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FORMULATION DESIGN AND EVALUATION OF LORATADINE AND EXTENDED RELEASE PHENYLEPHRINE HYDROCHORIDE TABLETS

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ABSTRACT

In the present work Loratadine and Phenylephrine Bilayer tablets were prepared by compressing Loratadine layer as direct compressible layer which is an immediate release layer and Phenylephrine hydrochloride by wet granulation method as sustained release layer which are compressed using Bilayer tableting machine. The tablets were evaluated for thickness, hardness, friability, and weight variation. In vitro dissolution studies were performed using USP apparatus –II (paddle method) in 900ml of 0.1N HCl at 50 rpm. The physical properties of the tablets did not show any significant variations and were found to have good physical integrity. Tablets with Loratadine layer containing Lactose DCL21, PG Starch showed better release and the Phenylephrine Hydrochloride layer containing DCP(21.6%), Natrosol (5%), HPMC K15M(10%) emerged as the overall best formulation based on the in-vitro drug release studies. Short term stability studies on the formulations indicated that there are no significant changes in drug content and drug release profile. Among all the formulations Trial 6 emerged as the overall best formulation found to be promising

KEY WORDS: Loratadine, Phenylephrine Hydrochloride, DCP (Dicalcium Phosphate), HPMC (Hydroxy Propyl Methyl Cellulose), PG Starch (Pregelatinized Starch), Lactose anhydrous (Directly compressible Lactose).

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INTRODUCTION

The millennium has dawned. Development of newer drugs and medicines will be the goal of scientists across the world. In order to achieve satisfying results, a drug has to be carefully formulated in proper dosage form. It is an established fact that the conventional immediate release drug delivery systems when taken frequently in a day can maintain drug concentration levels in therapeutically effective range. However, this results in significant fluctuations in plasma drug levels. Recently, several technical advancements have led to the development of various Novel Drug Delivery Systems (NDDS) that could revolutionize method of drug delivery and hence could provide definite therapeutic benefits. Till date, man has found remedies for almost all diseases; but still research is going on in order to improve the existing therapy. To bring a new drug molecule, it involves a lot more than investment of time and money. In the pre GATT era, if the patents of drug molecules or formulations were expiring, the new way of patenting the drug is to use "Novel Drug Delivery Systems" i.e. NDDS with improved bio-availability. To formulate a drug or to re-formulate it in a form of NDDS is not a herculean task if one goes methodically and skillfully. This is where the formulation development studies play an important role. An oral drug delivery system providing a uniform drug delivery can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn't take into account the site specific absorption rates within the gastrointestinal tract, therefore there is need for developing delivery system that release the drug at the right time, at the specific site and with the desired rate. The important objective for the development of sustained release dosage forms systems is to furnish an extended duration of action and thus assure greater patient compliance. Pharmacokinetically, it is often desirable to administer a single dose of medication, which release the active ingredient over an extended period of time rather than to administer a number of single doses at regular intervals. Literature also substantiates the patient preference of extended release tablets, as compared to immediate release tablets for the relief of nasal congestion[27] Loratadine is a piperdine derivative and is a long acting selective peripheral H1 antagonist which lacks CNS depressant effects used in the treatment of allergic skin disorder, specially atopic dermatitis and urticaria, allergic rhinitis, acute coryza, ocular allergies at the dose of 10 mg once a day in adult and 5 mg in 2-12 years children.[28] Phenylephrine is used as a decongestant oral medicine and is the most common OTC drug. Phenylephrine's effectiveness as a decongestant from its vasoconstriction of nasal blood vessels, thereby decreasing blood flow to the sinusoidal vessels, leading to decreased mucosal edema.

MATERIALS AND METHODS

Loratadine immediate release layer

Loratadine (Zydus Cadila), Anhydrous Lactose (Pharmatose DCL 21) from DMV, Microcrystalline cellulose (Avicel PH102) from FMC Biopolymer, Pregelatinized Starch (Starch 1500) from Colorcon, Magnesium stearate from Ferro Corporation.

Phenylephrine Hydrochloride Extended Release Layer

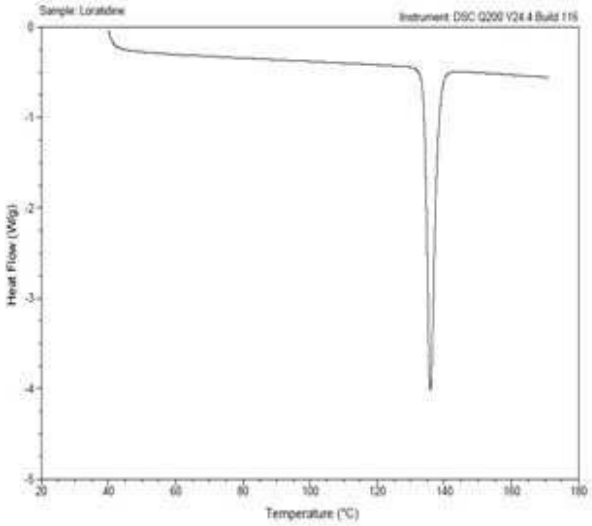
Phenylephrine Hydrochloride (Divi's Lab), Microcrystalline cellulose (Avicel PH 101) from FMC Biopolymer, Dicalcium Phosphate dihydrate (Calipharm D) from Innophose, Hydroxy propyl methylcellulose (Methocel K15M) from Colorcon, Hydroxyethyl cellulose Natrosol 250L from Ashland, Iron oxide red, Colloidal silicon dioxide (Aerosil 200 pharma) from Evonik, Stearic acid (Speziol L2SM Pharma) from Cognis and Opadry clear YS-IR-7006 from Colorcon.

EXPRERIMENTAL

Pre-formulation studies

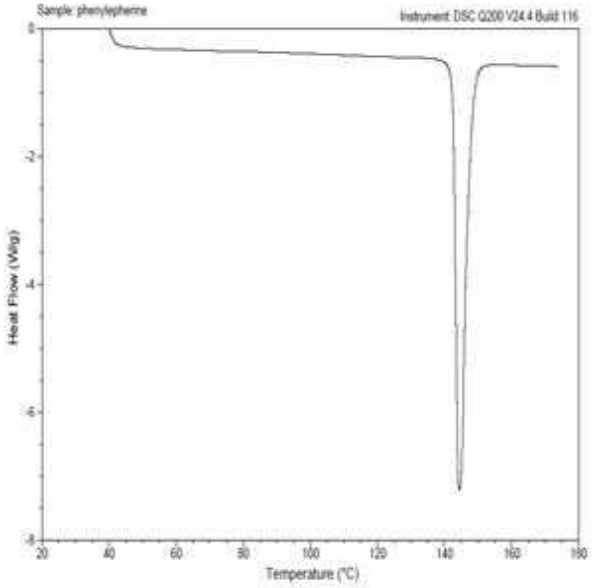
The drug along with the excipients was subjected to pre-formulation studied by mixing the drug and the excipients in different ratios of their composition to study the compatibility of drug with excipients. The mixture was mixed and

packed in glass vial and closed with rubber closure and sealed with Aluminum cap and subjected to accelerated condition at 40°C and 75% RH for 1 month and observed for any physical changes like color and appearance etc. The initial samples were subjected to differential scanning calorimeter and the results obtained showed no significant shift in the melting point of these drugs thereby ruling out incompatibility of these drugs with excipients.



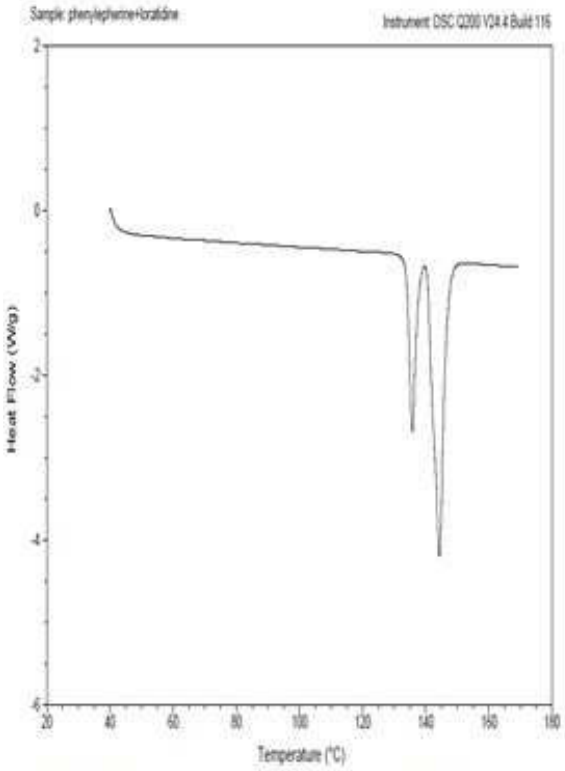
DSC Thermogram of Loratidine

Figure1



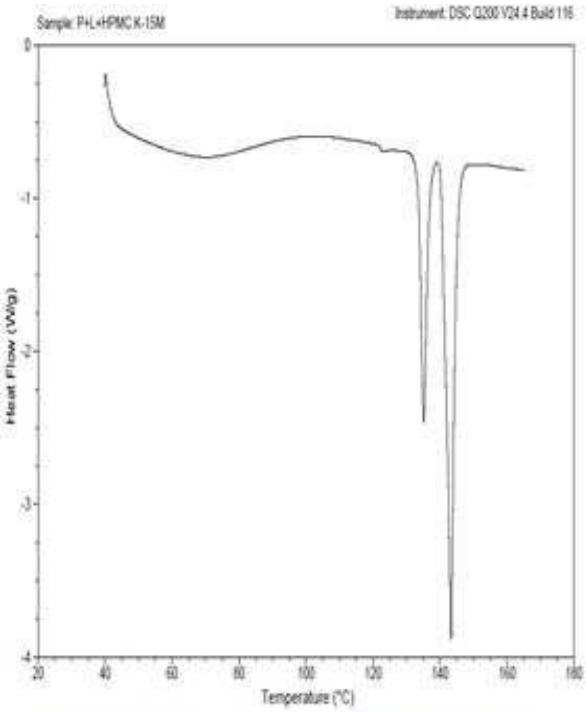
DSC thermogram of phenyl epherine

Figure 2



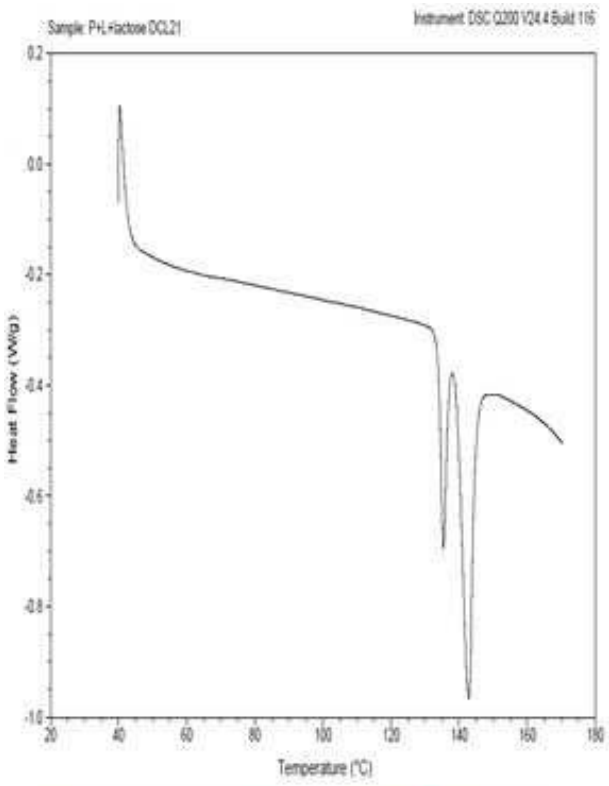
DSC thermogram of phenyl epherine + loratidine

Figure 3



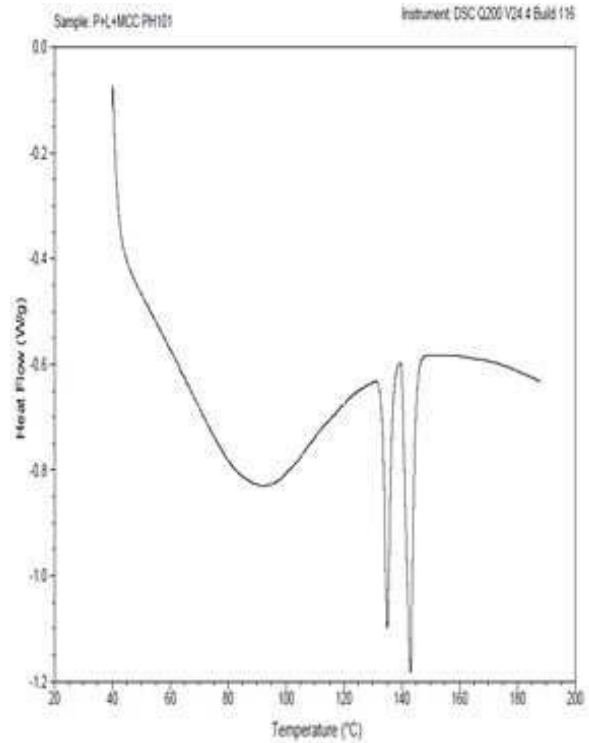
DSC thermogram of P+L+HPMC-K-15M

Figure 4



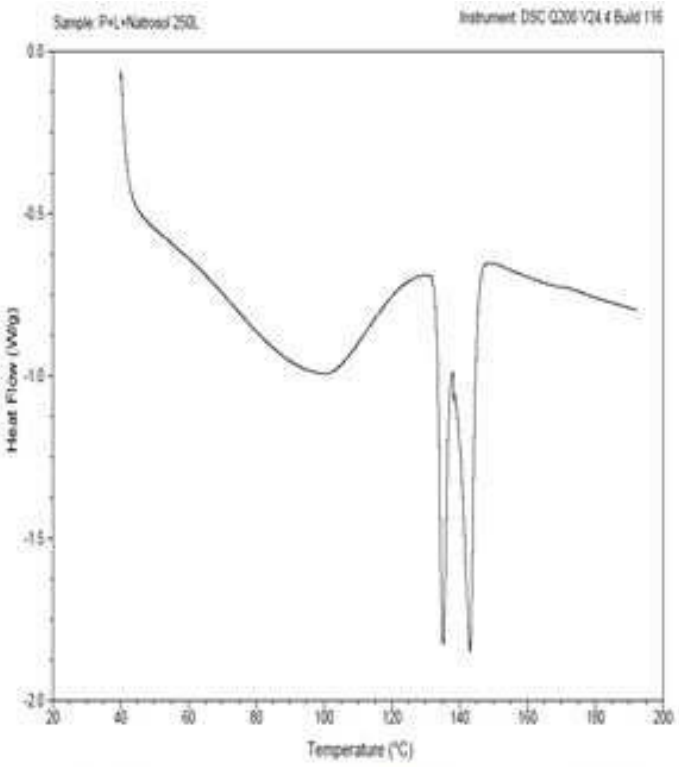
DSC thermogram of P+L+lactose DCL21

Figure 5



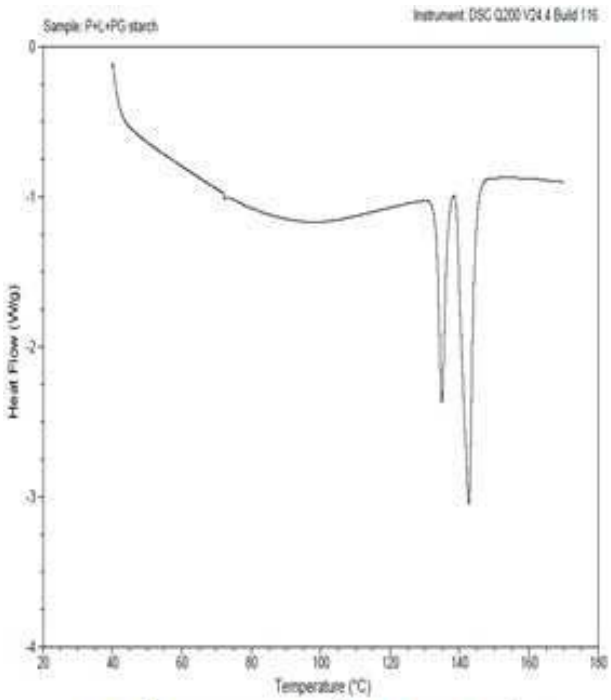
DSC thermogram of P+L+MCC pH 101

Figure 6



DSC Thermogram of P+L+Natrosol 250L

Figure 7



DSC Thermogram of P+L+PG Starch

Figure 8

Table 1
Unit Composition

Immediate release layer

Ingredients (mg/tab)	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6
Loratadine	10.0	10.0	10.0	10.0	10.0	10.0
Lactose anhydrous	99.0	85.0	80.0	90.0	95.0	90.0
Avicel PH102	76.0	90.0	95.0	87.0	80.0	85.0
Pre-gelatinized Starch	12.0	12.0	12.0	10.0	12.0	12.0
Magnesium Stearate	3.0	3.0	3.0	3.0	3.0	3.0
Total weight	200.0	200.0	200.0	200.0	200.0	200.0
Sustained Release Layer:						
Phenylephrine HCl	30.0	30.0	30.0	30.0	30.0	30.0
Avicel PH 101	148.6	152.6	157.6	153.6	158.6	163.6
Dicalcium Phosphate	65.0	68.0	66.0	70.0	70.0	65.0
HPMC K15M	15.0	15.0	12.0	12.0	15.0	22.0
Natrosol	15.0	15.0	15.0	15.0	10.0	-
Extra-granular(binder addition)						
HPMC K15M	15.0	8.0	8.0	8.0	-	-
Natrosol 250L	-	-	-	-	5.0	8.0
Iron oxide red	0.4	0.4	0.4	0.4	0.4	0.4
Purified Water	q.s	q.s	q.s	q.s	q.s	q.s
Pre-lubrication						
Aerosil-200	2.0	2.0	2.0	2.0	2.0	2.0
Lubrication						
Stearic acid	9.0	9.0	9.0	9.0	9.0	9.0
Total Weight (mg)	300.0	300.0	300.0	300.0	300.0	300.0
Coating						
Opadry clear YS-IR-7006	10.0	10.0	10.0	10.0	10.0	10.0
Purified water	q.s	q.s	q.s	q.s	q.s	q.s
Total Weight (mg)	310.0	310.0	310.0	310.0	310.0	310.0

Preparation of immediate release layer of Loratadine

All the ingredients were weighed according to the formula. The Loratadine, lactose, Avicel Ph102, and PG Starch were passed through sieve#30 and blended in an octagonal blender(Garson's Ltd)for 20 minutes, t hen Magnesium Stearate was passed through sieve #60 and lubrication was done for the blend for five minutes.

Preparation of Phenylephrine HCl Sustained Release Layer

Phenylephrine HCl Sustained Release Layer was prepared by wet granulation method according to the formula given in the table 1. All the intra-granular ingredients were passed through sieve#30 separately, weighed and mixed in geometrical order. Then HPMC K15 or Natrosol 250L was dispersed in required amount of purified water along with iron oxide red and wet granulation was done. The granules obtained were dried until the required LOD was reached. Then the granules were passed through sieve #20 and pre-lubricated with Aerosil which was passed through sieve#40 and blended for 10mins in the blender. Granules were lubricated for 5 minutes with magnesium stearate which was passed through sieve#60. Then the tablets were compressed using caplet shape punches on 10 station bilayer tablet compression machine Mini Press II MTDL (Karnavati).

Blend Parameters

Bulk density[07]

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. It is of great importance when one considers the size of a high – dose tablet or the homogeneity of a low dose formulation in which there are large differences in drug and excipient densities. In addition to bulk density, it is frequently desirable to know the true density of a powder for computation of void volume or porosity of packed powder beds. An accurately

weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. The graduated cylinder was closed with a lid and placed into the tap density testing apparatus (USP). The density apparatus was set for 500 taps after 750 taps and the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulae.

$$\textbf{Bulk density} = \frac{Weight\ of\ powder\ (g)}{Bulk\ volume\ (mL)}$$

Tapped density

Tapped densities the drug was determined by pouring gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. In USP TAP DENSITY TESTER, Tap density is measured in 500taps, 750 taps & 1250taps with drop/time-299-302. The tapped density was measured for 500 tapings and 750 tapings giving densities (V_a), and (V_b) with a drop time of 299 to 302 tapings per minute. If the percentage difference between the 'V_a' and 'V_b' exceed about 2% than 'V_c' is measured by 1250 tapings. Either 'V_b' or 'V_c' is taken as the final tapped density. The volume occupied by the sample after tapings were recorded and the tapped density was calculated by the formula below

$$\textbf{Tapped density} = \frac{\textbf{weight of powder (g)}}{\textbf{Tapped volume (mL)}}$$

Carr's compressibility index

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. High density powders tend to possess free flowing properties. A useful empirical guide is given by the Carr's index or compressibility index calculated from bulk density and tapped density. Carr's index of each formulation was calculated according to equation given below

$$Carr's\ index = \frac{Tapped\ density - Bulk\ density}{Tapped\ density}\ X\ 100$$

Hausner's ratio

Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value of indicates better flow and vice versa. Hausner's Ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density. It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to inter-particle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Table 2
Flow properties corresponding to compressibility index as per USP31- NF26

% Compressibility	Flow description
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Extremely poor

Table 3
Specifications of Hausner's ratio

HAUSNER RATIO	TYPE OF FLOW
Less than 1.25	Good Flow (20% Carr's index)
1.25 – 1.5	Moderate (33% Carr's index) (adding glidant normally improves flow)
Greater than 1.5	Poor Flow (Glidant has marginal effect)

Particle size distribution

Size, shape & surface morphology of drug particles affects the flow, formulation homogeneity, dissolution & chemical reactivity of drugs Particle size of drugs may affect formulation and product efficacy. Certain physical and chemical properties of drug substances are affected by the particle size distribution including: drug dissolution rate, bioavailability, content uniformity, taste, texture, color, stability, flow characteristics, and sedimentation rates. Particle size also has effect on the drug's absorption. Satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation. Particle size distribution was carried out in "Electromagnetic Sieve Shaker" (Electrolab EMS-8)

Table 4
Blend parameters of Loratadine

S.No	Parameter	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6
1	Bulk density	0.41	0.36	0.42	0.41	0.44	0.42
2	Tapped density	0.46	0.40	0.47	0.47	0.48	0.46
3	Compressibility index	10.86	10	8.51	12.7	8.33	8.69
4	Hausner's ratio	1.121	1.11	1.112	1.14	1.09	1.09

Table 5
Blend parameters of Phenylephrine HCl

S.No	Parameter	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6
1	Bulk density	0.61	0.64	0.67	0.62	0.59	0.68
2	Tapped density	0.72	0.73	0.74	0.72	0.66	0.76
3	Compressibility index	15.2	12..3	9.45	13.88	10.60	10.5
4	Hausner's ratio	1.18	1.14	1.10	1.16	0.94	1.11

Compression of tablet

The tablets were compressed using Cadmach Bilayer compression machine. The extended release layer of Phenylephrine HCl was compressed first followed by immediate release layer of Loratadine. Coating The Bilayer tablets were film coated with Opadry clear YS-IR-7006 supplied by Colorcon up to weight gain of 10mg in automatic coating machine (Neocota). The film coating of Bilayer tablet provided better appeal and gloss to the tablet increasing the aesthetic appearance of the tablet.

Evaluation of Tablets[11]

The tablets were selected at random and assessed individually using an electronic balance (Sartorius). The individual weights were compared with the average weight for the determination of weight variation. Tablets were also evaluated for the hardness using hardness tester (Dr.Schleuniger), friability using a Roche friability apparatus (Electrolab, India) and thickness using digital Vernier calipers.

In vitro drug release study

In vitro dissolution of the formulated Bilayer tablets were studied using USP Type II Apparatus (Electrolab) at 50rpm using 900ml of 0.1N HCl or de-ionized water at 37±0.5°c as dissolution media. Aliquots of dissolution medium (10ml) were withdrawn at specific intervals of time and analyzed for drug content by measuring absorbance at 283nm for Loratadine and at 214 nm for Phenylephrine HCl. Cumulative percentage drug release was calculated and plotted again st time. The release profile was found satisfactory with trial number 6, which was showed the best trial. Refer Tables 7, 8, 9, 10 and figure numbers 9,10,11,12..

RESULTS AND DISCUSSION

Table 6
Evaluation of Physical properties of Bilayer Tablet

Formulation	Thickness(mm)±5 SD	Hardness(N)±3SD	% Friability±2SD
Trial 1	5.24±0.15	94±8.48	0.25±0.05
Trial 2	5.23±0.20	94±12.36	0.32±0.04
Trial 3	5.17±0.16	97±4.74	0.2±0.08
Trial 4	5.22±0.28	94±9.48	0.35±0.07
Trial 5	4.86±0.14	107±4.74	0.38±0.06
Trial 6	4.95±0.22	104±8.74	0.31±.004

Loratadine and Phenylephrine HCl Bilayer tablets were prepared by Loratadine as immediate release layer and Phenylephrine HCl layer as sustained release. Loratadine immediate release layer was prepared by using Lactose DCL21, Avicel Ph102 as diluent, PG starch as binding agent and magnesium Stearate as lubricant. Then the Phenylephrine HCl sustained release layer was prepared by using Dicalcium phosphate, MCC 101 as diluent, HPMC K15M, Natrosol, Iron oxide red, Aerosil, Stearic acid as lubricant. A total of six formulations were designed. As the material was free flowing, there by the tablets obtained were of uniform weight with acceptable variation as per IP specifications i.e., below 7.5%. Hardness of the tablets were found to be about 94-107N. Friability below 0.38% was an indication of good mechanical resistance of tablets.

Table 7
Loratadine release profile in 0.1N HCl

Time(min)	Trial 1(%)	Trial 2 (%)	Trial 3(%)	Trial 4(%)	Trial 5(%)	Trial 6(%)
5	20.0±0.75	20.0±1.34	18.0±0.49	21.0±0.74	19.0±0.55	24.0±0.94
10	38.0±1.35	40.0±1.09	37.0±0.70	39.0±0.92	35.0±0.96	39.0±1.03
15	58.0±0.66	55.0±0.35	53.0±0.77	54.0±1.35	55.0±1.71	60.0±0.54
20	65.0±1.01	68.0±0.51	67.0±0.92	67.0±0.55	64.0±0.64	76.0±0.47
30	76.0±0.67	78.0±0.75	78.0±0.76	78.0±0.63	74.0±0.76	89.0±0.86
45	88.0±1.11	86.0±1.50	85.0±0.94	86.0±0.91	90.0±0.63	97.0±0.71

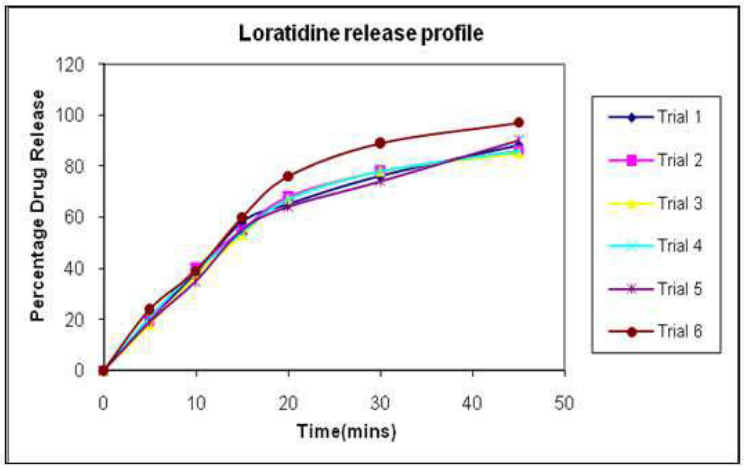


Figure 9
In vitro percentage drug release v/s time profile of Loratadine in 0.1N HCl.

Table 8
Phenylephrine HCl drug release profile in 0.1N HCl

Time(min)	Trial 1(%)	Trial 2(%)	Trial 3(%)	Trial 4(%)	Trial 5(%)	Trial 6(%)
5	0	0	0	1.0±0.25	3.0±0.37	4.0±0.45
10	1.0±0.44	0	1.0±0.26	3.0±1.0	5.0±0.22	6.0±0.50
15	3.0±0.28	2.0±0.42	3.0±0.22	6.0±0.27	8.0±0.42	7.0±0.31
20	4.0±0.40	3.0±0.40	5.0±0.33	7.0±0.42	11.0±0.49	9.0±0.30
30	5.0±0.15	5.0±0.19	7.0±0.38	8.0±0.50	13.0±0.62	10.0±0.47
45	7.0±0.58	7.0±0.29	8.0±0.22	10.0±0.58	15.0±0.62	15.0±0.50

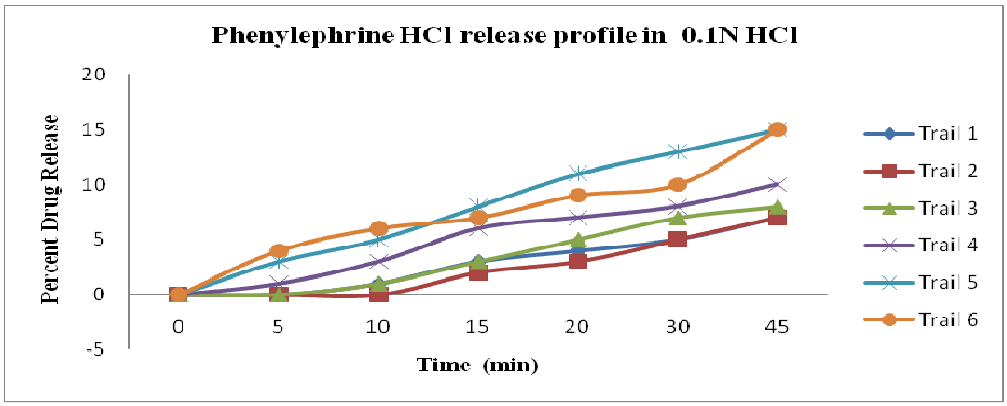


Figure 10
In vitro percentage drug release v/s time profile of Phenylephrine HCl in 0.1N HCl.

Table 9
Phenylephrine HCl Cumulative drug release profile in 0.1N HCl

Time(hrs)	Trial1(%)	Trial2(%)	Trial 3(%)	Trial 4(%)	Trial 5(%)	Trial 6(%)
1	10.0±0.73	10.0±0.73	11.0±0.43	12.0±0.39	16.0±0.40	16.0±0.40
2	15.0±0.36	16.0±0.74	17.0±0.39	18.0±1.00	25.0±0.49	20.0±0.72
3	31.0±0.78	31.0±0.78	31.0±0.78	33.0±0.56	31.0±0.59	33.0±0.69
4	43.0±0.46	43.0±0.46	51.0±0.59	54.0±0.49	52.0±0.67	54.0±0.51
5	54.0±0.41	52.0±0.49	66.0±0.47	70.0±0.63	68.0±0.50	71.0±0.52
6	67.0±0.52	65.0±0.44	79.0±0.52	82.0±0.50	81.0±0.51	84.0±0.58
7	74.0±0.47	72.0±0.44	85.0±0.38	87.0±0.53	85.0±0.31	91.0±0.58
8	81.0±0.76	83.0±0.64	93.0±0.55	95.0±0.44	94.0±0.59	98.0±0.76

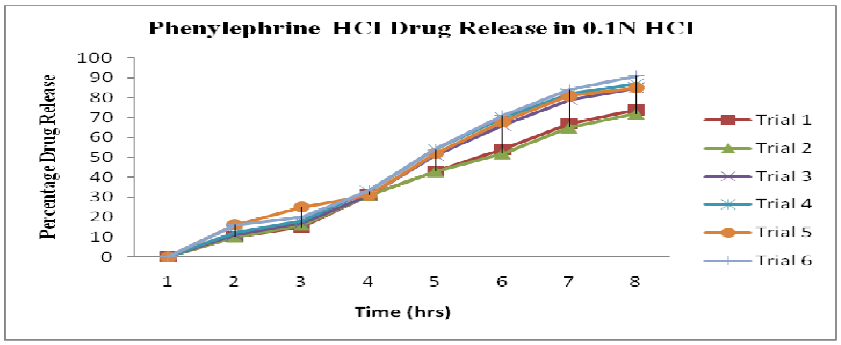


Figure 11
In vitro percentage cumulative drug release v/s time profile of Phenylephrine HCl in 0.1N HCl.

Table 10
Cumulative Percentage drug release of Phenylephrine HCl in De-ionized Water

Time(hrs)	Trial 1(%)	Trial 2(%)	Trial 3(%)	Trial 4(%)	Trial 5(%)	Trial 6(%)
1	15.0±0.74	10.0±0.73	14.0±0.60	18.0±0.45	27.0±0.45	22.0±0.54
2	23.0±0.31	16.0±0.40	24.0±0.49	28.0±1.00	35.0±0.59	30.0±0.83
3	31.0±0.91	31.0±0.78	31.0±0.78	33.0±0.56	44.0±0.52	46.0±0.56
4	40.0±0.72	43.0±0.46	43.0±0.59	41.0±0.72	56.0±0.64	58.0±0.54
5	48.0±0.50	52.0±0.49	51.0±0.47	54.0±0.49	69.0±0.78	69.0±0.78
6	56.0±0.44	65.0±0.44	66.0±0.52	70.0±0.63	78.0±0.62	82.0±0.50
7	62.0±0.52	72.0±0.44	79.0±0.35	82.0±0.50	85.0±0.46	89.0±0.51
8	70.0±0.64	83.0±0.64	85.0±0.35	87.0±0.53	94.0±0.93	96.0±0.77

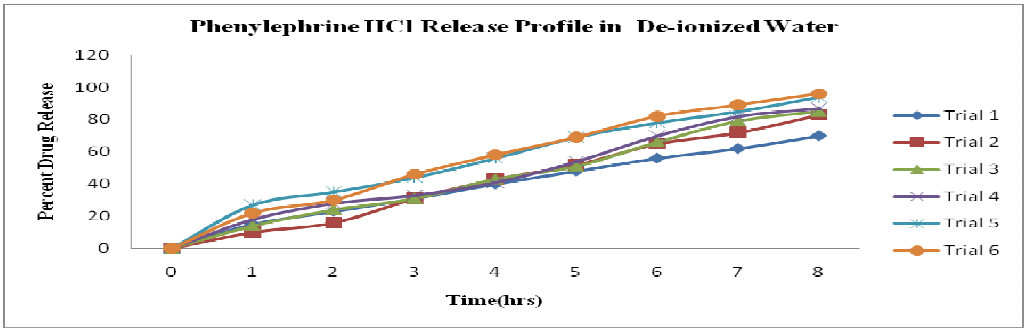


Figure 12
In vitro percentage drug release v/s time profile of Phenylephrine HCl in De-Ionized Water.

CONCLUSION

The Optimized formulation (Trial 6) has shown good release mechanism for both immediate release layer of Loratadine and extended release layer of Phenylephrine Hydrochloride. In this formulation of (Trial 6), Phenylephrine HCl has shown release effectively over a period of 8 hours. The tablets containing 10 mg of Loratadine as immediate release and 30 mg of Phenylephrine HCl as sustained release will definitely be a promising formulation in comparison to conventional release product. The formulation containing 22 mg of HPMC K15M and 8 mg of Natrosol 250L per tablet as a retarding polymer showed desirable invitro kinetic properties. The extended release profile of Phenylephrine HCl follows zero order kinetics by showing highest linearity and diffusion controlled mechanism following Higuchi model of drug release. This final formulation of Trial 6 provides an oral solid pharmaceutical combination comprising of non-sedative antihistamine like Loratadine and decongestant like Phenylephrine HCl in a bilayer tablet for prophylaxis and treatment of allergic rhinitis and improved patient compliance.

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