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Design and Evaluation of Labetalol Bilayered Tablets

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Abstract

Bilayered Tablets are used to produce repeat action or prolonged action by separating physically or chemically incompatible ingredients. The present study was carried out to exploit the feasibility of using controlled delivery bilayered tablets of labetalol as an alternative carrier for targeting adrenergic receptors. This tablet contains two layers, first immediate release layer using Ludiflash as Super disintegrant and second layer using polymers Sodium alginate, Carbopol, Ethyl Cellulose by varying concentrations for Controlled release for 10 hours. The drug products may be developed to reduce hypertension by blocking alpha adrenergic selectively and beta adrenergic non selectively. A total number of nine formulations have been taken to optimize and develop a robust and stable formulation and were evaluated. The kinetics of release was determined and fitted to an empirical equation. Among the formulations, tablets of formulation -4 was taken as optimized formula due to its higher rate of dissolution and complied all the other formulations and found to be first order in kinetics. Formulated Bilayered tablets of Labetalol were found to be potential drug delivery system for sustaining the release of the drug.

Keywords: Bilayered Tablets, Labetalol, Ludiflash, Sodium alginate, Carbopol, Ethyl cellulose

Contents

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1. Introduction

Usually conventional dosage form produce wide range of fluctuation in drug concentration in factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug

delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance [1, 2]. 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 [3, 4]. There is various application of the bi-layer tablet it consist of monolithic partially coated or multilayered matrices. In the case of bi-layered tablets drug release can be rendered almost unidirectional if the drug can be incorporated in the upper non-adhesive layer its delivery occurs into the whole oral cavity [5].

Formulation of layers from different polymers allows manipulation over more than one rate-controlling polymer, thus enabling different types of drug delivery of one or more drugs, i.e. where the drug may be released with a bolus and then at a controlled rate or by targeted drug delivery in the GI tract using pH dependant polymers [6-9]. The aim in designing sustained or controlled delivery systems is to decrease the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or provide uniform drug delivery. The main objective of sustained release drug delivery is to make sure safety and to improve effectiveness of drugs as well as patient compliance. But often this controls drug delivery system fails to achieve the stated advantages due to lack of releasing the initial bolus dose dumping and failure to achieve site specific drug delivery. Immediate release drug delivery system is intended to disintegrate rapidly, and exhibit instant drug release. It is associated with fluctuations in drug plasma levels, which leads to reduction or loss in drug effectiveness or increase incidence of side effects. A relatively constant plasma level of a drug is often preferred to maintain the drug concentration within the therapeutic window. However, it is difficult to achieve, especially for once-daily dosage forms, partly because the environment for drug diffusion and/or absorption varies along the gastrointestinal (GI) tract. On the basis of these considerations, bilayer tablets have being proposed [10-12].

Labetalol hydrochloride is an anti-hypertensive belongs to the class of alpha and beta blocking agents which is used to treat high blood pressure. It is slightly soluble in water and is well absorbed from the GIT. Labetalol hydrochloride is rapidly absorbed following an oral dose but undergoes extensive first pass metabolism, resulting in only 25% oral bioavailability. The drug is eliminated rapidly, so repeated daily administration are required to maintain the effective plasma levels. The half-life of Labetalol hydrochloride is approximately 4-6 hours [13]. Thus an attempt has been made to develop a bilayer tablet of Labetalol hydrochloride for improving and enhancing the bioavailability.

The main objective of the present study is to formulate and evaluate a bilayered drug delivery system for an anti hypertensive drug by using Ludiflash, Sodium alginate, Carbopol, Ethyl cellulose, Micro crystalline cellulose, Colloidal Silicon-dioxide polymers in various ratios thus can decrease the dose, dosing frequency and maintain prolonged therapeutic levels of the drug.

2. Materials and Methods

Materials:

Labetalol Hcl was obtained as a gift sample from Sigma-Aldrich. Sodium alginate, carbopol 934 p, ethyl cellulose, ludiflash, microcrystalline cellulose, aerosil, magnesium stearate were obtained from SD fine –chemicals private limited, Mumbai.

Methods:

Drug – Excipients Compatibility studies by FT-IR

A proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of both drug and excipients used in fabrication of the product. Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product. So before producing the actual formulation, compatibility of Labetalol with disintegrants, with polymer and other excipients were tested using the Fourier Transform Infrared Spectroscopy (FT-IR).

For this study, potassium bromide (KBr) pellet method was employed. The samples were thoroughly mixed with dry powdered potassium bromide. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded. The application of infra-red spectroscopy lies more in the qualitative identification of substances either in pure form or in the mixtures and as a tool in establishment of the structure. Since IR is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds.

Formulation of bilayer tablets of labetalol:

Development of bilayer tablet of Labetalol was carried out in three stages. Two layers (Immediate release layer and controlled release layer) were formulated separately using different concentration of polymers in different ratios as

given in the table 1 and 2. After optimization of individual layers by *in-vitro* studies, bilayer tablet was prepared using optimized formulae. Bilayer tablet was prepared on rotary tablet compression machine. First the extended release layer was precompressed on compression machine manually and the immediate release layer was loaded on top of precompressed layer and punched with 8mm punch on compression machine automatically.

Preparation of Immediate layer:

1. Drug and superdisintegrant (Ludiflash) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.
2. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min.

Preparation of Sustained layer:

1. Drug and polymer (Sodium alginate or Carbopol 934P or Ethyl cellulose) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.
2. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) to the above blend mix it for 2min.
3. Compressed the above lubricated blend by using 8mm round punches.

Table 1: Composition of Labetalol Sustained Release Layer

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Labetalol Hcl	200	200	200	200	200	200	200	200	200
Sodium Alginate	20	-	-	40	-	-	60	-	-
Carbopol 934p	-	20	-	-	40	-	-	60	-
Ethyl Cellulose	-	-	20	-	-	40	-	-	60
Micro crystalline cellulose	177	177	177	157	157	157	137	137	137
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Total Weight (mg)	400	400	400	400	400	400	400	400	400

Table 2: Optimized formulation of Immediate release layer

Ingredients	I1(Mg)	I2(Mg)	I3(Mg)
Labetalol Hcl	100	100	100
Ludiflash	8	16	24
Microcrystalline Cellulose	88	80	72
Aerosil	1	1	1
Magnesium Stearate	3	3	3
Total weight (mg)	200	200	200

Evaluation of Bilayer Tablets of labetalol

Pre Compression Parameters [14]:

The powder blend is evaluated for various precompression parameters such as bulk density, tapped density, angle of repose, hausner's ratio, compressibility index to determine the flow properties of the powdered blend.

Post compression parameters [14-16]:

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and *invitro*-dissolution characters.

1. Physical Appearance

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

2. Size & Shape

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

3. Weight variation test

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests. Twenty tablets were weighed

individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table 3: Limits for Tablet Weight variation test

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

4. Content Uniformity

Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 10mg of Labetalol HCl was transferred to 100ml volumetric flask containing 70ml of 7.4 pH phosphate buffer. It was shaken by mechanical means for 1hr then it was filtered through Whatman filter paper (no.1) and diluted to 100ml with 7.4 pH phosphate buffer. From this resulted solution 1ml was taken, diluted to 50ml with 7.4 pH phosphate buffer and absorbance was measured against blank at 302 nm.

5. Hardness /Crushing strength:

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The limit is toward the lower range in order to help early disintegration. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

6. Friability

Friction and shock are the forces that most often cause tablets to chip, cap or break. 20 tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

% friability = $(W_1-W_2) / W_1 X 100$

W_1 = Weight of tablets before test; W_2 = Weight of tablets after test

7. In vitro drug release study [17]

In vitro drug release was studied using USP II apparatus, with 900 ml of dissolution medium maintained at 37±1°C for 15 h, at 50 rpm. 0.1 N HCl (pH 1.2) was used as a dissolution medium for the first 2 h, followed by pH 7.4 Phosphate buffers for further 13 h. 5ml of sample was withdrawn in different time intervals, and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analyzed spectrophotometrically at 302 nm, and cumulative percent drug release was calculated. The study was performed in triplicate.

***Kinetic-model of* labetalol [18-20]**

In order to describe the DS release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models:

Zero order, first order, and Higuchi respectively.

$Qt = Q_0 + K_0 t$…….. (1)

where, Qt is the amount of drug released at time t; Q_0 the amount of drug in the solution at t = 0, (usually, Q_0= 0) and K_0 the zero order release constant.

$logQt = logQ\alpha + (K1 /2.303) t$…….. (2)

Qα being the total amount of drug in the matrix and K1 the first order kinetic constant.

$Qt = KH. t ½$……. (3)

where, KH is the Higuchi rate constant.

Further, to better characterize the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Krosmeyer and Peppas.

$Q (t-l) /Q\alpha = KK (t-l)n$……. (4)

where, Qt corresponds to the amount of drug released in time t, *l* is the lag time (*l* = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where $Q (t-l)/Q \alpha>0.6$, were only used. If n approaches to 0.5, the release mechanism can be Fickian. If n approaches to 1, the release mechanism can be zero order and on the other hand if $0.5<n<1$, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ‘‘best model’’ was the one with the highest coefficient of determination (r^2).

3. Results and Discussion

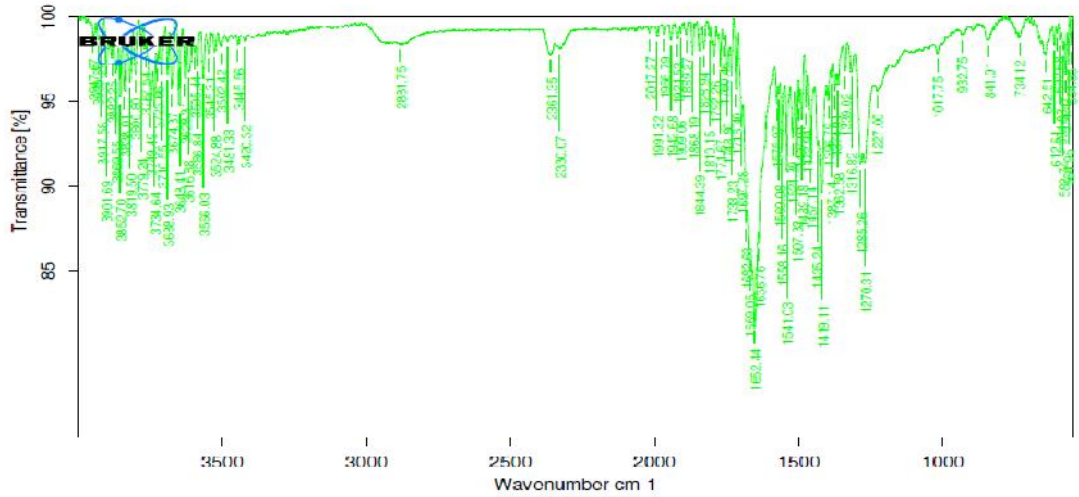

Figure 2: FT-IR of ludiflash

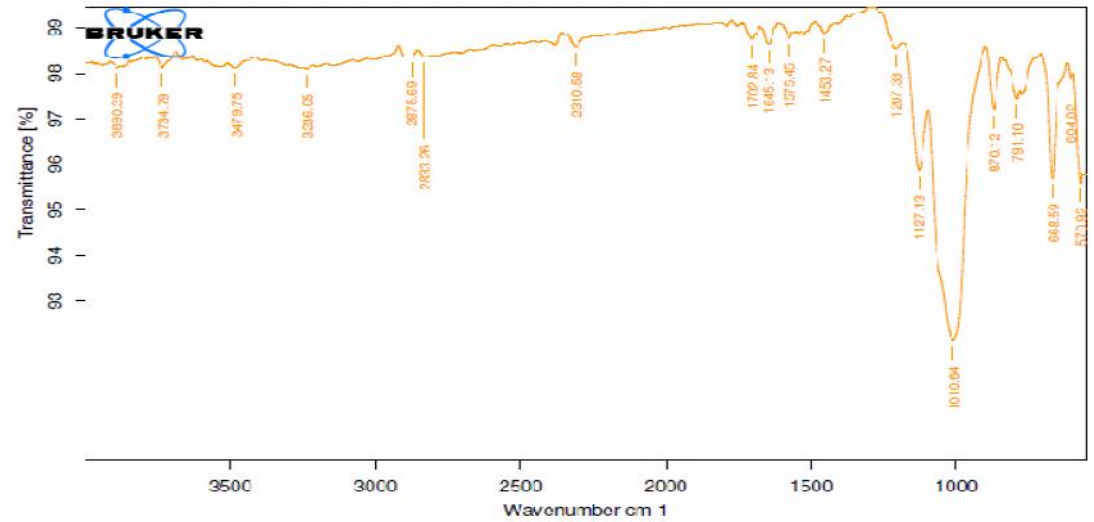

Figure 3: FT-IR of physical mixture of formula of immediate release layer

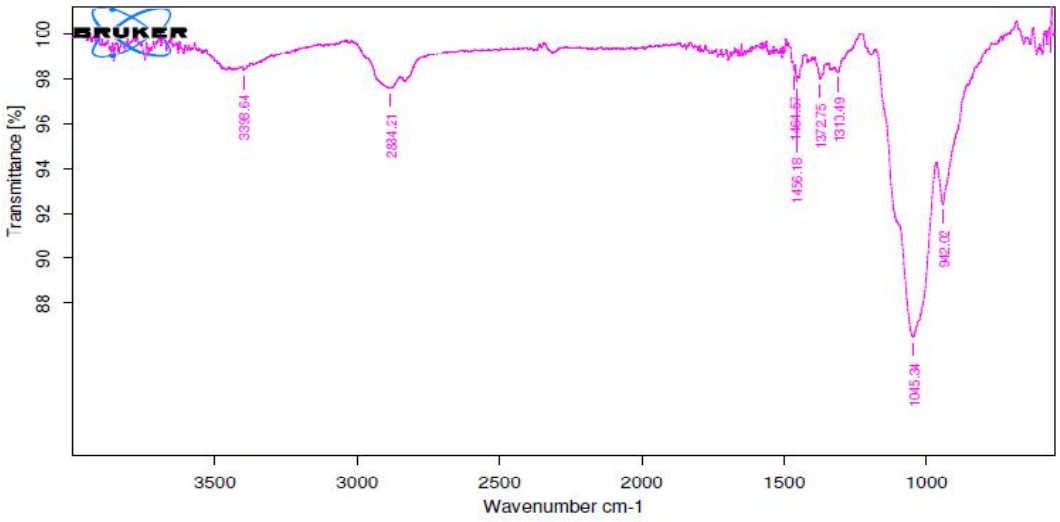

Figure 4: FT-IR of sodium alginate

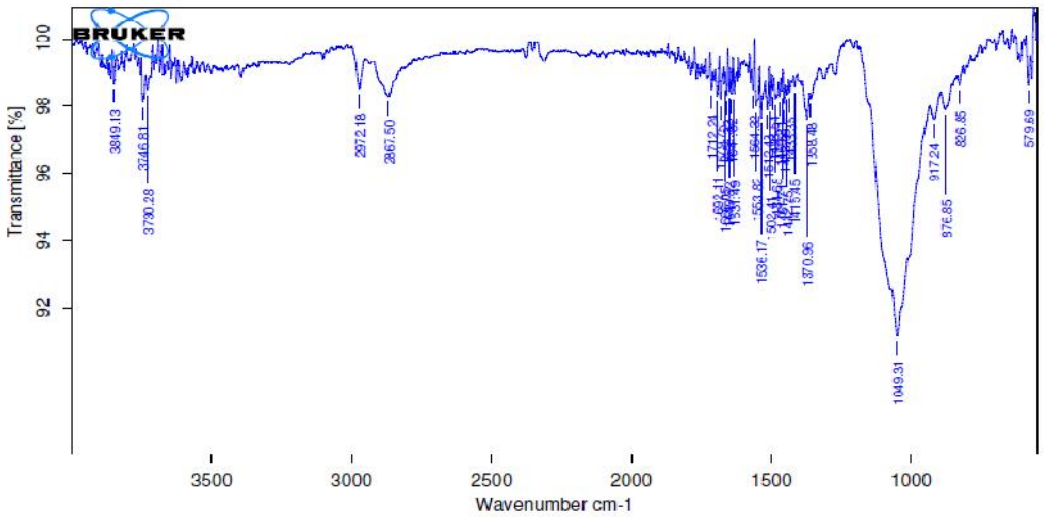

Figure 5: FT-IR of ethyl cellulose

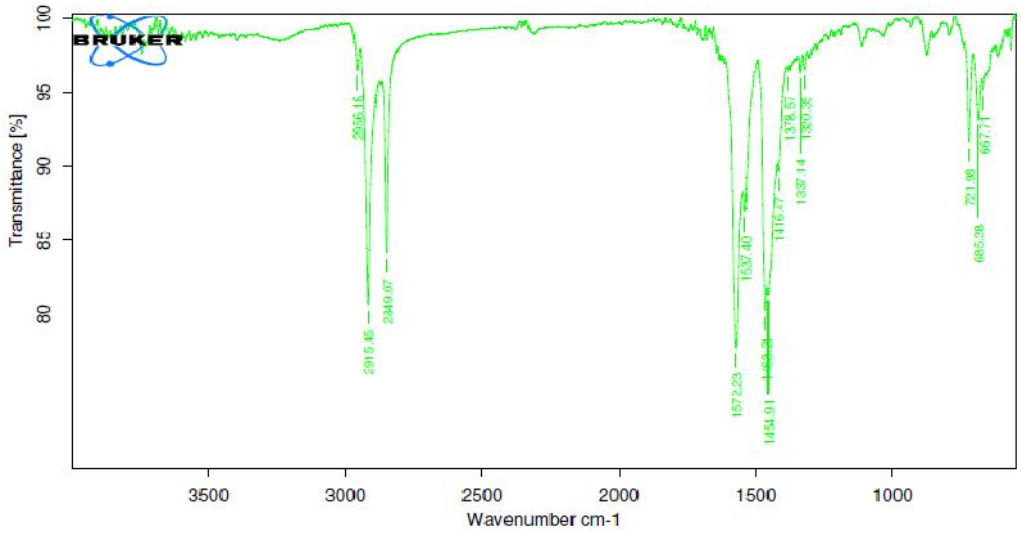

Figure 6: FT-IR of magnesium stearate

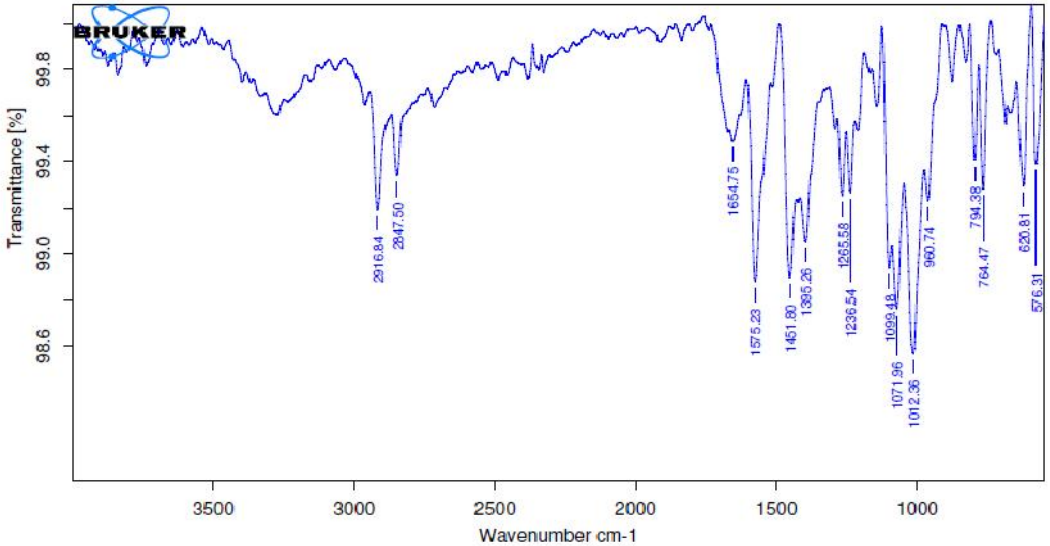

Figure 7: FT-IR of best formulation of sustained release formulation

Evaluation of precompression parameters:

Table 4: Precompression parameters for the blend

Parameter	Angle of repose (θ)	Bulk density (g/cc)	Tapped density (g/cc)	% Compressibility	Hausner's ratio
F1	27°55'	0.63	0.66	16.76	1.047
F2	29°39'	0.55	0.63	14.54	1.14
F3	23°31'	0.51	0.54	15.88	1.05
F4	28°81'	0.47	0.52	10.63	1.10
F5	28°65'	0.60	0.64	16.66	1.06
F6	26°74'	0.57	0.63	10.52	1.10
F7	28°39'	0.46	0.51	10.86	1.10
F8	21°81'	0.42	0.53	16.19	1.15
F9	24°81'	0.61	0.69	13.11	1.13

All formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the pharmacopeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table 5: Evaluation of Bilayered Tablets of Labetalol (F_1 to F_9)

Parameter	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability % w/w	Content uniformity %
F1	600±0.4	5.5±0.4	5.9±1.4	0.12±0.2	95.01±0.2
F2	599±0.3	5.6±0.4	4.4±1.2	0.16±0.23	96.4±0.4
F3	598±0.7	5.3±0.4	5.2±1.2	0.15±0.19	98.7±0.3
F4	600±0.1	5.6±0.4	5.5±0.9	0.15±0.26	98.8±0.2
F5	599±0.3	5.5±0.4	5.4±1.9	0.15±0.22	99.8±0.3
F6	600±0.2	5.5±0.3	5.1±1.7	0.12±0.1	99.19±0.2
F7	599±0.9	5.5±0.2	4.9±1.5	0.15±0.4	99.18±0.2
F8	600±0.8	5.5±0.1	5.3±1.6	0.10±0.5	99.88±0.2
F9	599±0.1	5.5±0.2	5.4±1.4	0.13±0.7	99.68±0. 2

Table 6: Results of Dissolution profile for Immediate Release layer of Bilayered Tablets of Labetalol (I-1 to I-3)

Time(min)	I-1	I-2	I-3
0	0	**0**	0
5	16.17	**26.92**	38.44
10	25.29	**43.13**	60.34
15	36.94	**56.50**	89.36
30	52.06	**77.81**	100
45	63.31	**88.78**	--
60	79.32	**99.87**	--

Table 7: Results of Dissolution profile for Sustained Release layer of Bilayered Tablets of Labetalol (F-1 to F-9)

Time	F1	F2	F3	F4	F5	F-6	F-7	F-8	F-9
0	0	0	0	**0**	0	0	0	0	0
1	48.17	56.82	46.44	**44.47**	53.11	41.87	42.24	48.91	37.80
2	59.29	68.93	53.11	**48.91**	59.66	49.78	46.94	50.89	43.23
4	67.94	91.41	65.47	**66.58**	82.51	61.39	61.88	77.82	60.90
6	79.06	99.81	82.14	**80.54**	90.92	73.37	73.25	91.41	69.67
8	89.31		89.43	**84.86**	100.18	79.67	78.69	99.69	73.25
10	99.32		100.06	**90.42**		84.61	83.63		78.69

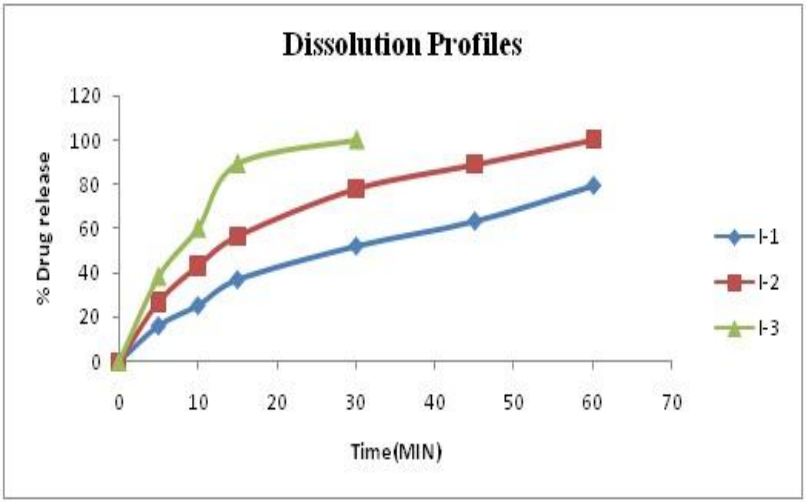

Figure 8: Dissolution Profiles of Formulations (I_1 to I_3)

Inference: we concluded that I-2 shows optimum results when compared with other two formulations.

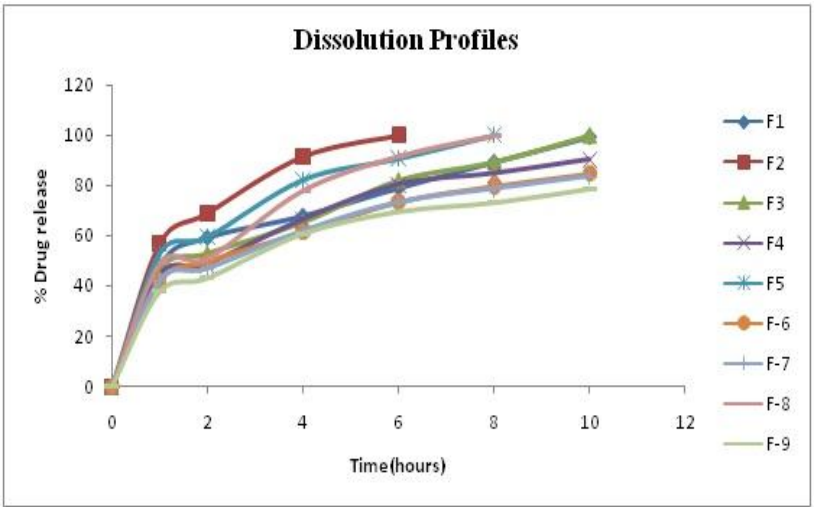

Figure 9: Dissolution Profiles of Formulations (F_1 to F_9)

Inference: we concluded that F4 shows optimum results when compared with other eight formulations.

Kinetic models of labetalol:

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using Higuchi equation.

Table 8: Kinetic model data

Formulation Code	Zero-order	First-order	Higuchi	kosermeyer-peppas	
	Regression Coefficient (r^2)	Regression Coefficient (r^2)	Regression coefficient (r^2)	Slope (n)	Regression coefficient (r^2)
F1	0.790	0.882	0.955	0.301	0.985
F2	0.718	0.004	0.931	1.361	0.328
F3	0.837	0.214	0.975	0.550	0.093
F4	**0.815**	**0.897**	**0.968**	**0.337**	**0.978**
F5	0.963	0.009	0.963	1.317	0.318
F6	0.819	0.953	0.968	0.320	0.991
F7	0.815	0.959	0.967	0.325	0.982
F8	0.805	0.212	0.963	0.546	0.089
F9	0.800	0.958	0.964	0.337	0.984

The release data were analyzed as per zero order, first order, Higuchi and Korsmeyer & Peppas models. The correlation coefficient (r^2) values in the analysis of release data as previous models are mentioned. Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from bilayered tablets formulated followed first order kinetics. The correlation coefficient (r^2) values were higher in first order model when compared to zero order models.

4. Conclusion

The main objective to design the bilayer tablets for labetalol has been achieved. Systematic studies were conducted using different concentration of rate releasing polymers like Sodium alginate, Carbopol and Ethyl cellulose for extending the drug release up to 10 hours and immediate layer prepared by using Ludiflash as a superdisintegrant. Preformulation studies have shown that the powder has good flow properties. Post compression evaluations for the prepared formulations have shown acceptable results. The weight variation of all formulations was found to be in the range of 598 ± 0.7 to 600 ± 0.8mg within range of 5% difference. The thickness was found to in the range of 5.3 ± 0.4 to 5.5 ± 0.4 mm. The hardness of tablets was found to be in the range of 4.9 ± 0.25 to 5 .5 ± 0.5 kg/cm^2. The loss of percentage of weight in friability was found to be 0.10% ± 0.5 to 0.16 ± 0.2 which is less than 1% which indicates tablets has good mechanical resistance. The release data were analyzed as per zero order, first order, Higuchi and Krosmeyer & Peppas models. The correlation coefficient (r^2) values were higher in first order model when compared to zero order models. Finally it was concluded that among all the formulations (F1-F9), it was observed that formulation-4 has shown better dissolution profile. So Formulation-4 was found to be the best formulation when compared with other prepared formulations as it showed the 90% of drug release for 10hrs.

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