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Research article

DESIGN AND *INVITRO* EVALUATION OF SUSTAINED RELEASE TABLETS OF DILTIAZEM HYDROCHLORIDE BY DRY GRANULATION METHOD

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ABSTRACT

The main objective of the experimental work under taken was to develop and in vitro evalution of Diltiazem hydrochloride sustained release dosage form by optimization of the developed formulation. Diltiazem hydrochloride can be increased in duration for long time in the body by formulating it in a sustained release dosage form using optimum amount of hypromellose, hydroxypropyl cellulose and methacrylic acid copolymer and tablets were prepared by dry granulation method, optimized on the basis of acceptable tablet properties and *in vitro* release..In this research work identification of pure drug, data analysis, pre compression parameters formulation, composition of formulations and post compression evaluation were discussed. The following assumptions have been made in developing these designs, drug disposition can be described by one compartment open model, absorption is first order and complete, the rate of release of the drug from maintenance dose should be zero, the release of drug from loading dose should follow first order kinetics. The granules prepared by melt granulation technique evaluated for characterization such as bulk density, tapped density, hausners ratio, angle of repose, cars index all granules shows good flow property. The tablet of Diltiazem HCL evaluated for characterization such as hardness, friability, weight variation and content uniformity all tablets shows sufficient hardness and friability shows that tablets are having sufficient strength. All results were satisfactory. The in vitro drug release studies for the prepared formulation were conducted for a period of 15 hr using an tablet dissolution tester (USP XXIII) Type - II apparatus (rotating paddle) set at 100 rpm and a temperature of 37 ± 0.5°C formulation was placed in the 900 ml of the medium. The results of dissolution studies indicated that formulation F5 was found to be most successful as it exhibits drug release pattern very close to theoretical release profile.

Key Words:- Diltiazem hydrochloride, Sustained release, Methacrylic acid copolymer, Hypromellose, Roller compactor.

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INTRODUCTION

The solubility and dissolution properties of any drug are vital determinants of its oral bioavailability. The simplest and least expensive way to control the release of the drug is to disperse it within an inert polymeric matrix. And hydrophyilic matrices are an interesting option when formulating an oral sustained release of a drug.

The dosage release properties of matrices devices may be dependent upon the solubility of the drug in the polymer matrix or in case of porous matrices, the solubility in the sink condition within the particles pore network (Basak *et al.*, 2009. Sustained drug therapy of matrices type offers potential advantages, improving clinical efficacy, reducing fluctuation in blood and providing cost

effectiveness (Shende *et al.,* 2009). Oral sustained release dosage forms are the most commonly formulated but still offer highest attention in the area of novel drug delivery systems.

Sustained release describes a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed /prolonged and its plasma profile in sustained in duration (Vyas *et al.*, 2003). Sustained drug have main aim to achieve a steady state blood or tissue level that is therapeutically effective and non toxic for extended period of time. Drugs are usually prescribed as a multiple of unit doses and the treatment. This is desirable because of the drug to be effective its blood level concentration is to be maintained for a definite duration of time when a dose is administered, the blood level of the drug is attained and subsequently falls and therefore to maintain the blood level concentration in the optimum therapeutic range over a definite duration of time calls for either sustained or prolonging the effect of the drug. This is achieved through the administration of an intial dose which is below the toxic level and folds up therapeutic level and providing for maintenance dose in such a manner that before the blood level falls to the lower limit of the desired therapeutic range the drug concentration increase but not above the therapeutic range (Vyas *et al.,* 2003). For oral solid delivery systems, drug absorption is unsatisfactory and highly variable between individuals despite excellent *in vitro* release pattern (Gattani *et al.,* 2008). The aim of the present study is to develop and *in vitro* evalution Dilitiazem hydrochloride sustained release dosage form by optimization of the developed formulations. Cardiovascular diseases are one of the most life threatening disease of the world. Hypertension and angina pectoris are the commonest cardiovascular diseases and require constant monitoring. Sustained drug delivery systems significantly improve therapeutic efficacy of drugs. Methacrylic acid copolymer, it is a solid white powder with dissolution above pH of 5.5, and is used in enteric coatings for fast dissolution in the upper bowel, for granulation of drug substances in powder form for controlled-release, and for site-specific drug delivery. It is typically released in the duodenum of the gastrointestinal tract. The present research endeavor was directed towards the development of a sustained release tablet formulation containing diltiazem hydrochloride tablet taken once rather than two or three times a day (Modi *et al.*,2010).

The aim of present project work was to design, process optimization and evaluation of sustained-release tablet of poorly soluble drug diltiazem. Greater attention has been focused on development of sustained or controlled release drug delivery systems with concomitant recognition of the therapeutic advantages of controlled drug delivery. A simple dosing scheme with a once- or twice daily administration of the antihypertensive agent is known to increase patient compliance.

For this reason, the pharmaceutical industry is intensively searching for longer acting antihypertensive drugs, either by the development of novel agents with a longer elimination half-life, or by the improvement of the dosage form of existing shorter-acting compounds, so that plasma concentrations compatible with a blood-pressure-lowering activity are maintained during the whole day. The present research endeavor was directed towards the development of a sustained release tablet formulation containing diltiazem hydrochloride tablet taken once rather than two or three times a day.

MATERIALS AND METHODS

Dilitiazem hydrochloride which is obtained as gift sample from Ranbaxy Lab Ltd Dewas and hydroxyl propyl cellolose, hypromellose and methacrylic acid copolymer from Ranbaxy Lab Ltd Dewas. And all other chemicals used in this study are of analytical reagent grade.

Dry Granulation using Roller compactor (Chowdary *et al.*, 2003)

The dry granulation process issued to form granules without using a liquid solution because the product to be granulated may be sensitive to moisture and heat. Forming granules without moisture requires compacting and densifying the powders. Dry granulation can be conducted on a tablet press using slugging tooling or on a roller compactor commonly referred to as a chilsonator, when a tablet press is used for dry granulation. The powders may not possess enough natural flow to feed the product uniformly into the die cavity, resulting in varying degrees of densification. The roller compactor uses an auger feed system that will consistently deliver powder uniformly between two pressure rollers. The powders are compacted into ribbon or small pellets between these rollers and milled through a low shear mill. When the product is compacted properly, then it is passed through a mill and final blend before tablet compression. The process may require compaction steps to attain the proper granulator end point. If fines are not removed or processed then the batch may contain too many of them, a situation that can contribute to capping (Kedzierewicz et al., 1995), lamination (Chawla *et al.,* 2003), weight and hardness problems (Dortune *et al.,* 1994) on the tablet press. Roller compacting the complete formula is not necessary.

The objective is to densify powders and form granules of the products in the formula that must be compacted, milling the granules and finally wending back with the rest of the formulas ingredients. Dry granulated products do not have problems with picking (Cui et al.,

2008) and sticking (Coasta *et al.*, 2001) because moisture is not present.

PRECOMPRESSIONPARAMETERS (Dortune *et al.*, 1994): The following tests were performed for polymer as well as for drug substance.

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation. The specifications of angle of repose as per IP is given in table no1

$$\tan \theta = h/r$$

Where, h = height of the powder cone, r = radius of the powder cone, ɵ=angle of repose

Bulk density (Bodea *et al.*, 1997)

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/ cm3.The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. A sample of about 50 cm3 (blend) is carefully introduced in a 100ml graduated cylinder. The cylinder is dropped onto a hard wood surface three times from a height of 1 inch at two second interval. The bulk density is then obtained by dividing the weight of sample in gms by final volume in cm3.
The bulk density is calculated by given formula,
Bulk density (Bd) = Mass of the powder (M) / Bulk volume (VB)

Tapped density (Bodea *et al.*, 1997)

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured was measured by tapping the powder for 500 times. The mechanical tapping of the cylinder was carried out using tapped density tester and the tapped volume was noted. It is expressed by given formula, Tapped density (Td) = Mass of the powder (M) / Tapped volume (VT)

Carr's index or % compressibility (Bodea *et al.*, 1997)

The Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, are measures of the relative importance of inter particulate interactions In a free-flowing powder, such interactions are generally less significant and the bulk and tapped densities will closer in value. For poorer flowing materials there are frequently greater inter particle interactions, and a greater difference between the bulk and tapped densities will be observed. Carr's index indicates powder flow properties. It is the simple test to evaluate the bulk density and tapped density of a powder and the rate at which it packed down. It is expressed in percentage and is given by

$$\% \text{ Compressibility } (\% I) = Td - Bd / Td \times 100$$

Where, Td and Bd are tapped density and bulk density respectively.

STANDARD CURVE OF DILTIAZEM HCL

Diltiazem HCL has been quantitatively analysed by various techniques. In the present study, Diltiazem HCL was estimated by UV spectro photometer.

Preparation of standard curve in 0.1N HCL

An accurately weighed quantity of Diltiazem HCL (100mg) was dissolved in 100mlof 0.1N HCL to generate a stock solution having concentration of 1mg/ml.2ml of stock solution was further diluted to100ml to produce standard solution having cocncentration of 20µg/ml. The standard solution was serially diluted with 0.1N HCL to get working standard solution having concentration of 2, 4, 6,8,10,12,14,16.18 and20 µg/ml. The absorbance of the solution was measured at 240 nm using double beam UV spectrophotometer against 0.1N HCL as a blank. The plot of absorbance v/s concentration (µg/ml) was plotted and data was subjected to linear regression analysis in Microsoft excel.

FORMULATION

Dilitiazem HCL, Hypromellose, Hydroxy propyl cellulose, Methacrylic acid copolymer and purified talc were taken in quantities as per table no 2 and passed through 44 mesh separately and lactose, magnesium stearate and colloidal anhydrous silica were taken in quantities as and passed through 60 mesh separately. The drug and polymer blend in 20 min, after add excipients blend in 10 min and dry granulation using Roll compactor process.

The mixture was blended with magnesium stearate, silica and talc for 10min to improve flow property. The powder was compressed into tablet weighing 225 mg using 8.75mmshallow biconcave

punches in a rotary tablet press to a hardness of 2-4 kg.

POST COMPRESSION PARAMETER:

All the prepared matrix tablets were evaluated for following official and unofficial parameters.

Tablet Thickness and Diameter (Modi *et al.*, 2010).

Thickness and diameter of tablets were important for uniformity of tablet size, thickness and diameter were measured using dial vernier calliper.

Hardness (Modi *et al.*, 2010).

The resistance of tablets to shipping or breakage, under conditions of storage, transporation and handling before on its hardness. The hardness was measured in terms of kg/cm^3.

Friability (Modi *et al.*, 2010).

Friability is the measure of tablet strength. Roche friability was used for testing the friability using the following procedure. Twenty tablets were weighed and placed in the tumbling apparatus that revolves at 100rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentages loss in weight was determined.

% loss =

$$\frac{\text{Initial weight of tablets - Final weight of tablets}}{\text{Initial weight of tablets}} \times 100$$

The percentage loss of a tablet ranges from 0.5-1.0%.

Weight variation (Modi *et al.*, 2010).

Weigh 20 tablets selected at random and calculate the average weight. Not more than the percentage as given in IP and none derivatives by more than the percentage as given in USP and none derivates by, more than twice that percentage.USP Standards of uniformity of weight is given in table no3.

Drug Content

Ten tablets were weighed and average weight is calculated. All the ten tablets were crushed in mortar. Powder equivalent to50 mg Diltiazem HCL was dissolved in 250ml 0.1NHCL and shaken for 20min.Solution was filtered and 5ml filtrate was diluted to the 100mlusing a 0.1NHCL.Absorbanceof resultant solution is measured at 240 nm using 0.1N HCL as blank. Amount of drug present in one tablet is calculated.

***In vitro* dissolution studies (Modi *et al.*, 2010**

Dissolution of the tablet of each batch was carried out using USP XXIII type apparatus using paddle.900 ml of 0.1N HCL (Ph 1.2) was filled in a dissolution vessel and the temperature of the medium was at 37±0.5)^{0}C. One tablet was placed in each dissolution vessel and the paddle rotational speed was set at 100rpm.5mlof sample was withdrawn at every hour and same volume of fresh medium was replaced every time. The samples were analysed for drug content 0.1 N HCL as a blank at wavelength of 240 nm using double beam uv spectrophotometer. The content of drug was calculated using the equation generated from standard curve. The % cumulative drug release was calculated.

Data Analysis

To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted into Higuchi and Krosmeyer and Peppas release model. The dissolution data obtained from the above experiments were treated with the different release kinetic equations.

Zero order release equation:

$$Q=K_0 t$$

Higuchi's square root of time equation:

$$Q=K_H t^{1/2}$$

Korsmeyer and Peppas equation;

$$F= (M_t/M) =Km\ t^n$$

Where Q is the amount of drug release at time t, $M_{t\ is}$ drug release at time t, M is total amount of drug in dosage form, F is fraction of drug release at time t, K_0 is zero order release rate constant, K_H is Higuchi square root of time release rate constant, K_M is constant depend on geometry of dosage form and n is diffusion exponent indicating the mechanism of drug release.

RESULTS AND DISCUSSIONS

Standard graph of Diltiazem HCL

The standard calibration curve of drug in 0.1 N HCL is depicted in Figure 1.Thedataof absorbance was shown in Table no 4.The data had correlation coefficient of 0.999.

In process evaluation

Pre compression parameters of Diltiazem HCL

Powder blend were evaluated for the following pre compression parameters such as bulk density, angle of repose, tapped density Hausners ratio and Compressibility index as per official requirement. Angle of repose was found in the range of 21º to24 º.Bulk density is found in the range of 0.521 to 0.582 g/cm^3.Tapped density is found in the range of 0.521 to 0.661 g/cm^3.Hausners ratio is found in the range of 1.06 to 1.13.Compressibility index is found in the range of 6.86-10.94%. Allpara meters

were found to be acceptable range indicating fair to good flow properties, and pre compression parameters are shown in table no 5 and graphical representation is shown in figure 3 and 4.

Post compression parameter of Diltiazem HCL

The tablets were evaluated for post compression parameters such as dug content, hardness, friability, *in vitro* dissolution study and deviation in weight variation test. Table 6 represents the results of physiochemical parameters of all tablet formulation of diltiazem HCL and graphical representation is shown in Figure 4 and 5..All the prepared tablets were located in the acceptable range as per the specifications given IP .Drug content was found in the range of 95.3% to 98.89 %.Hardness was found in the range of 4.3to 4.9kg/cm^2 and friability in the range of 0.70 to 0.87%

***In vitro* evaluation**

The in vitro drug release data of different batches of tablets are shown in Table7 to 12.The plots of % drug release v/s time (hrs) for tablet of different batches are depicted in figure 6. When comparing the formulations from F1to F6, the best formulation (F5) has shown a drug release NLT 86% in 20hr was in accordance with the USP dissolution criteria for extended release diltiazem hydrochloride formulation. The *in vitro* drug release for 15 hr of F1to F6 formulation was shown in table. *In vitro* release form all formulation was fitted into different kinetic equation (zero order, first order and Higuchi equation and Korsmeyer Peppas).The curve fitting result of the release rate profile of the formulation gave an idea on the release rate and mechanism of drug release. Here in this study it was indicated that the most of the formulation follows the zero order release kinetics. Fitting of the release data to Korsmeyer peppas model it was reported that the diffusion coefficient (n) was found to be more than 0.80 in most cases, it is given in table13.

Data Analysis

The result of kinetic treatment applied to dissolution profile of tablet of each batch was shown below in table no.13The curve fitting result of the release rate profile of the formulation gave an idea on the release rate and mechanism of drug release. Here in this study it was indicated that the most of the formulations follows zero order release kinetics. Fitting of the release data to korsmeyer peppas model it was reported that the diffusion coefficient (n) was found to be more than 0.80 in most cases.

Figure 1. Standard graph of Diltiazem HCLIin 0.1NHCL

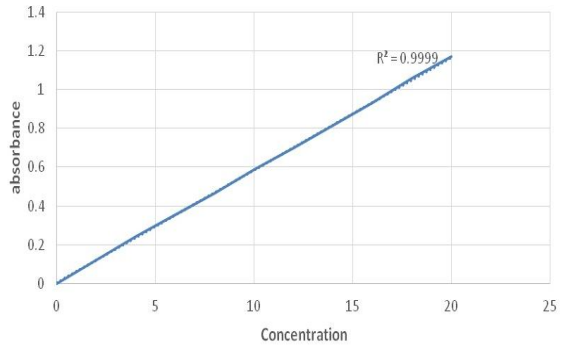


Figure 2. IR spectrum of Diltiazem HCL

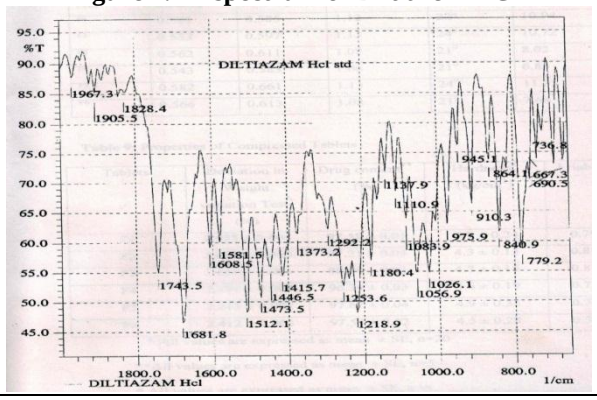
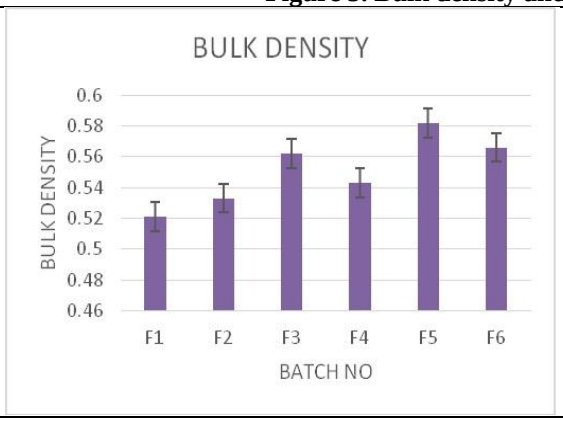


Figure 3. Bulk density and tapped density of formulations



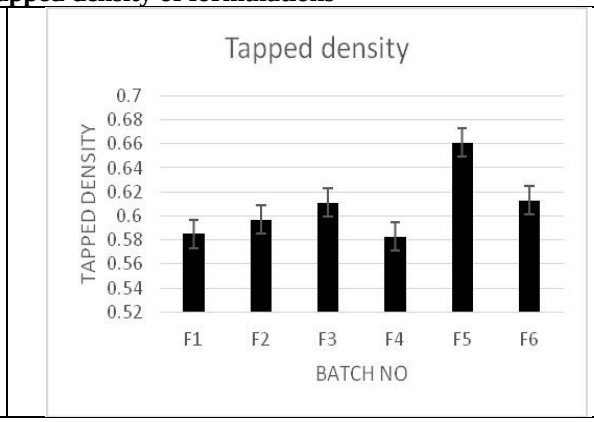


Figure 5. Hausner's ratio and compressibility index of formulations

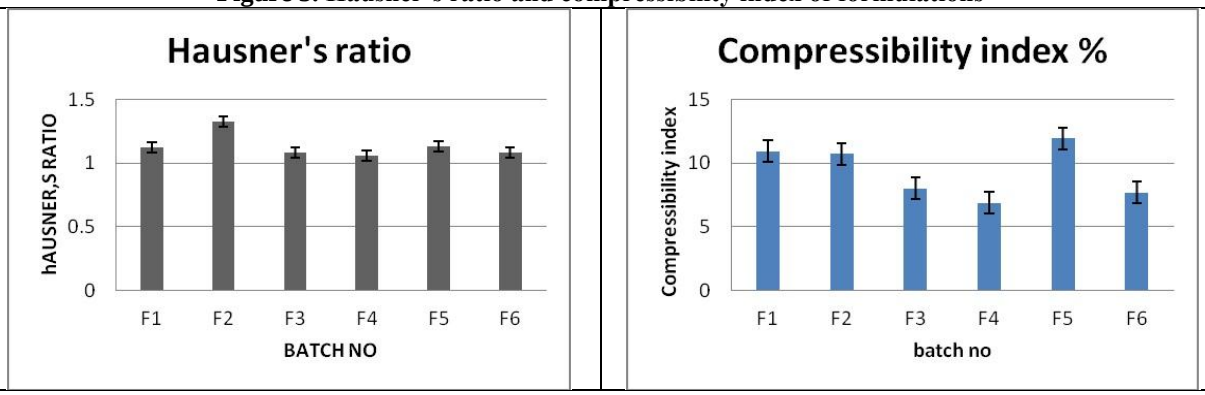


Figure 6. Hardness and drug content of formulations

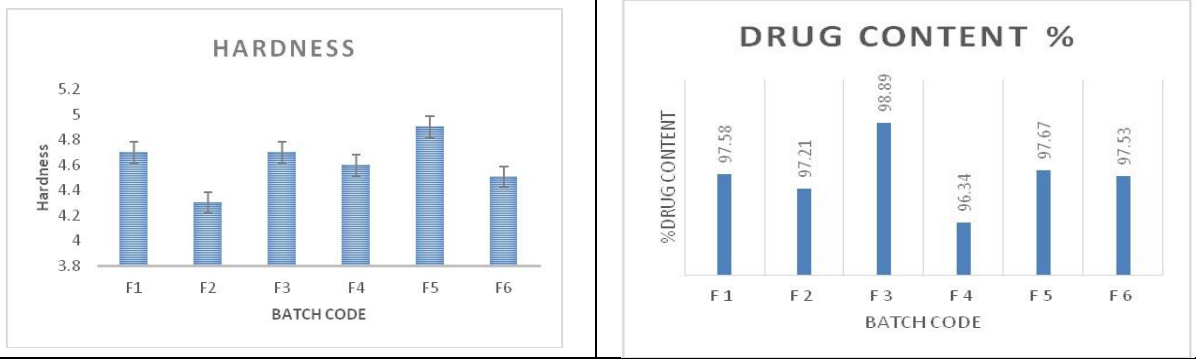


Figure 7. Friability and weight variation of formulations

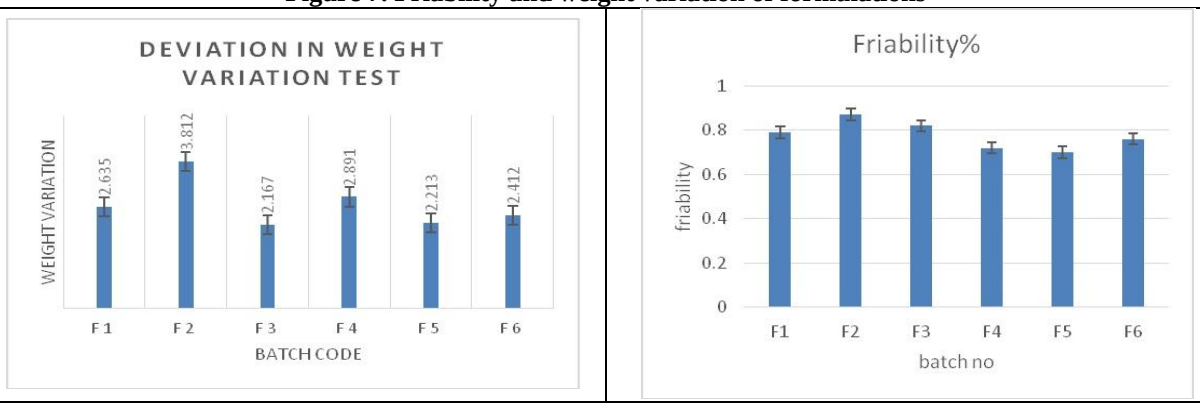
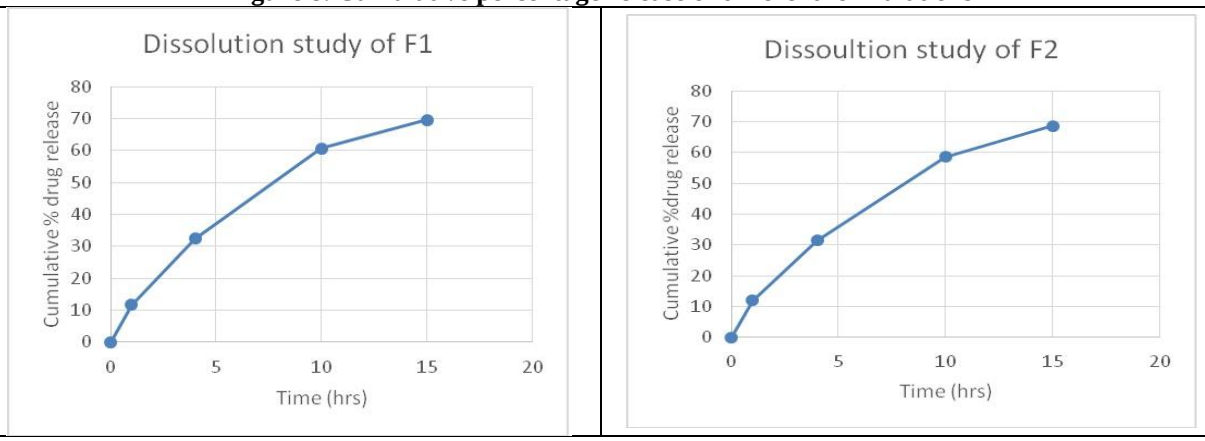


Figure 8. Cumulative percentage release of different formulations



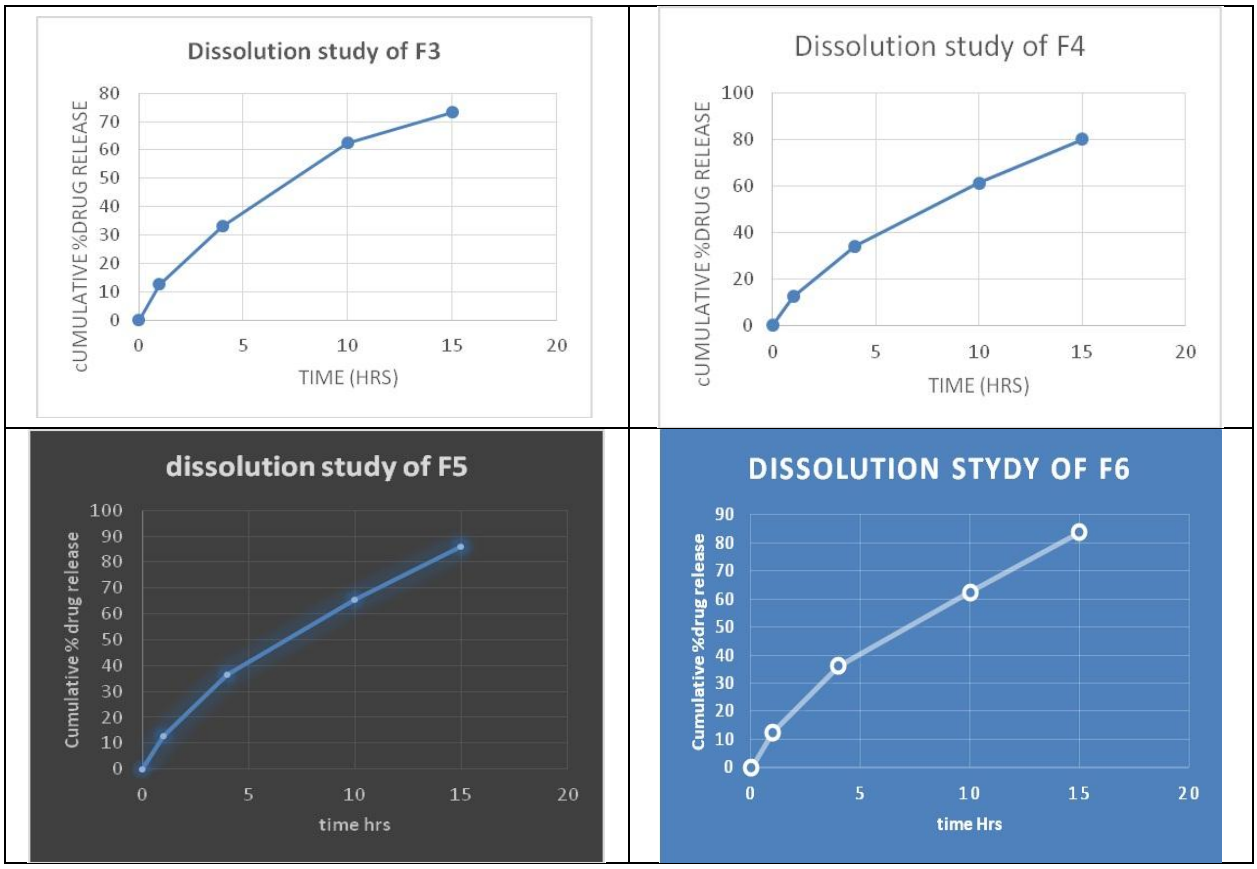


Table 1. Specification of Angle of repose for granules as per IP [9, 5]

No.	Angle of repose (degree)	Types of flow
1	Less than 25	Excellent
2	25-30	Good
3	30-40	Possible
4	Above 40	Very poor

Table 2. Composition of Formulation

Ingredients	F1	F2	F3	F4	F5	F6
Diltiazem Hydrochloride	120.6	120.6	120.6	120.6	120.6	120.6
Hypromellose	77.5	72.5	67.5	62.5	57.5	55
Hydroxypropyl Cellulose	52.5	57.5	62.5	67.5	72.5	75
Methacrylic acid co polymer	19.98	19.98	19.98	19.98	19.98	19.98
Lactose	19.46	19.46	19.46	19.46	19.46	19.46
Magnesium Stearate	3	3	3	3	3	3
Colloidal anhydrous Silica	3	3	3	3	3	3
Purified talc	3.69	3.69	3.69	3.69	3.69	3.69
TOTAL WEIGHT	300	300	300	300	300	300

Table 3. USP Standards of uniformity of weight [5]

NO	Average Weight Of Tablets	%of deviation
1	130 0r less	10
2	130-324	7.5
3	More than 324	5

Table 4. Standard curve of Diltiazem HCL in 0.1N HCL at 240 nm

Concentration	Absorbance
0	0
2	0.121
4	0.242
6	0.355
8	0.468
10	0.585
12	0.699
14	0.815
16	0.93
18	1.057
20	1.169

Table 5. Properties of granules

Batch no	Bulk density	Tapped density	Hausner's ratio	Angle of repose	Compressibility index %
F1	0.521	0.585	1.12	22˚	10.94
F2	0.533	0.597	1.33	24˚	10.72
F3	0.562	0.611	1.08	21˚	8.02
F4	0.543	0.583	1.06	21˚	6.86
F5	0.582	0.661	1.13	24˚	11.95
F6	0.566	0.613	1.08	21˚	7.68

Table 6. Properties of Compressed tablets

Tablets	Deviation in weight variation test *	Drug content % **	Hardness kg/cm2 #	Friability% #
F1	2.635±0.004	97.58±0.01	4.7±0.24	0.79±0.12
F2	3.812±0.005	97.21±0.05	4.3±0.13	0.87±0.09
F3	2.167±0.001	98.89±0.01	4.7±0.16	0.82±0.06
F4	2.891±0.003	96.34±0.03	4.6±0.19	0.72±0.04
F5	2.213±0.002	97.67±0.02	4.9±0.33	0.7±0.06
F6	2.412±0.003	97.53±0.02	4.5±0.28	0.76±0.08

*All values are expressed as mean ± SE n=20; ** All values are expressed as mean ± SE n=5;
All values are expressed as mean ± SE n=6

Table 7. Percentage cumulative drug release profile of batch F1

Time(hrs)	Absorbance	Concentrationµg/ml	Amt.in 5ml (mg/ml)	Amt in 900 ml(mg/ml)	Cumulative % drug release
0	0	0	0	0	0
1	0.109	1.56	0.078	14.1	11.75
4	0.242	4.38	0.216	38.9	32.48
10	0.585	8.06	0.403	72.6	60.75
15	0.871	9.2	0.46	82.8	69.58

Table 8. Percentage cumulative drug release profile of batch F2

Time(hrs)	Absorbance	Concentration µg/ml	Amt.in 5ml (mg/ml)	Amt in 900 ml(mg/ml)	Cumulative % drug release
0	0	0	0	0	0
1	0.11	1.58	0.079	14.3	11.92
4	0.239	4.18	0.209	37.7	31.42
10	0.526	7.78	0.389	70.1	58.65
15	0.832	9.08	0.454	81.8	68.73

Table 9. Percentage cumulative drug release profile of batch F3

Time(hrs)	Absorbance	Concentration µg/ml	Amt.in 5ml (mg/ml)	Amt in 900 ml(mg/ml)	Cumulative % drug release
0	0	0	0	0	0
1	0.112	1.62	0.081	14.6	12.6
4	0.242	4.34	0.217	39	33.17
10	0.592	8.32	0.416	74.8	62.58
15	0.812	9.68	0.484	87.1	73.28

Table 10. Percentage cumulative drug release profile of batch F4

Time (hrs)	Absorbance	Concentration µg/ml	Amt.in 5ml (mg/ml)	Amt in 900 ml(mg/ml)	Cumulative % drug release
0	0	0	0	0	0
1	0.114	1.64	0.082	14.7	12.25
4	0.246	4.46	0.223	40.2	33.98
10	0.532	8.14	0.407	73.2	61.26
15	0.546	10.46	0.523	94.2	79.97

Table 11. Percentage cumulative drug release profile of batch F5

Time (hrs)	Absorbance	Concentration µg/ml	Amt.in 5ml (mg/ml)	Amt in 900 ml(mg/ml)	Cumulative % drug release
0	0	0	0	0	0
1	0.118	1.68	0.084	15.1	12.58
4	0.258	4.86	0.243	43.8	36.57
10	0.594	8.68	0.434	78.2	65.44
15	0.897	11.41	0.572	102.6	86.05

Table 12. Percentage cumulative drug release profile of batch F6

Time (hrs)	Absorbance	Concentration µg/ml	Amt.in 5ml (mg/ml)	Amt in 900 ml(mg/ml)	Cumulative % drug release
0	0	0	0	0	0
1	0.121	1.66	0.083	14.9	12.42
4	0.261	4.8	0.24	43.2	36.07
10	0.532	8.3	0.415	74.7	62.51
15	0.882	11.09	0.554	99.78	83.76

Table 13. Kinetic data modelling of tablets of batch F1 TO F6

Batch	Zero order		Higuchi		Korsmeyer Peppas		
	K_o	r^2	K_H	r^2	N	r^2	K_m
F1	12.789	0.3335	35.193	0.9258	0.324	0.9952	48.65
F2	7.376	0.988	19.331	0.9133	0.856	0.9992	9.84
F3	13.187	0.6216	39.456	0.5383	0.138	0.8341	76.09
F4	6.765	0.9951	17.45	0.8356	1.285	0.9842	3.96
F5	6.695	0.9859	17.14	0.7977	1.243	0.9966	4.1
F6	6.051	0.9957	15.71	0.8674	1.166	0.9791	4.5

CONCLUSION

The main objective of the experiment work undertaken was to develop and *in vitro* evalution of Diltiazem hydrochloride sustained release dosage form by optimization of the developed formulations. Diltiazem hydro chloride can be increased in duration for long time in the body by formulating it in a sustained release dosage form using optimum amount of Hypromellose, Hydroxy propyl cellulose, Methacrylic acid copolymer. The produced tablets exhibited good sustained release over a period of 15hours.In conclusion, in the present research, sustained release tablet formulations of diltiazem hydrochloride were successfully prepared for a once daily administration.

When comparing the formulations from F1to F6, the best formulation (F5) has shown a drug release NLT 86% in 20hr was in accordance with the USP dissolution criteria for extended release diltiazem hydrochloride formulation. The number of experimental trials carried out to produce the optimized formulation was reduced there by substantially cutting down the expenditure on time and cost effective.

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CONFLICT OF INTEREST:
The authors declare that they have no conflict of interest.

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