Formulation and Evaluation of Lisinopril Double Layer Tablet

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Abstract

Lisinopril is an antihypertensive drug that is primarily used in the treatment of hypertension, congestive heart failure, heart attacks and also in preventing renal and retinal complication of diabetes that acts by inhibiting angiotension converting enzyme (ACE). The present investigation deals with the formulation of lisinopril double layer tablet containing 100 mg fast release layer and 100 mg sustained release layer to be formulated using wet granulation method.

Twelve formulations are prepared for bilayered tablets; 6 formulas for fast release layer study (FF1 to FF6) and another 6 formulas for the sustained release layer study. Friability of all formulation was less than 1%, which indicates the tablets had good mechanical resistance. Drug content was found to be uniform in all formulas. The tablet thickness was found to be 5.12 to 5.31 mm. Acceptable weight variation and content uniformity. Hardness was low for fast release lisinopril layer formulas FF1 to FF6, while it was high for formulas used to study the sustained release layer (SF1 to SF6). On the other hand disintegration time was short for formulas containing super disintegrant as crospovidone 15, and 10 seconds, croscarmelose 27, and 24 seconds and sodium starch glycolate 24, and 19 seconds and the shortest time for disintegration was for crospovidone containing formulas (FF1, and FF4); 15, and 10 seconds respectively for fast release layer study with no disintegration for the formulas used to study the sustained release of lisinopril. At the same time the release study for formulas containing crospovidone was within 20 minutes, while formulas containing HPMC K100 was 12 hours release. To be concluded that double layer tablets were attempted to be prepared for controlled drug delivery. The first layer of lisinopril provides the initial drug release while the second layer provides sustained release of lisinopril for increase patient compliance and decrease frequency of dosing for more control of hyper tension.

Keywords: Lisinopril, Bi-layered tablets, Wet granulation process.

تصييغ و تقييم اقراص اللايسينوبريل ثنائية الطبقة

شيماء نزار عبدالحميد صالح

الملخص

اللايسينوبريل هو دواء يستعمل اولا في معالجة ارتفاع ضغط الدم، عجز القلب ، و النوبات القلبية و ايضا في منع التعقيد الكلوي و الشبكي من مرض السكر. يعمل على منع الانزيم المحول للانجيوتينسين. الدراسة الحالية تعمل على تصييغ اقراص اللايسينوبريل ثنائية الطبقة الحاوية على 100 ملغم في الطبقة سريعة التحرر و 100 ملغم في الطبقة ثابتة التحرر مصاغة بطريقة التحبيب الرطبة.تم تحضير 12 صيغة دوائية للاقراص مضاعفة الطبقة 6 صيغ دوائية لدراسة طبقة التحرر السريع و ست صيغ دوائية اخرى لدراسة طبقة التحرر البطئ. هشاشة كل الصيغ كانت اقل من

1% مما يشير الى ان الاقراص لديها مقاومة ميكانيكية جيدة كما وجد ان محتوى الدواء متقارب في جميع الصيغ الدوائية. سمك الاقراص كان بحدود 5و12-5و31 مليمتر. ايضا كان اختلاف الوزن مقبول في جميع الصيغ الدوائية المحضرة.كما ان صلابة الحبة كانت قليلة للاقراص ذات الطبقة سريعة التحرر1-6 و عالية للاقراص بطيئة التحرر من الناحية الاخرى كان وقت التفكك قصيرا للصيغ التي تحتوي على مفتت سريع كما في الكروس بوفيدون 10و 15 كذلك الكروس كارميللوز 27 و 24 و ايضا صوديوم ستارج كلايكوليت 24 و 19. و الوقت الاقصر للتفكك كان للصيغ التي تحتوي على الكروس بوفيدون. ففـ1 و ففـ4 كان 15 و 10 بالتتابع للطبقة ذات الاطلاق السريع.مع عدم تفكك الصيغ ذات الاطلاق الثابت في الوقت نفسه فان تحرر الدواء للصيغ الدوائية التي تحتوي على الكروس بوفيدون كان عشرين دقيقة غير ان الصيغ الدوائية التي تحتوي على الهايدروكسي بروبيل مثيل سليلوز كان اثنى عشر ساعة . كخاتمه ان الاقراص مضاعفة الطبقة ممكن تصنيعها للسيطرة على تحرر اللايسينوبريل حيث تكون الطبقة الاولى للاقراص سريعة التحرر و تكون الطبقة الثانية للاقراص بطيئة مسيطرة التحرر لزيادة تقبل المريض و تقليل عدد مرات استعمال الدواء و للسيطرة على ارتفاع ضغط الدم.

Introduction

Multilayered systems (bilayered, triple-layered, quadruple-layered, etc.) are becoming increasingly recognized as controlled-release drug delivery systems [(1)]. While the term Bi- layered tablets, refer to tablet containing subunits that may be either the same or different. Bilayered tablets allows for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release while second layer designed to release drug latter, either as second dose or in an extended release manner [(2- 4)].

Lisinopril (Figure 1), is a synthetic peptide derivative, is an oral long acting angiotensin converting enzyme inhibitor (ACE) [(5)]. It is widely used in treatment of hypertension; it has the biological half-life of 12.6 hr. Its bioavailability is 25% and it is mainly excreted in urine [(6, 7)].

Lisinopril cause reduction in angiotensin II also leads to reduced aldosterone secretion, which decreases sodium and water reabsorption, decreasing angiotensin II and aldosterone also decreases ventricular re-modeling, myocardial fibrosis, myocyte apoptosis, cardiac hypertrophy and nor epinephrine release[(8)]. The decrease in aldosterone can lead to an increase in serum potassium, also causes vasodilatation of the renal efferent arteriole which can decrease protein urea (especially in patients with diabetic nephropathy) and is considered renal protective. It is used alone or in combination with other classes of antihypertensive agents in the management of mild-to severe hypertension [(9)]. The **aim** of this study was to formulate the bilayered tablets of fast release layer and slow release layer of lisinopril using povidone k-30 as a binder.

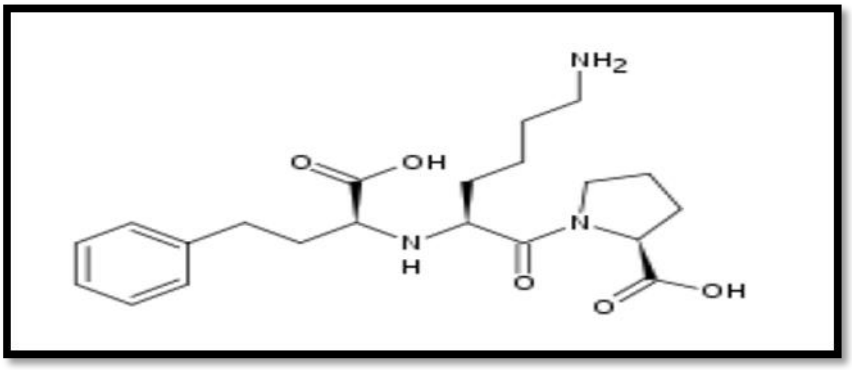

Figure 1: Structure of lisinopril

Materials and Methods

Materials

Lisinopril was obtained as a gift sample from Lincoln Pharmaceutical Ahmedabad, India. Hydroxyl propyl methyl cellulose (HPMC K-4M), sodium carboxyl methylcellulose (Na CMC) was obtained from Sigma Chemicals, USA. Ethyl cellulose was obtained from Strides Arco Labs, Bangalore, India. Mannitol, magnesium stearate were supplied from Loba Chemie Mumbai, India. Hydrochloric acid GCC, U.K and ethanol BDH, England All other ingredients used were of analytical grade.

Method

Determination of λ_{max}

Solution of 0.1 mg/ml lisinopril in 0.1 N HCl was scanned by a UV spectrophotometer from 400 to 200nm, and the λ max was determined.

Preparation of Calibration Curve

Calibration curve for lisinopril in 0.1 N HCl was constructed by preparing serial dilutions of the drug from a stock solution (0.1 mg/ml), samples were then analyzed spectrophotometrically for lisinopril at its λ max. The determined absorbance were plotted versus the concentration.

Preparation of Bi-layer Tablets

Bi-layer tablets were prepared by wet granulation process according to the formula given in table1 and 2. Up to 12 formulations are prepared for bilayer tablet. First sustained release layer is prepared (SF1-SF6) by sifting the materials shown in table 1, through the sieve separately. Then binding agent is prepared by dissolving 1% PVP k-30 in specified quantity of ethanol. Load the sifted contents in a mortal. Add the binding agent which is previously prepared with mixing until ball test is achieved. Then pass the wet granules through sieve no 1.Then dry in the oven for 2 hours then homogenize the granules in sieve no 2 and mix the above granules with lubrication (1% magnesium stearate) for 1 min and compress into tablet. Similarly lisinopril fast release layer is prepared (FF1-FF6) by sifting all the material shown in table 2, then mix content geometrically. mannitol & super disentegrant to it. Then binding agent is prepared by dissolving 1% PVP in specified quantity of ethanol, also dissolve color into it. Add the binding agent which is previously prepared with mixing until ball test is achieved. Then pass the wet granules through sieve no 1.

Then dry in the oven for 2 hours then homogenize the granules in sieve no 2 and mix the above granules with lubrication (magnesium stearate) for 1 min. Then the tablets were compressed into a 7.6 mm diameter tablets using a single punch tablet machine of 7.6mm diameter die at a compression force of (37 kN) to get the tablets.

Table 1: Composition of Different Formulas of Lisinopril Granules as Sustained Release Layer of Lisinopril Tablet

Ingredients (mg)	SF1	SF2	SF3	SF4	SF5	SF6
Lisinopril	10	10	10	10	10	10
Lactose				40	40	40
HPMC	85			45		
CMC		85			45	
EC			85			45
PVP	4	4	4	4	4	4
Mg stearate	1	1	1	1	1	1
Total WT	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

Table 2: Composition of Different Formulas of Lisinopril Granules as Fast Release Layer of Lisinopril Tablet

Ingredients (mg)	FF1	FF2	FF3	FF4	FF5	FF6
Lisinopril	10	10	10	10	10	10
Mannitol	65	65	65	55	55	55
crospovidone	20			30		
croscaramellose		20			30	
Sodium starch glycolate			20			30
PVP	4	4	4	4	4	4
Mg stearate	1	1	1	1	1	1
Total WT	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg

Evaluation of the Tablets

Evaluation of Physicochemical Parameters of Tablets Hardness

The hardness of three randomly selected tablets from each formulation sustained release layer (SF1 to SF6) and fast release layer (FF1-FF6) was determined by placing each tablet diagonally between the two plungers of Monsanto hardness tester and applying pressure until the tablet broke down into two parts completely and the reading on the scale was noted down in $Kg/cm^2$and the average reading noted.

Friability

The friability of tablets was determined using Roche friabilator for all formulas. It is expressed in percentage (%). Ten tables were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W final). The percentage friability was then calculated using the following equation.

$$F = \frac{I_{nitial} - F_{inal}}{I_{nitial}} \times 100$$

% Friability of tablets less than 1% are considered acceptable [10].

Weight Variation

Randomly, twenty tablets were selected after compression for each formula and the mean weight was determined. None of the tablets deviated from the average weight by more than ±7.5% (USP XX).

In-vitro Disintegration Test

The in-vitro disintegration time was determined for the fast disintegration layer (FF1-FF6) using the USP disintegration apparatus, the basket rack assembly containing six open ended tubes and 10- mesh screen on the bottom was used, and the six tubes are filled with 0.1 N HCl. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds [11].

Drug Content

Twenty tablets were weighed and powdered from each formula. An amount of the powder equivalent to 20mg of Lisinopril was dissolved in 100ml of 0.1N hydrochloric acid, filtered, diluted suitably and analyzed for drug content at 246nm using UV-Visible spectrophotometer (UV 160 Shimadzu, Japan) [12].

Thickness

The thickness of the tablet is measured by vernier calipers scale. Thickness of the tablet related to the tablet hardness and can be used an initial control parameter.

Results and Discussion

Determination of λ_{max}

The UV spectrum showed a peak at 246 nm and it represents the λ_{max} as stated in European pharmacopeia.

Preparation of Calibration Curve

Figure (2) shows the calibration curve of lisinopril in 0.1N HCl. A straight line was obtained as a result of plotting the absorbance versus concentration, which indicates that the calibration curve obeys Beer's-Lambert law within the concentrations used.

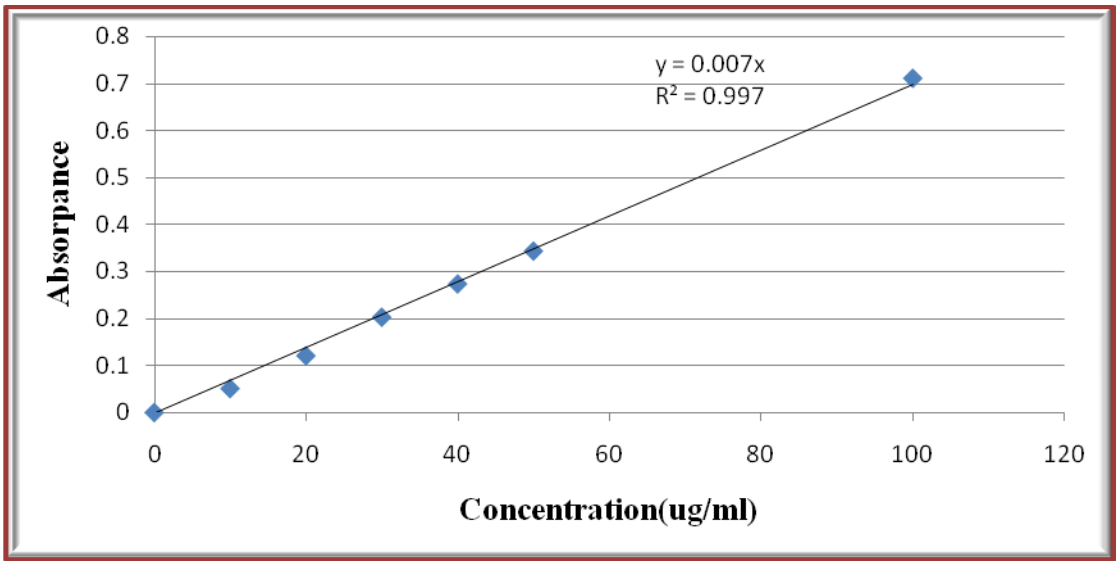

Figure 2: Calibration curve of Lisinopril in 0.1N HCL.

Physical Properties of the Prepared Tablets

Physical Properties of the Prepared Fast Release Layer

The results for FF_1- F_{F6}, which they were utilized to study the effect of the superdisintegrant type (crospovidone, croscarramelose sodium, and sodium starch glycolate) are shown in table 3.

Regarding in vitro disintegration test, when comparing these three superdisintegrants it was found that crospovidone gives the best result followed by croscarramelose sodium and then sodium starch glycolate.

The results for the inner sustained release layer were shown in table 3.

Figure 3: Picture shows double layer tablet

Table 3: Physical Properties of the Outer Fast Release Layer

Formula No.	In-vitro Disintegration time (sec)	Hardness(kg/cm^2)	Friability (%)
FF1	15±2	4	0.95
FF2	27±3	6	0.61
FF3	24±3	6	0.49
FF4	10±2	4.5	0.9
FF5	24±3	6	0.56
FF6	19±1	7	0.39

Hardness Test for Fast Release Layer

The hardness test was perform in which three tablets from each formulation batch were tested randomly and the average reading was recorded, using Monsanto hardness tester in which the hardness was expressed as a force in kg/cm^2 required to crush the tablet. The results were shown in table 3 [(12)].

Tablet Friability for Fast Release Layer

The friability of the tablets was measured in a Roche friabilator for 4 minutes as shown in table 3 [(13)].

Hardness Test for Sustained Release Layer

The hardness test was performed in which three tablets from each formulation batch for SF1, SF2, SF3, SF4, SF5, and SF6 were tested randomly and the average reading was recorded as shown in table 4.

Tablet Friability for Sustained Release Layer

The friability of the tablets was measured in Roche friabilator for 4 minutes for sustained release formulas (SF1, SF2, SF3, SF4, SF5, and SF6) as shown in table 4.

Table 4: Friability, and Hardness of the Inner Sustained Release Layer

Properties Formula No.	Hardness(kg/cm^2)	Friability (%)
SF1	9	0.079%
SF2	12	0.061%
SF3	15	0.031 %
SF4	8	0.065%
SF5	9	0.053%
FF6	12.5	0.037%

Uniformity of the Dosage Units

From each formula (FF1-FF6), and inner layer; ten tablets were randomly selected from prepared formulas and pulverized to a fine powder. Weighed aliquots containing an amount of powder equivalent to a single dose were taken in triplicate and assayed for the drug content utilizing a UV spectrophotometer. All results were accepted and within the range.

Table 5: Lisinopril Content per Layer for Fast and Sustained Release Layers

Formula Number	%Lisinopril/ Tablet
FF1	99.2
FF2	97.8
FF3	99.1
FF4	93.5
FF5	96.9
FF6	96.6
SF1	94.1
SF2	96.6
SF3	96.7
SF4	97.9
SF5	96.3
SF6	99.5

Weight Variation for Outer Fast and Inner Sustained Release Layer

Weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weight to the average. The results were within the range for all formulas. All the tablets passed weight variation test as the percentage weight variation was within the pharmacopoeial limits [13].

Disintegration Test

Disintegration test measured for the outer layer occur within less than 1 minute. On the other hand no disintegration occurs for the inner layer tablet.

For FF1 to FF6, formulas contain crospovidone gave the fastest disintegration time and this is because crospovidone unlike other superdisintegrants, which rely principally on swelling for disintegration, crospovidone disintegrants use a combination of mechanisms to provide rapid disintegration. Although crospovidone polymers swell by 95% to 120% upon contact with water, swelling is not the only mechanism for tablet disintegration. Swelling or swell volume is mainly a measure of the change in volume of the disintegrant after it is introduced to an aqueous solution and the system has reached equilibrium. However, swell volume does not measure the rate at which a disintegrant absorbs water and swells or the pressure generated by swelling. Crospovidone polymers, with their porous particle morphology rapidly absorb water (wicking) via capillary action. As the deformed crospovidone particles come in contact with water that is wicked into the tablet, the crospovidone particles recover their normal structure and then swell, resulting in rapid volume expansion and high hydrostatic pressures that cause tablet disintegration [14].

In addition, an acidic medium significantly reduce the liquid uptake rate and capacity of sodium starch glycolate and croscarmellose sodium but not crospovidone, where a significant reduction in swelling capacity is also observed for croscarmellose, sodium in 0.1 N HCL ,which swells to half that in water. The strong decrease in swelling capacity of chemically modified starches and celluloses may attribute to the converting of the carboxyl methyl sodium moieties. Since the acid form has less hydration capacity than its salt form, the liquid holding capacity of the disintegrant particle reduces after deionization in the acidic medium [15]. While for sustained release layer no disintegration occurs.

Dissolution Test

For the fast release layer, the release was done for the selected crospovidone containing layer (FF1) and it was very fast as shown in figure 4. Within about 20 minutes the entire drug release from the fast release layer which is required for the fast onset on lisinopril tablet as antihypertensive.

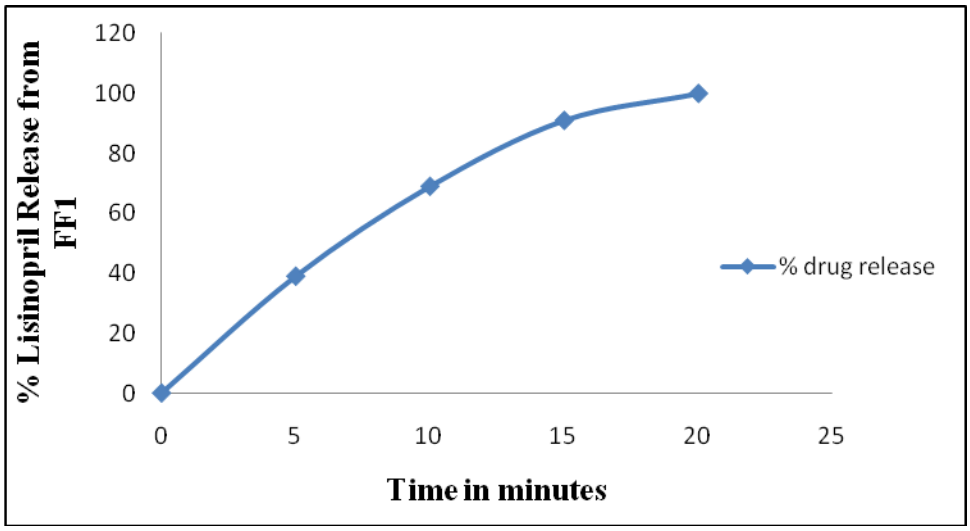

Figure 4: Dissolution rate of outer fast release layer of Lisinopril tablet in 0.1 N HCl and temperature 37 C°.

The goal of sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtain zero order release from the dosage form. In zero order release drug release is independent of the concentration of drug in the delivery system (a constant release rate) [16]. HPMC polymer was selected for release study [17], and the dissolution test for the sustained release layer was 12 hours for SF1as it is shown in figure 5.

This is consistent with the findings of Arunprasad B. et al [18].

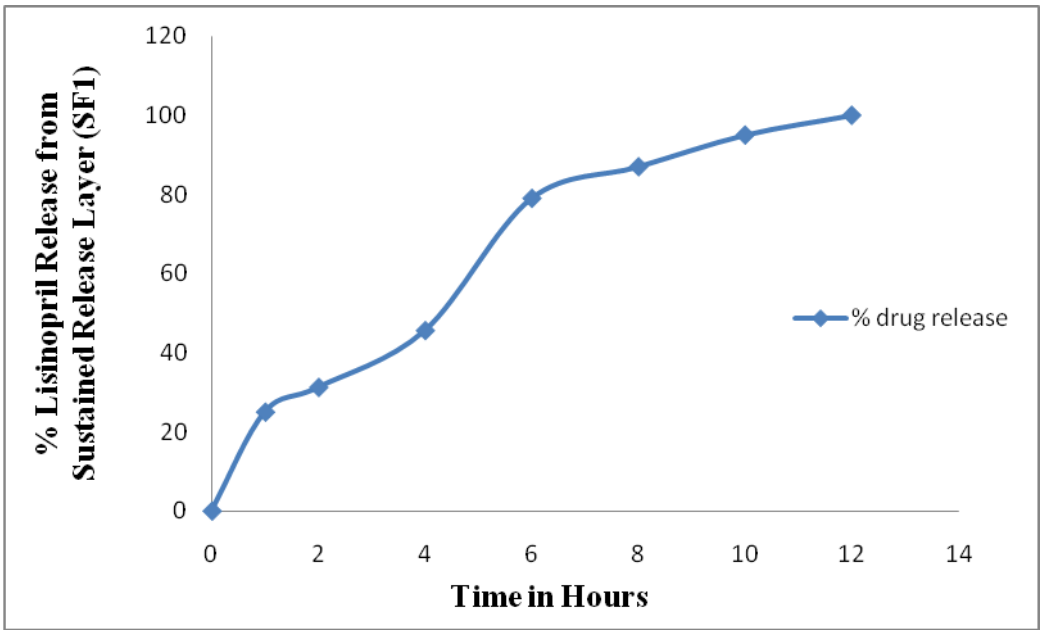

Figure 5: Dissolution rate of inner sustained release layer of lisinopril tablet in 0.1 N HCl and 37 C°.

Friability of all formulation was less than 1%, which indicates the tablets had good mechanical resistance.

Drug content was found to be uniform in all formulations. The tablet thickness was found to be 5.12 to 5.31 mm. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ± 7.5 %, which provide good uniformity in all formulations.

Conclusion

Bilayered tablets containing 100 mg fast release layer and 100 mg sustained release layer of Lisinopril were successfully prepared by wet granulation method.

Initially fast release layer was optimized based on hardness, friability, and disintegration studies of 6 trials. Then dissolution time studied for FF1 as the best fast release layer. On the other hand sustained release layer of Lisinopril were formulated based on 6 trials SF1-SF6), then the HPMC polymer selected as the most appropriate layer and used for further release study.

As a conclusion double layer tablets were attempted to be prepared for controlled drug delivery. The first layers of tablets providing the initial drug release while the second outer layer provide sustained release of lisinopril for increase patient compliance and decrease frequency of dosing for more control of hyper tension.

References

1-Narendra C. et al. Development of three layered buccal compact containing metoprolol tartrate by statistical optimization technique. Int. J. Pharm. 2005; 304: 102-114.

2- Podczeck F., Drake K.R., Neton J.M., and Harian I., The strength of bi layered tablet. Europian Journal of Pharmaceutical Sciences 2008; 1: 1- 14.

3- Jadhav R T, Patil P H, Patil P R. Formulation and evaluation of bilayered tablet of Piracetam and Vinpocetine. J. Chem. Pharm. Res., 2011, 3(3):423-431.

4-Remya P N, Damodharan N, Kumar C V. Formulation and evaluation of bilayered tablets of ibuprofen and methocarbamol. Int.J. PharmTech Res 2010; 2(2): 1250-1255.

5-Nayak S, Ashish J, Rathore P, Sumbate S, Nayak S.A. Comparative study of Lisinopril from different vehicle Int.J.of pharmacy & pharma.sci. 2009; 1: 213- 218.

6-Guda A, Gudas GK, Bingi M, Subal D, Rajesham VV. Design and evaluation of controlled release mucoadhesive buccal tablets of Lisinopril. Int.J.pharma.Res. 2010; 2(4): 24-27.

7-Viswanadhan P V, Padole A, Abraham A. Buccal tablets of lisinopril by direct compression method for buccal drug delivery. International Research Journal of Pharmaceuticals 2012; 2(02): 30-38.

8- Patil B, Motagi A, Kulkarni U, Development and evaluation of time controlled pulsatile release Lisinopril tablets. JPSBR 2012: Volume 2, Issue 1: Jan Feb (30-35).

9- Panigrahi R, Chowdary K.A. , Mishra G, Bhowmik M, Behera S. Formulation of fast dissolving tablets of Lisinopril using combination of synthetic superdisintegrants. Asian J. Pharm. Tech. 2012; 2(3): 94-98.

10-Veeraveni R, Nampalli Sh, Ganesh Kumar P.C.Krishna and Shiva Prasad M.S. Design and evaluation of orodispersible taste masked valdecoxib tablets. J Chem Pharm Res. 2011; 3(4): 882-892.

11- Radke R.S. JJK, Chajeed M.R.. Formulation and evaluation of orodispersible tablets of baclofen. International Journal of ChemTech Research 2009; 1(3): 517-521.

12- Aulton ME, Wells TI. Pharmaceutics: The Science of Dosage form design, London, England: Churchill Livingstone, 2nd edition, 2002, Pages. 1-13, 136, 20-207.

13- Gilbert S. Banker, Neil R. Anderson., tablets. In Leon Lachman, Herberta Liebermann, Joseph L Kanig. (Edition), the theory and practice of Industrial pharmacy, 3rd ed. Lea and Febiger, Philadelphia, 1987, page. no. (a) 293-294, (b) 330-331, (c) 430-431.

14-Mangal ST, Goswami M, Ghai P. Superdisintegrants: an updated review. Int. J. Pharm. Pharm. Sci. Research 2012.

15- Zhao N, Augsburger LL. The influence of swelling capacity of superdisintegrants in different pH media on the dissolution of hydrochlorothiazide from directly compressed tablets. AAPS PharmSciTech 2005; 6(1): E120-E126.

16-Herbert A. Liebermann. Pharmaceutical Dosage forms –Tablets - Vol.1, Marcel Dekker publications, 2nd edition, Pages. 179-181.

17- S.S basak, B.M jaya kumar reddy. Formulation and release behavior of sustained release of Ambroxol hcl HPMC matrix tablets.Indian journal of pharmaceutical sciences, 2006; 4: 594-598.

18-Arunprasad B, Teja. Design and evaluation of bilayered tablets to treat respiratory tract infections. International Journal of Pharmacy and Pharmaceutical Sciences 2013; 5(1): 250-255.