31.27± 2.4
F8	0.33± 0.04	0.4± 0.030	17.5± 1.30	1.21± 0.090	30.72± 1.5
F9	0.29±0.01	0.33±0.04	17.5±1.30	1.11±0.015	30.49± 2.4
F10	0.30±0.02	0.4±0.030	17.5±1.30	1.12±0.014	31.27± 2.4
F11	0.34± 0.01	0.33 ±0.04	12.1±1.04	1.21±0.090	31.27± 2.4
F12	0.33±0.04	0.39±0.03	16.1±0.36	1.11 ±0.015	30.72± 1.5
F13	0.29±0.01	0.33±0.04	17.1±1.30	1.11±0.015	29.45± 1.7
F14	0.30±0.02	0.4±0.030	17.5±1.30	1.12±0.014	31.27± 2.4
F15	0.29±0.01	0.33±0.04	9.09±0.83	1.21±0.090	30.49± 2.4
F16	0.33+ 0.04	0.4+ 0.030	17.5+ 1.30	1.21+ 0.090	30.72±1.5
F17	0.33+ 0.04	0.4+ 0.030	17.5+ 1.30	1.21+ 0.090	29.45±1.7
F18	0.29+ 0.05	0.33+ 0.04	12.1+ 1.04	1.13+ 0.020	30.72+ 1.5

Post-compression Evaluations for Batches F1 to F18

The formulations were evaluated for different parameter like hardness, friability, drug content, weight variation. The hardness of formulations F1-F18 tablets was found to be in range of 6± 0.60 to 6.8± 0.95 (kg/cm^2). The friability of formulations F1-F18 was found to be less than 1%. So it met the acceptance criteria According to I.P. 2007. Drug content of all the batches complied the IP standard. The average weight variation of all the formulations was found to be closed to 400 mg which complied the IP standards.

Table 6: Result of evaluation of Formulation batches F1 to F18

Batches	Hardness* (Kg/Cm^2)(n=3)	Friability (%)	Weight variation(mg) (%S.D ≤ 10%)	Drug Content(%)(n=3)
F1	6.0±0.60	0.23	401.22±0.68	99.54±0.31
F2	6.5±0.90	0.19	399.21±0.34	99.12±0.40
F3	6.0±0.60	0.14	400.89±1.01	99.82±0.12
F4	6.5±0.90	0.17	399.71±0.54	99.54±0.31
F5	6.8±0.95	0.16	398.71±1.21	99.89±0.58
F6	6.8±0.95	0.13	399.45±1.35	99.64±0.60
F7	6.7±0.34	0.14	400.5±0.32	99.85±0.12
F8	6.2±0.72	0.12	400.72±1.45	99.56±0.34
F9	6.2±0.72	0.11	399.97±1.11	98.57±0.87
F10	6.3±0.91	0.16	401.22±0.68	98.9±0.65
F11	6.3±0.91	0.15	399.21±0.34	99.4±0.14
F12	6.7±0.43	0.13	400.89±1.01	99.89±0.10
F13	6.3±0.91	0.14	399.71±0.54	99.89±0.10
F14	6.5±0.90	0.13	398.71±1.21	99.89±0.10
F15	6.5±0.90	0.13	399.45±1.35	99.89±0.10
F16	6.5±0.90	0.15	400.5±0.32	99.4±0.14
F17	6.3±0.91	0.19	400.72±1.45	99.12±0.40
F18	6.5±0.90	0.13	399.97±1.11	99.64±0.60

In Vitro Dissolution Study

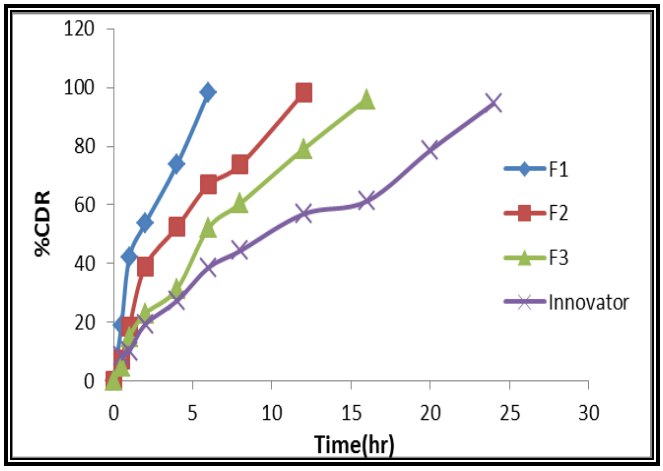

Figure 10: Comparative dissolution profile of trial F1 to F3 with innovator

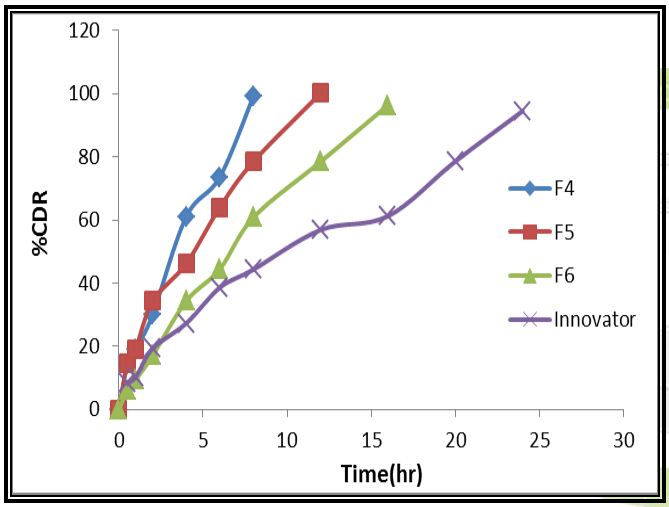

Figure 11: Comparative dissolution profile of trial F4 to F6 with innovator

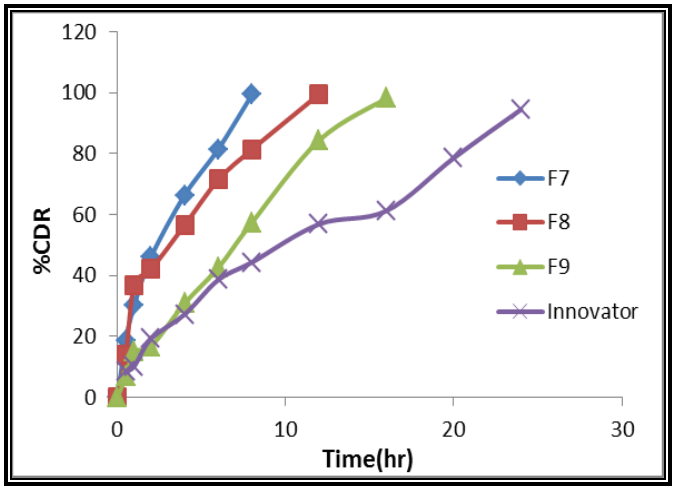

Figure 12: Comparative dissolution profile of trial F7 to F9 with innovator

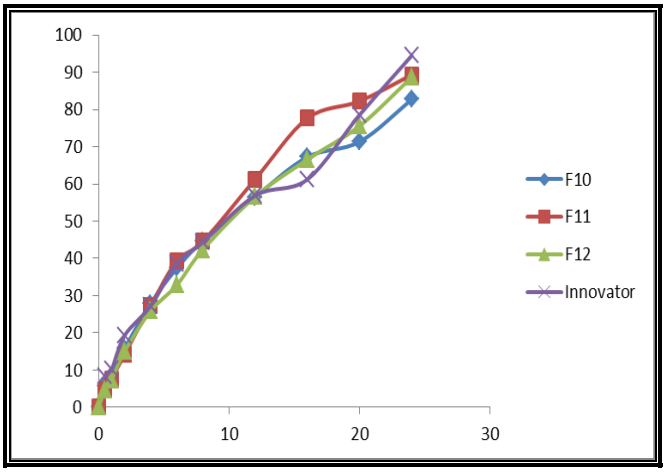

Figure 13: Comparative dissolution profile of trial F10 to F12 with innovator

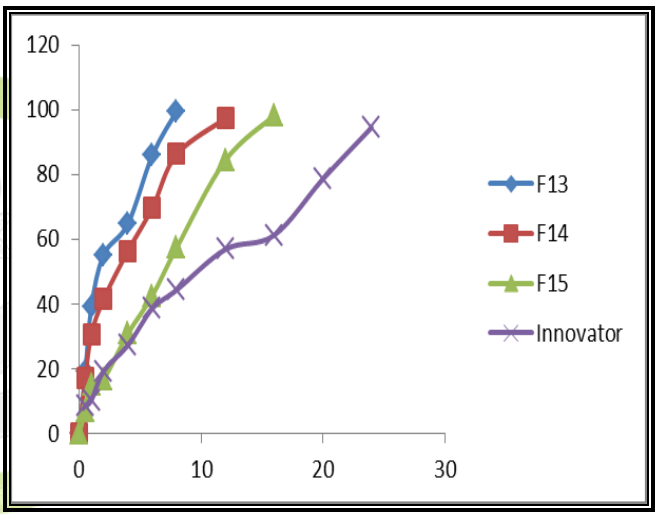

Figure 14: Comparative dissolution profile of trial F13 to F15 with innovator

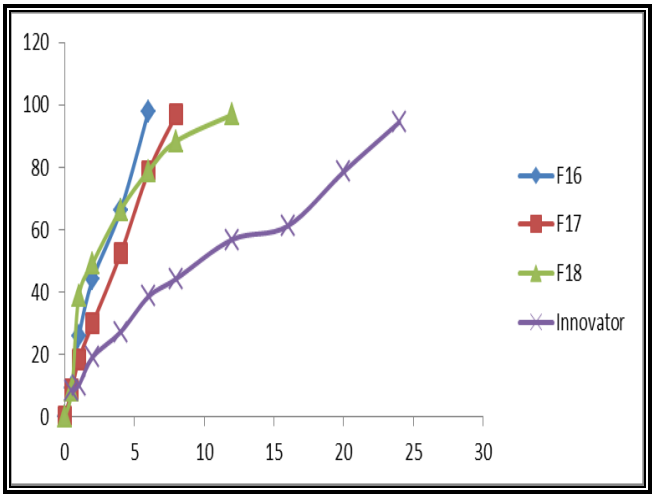

Figure 15: Comparative dissolution profile of trial F16 to F18 with innovator

From the above different drug release profile of all the formulation were showed the effect of different hydrophilic and hydrophobic polymer concentration to the release rate of the Diltiazem HCl. Glyceryl dibehanate retard the drug release up to 24 hrs. An HPMC different viscosity grade shows different release. As the concentration of polymer increases the sustained action increases in all batches. Higher viscosity of polymer shows high swelling index which retard the drug release. Batch F11 shows desired release up to 24 hrs.

Kinetic Modelling of Optimized Batch

Table 7: Release Pattern of F11 Batch

Optimized batch	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer Peppas R^2
F11	0.9563	0.6488	0.9826	0.9271

CONCLUSION

The extended release tablets of Diltiazem HCl were formulated by direct compression using various polymers like HPMC K4M, HPMC K15M, HPMC K100M, Glyceryl Dibehanate, Glyceryl Palmosterate and Ethyl Cellulose. The formulations were evaluated for various parameters like Hardness, Friability, Weight variation, *In vitro* release study, Drug content, etc. From the results obtained, it was concluded that the optimized formulation containing Glyceryl Dibehanate shows better release with extended drug release properties. Hence Glyceryl Dibehanate is a potential polymer for formulation of extended release tablets.

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