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Research Article

A Study on Bilayer Tablets for the Anti-Allergic Drug

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Abstract:

The bilayer tablet formulations used for each individual layer should be compressible (i.e., the capacity of a material to undergo a reduction in volume as a result of an applied pressure) and compactable (i.e., the capacity of a powder to be transformed into tablets with strength during densification) on their own, i.e., they should show satisfactory reduction in volume and form mechanically sound and coherent solid bodies. A bigger contact area exists between the layers as a result of the increased surface roughness, which improves interlayer adhesion. Bilayer tablet characterisation in early formulation development has certain advantages, including Bilayer tablet interfacial strength should be quantified, unusual or extreme properties of compacted layers should be identified, lot-to-lot consistency of the produced tablets should be ensured, rational formulation development strategy followed, material failure mechanisms during tablet manufacturing should be explained, and tablet-specific factors' effects should be understood.

Keywords: Tablets, bilayer tablet, physical mechanisms, drugs, Anti-Allergic, Allergic Rhinitis.

Introduction

An allergic inflammation of the nasal airways is known as allergic rhinitis. It happens when a person with a hypersensitive immune system inhales an allergen such as pollen, dust, or animal dander (particles of lost skin and hair). Seasonal or ongoing allergic rhinitis are both possible. Seasonal allergic rhinitis symptoms might appear in the spring, summer, or early fall. They are typically brought on by an allergic reaction to weed, grass, or tree pollen, or to mould spores in the air. All year long, those who have perennial allergic rhinitis endure symptoms. Sensitivity to household dust mites, animal dander, cockroaches, and/or mould spores is typically the reason. Rarely do underlying or concealed food allergies result in persistent nasal problems.

Solid oral dosage forms, such as controlled release (Conte et al., 1993; Nangia et al., 1995; Chidambaram et al., 1998; Abdul and Poddar, 2004), [1] osmotic pumps (Wong et al., 2002), and compression-coated tablets (i.e., tablet within a tablet), are still the most frequently used formulations for new and

existing complex-configuration dosage forms (Shivanand and Sprockel, 1998; Zerbe and Krumme, 2002; Ozeki et al., 2004). [2] In comparison to what is feasible with conventional measuring methodologies, the mechanical testing, characterisation, and monitoring techniques needed for controlled-drug delivery systems are often more demanding (Mashadi and Newton, 1987; York et al., 1990; Hancock et al., 2000). [3] Pharmaceutical medication product producers have recently focused their product development efforts on fixed dosage combos (FDCs) for treatments for HIV/AIDS, type 2 diabetes, hypertension, pain, and other conditions, to name a few. For example, multilayer tablets (Benkerrour et al., 2004), [4] compression coating, active coating (Desai et al., 2013; Charlton and Nicholson, 2010) [5] , bilayer floating tablets (Ranade et al., 2012; Lalita et al., 2013), [6] and buccal/mucoadhesive delivery systems are all used to deliver FDC products to patients (Park and Munday, 2002; Yedurkar et al., 2012). Among these strategies, the use of multilayer tablets for medication administration is growing in popularity, and the bilayer technology in particular has caught the attention of manufacturers for the creation of products for life cycle management (LCM). Bilayer tablets that are improperly made might split apart, which would be a very serious flaw since it would prevent a patient from obtaining one of the intended medicinal components. The distribution of residual stress in the tablet is thought to be a key factor in the inhomogeneity that results un the tablet's fracture and disintegration (Inman et al., 2007). Multilayered tablets frequently shatter as a consequence of an interfacial crack that propagates a finite distance within the tablet and is caused by residual strains in the tablet. After compaction, this causes capping and lamination, which may not always be immediately obvious (Hiestand et al., 1977; Abdul and Poddar, 2004; Inman et al., 2007) [7] . It is understood that when an interface fracture or crack occurs, the total elastic stiffness (Young's modulus) is decreased, making stacked tablets more brittle and prone to failure. As a result, even while the therapeutic (chemical/pharmaceutical) activities of multilayered tablets are essential, they also need to be strong enough mechanically and tough enough to withstand pressures associated with routine production, handling, packing, and shipping. Knowing the factors that affect a multilayered tablet's stress state and mechanical characteristics as well as creating specific methods for assessing those characteristics will help us comprehend how and why defects like capping, delamination, and cracking take place. Understanding and forecasting the mechanical strength of bilayer tablets, according to Wu and Sevilla (2009), has economic significance since bilayer tablet failures (delamination) caused by poor mechanical strength can result in significant financial losses. This review mainly focuses on the advantages and the main challenges associated with bilayer compaction technology including impact of material mechanical properties, characterization techniques for interface between layers, compression parameters, as well as features offered by commercial bilayer compression machines.

Key advantages of bilayer tablets

The bilayer technique has a number of benefits, according to the literature. This is a list of the key ones.

• A bilayer formulation containing two chemistically incompatible active pharmaceutical ingredients (APIs) is possible. An intermediary layer may occasionally be required to create physical separation between the two levels, depending on the severity of the mismatch between the two APIs (Li et al., 1995; Benkerrour et al., 2004; Efentakis and

Peponaki, 2008; Vaithiyalingam and Sayeed, 2010). [8]

• Drugs having extended release and instant release profiles, for example, can be administered as a single bilayer tablet together with another API that has a distinct release profile (Zerbe and Krumme, 2002; Nirmal et al., 2008; Shiyani et al., 2008).[9]

• Combining two or more APIs in a single bilayer tablet minimises the dosage unit load hence improves patient compliance (La Force et al., 2008; Charman and Charman, 2002; Bangalore et al., 2007).

• As most bilayer tablets are created as part of a Life Cycle Management programme, the bilayer technology offers the potential to extend a drug product's patent life (Veroma and Garg, 2001; Abebe et al., 2010). [9]

• The active ingredients' increased effectiveness as a result of their synergistic interaction (Serebruany et al., 2004; Benkerrour et al., 2004). [11]

Review of Literature:

According to Masahiro Niwa et al., [12] layer separation is a serious flaw in several bilayer tablets. Few researches have looked at its underlying causes despite how important it is for product quality. We compared terahertz pulsed imaging (TPI) to various analytical techniques, including tensile strength measures, friability testing, scanning electron microscopy (SEM), and X-ray computed tomography, to evaluate bilayer tablets with varied layer separation tendencies (XRCT). Friability testing was utilised to assess the risk of layer separation, and it was discovered that this risk was connected to the final compression pressure applied during the production of bilayer tablets. Layer separation-causing fissures between the component layers might be found by TPI without causing any damage. The interface index, a distinct value obtained from the time-domain terahertz signal, was used to measure the adhesion integrity of the interface. The interface index distinguished between seven batches of bilayer tablets with different interface quality and shown a strong association to the likelihood of layer separation. SEM and XRCT, on the other hand, may identify structural flaws but not batches with high or low layer separation risk. The link between compression pressure and interface quality was made clear by TPI. As a result, TPI can help with quality control by offering an accurate assessment of the layer separation risk and robust quality of bilayer tablet development with a better knowledge of layer separation.

According to Mohana Raghava Srivalli K et al2013 [13].'s paper, the BCS class II medication lamotrigine has a pH-dependent solubility. The lamotrigine bilayered gastric mucoadhesive tablets were created with the medication and controlled release polymers in the upper layer and the mucoadhesive polymers in the lower layer. The medication and the control release polymer (either HPMC K15M or polyox) were the main elements used for the top layer, whilst Carbopol 974P was primarily used in the bottom MA layer. The tablets were optimised for factors including tablet size, shape, ex vivo mucoadhesive characteristics, and unidirectional drug release using a 23 complete factorial design. The ideal size was determined to be 14 mm in diameter for oval tablets. When combined with a synergistic resin polymer, carbopol was able to obtain the highest mucoadhesive binding strength of 79.3 0.91 * 103dyn/cm2. Every formulation that was examined had a mucoadhesion time of more than 12 hours. The addition of methacrylic polymers in the bottom layer ensured unidirectional drug release from the bilayered tablets. By contrasting the dissolution outcomes of the paddle approach with those of a modified basket method, the unidirectional drug release was confirmed. The comparison of the findings of the dissolution was done using model independent similarity and

dissimilarity factor approaches. Using polyox and HPMC K15M, which showed t90% at 6th and 12th hours, respectively, controlled drug release patterns with zero order kinetics were established. For polyox, the "„n" value was 0.992, and with HPMC K15M, it was 0.946, suggesting a roughly case II transport. In addition to reporting the best tablet physical properties and greatest mucoadhesive strength, these two formulations demonstrated the potential for oral administration of lamotrigine as bilayered gastric mucoadhesive tablets by yielding the highest similarity factor values, 96.06 and 92.47, respectively, between the paddle and modified basket method dissolution release profiles.

Fridrun Podczeck (2011) [14] shown that delamination is a significant issue in the manufacture of multilayer tablets, but little is known about the underlying physical causes of this to happen. The purpose of this research was to establish an experimental technique to identify delamination tendencies in bilayered tablets and to investigate the theoretical effects of thermal stresses and strains that may arise during tableting. According to theoretical analysis, thermal stresses caused by heat buildup during powder compaction can cause delamination. This impact is amplified by the bigger the Young's modulus for the individual layer materials. Elastic mismatch raises the propensities for delamination. A model medicine (acetylsalicylic acid) and a model excipient (lactose monohydrate) have only minimal adhesion between their particle surfaces, according to experiments on mixed powder beams, which is a sign of low adhesion between comparable interfaces in stacked tablets. To calculate the far field stress intensity factor for bilayered compacts, a three-point bending test was created. Lactose monohydrate exhibited brittle behaviour under the test conditions, whereas acetylsalicylic acid displayed ductility. As a result, the far field stresses intensity factor values varied significantly depending on whether the excipient or the drug formed the downward facing layer during the bending test. As the medication created the downward-facing layer during the test, lactose monohydrate must do the same for bilayer tablets manufactured from these two powders since ductile phase toughening was seen. The far field stress intensity factor properly predicted the realistically observed delamination between the two material layers when used with the proper test configuration. As a result, the suggested fracture mechanics technique may be used as a formulation tool for bilayered tablets.

The purpose of this study, according to Fridrun Podczeck and Emad Al-Muti, was to ascertain the tensile strength of bilayered tablets manufactured from various grades of microcrystalline cellulose. While having the same chemical composition, these grades have vastly different particle sizes and mechanical characteristics, including Young's modulus of elasticity. Tablets were produced in the shape of beams of similar dimensions using uniaxial compression, and solid beams made from one material only were compared with bilayered beams made from various combinations of powders. It was found that in the production of layered tablets it is important for the purpose of quality assurance and control that the upper and lower layer of the compact can be identified. Otherwise, tensile strength measurements will result in large variability depending on which layer faces upwards during the test. Both particle size and Young‟s modulus of elasticity influenced the overall strength of layered tablets. If the material forming the lower layer was more elastic, then the beam strength was reduced due to tension introduced into the system, acting especially at the layer interface and potentially causing partial or complete

delamination. Larger differences in the particle size of the materials forming the tablet layers resulted in an overall reduced compact tensile strength.

Anuar MS and Briscoe BJ (2010) claimed that the feasibility of a bi-layered tablet as a candidate for a controlled release solid drug delivery device is diminished by its propensity to fail in the interface area after its first production in the compaction process. So, in order to enhance the overall mechanical integrity of the bi-layered tablet, a basic understanding of the regulating process that results in the weakening of the interfacial bonds within the bi-layered tablet is essential. This research has demonstrated that when the interface strength of the bi-layered tablet increases, the incidence of elastic relaxation in the interface area during the ejection stage of the compaction process reduces. This is thought to be caused by an increase in plastic bonding in the area between the faces. The tablet height elastic relaxation is influenced by the tablet diametrical elastic relaxation, and the tablet height expansion is impeded when the interface area expands diametrically. [15-16]

Objectives:

1. Preformulation research DSC analyses are used to investigate potential chemical interactions between the medicine and the excipient.
2. Making the Loratadine rapid release layer
3. Blend evaluation: Bulk density, Tapped density, Carr compressibility index, Hausner's ratio, and particle size distribution
4. Tablet evaluation: hardness, friability, and thickness
5. Making a coating of sustained-release phenylephrine HCl
6. Blend evaluation: Particle size distribution, bulk density, tapped density, Carr's compressibility index, and
7. Tablet evaluation: hardness, friability, and thickness
8. Using the USP Dissolution Apparatus 2, evaluate the in vitro release characteristics (paddle).
9. The improved formulation will undergo accelerated and intermediate stability tests in accordance with ICH Guidelines.

Evaluation of Bilayer Tablets (Gandhi PP et al., 2010) [17]

All the batches of tablets were evaluated for various physical parameters like thickness, weight variation, friability, hardness, drug content and dissolution as per pharmacopoeial standards.

Thickness (United State Pharmacopoeia-30, 2007)

For consistency in tablet size, the thickness of the tablet is crucial. Due to variations in the granulation's density, the pressure applied to the tablets, the speed of the compression machine, and other factors, tablet thickness can alter without affecting weight. Vernier callipers were used to measure and record the thickness of ten randomly chosen tablets.

Crushing strength (United State Pharmacopoeia-30, 2007)

Tablets need to be strong enough to endure mechanical manipulation during production, packing, and delivery. They also need to be resistant to friability. The strength of a tablet's crushing is often measured by hardness. Different properties of disintegration and dissolution are brought by by changes in hardness. Using a Schleuniger hardness tester, the tablet's crushing strength was ascertained.

Friability test (United State Pharmacopoeia-30, 2007)

The Roche Friabilator was used to assess the friability of tablets (Electrolab, Mumbai). The tablets were dropped from a height of six inches in each rotation while being

exposed to the combined effects of abrasions and shock in a Friabilator at a speed of 25 rpm. A friabilator was filled with a pre-weighed sample of tablets and rotated 100 times. A delicate muslin cloth was used to dust the tablets, and they were reweighed. The following formula determines the friability:

F= (1-Wo/W) X 100

Where, Wo is the weight of the tablets before the test and W is the weight of the tablet after the test.

%Friability = (Loss in weight / Initial weight) X 100

In Vitro Drug Release Study

The formed bilayer tablets' in vitro dissolution was investigated using a USP Type II Apparatus (Electrolab), a paddle stirrer at 50 rpm, and dissolution fluid of 900mL of 0.1N HCl at 370.5°c. At predetermined intervals, aliquots of the dissolving media (10 mL) were taken out and their drug concentration was determined by measuring absorbance at 214 nm for phenylephrine HCl and 283 nm for loratadine. Every time a portion was extracted, a new portion of the dissolving media was added. Drug release cumulative percentage was determined and shown against time. Short term stability tests (at 40oC/75%RH for a month) and in vitro drug release experiments (in 0.1N HCl as dissolving medium) were carried out for all trials. Trial 6 stood out among all the formulations as being the best one overall.

Stability Studies

The stability of a few loratadine and phenylephrine bilayer pills was also accelerated for up to three months at 400C and 75% RH. The goal of stability testing is to establish a retest period for the drug substance or a shelf life for the drug product as well as recommended storage conditions. Stability testing provides evidence on how the quality of a drug substance or drug product changes over time under the influence of various environmental factors, such as temperature, humidity, and light (ICH guideline 1996).s

Result and Discussion:

Evaluation of Bilayer Tablets

Moreover, tablets were assessed for hardness using a Schleuniger hardness tester, friability using an Electrolab, India, Roche friability instrument, and thickness using digital vernier callipers. It was discovered that tablets ranged in thickness from 4.85 to 5.26 mm. It was discovered that the hardness ranged from 90 to 110N for several formulations, demonstrating adequate mechanical strength. All of the formulations had friability levels below 0.8%, which is a sign of the tablet's strong mechanical resilience. The percentage of drugs was discovered to be between 96 and 105%, which is within safe levels. [18]

Table 1: The physical properties of Loratadine and Phenylephrine bilayer tablet

Formulation	Thickness(mm)	Hardness(N)	Friability (%)
Trial 1	5.23-5.26	90-110	0.65
Trial 2	5.20-5.25	90-110	0.75
Trial 3	5.15-5.18	90-110	0.62
Trial 4	5.21-5.24	90-110	0.72
Trial 5	4.85-4.88	90-110	0.77
Trial 6	4.9-5.0	90-110	0.75

In Vitro Drug Release Study

Loratadine release profile

Results of in vitro dissolving tests on formulation T-1 revealed that 20% of the medication was released after 5 minutes and 88% at 45 minutes. Results of dissolving experiments on formulations T-02 and T-03 revealed that 20% and 18% of Loratadine were released after 5 minutes and 86% and 85% were released after 45 minutes, respectively. According to dissolving experiments, formulations T-04, T-05, and T-06 released 21%, 19%, and 24 of the drug after 5 minutes and 86%, 90%, and 97% after 45 minutes . Figure 5 displays the results of the dissolving investigations. [19]

Table 2: In vitro Dissolution studies of Loratadine release profile

Time(mins)	Trial 1 (%)	Trial 2 (%)	Trial 3 (%)	Trial 4 (%)	Trial 5 (%)	Trial 6 (%)
5	20.0	20.0	18.0	21.0	19.0	24.0
10	38.0	40.0	37.0	39.0	35.0	39.0
15	58.0	55.0	53.0	54.0	55.0	60.0
20	65.0	68.0	67.0	67.0	64.0	76.0
30	76.0	78.0	78.0	78..0	74.0	89.0
45	88.0	86.0	85.0	86.0	90.0	97.0

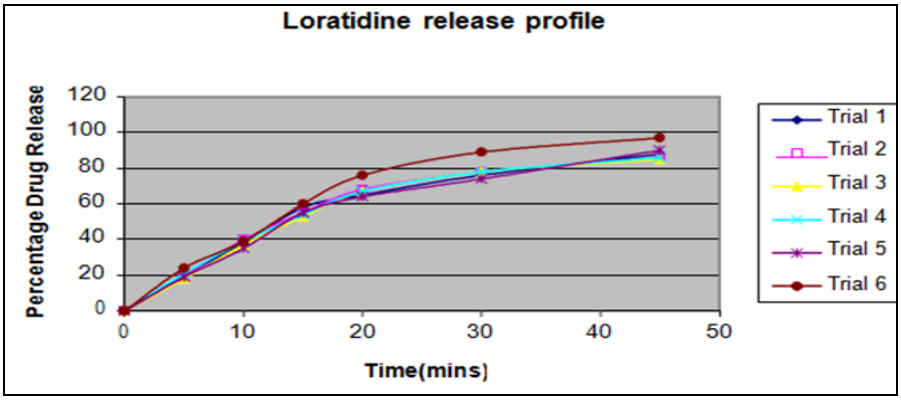

Figure 1: In vitro percentage drug release Vs time profile of Loratadine IR layer

Phenylephrine HCl drug release profile

The findings of in vitro dissolving tests on formulation T-1 revealed that at the end of 1 hour, 7% of phenylephrine HCl was released, and at the end of 8 hours, 81%. Results of dissolving investigations on formulations T-02 and T-03 revealed that 7% and 8% of phenylephrine HCl were released after one hour, while 83% and 93% were released after eight hours. Results of dissolving experiments on formulations T-04, T-05, and T-06 revealed that at the end of 1 hour, 8%, 8%, and 9% of phenylephrine HCl were released, and at the end of 8 hours, 95%, 94%, and 98% of the medication. In Figure 1, the dissolving studies are displayed.

Table 3: In vitro Dissolution studies of Phenylephrine HCl release profile

Time(hrs)	Trial 1 (%)	Trial 2 (%)	Trial 3 (%)	Trial 4 (%)	Trial 5 (%)	Trial 6 (%)
1	7.0	7.0	8.0	8.0	8.0	9.0
2	15.0	16.0	17.0	18.0	17.0	18.0
3	31.0	31.0	31.0	33.0	31.0	33.0
4	43.0	43.0	51.0	54.0	52.0	54.0
5	54.0	52.0	66.0	70.0	68.0	710
6	67.0	65.0	79.0	82.0	81.0	84.0
7	74.0	72.0	85.0	87.0	85.0	91.0
8	81.0	83.0	93.0	95.0	94.0	98.0

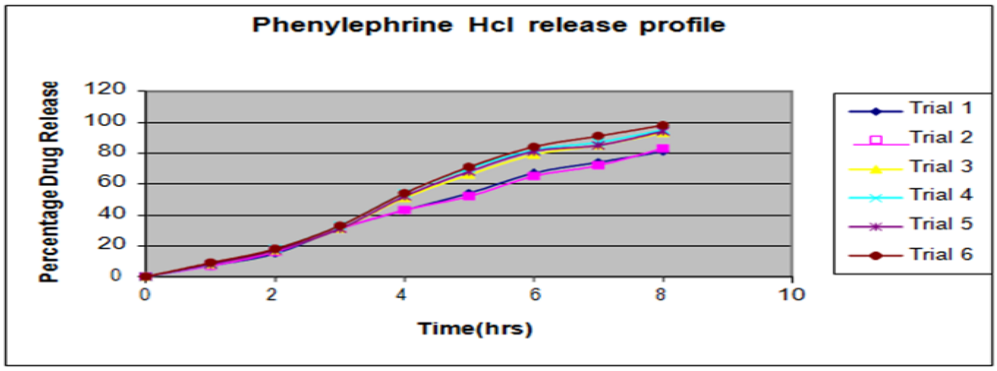

Figure 2: In vitro percentage drug release Vs time of Phenylephrine HCl SR layer

Both the Loratadine rapid release layer and the phenylephrine hydrochloride prolonged release layer have demonstrated satisfactory release mechanisms in the optimised formulation (Trial 6). Phenylephrine HCl has demonstrated an efficient 8-hour release in this formulation of (trial 6). In compared to typical release products, the tablets containing 30 mg of phenylephrine HCl as sustained release and 10 mg of loratadine as quick release will undoubtedly be a good composition. The formulation, which included 8 mg of Natrosol 250L and 22 mg of HPMC K15M as a retarding polymer per tablet, had favourable in vitro kinetic characteristics. The prolonged release profile of phenylephrine HCl exhibits the maximum linearity and diffusion regulated mechanism in accordance with the Higuchi model of drug release and follows zero order kinetics. This trial's sixth and final formulation offers a bilayer tablet containing a non-sedating antihistamine like Loratadine and a decongestant such phenylephrine HCl for the prevention and treatment of allergic rhinitis and to increase patient compliance.

Stability Studies

The ideal batch of Loratadine and Phenylephrine HCl Extended Tablets is packaged appropriately and kept in storage for the duration specified by ICH recommendations (40°C 2°C and 75 5%RH). After 6 months, the extended-release tablets of loratadine and phenyl ephedrine HCl were extracted and the percentage release data was compared to the initial release rate.

Table 41: Stability studies of Loratadine and phenylephrine HCl ER tablets

Stability data								
Product : Loratadine and extended release Phenylephrine hydrochloride tablets 10mg/ 30mg								
Pack: HDPE container (60cc with 1g silica bag)								
Batch no: Trial no 6								
Description	White and pink colored, bilayer, biconvex, capsule shaped, film coated tablet							
Test parameters	Limit (%w/w)	Initial	1 Month $40^0C/75\%RH$	2 Month $40^0C/75\%RH$	3 Month $40^0C/75\%RH$	6 Month $40^0C/75\%RH$	3 Month RT	6 Month RT
Description	As above	As above	As above	As above	As above	As above	As above	As above
Assay - Loratadine	95-105%	101.1	100.2	99.8	99.7	98.6	99.8	99.7
Assay- phenylephrine	95-105%	100.2	99.8	99.7	99.6	99.6	99.8	99.7
Loss on drying	NMT 4.0%	2.5	2.45	2.11	2.05	2.12	2.01	2.05
Dissolution	Loratidine immediate release layer							
Dissolution condition: 900ml, 0.1N HCl, 50 rpm, USP Type II	Time (min)	% Release	% Release	% Release	% Release	% Release	% Release	% Release
	0	0	0	0	0	0	0	0
	5	24.0±0.94	25.0±1.8	24.0±2.2	25.5±2.6	23.5±4.5	23.6±5.4	23.5±4.4
	10	39.0±1.03	44.0±0.7	45.1±0.8	44.2±1.2	41.2±3.5	37.4±4.1	35.4±3.8
	15	60.0±0.54	55.0±1.0	56.2±1.1	54.6±0.8	51.6±2.8	55.6±3.3	55.1±3.2
	20	76.0±0.47	62.0±1.9	63.3±0.8	63.1±0.9	60.4±2.4	73.1±1.8	79.2±2.5
	30	89.0±0.86	83.0±1.0	84.5±1.1	85.1±1.2	82.3±2.1	93.5±1.4	91.2±1.9
	45	97.0±0.71	96.0±0.6	95.3±0.8	93.2±0.8	90.1±1.5	96.5±0.5	95.5±1.1
Dissolution	Phenyl ephrine hydrochloride Sustained release layer							
Dissolution condition: 900ml, 0.1N HCl, 50 rpm, USP Type II	Time (hr)	% Release	% Release	% Release	% Release	% Release	% Release	% Release
	0	0	0	0	0	0	0	0
	1	16.0±0.4	23.0±8.5	21.1±5.6	22.4±4.5	20.6±4.5	22.5±3.8	22.5±3.8
	2	20.0±0.72	37.0±4.5	35.1±5.1	36.1±4.2	36.5±3.7	34.1±3.3	34.1±3.3
	3	33.0±0.69	48.0±3.4	46.5±2.5	45.6±7.6	44.2±3.3	46.1±2.4	46.1±2.4
	4	54.0±0.51	67.0±2.3	68.1±2.1	68.5±2.2	61.5±2.4	65.2±1.8	65.2±1.8
	5	71.0±0.52	70.0±0.9	74.5±1.2	72.5±1.5	71.5±2.1	72.6±0.9	72.6±0.9
	6	84.0±0.58	78.0±1.1	79.2±1.2	83.1±0.6	79.8±1.4	80.5±0.9	80.5±0.9
	7	91.0±0.58	92.0±1.1	93.6±0.5	92.5±0.8	86.5±1.1	89.3±0.7	89.3±0.7
	8	98.0±0.76	98.0±0.8	97.1±0.1	96.5±0.4	96.5±0.5	97.2±0.4	96.1±0.4

Figure 3: Loratadine and Phenylephrine Hydrochloride extended release Bilayer tablets [20]

Conclusion:

Using a Cadmach bilayer compression machine, the tablets were compressed. The quick release layer of Loratadine was squeezed after the prolonged release layer of phenylephrine HCl. With an automated coating machine, Opadry clear YS-IR-7006 from Colorcon was film coated onto the bilayer tablets up to a weight increase of 10mg per tablet (Neocota).

The bilayer tablet's film covering improved the tablet's attractiveness and gloss, enhancing its attractive look.

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