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Formulation and Development of Diltiazem Hydrochloride Bilayer Tablet

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ABSTRACT

Diltiazem hydrochloride is the most widely used calcium channel blocker, which inhibits the entry of C++ from extracellular to intracellular passage. Diltiazem hydrochloride is the salt form of diltiazem, which is used to prevent heart disease, heart attack, stroke. It is also used to prevent chest pain caused by angina as well as Reynaulds phenomenon. It can also be used in anal fissure suppression. The bilayer tablets were prepared by direct compression method using HPMC K100, Microcrystaline Cellulose, PVPK-30, ethyl cellulose, mg. Sterate,Talc.. The bilayer tablets were evaluated for preformulation studies, UV spectroscopy, FTIR study, invitro drug release study. The drug release date fitted in the standard kinetic data. The optimised F2 batch formulation shows first order kinetic and accelerated studies were performed for bilayer tablets. The Sustained release bilayer tablet was prepared to modulate the rate of drug distribution and increase bioavailability and stability. All the invitro studies were carried out in phosphate buffer (6.8pH) + -37.05°C. In-vitro dissolution was carried out using USP type - 2 at 50 rpm. The IR spectrum of diltiazem was obtained in KBr pellet using Agilent Cary 630 ATR FTIR Spectrophotometer. The FTIR spectra was recorded in the region of 400 - 4000 cm-1 . Stability studies of optimzed to ICH, changes in physical characteristics drug dissolution and drug content. The drug was found at maximum wavelength of 237 nm. The results obtained were found to be in limits.

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INTRODUCTION

Oral route of drug administration is the most important method of administering drugs for systemic effects. Nevertheless, it is probable that at least 90% of all drugs for systemic effects are administered by the oral route. When a new drug is discovered, one of the firstquestions a pharmaceutical company asks is whether or not the drug can be effectively administered for its intended effect for the oral route. If patient self-administration cannotbe achieved, the sale of the drug constitutes only small fraction of what the market would be otherwise of drugs that are administered orally, solid oral dosage forms represent the preferred class of product. Tablets and capsules represent unit dosage form in which one usual dose of the drug has been accurately placed. [1]

Now a day's various developed and developing countries are moving towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension, Diabetes and Rheumatoid arthritis. The problem of dose dependent side effects is minimized by combination therapies and is advantageous over mono therapy from last few years , interest in developing a combination of two or more active pharmaceutical ingredients in a single dosage form has increased in pharmaceutical industry. Bi-layer tablets can be a primary option to avoid incompatibilities between APIS by physical separation.

Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. There are various applications of the bi-layer tablet as it consists of monolithic partially coated or multilayered matrices. Bi-layer tablets are made by compressing two different granulationsfed into a die succession, one on top of another, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet press can be setup for two layers. More layers are possible but the design becomes very special. Bi-layer tablets are composed of two layers of granulation compressed together. They have the appearance ofa sandwich because the edges of each layer are exposed.[2]

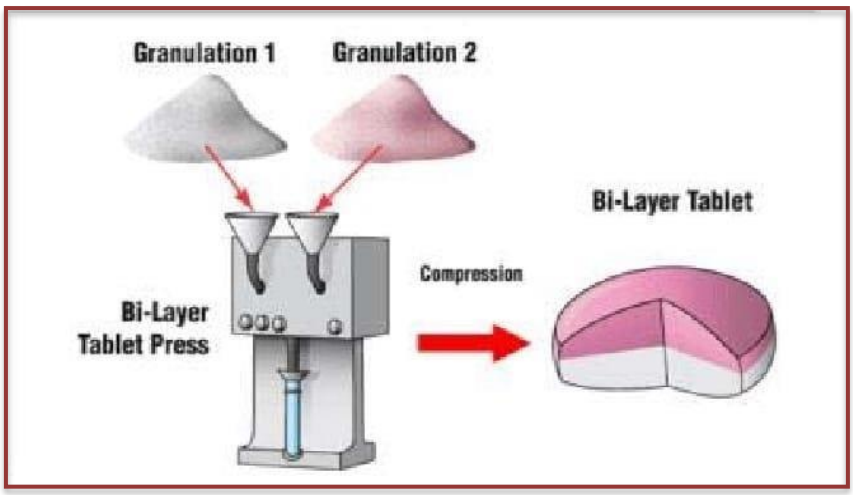

Figure No. 1 General concept of bi-layer tablet

Generally conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with undesirable toxicity and poor efficiency. This factor repetitive dosing and unpredictable absorption led to concept of controlled drug delivery system.The goal in designing sustained or controlled delivery systems is to reduced frequency of dosing or to increase effectiveness of the drug by localization at the site of action reducingthe dose required or providing inform drug delivery. Primary objective of sustained release delivery is to insure safely and to improve efficacy of drugs as well as patient compliance[3]

MATERIALS & METHODS

Table No. 1: List of Reagents and Chemicals

Sr. No.	Materials	Source
1	Diltiazem HCL	SWAPNROO Drugs and PharamaceuticalsAurangabad
2	Ethyl Cellulose	Thomas Baker Pvt. Ltd. Mumbai
3	HPMC K100M	Research-Lab Fine Chem Industries, Mumbai.
4	Lactose	Thomas Baker Chem.Pvt Ltd.
5	Microcrystalline Cellulose	Research-Lab Fine Chemind.
6	Cross povidone	Basf GERMANY
7	Sodium starch Glycolate	N. B. Enterprises
8	Croscarmellose sodium	FMC-Ireland
9	PvpK-30	Research -Lab Bombay.
11	Isopropyl Alcohol	Thomas Baker Chem.Pvt Ltd
12	Aerosil	Venus Enterprises
13	Talc	Research-Lab Fine Chem Industries.
14	Magnesium stearate	S. Kanth Health Care Ltd.
15	Methylene Blue	Research-Lab Fine Chem industries

Table No. 2 : List of Major Instruments :

Sr. No.	Equipment's	Source
1	Dissolution Test Apparatus	Electro lab. Mumbai.
2	Electronic Balance	Citizen, Mumbai
3	UV-Visible Spectrophotometer	Agilent Cary 60 Spectrophotometer
4	pH Meter	Hanna Instruments
5	Hot Air oven	Shital Scientific Industries, Mumbai
6	Distillation Apparatus	Fill-Well
7	Vernier Caliper	ICI checking instruments
8	Single punch Tablet Machine	Cadmach Ahmadabad
9	Roche Friability Tester	Labhosp
10	Monsanto Hardness Tester	Dolphin Mumbai.
11	Laboratory Sieves	Unique
12	Disintegration Test Apparatus	Veego
13	FTIR	Agilent Cary 630 ATR FTIR Spectrophotometer.

EXPERIMENTAL

Formulation and optimization of bilayer tablet containing release layer & sustained release layer of Diltiazem Hydrochloride.

Development of sustained release layer by direct compression

Weight all the Required quantities of drug polymer and diluent were mixed thoroughly talc and magnesium stearate were finally added as glidant and lubricant mixed well with powder blend for 5 minutes.

Development of immediate release layer by direct compression

Weigh the all Required quantities of drug and polymer and diluent were mixed thoroughly talc and magnesium stearate were finally added as glidant and lubricant mixed well with powder blend for 5 minutes

Compression of Bilayer Tablet

In the present study bilayer tablet was prepared manually using single station punching machine. Accurately weighed amount of SR powder mixture was fed manually into die cavity. SR layer was compressed at mild compression force (3-4 kg/cm2). After that accurately weighed IR powder mixture was manually fed intothe die on SR layer and compress using 9 mm circular punch. Both the layer was identified on the basis of colour since the immediate release layer has

Table No .3. Formulation of Sustained release layer

Ingredients	D1	D2	D3	D4	D5	D6
Diltiazem HCL	60	60	60	60	60	60
HPMC K100M	60	30	23.33	36.66	15	-
Ethyl Cellulose	-	30	36.66	23.33	45	60
MCC	60	60	60	60	60	60
PVP K -30	10	10	10	10	10	10
Mg. Stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total	200	200	200	300	200	200

Table No .4. Formulation of Immediate release layer

Ingredients	R1	R2	R3	R4	R5	R6
Diltiazem HCL	60	60	60	60	60	600
Lactose	10.25	10.25	10.25	10.25	10.25	10.25
MicrocrystallineCellulose	19	16	19	16	19	16
PVP K - 30	5	5	5	5	5	5
IsopropylAlcohol	q.s	q.s	q.s	q.s	q.s	q.s
SSG	3	3	-	-	-	-
CCS	-	-	3	3	-	-
CP	-	-	-	-	3	3
Aerosil	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Mag. stearate	0.6	0.6	0.6	0.6	0.6	0.6
Methylene Blue	0.15	0.15	0.15	0.15	0.15	0.15
Total	100	100	100	100	100	100

RESULTS & DISCUSSION

Organoleptic characterization and Melting point determination

Table No.5: the physicochemical characteristics of Diltiazem Hydrocloride

Sr. No.	Test	Observations
1.	Colour	White Crystalline Powder
2.	Odour	Odourless
3.	Taste	Bitter
4.	Melting Point	210^0– 215^0c
5.	pH	4.5 – 6.0

The organoleptic character and melting point was found to be as per standard drug so drug used in the formulation was found to be pure according to I.P. specification.

Cumulative percentage release from immediate release layer of tablet

Table No 6: In vitro dissolution data immediate release layer

Time (min)	R1 (%)	R2 (%)	R3 (%)	R4 (%)	R5 (%)	R6 (%)
0 min	0	0	0	0	0	0
5 min	71.27	74.54	61.53	72.09	70.99	72.09
10 min	73.75	76.45	64.30	74.54	74.81	77.54
15 min	75.90	80.27	80.27	77.81	79.45	82.18
20 min	79.36	87.81	84.00	79.63	87.54	89.98
25 min	84.27	92.45	89.72	84.27	89.72	93.00
30 min	85.63	96.27	95,81	91.18	91.99	98.27

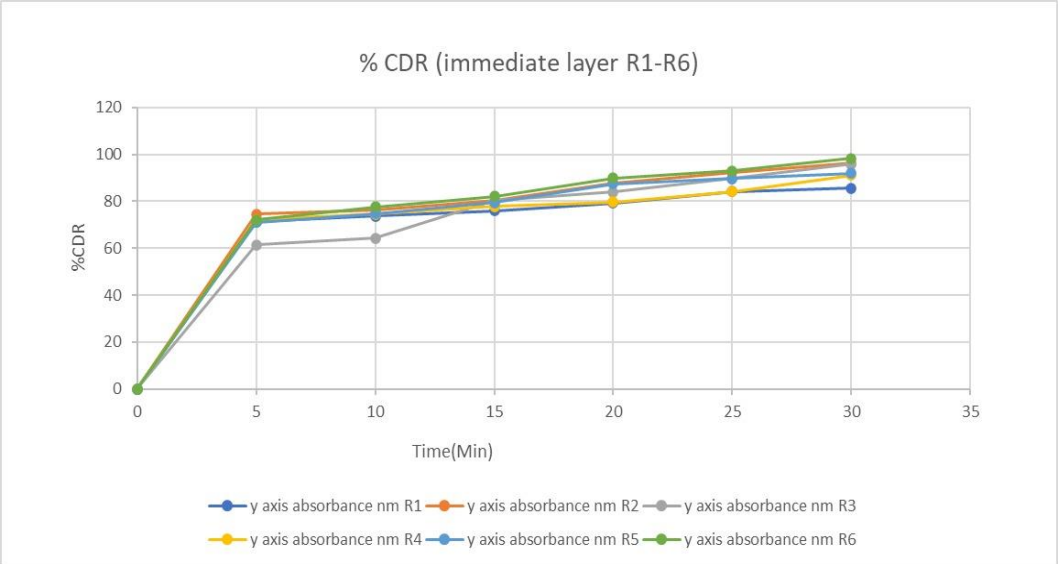

Fig No.2: In vitro dissolution data

Cumulative percentage release from sustained release bilayer tablets

Table No 6: In vitro dissolution data sustained release layer

Time (Hr)	D1 (%)	D2 (%)	D3 (%)	D4 (%)	D5 (%)	D6 (%)
0 hr	0	0	0	0	0	0
1hr	11.97	11.58	10.97	13.02	14.44	19.02
2 hr	23.39	24.29	22.05	24.85	26.03	36.94
3 hr	34.58	33.35	28.59	40.85	37.05	54.85
4 hr	43.32	43.32	43.43	57.98	49.02	68.39
5 hr	56.08	50.00	57.27	71.41	66.09	82.27
6 hr	67.16	59.05	71.52	82.72	79.02	90.00
7 hr	71.19	65.02	81.71	88.43	82.08	93.47
8 hr	78.13	70.71	88.18	90.00	91.08	95.62

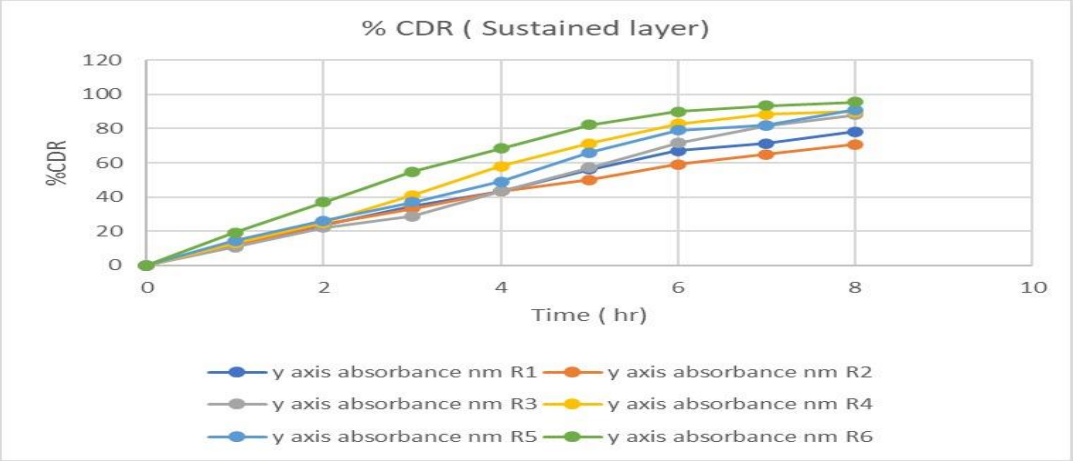

Fig No. 3: In vitro dissolution data

The comparative dissolution profile of D1-D6 shown in table 21. Batch D6 give maximum release compare to D1-D6 batches, and it also give the same release profile as per dissolution profile. Optimized batch D6 has passed all the specified range of parameter. D6 batch give weight variation in the range of 300 mg +0.98 mg It had also sufficient hardness 7.0 kg/cm² to stand mechanical shock, which was the optimized for the further study because less than the above value then the tablet layer become separated during the friability study. Drug content and friability of batch D6 was found 98.84 ± 0.75% and 0.36 ± 1.24, which was desirable for our formulation. Therefore, D6 batch is considered optimized batch for the SR layer.

Evaluation Parameter of Optimized Formulation

Table No.7: Evaluation Parameter of Optimized Formulation

Sr. No.	Parameter	Observation
1	Hardness	7.0 Kg/cm^2
2	Friability	0.3%
3	Thickness	0.5 mm
4	Diameter	1mm
5	Weight Variation test	Passed
6	Description	A circular, flat edged, concave, uncoated bilayer tablets of which one layer is methylene blue Colored
7	Disintegration test	45 min for sustained released 05 min for immediate release

SUMMARY & CONCLUSION

The aim was to design bilayer tablets of Diltiazem hydrochloride to give immediate release and sustained release of diltiazem hydrochloride. The immediate release of was prepared of Diltiazem hydrochloride with different super disintegrants like Cross povidone. sodium starch glycolate and croscarmellose sodium and Diltiazem hydrochloride the sustained release layer prepared by direct compression techniques using different polymer HPMC K100M and ethyl cellulose (with different ratio of HPMC K100M and ethyl cellulose) as the release retarding polymers. Preformulation studies were performed prior to compression. The bilayer tablets were evaluated for various parameters. Thickness of bilayer tablets 0.5 mm The hardness of these bilayer tablet ranges between 6.8- 7.0 kg/cm Percentage buoyancy was in the range of 88- 99.27%. Results of the in vitro drug release indicated that immediate released in 30 min & Diltiazem Hydrochloride sustained released in 8 Hrs. Results of in-vitro release profile indicated that Immediate release layer formulation R2, R5 and R6, and Sustained release layer formulation D3, D5 and D6 were the most promising formulations as the extent of drug release from this formulation was high as compare to other Immediate release layer formulations up to 30 mins. Sustained release layer formulations up to 8 hrs. The in vitro release of Bilayer tablet of Diltiazem Hydrochloride were found in the release of drug from the bilayer tablet depends on the different super disintegrants and different concentration of polymer were used As per all satisfactory evaluation parameters, the batch R6 and D6 is found to be optimized batch The IR spectrum studies revealed that there was no disturbance in the principal peaks of pure drugs. This further confirms the integrity of pure drugs and no incompatibility of them with excipients**.**

The stability studies were carried out for the optimized batch for one month and it showed that there was no change in the formulation after 30 days.

It can be concluded that the preparation of bilayer tablets diltiazem hydrochloride with immediate release and sustained release of the later has been achieved for the treatment of antihypertensive . By using this polymer HPMC K100M and ethyl cellulose concluded that increase the drug release of diltiazem Hydrochloride up to 08 hrs. and croscarmellose sodium as a super disintegrant for immediate release diltiazem HCl of up to 30 min. The various pre-formulation studies like bulk density, tapped density, Carr's index, powder drug and polymer are compatible with each other that studied by FTIR Spectroscopy. By formulating diltiazem HCl we can improve stability of formulation, fixed dosing, increase patient

compliance & also bioavailability of drug.

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