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DESIGN AND EVALUATION OF BILAYER FLOATING TABLETS OF DILTIAZEM HCL

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Abstract:
The present investigation concerns design and evaluation of bilayer floating tablets of Diltiazem HCl Diltiazem HCl is Class I drug, though its reported bioavailability is only 40 %. It is having very short half life of 3 to 4 hrs. Hence many sustained release formulations were developed for Diltiazem HCl.
A direct compression method was used to formulate all batches. 32 factorial design was applied to study % cumulative drug release and hardness. Super disintigrants like Sodium starch glycolate was used for immediate release layer and HPMC K200 M, Xanthan gum like polymers were used in floating layer for sustain release layer.Optimisation study was performed by using design expert software. Successful formulation was developed having floating lag time as low as 14 sec and drug release was sustained up to 12 hrs. A biphasic drug release can be obtained by using bilayer tableting technology which involved compression of immediate and sustained release layer together. The variables HPMC K200M and Xanthan Gum evaluated in this study exhibited significant affected the release profile.
Keywords: *Bilayer floating tablets, Diltiazem HCl, HPMC K 200 M, Xanthan gum, % drug release.*

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INTRODUCTION:

The oral route is the most promising and convenient route of drug administration. Conventional immediate release system achieves as well as maintains the drug concentration within the therapeutically effective range, but one has to take such formulations several times a day. This results in significant fluctuations in plasma drug levels and also the frequency of administration leads to patient non-compliance. Recently, several technical advancements in the pharmaceutical field have led to the development of many novel drug delivery systems that could revolutionize the method of medication and provide a number of therapeutic benefits [1,2].

Floating Drug Delivery Systems

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids thus, remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly and almost completely at a desired rate from the system. After the release of the drug, the residual system becomes liable to be emptied from the stomach.

Bilayered Tablets

A bilayered tablet is one made up of two separate layers, with each layer intended for a specific result, layers can be formulated to separate physically or chemically incompatible ingredients or to produce repeat action or to dissolve at different times or to deliver the product to different locations or to give different pharmacological effects [3].

The biphasic system may contain one or two drugs for immediate release and sustained release layer [6,7,8,9]

Diltiazem HCl is among the most extensively prescribed calcium channel blocker for hypertension & angina pectoris. The plasma half life of diltiazemHCl is 3 to 4 hours. It is BCS class I drug with high solubility and high permeability, belonging to the benzothiazepine family. Diltiazem HCl undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A, [2] which results in less than 4% of its oral dose being excreted unchanged in urine. Bioavailability of diltiazem HCl is 30-40% owing to an important first pass metabolism.It has an elimination half-life of 3.5 hours and has an absorption zone from the upper intestinal tract above the absorption zone. Diltiazem HCl requires multiple daily drug dosage in order to maintain adequate plasma concentrations. Therefore, it is a suitable model candidate for gastroretentive formulation [10-12].

MATERIALS AND METHOD

Diltiazem HCl was obtained as a gift sample from J.B. Chemicals Pvt.ltd. Ankleshwar, Gujarat. HPMC K200M, Xanthan gum, Sodium starch glycolate, Calcium phosphate, Sodium bicarbonate, Lactose, Mg. stearate, Talc. From Research Lab Fine Chem. Ltd. Mumbai.

Formulation Development

Bilayer tablets of diltiazem HCl contains two layers i.e. immediate release layer and sustained release layer. Both layers separately optimized. Accurately weighed 150 mg of immediate release blend and 260 mg of sustained release blend individually. Various batches of bilayer floating tablets were prepared by direct compression method. Initially, immediate release layer blend was fed manually in the die, compressed at low compression force to form uniform layer. Subsequently sustained release layer was added over it, completely compressed on bilayer tableting machine (Rimek Mini Press-II, Karnavati Engineering Ltd.) by using 09 mm flat punch [14].

Table1: Formulation of bilayer floating tablet

Ingredients (mg/ Tablet)	Formulation Code								
	B1	B2	B3	B4	B5	B6	B7	B8	B9
Immediate release layer									
Diltiazem Hydrochloride	30	30	30	30	30	30	30	30	30
Sodium starch glycolate	5	8	6	5	8	6	5	8	7
Calcium phosphate	113	110	112	113	110	112	113	110	111
Mg. sterate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Sustaine release layer									
Diltiazem Hydrochloride	90	90	90	90	90	90	90	90	90
HPMC K200M	60	70	80	60	70	80	60	70	80
Xanthum gum	10	10	10	20	20	20	30	30	30
Citric Acid	10	10	10	10	10	10	10	10	10
Sodium Bicarbonate	15	15	15	15	15	15	15	15	15
Lactose	27.5	35.5	47.5	57.5	47.5	37.5	67.5	57.5	47.5
Mg. stearate	5	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
TOTAL	**410**	**410**	**410**	**410**	**410**	**410**	**410**	**410**	**410**

Evaluation of Bilayer Floating Tablet
Hardness (Lachman et al., 1990)
Tablet requires certain amount of strength or hardness, measured by Monsanto hardness tester**.** Ten tablets were randomly picked from each formulation and evaluated for hardness during manufacturing and expressed in Kg/cm^2 .

Friability
Friability was performed by using Roche friabilator; normally preweighed 20 tablets were placed in the plastic chamber of friabilator. This was then operated for 100 revolutions. Tablets dropping from a distance of six inches with each revolution. Tablets are then dusted and reweighed.

$$F\ (\%) \quad \frac{\text{Initial wt.} - \text{Final wt.}}{\text{Initial wt.}} \times 100$$

Disintegration Test (IP 1996)

Six tablets were selected randomly from each batch for the disintegration test. Disintegration test was performed in simulated gastric fluid using Electrolab Disintegration tester (USP). Disintegration time (DT) was measured for immediate release layer tablets**.**

Drug content uniformity
Ten tablets were finely powdered and an amount equivalent to 40 mg of Diltiazem HCL was accurately weighed and transferred to a 100 mL volumetric flask, then 70 mL of methanol was added. The flask was shaken for 10 min. Finally, the volume was made up to the mark with methanol. The mixture was then filtered and 1 mL of the filtrate was suitably diluted with methanol to obtain a solution containing about 40 μg mL–1 of Diltiazem hydrochloride and analyzed for Diltiazem hydrochloride content at 236 nm using a double beam UV/Visible and methanol as blank.

Weight Variation (Lachman et al., 1990)
Twenty tablets were selected randomly and weighed individually. Calculated average weight and compared the individual tablet weight to the average

Table 2: Weight variation tolerances for uncoated tablets

Average weight of tablets (mg)	Maximum percent difference allowed
130 or less	10
130 – 324	7.5
More than 324	5

Thickness and Diameter
Thickness and diameter of tablets were accurately measured by using digital verniercaliper .

***In-vitro* Buoyancy Studies:**
The in-vitro buoyancy was determined by floating lag time. The time required for the tablet to rise to the surface and float was determined as floating lag time. In this the tablets were placed in 100 ml beaker containing 0.1 N HCL.

***In-vitro* Drug Release Study**
In vitro drug release of Diltiazem hydrochloride was determined using a USP (XXI) six stage dissolution rate test apparatus I (VeegoScientific) at 50 rpm. The dissolution rate was studied using 900 ml of 0.1 N Hydrochloride (pH 1.2). The temperature was maintained at 37± 0.20°C. The sample (5 mL) was withdrawn at different time intervals, *i.e*. 5,10,15,20,25,30 60, 120, 180, 240, 300, 360, 480, 600 and 720 min, filtered through Whatman filter paper and replaced by an equal volume of dissolution medium. Samples were suitably diluted and analyzed for propranolol hydrochloride content at 236 nm.

RESULTS AND DISCUSSION:
Preformulation study
Identification and characterization of drug
Organoleptic properties
Diltiazem HCl is a white crystalline powder with no odor.

Melting point
Melting point of Diltiazem HCl was found in the range of 210-212°C, which complies with given literature value (211°C).

UV spectra
Diltiazem hydrochloride methanolic solution was scanned at 400 nm to 200 nm, one maximas was observed at 236 nm. This was confirmed with reported UV spectrum of Diltiazem HCL.
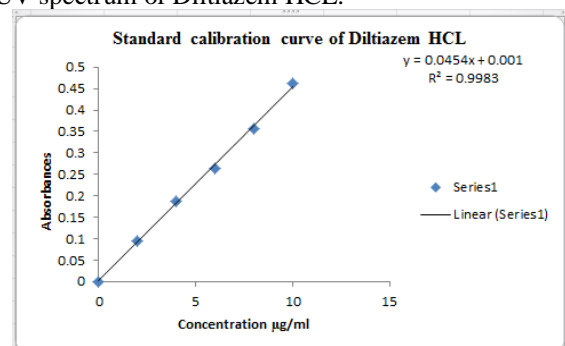

Fig 1: Spectrum of Diltiazem HCl at λ max 236 nm

Infrared Spectrum
The FT-IR spectrum was measured in the solid state as potassium bromide dispersion. The FT-IR spectrum of Diltiazem hydrochloride presented in **Figure 2**
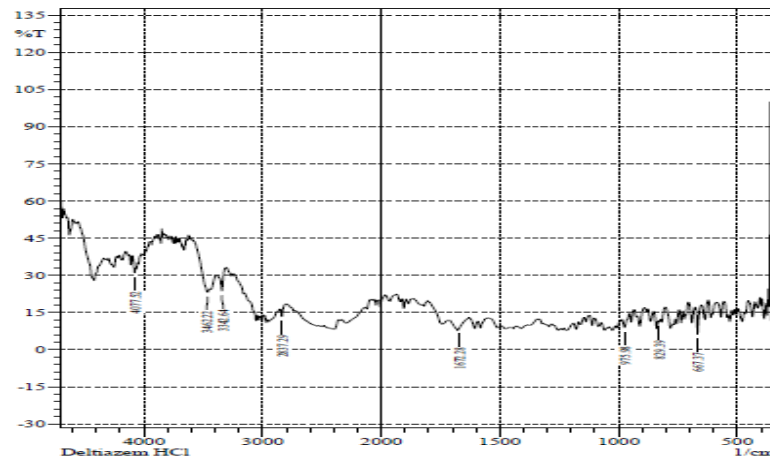
Fig 2: FT-IR spectrum of Diltiazem hydrochloride

Drug-Polymers Interaction Study

The FT-IR spectrum of drug and polymers revealed that major frequencies of functional groups of pure drug remain intact in granules containing different polymers; hence, there is no major interaction between the drug and polymers used in the study.
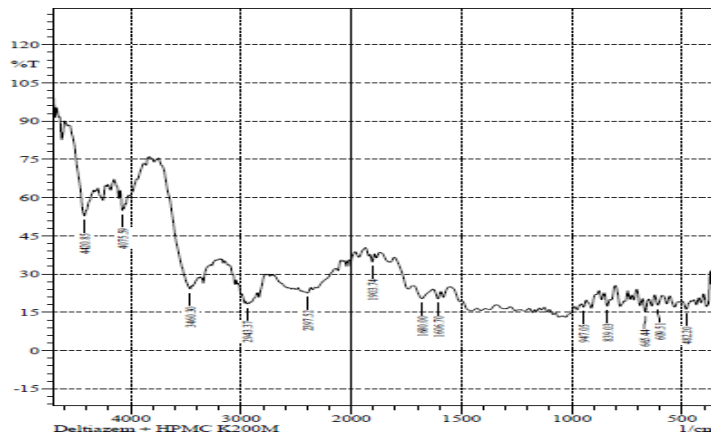

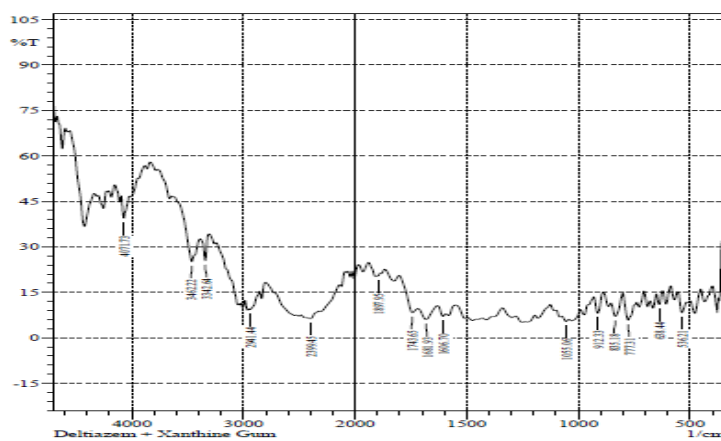**Fig 3: FT-IR spectrum of Diltiazem HCL and HPMC K200M**

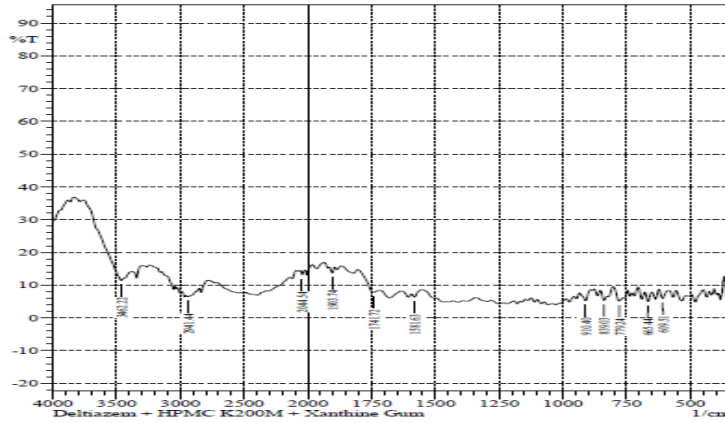**Fig 4: FT-IR spectrum of Diltiazem HCL and Xanthan gum**

Fig. 5: FT-IR spectrum of mixture of bilayer floating tablet of Diltiazem HCL

Table 3: FTIR peaks of various functional groups of Diltiazem HCl

Sr. No.	Energy (wave numbers cm-1)		Assignment
	Reported29	**Sample**	
1	3056	3055.24	Aromatic C-H stretch
2	3035	3034.03	Aromatic C-H stretch
3	2966	2966.52	Aliphatic C-H stretch
4	2837	2837.29	O-CH3-CH stretch
5	2393	2351.23	Amine HCl –N stretch
6	1743	1745.58	Acetate C=O stretch
7	1679	1680	Lactum C=O stretch
8	1839	1905	O- substituted Aromatic C-H stretch
9	781	778	P- substituted out of plane deformation

Differential Scanning Calorimetry

DSC thermogram of Diltiazem HCl showed endothermic peak of fusion, having peak maximum of 218.84°C. This was in accordance with the reported. DSC thermogram is shown in Figure. 6
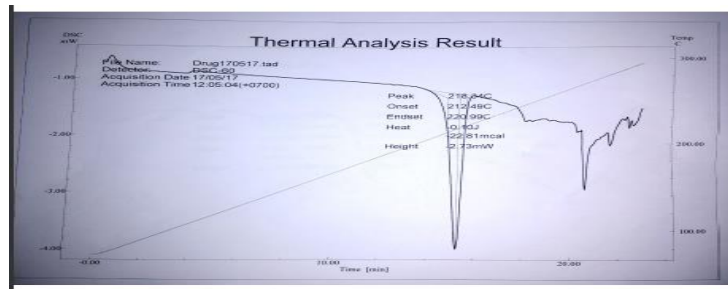

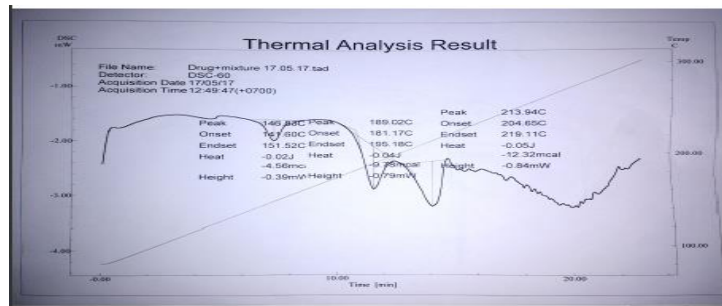**Fig 6: DSC Thermogram of Diltiazem HCL**

Fig 7: DSC Thermogram of Diltiazem HCL + HPMC K200M +Xanthan gum +Excipients

Table 4: Evaluation of bilayer floating tablet factorial design batches B1-B9

| Batches	Weight Variation* (mg)	Thickness* (mm)	Hardness (Kg/cm2)	Friability (%)	Drug Content Uniformity* (%)
B1	408.1±3.49	2.5	5.5	0.127±0.015	98.27±1.26
B2	404.9±3.30	2.5	5.5	0.728±0.021	97.11±0.56
B3	405.4±2.68	2.0	5.5	0.519±0.013	97.46±0.83
B4	403.40±3.18	2.5	6.0	0.224±0.012	98.57±0.63
B5	407.65±1.46	3.0	6.5	0.041±0.022	97.89±0.94
B6	406.40±1.60	2.5	6.0	0.037±0.021	96.49±0.61
B7	406.15±2.08	2.5	5.5	0.054±0.011	99.63±0.79
B8	405.40±2.16	2.0	5.8	0.022±0.020	98.84±0.53
B9	404.15±1.42	2.0	5.5	0.264±0.030	98.73±0.81

The data are presented as (n = 3) mean value ± S.D.

Table 5: *In-vitro* buoyancy study of bilayer floating tablets

Formulation batch code	Floatinglag time(sec)	Total floating Time(hrs)
B1	17.23±0.52	12
B2	15.00±1.12	12
B3	14.43±0.47	12
B4	17.00±1.30	12
B5	15.66±1.08	12
B6	16.00±1.40	12
B7	16.56±0.15	12
B8	15.56±1.52	12
B9	17.68±1.55	12

The *in-vitro* dissolution study of bilayer floating tablets of batches B1-B9

The *in-vitro* dissolution study of Diltiazem hydrochloride bilayer floating tablets was carried out by using USP dissolution type II apparatus (Paddle) (VeegoScientific, DA-6D)
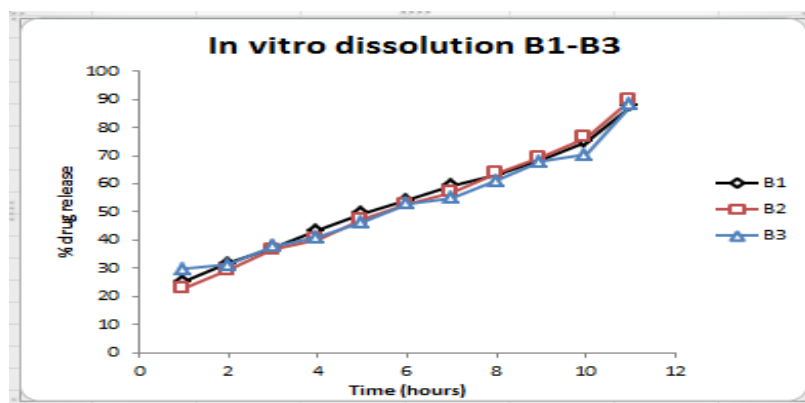
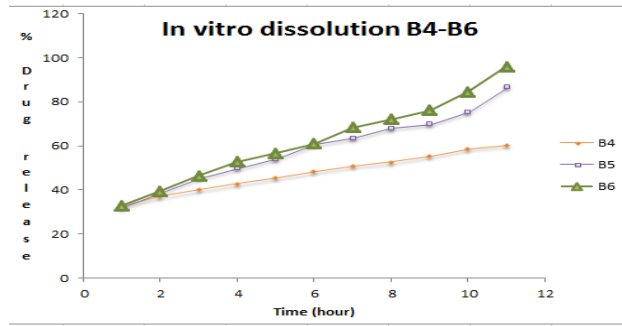Fig 7: Comparison of the release profiles of bilayer floating tablets of batches B1 to B3.

Fig 8: Comparison of the release profiles of bilayer floating tablets of batches B4 to B6.
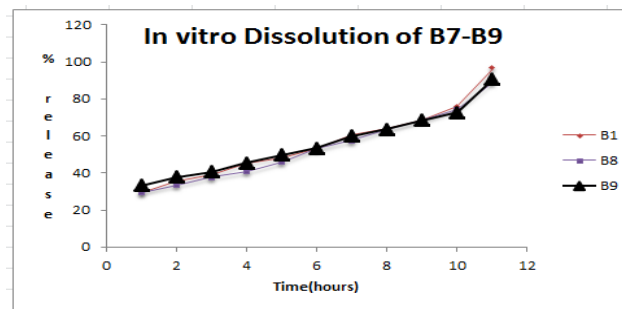

Fig 9: Comparison of the release profiles of bilayer floating tablets of batches B7 to B9.

Data Analysis

Table 6: In vitro Drug release data Analysis

Batch	Zero order		First order		Matrix		Korsmeyer-peppas		Hixson-Crowell	
B7	R^2	**Slope**	R^2	**Slope**	R^2	**Slope**	R^2	**Slope**	R^2	**Slope**
	0.8980	0.453	0.8077	4.332	0.9679	12.178	0.9574	10.481	0.8971	6.422
							n=11.434			

Optimisation

Table 7: Result of ANOVA

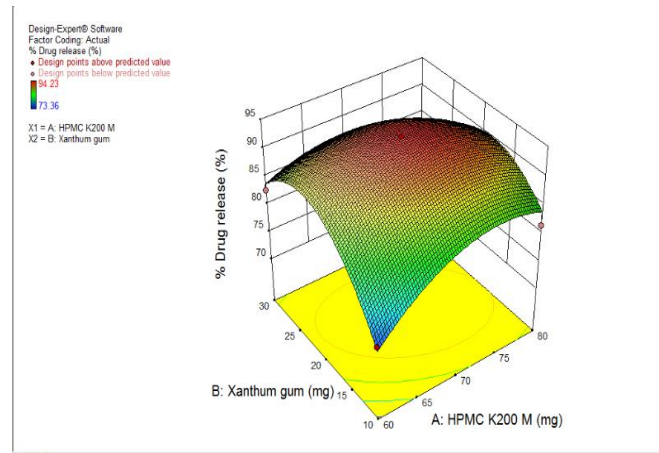| Response model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Model significant/non-significant
%Drug release (hours)	811.05	12	159.07	19.25	0.0006	0.9322	Significant
Hardness (Kg/cm²)	1.26	12	0.243	18.34	0.0007	0.9291	Significant

Fig 9: A response surface plot showing effect of concentration of independent   variables on the % Drug release.
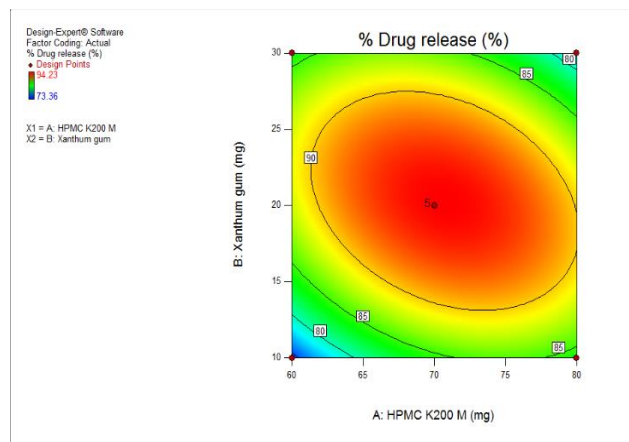

Fig 10: A counter plot showing relationship between various levels of independent variables to gain fixed value of % Drug release.
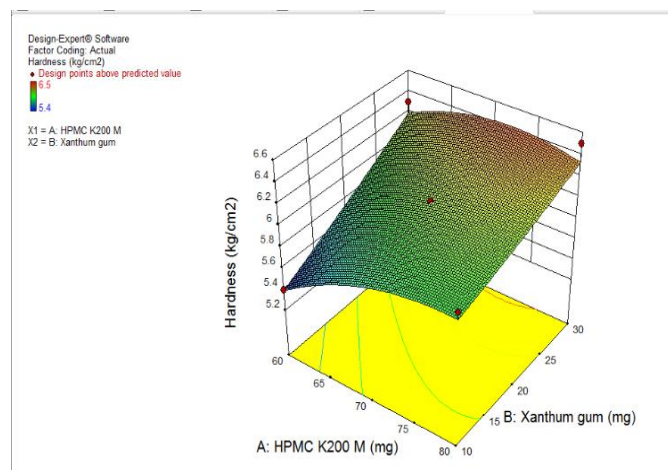

Fig 11: A response surface plot showing effect of concentration of independent variables on the Hardness.
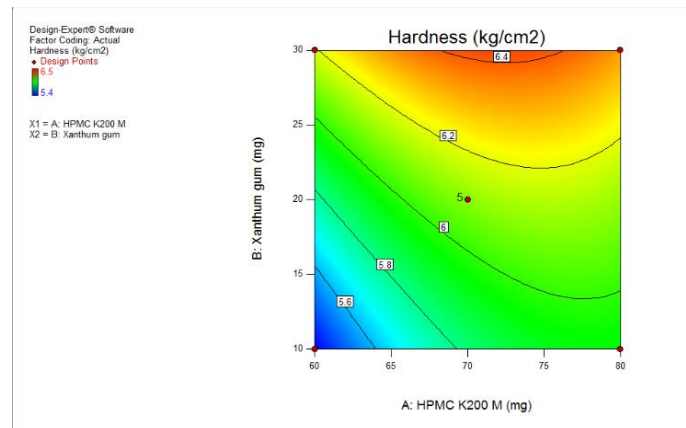
Fig 12: A counter plot of showing relationship between various levels of independent variables to gain fixed value of Hardness.

Final Equation in Terms of Coded Factors:	
% Drug release $= + 94.23 +0.89* A +0.85* B -3.94*AB -5.26*A^2 -9.00*B^2$	(1)
Final Equation in Terms of Coded Factors:	
Hardness $= + 6.10 + 0.17* A +0.30* B-0.10*AB-0.16*A^2 +0.019*B^2$	(2)

Stability Study

After storage the formulation was analyzed for various physical parameters, results are showed in **Table No.8**. No major difference was found between evaluated parameters before and after ageing / storage and all are in acceptable limits

Table 8: Evaluation parameters of stability batch (B7)

Evaluation parameters	Before stability Storage	After 3 months storage
Hardness (kg/cm^2)	5.5±0.0	5.2±0.15
Friability (%)	0.054±0.0	0.051±0.00
Weight variation (mg)	405.66± 0.57	403.66 ± 0.5
Disintegration time (sec)	91 ± 0.57	89 ± 1
Drug content (%)	98.90 ± 0.58	97.83 ± 1.0
Percent drug release	96.49 ± 0.49	95.28 ± 0.49

The data are presented as mean value ± S.D. (n = 3)

CONCLUSION:

A biphasic drug release can be obtained by using bilayer tableting technology which involved compression of immediate and sustained release layer together.Successful formulation was developed having floating lag time as low as 14 sec and drug release was sustained up to 12 hrs. The variables HPMC K200M and Xanthan Gum evaluated in this study exhibited significant effect on the responses FLT and B7 of the formulations; however the NaHCO3 markedly affected the FLT while the HPMC K200M affected the release profile of Dilitzam .

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