Original Article

Formulation Development And Evaluation Of Bilayer Tablets Of Lisinopril For Immediate Release And Simvastatin For Sustained Release

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Abstract

The development of innovative combination therapy is highly desired to deliver Lisinopril and Simvastatin for to prepare bilayer tablets that can perform as quick/slow biphasic release systems of a poorly soluble drug[1]. This formulation approach is of particular interest for treatments that require a rapid action followed by sustained therapeutic levels[2]. Lisinopril one of the most widely prescribed angiotensin –converting enzyme inhibitor for hypertension therapy was used as a model of a BCS III drug. The Sodium Starch Glycolate was chosen various concentration of (2%,3%,4%)[3] in the rapid release layer, HPMC K4M,HPMC K100M,was tested as controlled release agent in the sustained release layer and Sodium starch glycolate was utilizing as super in disintegrant in the rapid release layer and magnesium state was applied anti-adhered lubricant in both layer. In bilayer tablets[4] were characterized through several technique. The result feasibility of the preparation method of wet granulation with sodium starch glycolate in the rapid release to achieve fast dissolution for the first 45 minutes and HPMC K4M,HPMC K100M as a controlling agent in the sustained release layer of the bilayer tablets[5] to obtain a prolonged release during 1440 min.In conclusion, combinations of Sodium starch glycolate and HPMC K4M,HPMC K100M may help addressing the formulation of poorly soluble drugs in bilayer tablets as a fast/slow biphasic release system[6].

Key Words: Sodium Starch Glycolate, Lisinopril, Dyslipidemia, potassium bromide, *in-vitro*, Higuchi model.

1. INTRODUCTION

In recent decades, the pharmaceutical industry has explored potential improvements to currently available drugs, such as increasing the safety and efficacy of their use or reducing the side effects of their treatments[7]. The work carried out in this direction also aims to make it easier for patients to access the latest treatments and to follow the instructions of their doctors. In particular, new pharmaceutical applications (forms, routes of administration) and cheaper and improved techniques for their production are being developed[8]. Combination drugs, which combine two or more active ingredients, are gaining in importance. Such products are intended to increase patient tolerance to drugs, reduce side effects[9], promote patient-physician cooperation, and sometimes increase drug efficacy[10]. Some studies have shown that taking combination medications (combinations of active ingredients) is more effective than using the individual active ingredients of a drug[11]. These improvements may seem like simple modifications to existing drugs, but developing such modifications while preserving the drug's properties is time consuming and costly[12]. Patients will benefit from having safer, easier to use and "easier to use" medicines at their disposal.

Bilayer tablets are a novel drug delivery system that improves patient compliance, prolongs drug action and avoids serrated kinetics by combining two or more drugs with different release profiles into one entity, resulting in effective therapy and improved plasma drug control[13]. Bilayer tablets are suitable for combining two drugs for separate and sequential release from two miscible substances[14]. It is also suitable for sustained release tablets, where one layer is the initial dose for immediate release[15] and the second layer is the maintenance dose. Therefore, the current study attempted to prescribe a bilayer tablet of lisinopril and simvastatin as a bimodal delivery system to treat diabetes mellitus[16]and overcome diabetic complications such as hypertension and nephropathy[17].

Cardiovascular disease is the leading cause of mortality and morbidity in developed countries and is becoming the leading cause of mortality and morbidity worldwide. Although cardiovascular risk factors are well known[18], their management is suboptimal even in developed countries[19]. Undoubtedly, dietary and lifestyle changes reduce cardiovascular risk. Still, not enough work has been done to determine the most efficient and cost-effective ways to implement these lifestyle changes[20] cost is increasing. The authors analyzed which patients were most suitable for taking polypills. Candidates are patients who have experienced acute coronary syndrome or ischemic stroke[21], stable chronic angina, transient ischemic

episodes and diabetic patients[22]. Age is the most important factor in populations with no history of cardiovascular disease. Because 96% of deaths from acute coronary syndrome or jaundice occur in people over the age of 55, preventive treatment for people over the age of 55 can prevent almost all of these deaths[23].
That said, the best strategy is to treat all patients with ischemic disease and all people over the age of 55. In this direction, several patents have been published on polypills for cardiovascular prophylaxis. It has been Simvastatin is very sensitive to light and moisture[24]. Therefore, in the tablet of the present invention, this compound is segregated into a compartment different from that occupied by lisinopril[25].
Therefore, a combination of simvastatin and lisinopril provided in a single dosage form with the optimal doses of the three active agents appears to be recommended for stroke prevention in high-risk populations is 55 years or older[26], angina pectoris, stroke, atherosclerosis, claudication, diabetes, coronary artery disease, peripheral vascular disease, altered platelet function, hemodialysis, hypercholesterolemia, hypertension, myocardial infarction, Congestive patient[20]. Heart failure, ischemia, nephropathy, high serum homocysteine levels, cardiac arrest or restenosis, smokers, obese and sedentary populations[27].

2. MATERIAL AND METHODS

2.1 MATERIAL

Lisinopril hydrochloride,Simvastatin, Madras Pharmaceutical,Chennai,TamilNadu. HPMC K 4M, HPMC K100M, Mcrocrystalline Cellulose,Starch,Sodium starch Glycolate, Saimirra Innova Pharma Pvt Ltd.,Chennai,Tamil Nadu. Polyvinyl pyrolidone K30,Isopropyl alcohol,Talc,Magnesium Stearate and Poncheau 4 R are purchased from Sigma-Aldrich.

2.2 METHODS

2.2.1 PREFORMULATION STUDIES

Preformulation studies are the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation studies is to the formulator in developing stable and bioavailable dosage forms that can be mass produced[28].

A.ORGANOLEPTIC PROPERTIES

The colour,odour and taste of the drugs were studied.

B. SOLUBILITY ANALYSIS[29]

Solubility is an important parameter for preformulation studies because
1. It affects the dissolution of the drug.
2. Bioavailabilityof drug is directly affected by oral administration and also by dissolution.

METHOD:

weighed quantity of drug was added to the suitable volume of solvent and solubility checked.

C. LOSS ON DRYING(%) 1g of drug was accurately weighed and dried in an oven at 105˚ C for 3 hours. By gentle sidewise shaking, the sample was distributed at the specified temperature for constant weight. The drug was allowed to come to room temperature in a dessicator before weighing. The difference between successive weights should not be more than 0.5 mg. The loss on drying is calculated by the formula:[30]

%LOD=W3-W2⁄W2-W1X100

Where, W1-Weight of empty weighing bottle
W2-Weight of weighing bottle +sample
W3-Weight of weighing bottle+ dried sample

2.2.2 DRUG EXCIPIENT COMPATIBILITY STUDY

The drug and the excpients chosen for the formulation were screened for compatibility by physical methods and Fourier Transform Infrared (FTIR) spectroscopic studies[31].

2.2.3 CHEMICAL COMPATIBILITY STUDY BY FTIR

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drugs, polymers, excipients, drug excipient mixture was subjected to FTIR studies to investigate the drug- excipients interactions. The IR spectra of the test samples were obtained by pressed pellet technique using potassium bromide[32].

2.2.4 PREPARATION OF BUFFER SOLUTIONS

2.2.4.1 Preparation of 0.1MHydrochloric acid: 8.5ml of the hydrochloric acid was taken, dissolved in water and made upto 1000ml to get 0.1M hydrochloric acid.

2.2.4.2 Preparation of 0.2M potassium dihydrogen phosphate: 27.218g of potassium dihydrogen phosphate was dissolved in distilled water and the volume was made upto 1000ml using distilled water.

2.2.4.3 Preparation of 0.2 M Sodium hydroxide: 8g of Sodium hydroxide was dissolved in distilled water and made upto 1000 ml with distilled water.

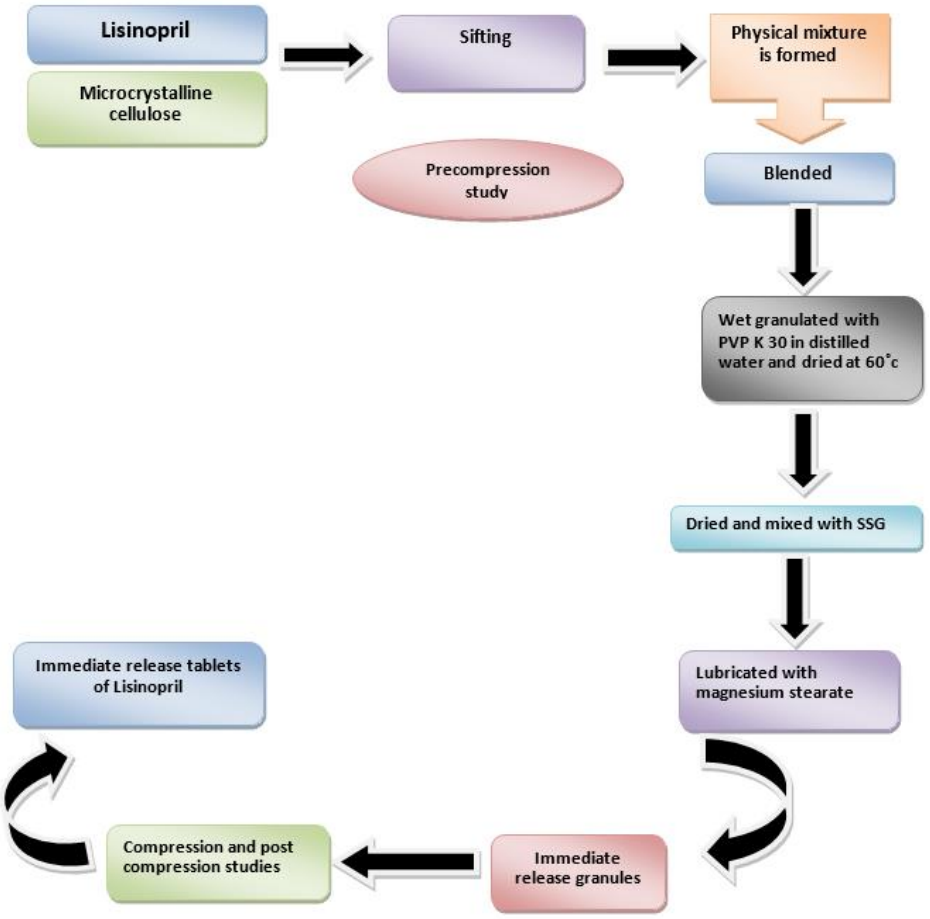
2.2.4.4 Preparation of pH 6.8 phosphate buffer solution: Take 50ml of 0.2M potassium dihydrogen phosphate in a 200ml volumetric flaskand add 22.4ml of 0.2M sodium hydroxide solution, then the volume was made upto 200ml using distilled water.

2.2.5 FORMULATION DEVELOPMENT[33]

2.2.5.1 FORMULATION OF IMMEDIATE RELEASE GRANULES OF LISINOPRIL

S.NO	INGREDIENTS	L1 (mg)	L2 (mg)	L3 (mg)
1	Lisinopril	10	10	10
2	Microcrystalline cellulose	95.31	94.4	93.49
3	Ponceau 4R	0.01	0.01	0.01
4	PVP K30	2.72	2.72	2.72
5	Distilled water	q.s	q.s	q.s
6	Sodium starch glycolate	1.81	2.72	3.63
7	Magnesium stearate	0.1	0.1	0.1
8	Talc	0.05	0.05	0.05
TOTAL WEIGHT		110.0	110.0	110.0

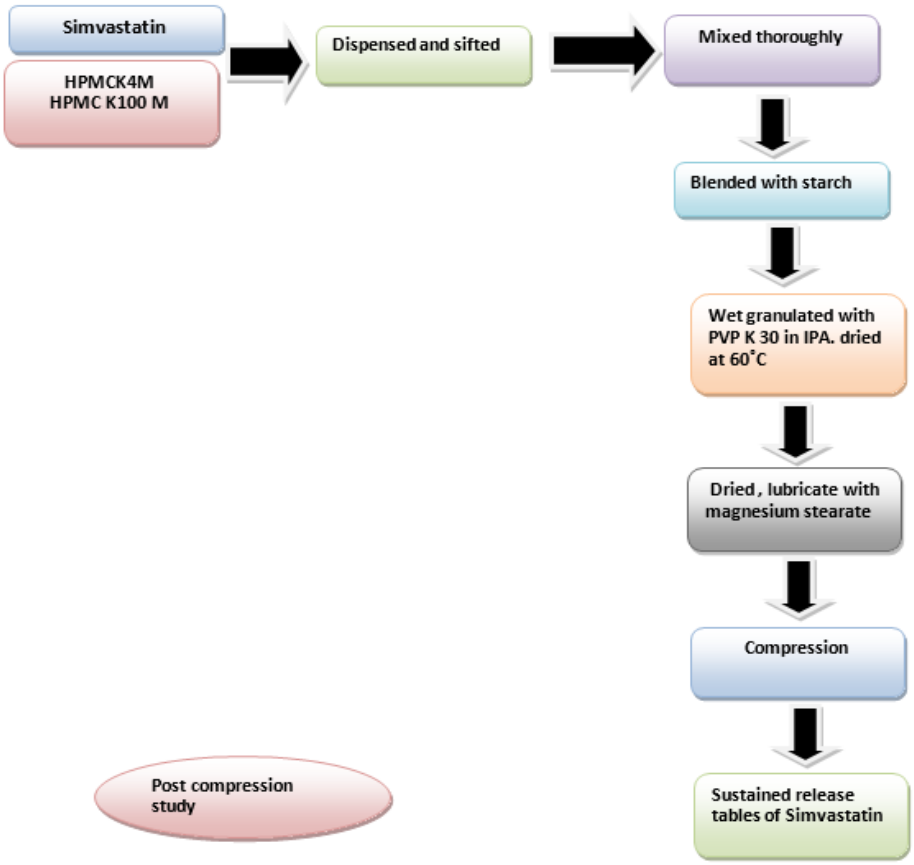
Flowchart For Formulation Of Lisinopril IR Tablets[34] :



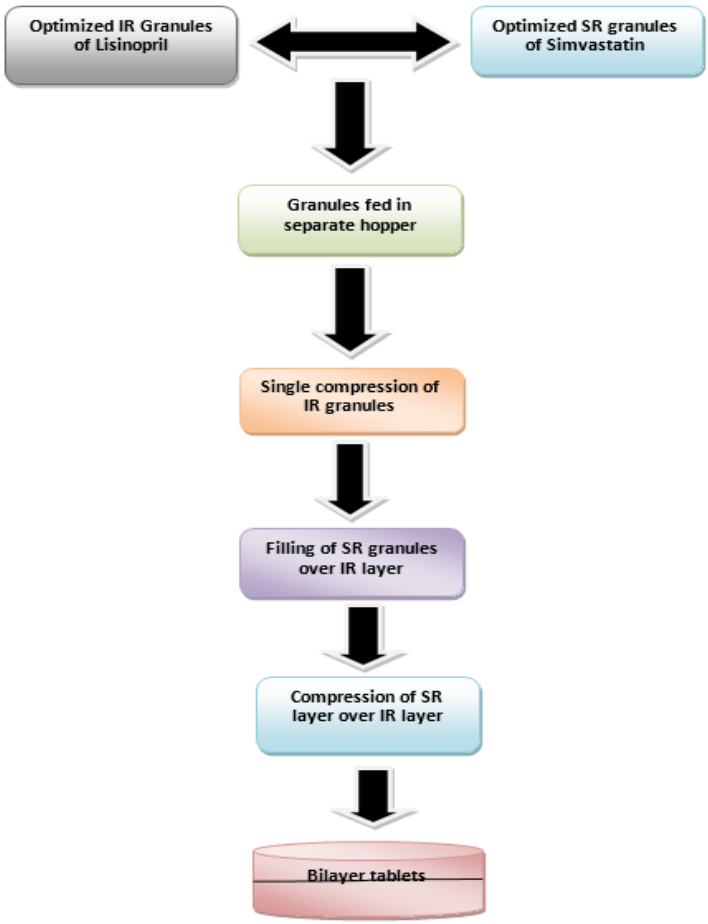
Formulation Of Simvastatin Sustained Release Tablets

S.NO	INGREDIENTS	S1 (mg)	S2(mg)	S3 (mg)	S4 (mg)	S5(mg)
01	Simvastatin	20	20	20	20	20
02	Starch	65.78	65.78	65.78	65.78	65.78
03	HPMC K4M	20	-	10	15	5
04	HPMC K100M	-	20	10	5	15
05	PVP K30	2.72	2.72	2.72	2.72	2.72
06	Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s
07	Magnesium stearate	1	1	1	1	1
08	Talc	0.5	0.5	0.5	0.5	0.5
TOTAL WEIGHT		110	110	110	110	110

Flowchart For Formulation Of Simvastatin Sustained Release Tablets[35] :



Flowchart for bilayer tablets of Lisinopril and Simvastatin



2.2.6 RESULTS AND DISCUSSION

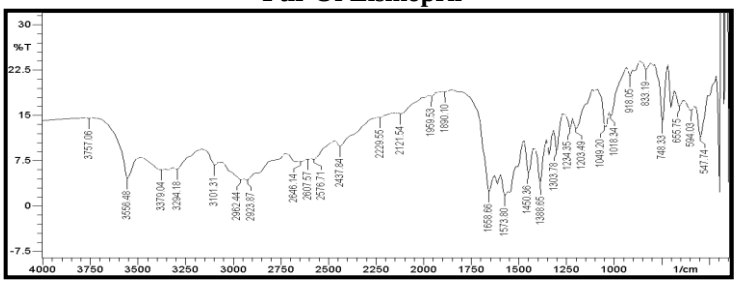
The present work was aimed to formulate bilayer tablets of immediate release Lisinopril and sustained release Simvastatin. The therapy with these drugs offers a good improvement for patient who suffer from hypertension and Dyslipidemia[36].

2.2.7 DRUG-EXCIPIENT COMPATIBILITY STUDY

2.2.7. Chemical compatibility study

All the sample were scanned at the wave number 4000-400 cm^{-1} using KBr disc method. This KBr discs were formed by taking Drug and KBr in a ratio of 1:100 respectively. Then this mixture was mixed well in mortal for three to five min. A very small amount of this mixture was uniformly spread and sandwiched between the pellets and pressed using KBr pellet press at a pressure of 20,000 psi for 1 min[37]. The pressure was then released and pellet was placed into the pellet holder and thus scanned in the IR region. The results are given below

Ftir Of Lisinopril



IR Spectral Interpretation Of Lisinopril

Functional group	Characteristic peak		Observed peak	
	Stretching	Bending	Stretching	Bending
N-H (primary amine)	3400-3500cm^{-1}	-	3556cm^{-1}	-
C-H (alkane)	2960-2850cm^{-1}	-	2923cm^{-1}	-
O-H (acid)	3590-3700 cm^{-1}	-	3757cm^{-1}	-
C=C(Alkenes)	1680-1620cm^{-1}	-	1658cm^{-1}	-

FTIR OF SIMVASTATIN

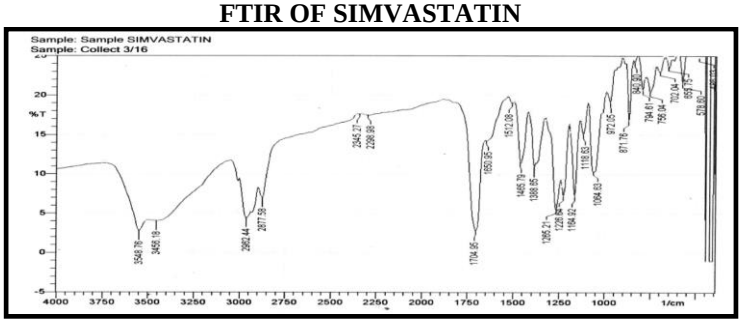


Table 12 :IR Spectral Interpretation Of Simvastatin

Functional group	Characteristic peak		Observed peak	
	Stretching	Bending	Stretching	Bending
C=O(Acid)	1700-1725cm^{-1}	-	1704cm^{-1}	-
O-H(Phenol)	3500-3650cm^{-1}	-	3456cm^{-1}	-
C=C(Alkene)	1650-1620cm^{-1}	-	1650cm^{-1}	-
C-H(Alkane)	1340cm-1	-	1388cm-1	-

FTIR OF LISINOPRIL AND SIMVASTATIN

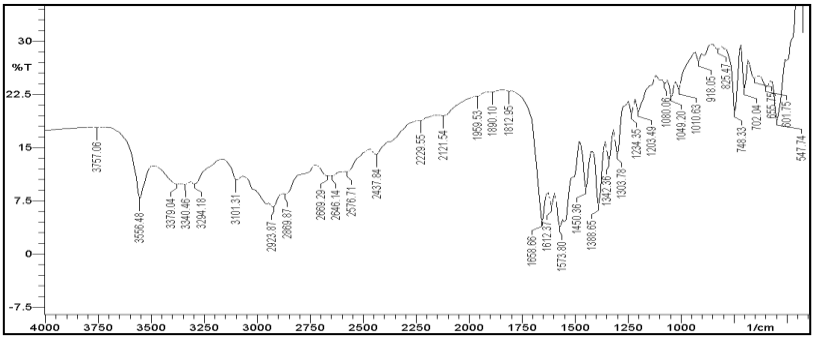
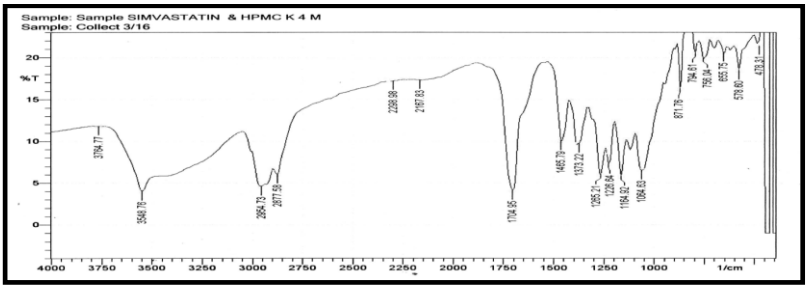


Table 13:IR Spectral Interpretation Of Lisinopril And Simvastatin

Functional group	Characteristic peak		Observed peak	
	Stretching	Bending	Stretching	Bending
N-H (Primary amine)	3400-3500cm^{-1}	-	3556cm^{-1}	-
O-H (Phenol)	1200cm^{-1}	-	1203cm^{-1}	-
C=O(Acid)	1650-1700cm^{-1}	-	1658cm^{-1}	-
C-H (Alkane)	2960-2850cm-1	-	2962 cm^{-1}	-

INFERENCE: No shift and no disappearance of characteristic peaks suggesting that there is no interaction between two drugs.

FTIR OF SIMVASTATIN& HPMC K 4 M

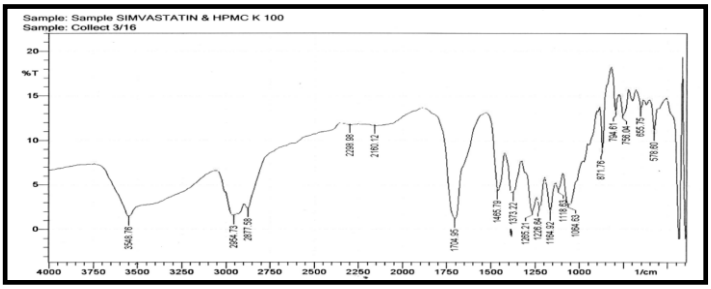


IR Spectral Interpretation of Simvastatin and HPMC K4M

Functional group	Characteristic peak		Observed peak	
	Stretching	Bending	Stretching	Bending
C=O(Acid)	1700-1725cm^{-1}	-	1704cm^{-1}	-
O-H(Phenol)	3500-3650cm^{-1}	-	3548cm^{-1}	-
C=C(Alkene)	1650-1620cm^{-1}	-	1650cm^{-1}	-
C-H(Alkane)	1340cm-1	-	1373cm-1	-

INFERENCE: No shift and no disappearance of characteristic peaks suggesting that there is no interaction between drug and polymer.

FTIR of Simvastatin and HPMC K100 M



IR Spectral Interpretation of Simvastatin and HPMC K100M

Functional group	Characteristic peak		Observed peak	
	Stretching	Bending	Stretching	Bending
C=O(Acid)	1700-1725cm^{-1}	-	1704cm^{-1}	-
O-H(Phenol)	3500-3650cm^{-1}	-	3548cm^{-1}	-
C=C(Alkene)	1650-1620cm^{-1}	-	1650cm^{-1}	-
C-H(Alkane)	1340cm-1	-	1373cm-1	-

INFERENCE : No shift and no disappearance of characteristic peaks suggesting that there is no interaction between the drug and polymer.

POST COMPRESSION STUDY FOR TABLETS

UNIFORMITY OF WEIGHT

Uniformity of weight of formulated tablet

Formulation	**Uniformity of weight (mg)***
Specified limit	**101.75- 118.25**
L1	110.4±1.140
L2	109.8±1.094
L3	110±1.0

***mean±SD (n=5)**

The tablets comply with the test for uniformityof weight.

Thickness and diameter of formulated tablets

Formulation	Thickness(mm)*	Diameter(mm)*
L1	3.200±0.1140	7.969±0.0198
L2	3.090±0.1140	8.054±0.3881
L3	2.954±0.0784	7.978±0.1121

***Mean±SD (n=5)**

The tablets were found to be uniform in thickness and diameter.

Hardness of formulated tablets

Formulation	Hardness (Kg / $cm^{2)*}$
L1	4.00±0.2214
L2	3.99±0.2729
L3	4.16±0.1239

***mean ±SD (n=5)**

All the formulated tablets showed sufficient mechanical strength to resist the transportation.

Friability of formulated tablets

Formulation	% friability*
Specified limit	**Not more than 1.0%**
L1	0.129±0.0130
L2	0.226±0.0119
L3	0.397±0.1508

***mean ±SD (n=5)**

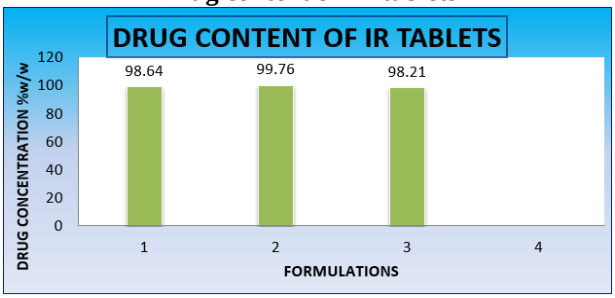
The percentage friability of all the formulations was within the acceptable limits. i.e NMT 1%.

Drug content of formulated IR tablets

Formulation	%w/w drug content *
Specified limit	**90-110%**
L1	98.641±0.8040
L2	99.160±0.1620
L3	98.219±0.2601

***Mean ±SD (n=5)**

Drug content of IR tablets



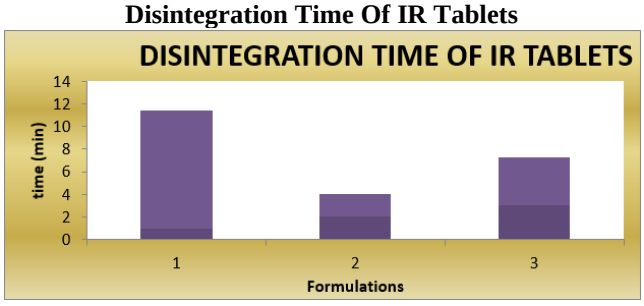
The drug contents of all three IR formulations were found to be within the limit.(NLT 90% and NMT 110%. As per IP :2010.

Disintegration Time Of Ir Tablets

FORMULATION	DISINTEGRATION TIME (min)*
L1	10.45±0.4147
L2	2.05±0.3991
L3	3.30±0.4493

*Mean ±SD (n=5)

Disintegration Time Of IR Tablets



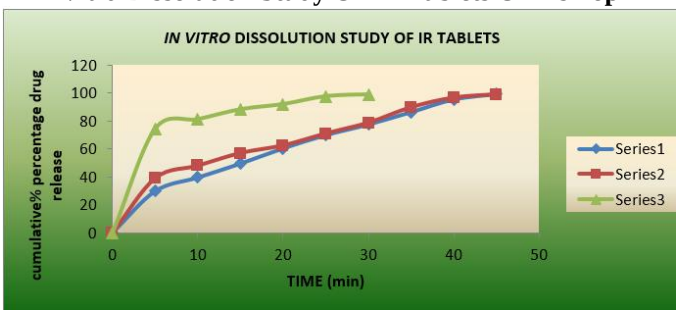
The disintegration time of the IR tablets ranged from 10 mins 45 secs to 02 mins 05 secs. The disintegration time of the IR tablets containing 3% sodium starch glycolate was found to have optimum disintegration time[38].

In Vitro Dissolution Study Of Immediate Release Tablets

Time (min)	Cumulative % drug release*		
	L1	L2	L3
0	0±0.000	0±0.000	0±0.000
10	69.84±0.5300	74.78±0.4010	72.00±0.2580
20	80.15±0.5560	83.85±0.2500	82.07±0.2900
30	87.24±0.2289	91.30±0.2860	86.12±0.2986
40	93.50±0.3680	96.24±0.2153	89.13±0.3135
50	96.58±0.5340	98.52±0.2300	92.61±0.3160
60	99.20±0.4812	100.91±0.3600	97.20±0.3058

***mean ±SD(n=3)**

In Vitro Dissolution Study Of IR Tablets Of Lisinopril



The *in vitro* dissolution study of IR tablets showed that 3% concentration of sodium starch glycolate was found to be optimum for immediate release of Lisinopril.therfore formulation L2 was optimized and selected for final bilayer tablets[39].

POST COMPRESSION STUDY

Uniformity Of Weight Of Formulated Tablets

Formulation	Uniformity of weight(mg)*
Specified limit	101.75- 118.25
S1	110±1.140
S2	109.8±1.094
S3	110±1.0
S4	110±1.140
S5	109.8±1.094

***mean ±SD(n=5)**

The tablets complies with the test for uniformity of weight.

Thickness and diameter of formulated tablets

Formulation	Thickness (mm)*	Diameter(mm)*
S1	3.98± 0.1140	7.969 ± 0.0198
S2	3.182± 0.9191	7.932 ±0.3881
S3	3.017 ±0.0784	7.978 ±0.1121
S4	3.983 ±0.1410	7.915 ±0.3521
S5	3.012 ±0.0762	7.922 ±0.2210

***mean ±SD (n=5)**

The tablets were found to be uniform in thickness and diameter.

Hardness Of The Formulated Tablets

Formulation	Hardness Kg/cm^2
S_1	4.00± 0.2214
S_2	3.99 ±0.2729
S_3	4.16± 0.1239
S_4	4.05± 0.2214
S_5	3.99 ±0.2729

Mean±S.D(n=3)

All the formulation tablets showed sufficient mechanical strength to resist the transportation.

Friability Of Formulated Tablets

Formulation	Friability(%)*
Specified limit	**Not More Than 1.0%**
S1	0.129± 0.0130
S2	0.226 ±0.0119
S3	0.397± 0.1508
S4	0.414 ±0.0065
S5	0.493± 0.0080

*Mean±S.D(n=3)

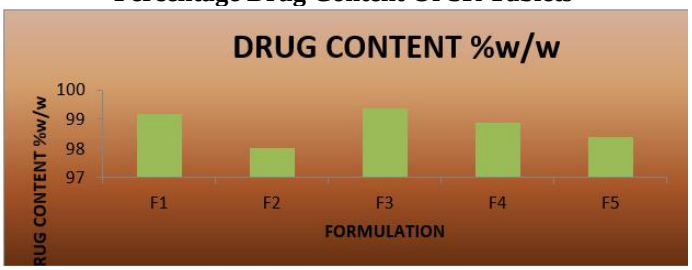
The percentage friability of all formulations was within the acceptable limits .i.e not more than 1%

Drug Content (%W/W) Of Formulated SR Tablets

Formulation	Dug content (%w/w)*
Specified limit	90%- 110%
S1	99.17± 0.0820
S2	98.02± 0.0930
S3	99.35± 0.0802
S4	98.88± 0.0900
S5	98.40 ±0.2660

*mean ±SD(n=3)

Percentage Drug Content Of SR Tablets



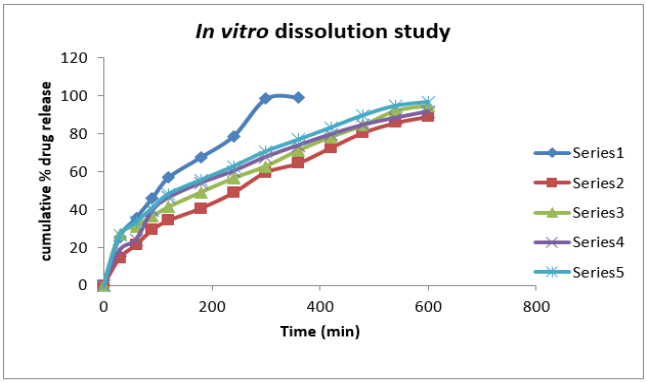
The drug content of all five SR formulations were found to be within the limit i.e the drug content was not less than 90% and not more than 110%.

Time (mins)	Specified limit(IP:2010)	S1*	S2*	S3*	S4*	S5*
0		0 ±0.0000	0 ± 0.0000	0±0.000	0± 0.0000	0 ±0.0000
30		25.46 ±0.0500	14.39 ±0.1500	26.88± 0.0200	18.48± 0.6600	26.18± 0.0500
60	NLT 25%& NMT 50%	35.37 ±0.1300	21.24 ±0.0800	31.12± 0.7200	24.04 ±0.0600	33.21± 0.0550
90		45.85± 0.0900	29.16 ±0.7200	36.26± 0.1500	39.17± 0.1400	40.59± 0.3400
120		56.82± 0.2900	34.19± 0.1700	41.21± 0.1600	46.18 ±0.4500	48.11 ±0.3200
180	NLT 45% &NMT75%	67.54 ±0.5100	40.61 ±0.1600	48.99± 0.0800	53.91± 0.1700	55.56± 0.5000
240		78.69 ±0.2600	48.81± 0.3000	56.44± 0.4800	60.18 ±0.4500	62.71± 0.0500
300		98.51 ±0.2300	59.61 ±0.6060	62.72± 0.3900	67.66± 0.1100	70.66± 0.50000
360		99.01 ±0.4200	64.45 ±0.4200	71.05± 0.1300	73.73 ±0.1400	76.81± 0.2700
420			72.58± 0.0250	78.11± 0.2200	79.55± 0.3200	83.18± 0.2100
480			80.61 ±0.2900	84.33± 0.4800	84.61 ±0.1300	89.73± 0.2100
540			85.85± 0.9630	91.96± 0.3900	88.28± 0.0800	94.72± 0.2360
600	NLT 80%		89.08 ±0.6320	94.76± 0.1400	91.63 ±0.2600	96.78± 0.0200
1440			95.61 ±0.0600	98.71± 0.1400	94.66± 0.2200	98.65± 0.3600

*mean ±SD(n=3)

IN VITRO DISSOLUTION STUDY

In vitro dissolution study of SR tablets



The results of in vitro dissolution SR tablets showed that [40]:

- The Formulation S1 containing HPMC K4M (20%) had released the drug completely in 6hours.
- The formulation S2 containing HPMC K 100M(20%) retarded the release, but did not meet the IP Specifications.
- In S3,S4,and S5 formulations the release of the drug obeyed 1,3,10 hour release specifications as per IP :2010,but the release profile of S3 was sustained when compared to the release profile of others.
- The formulation S3 containing HPMC K4M and HPMC K100M(1:1) retarded the release and met with the IP specifications.
- Based on the comparative release profile, formulation S3 was selected for the final bilayer tablets.

PREPARATION OF BILAYER TABLETS

FORMULATION DEVELOPMENT[41]

1.Optimised immediate layer of Lisinopril was prepared by wet granulation method.
2.Optimised sustained release layer of Metformin hydrochloride was prepared by wet granulation method.
3.The granules were compressed on a bilayer tablet compression machine .

POST COMPRESSION STUDY OF BILAYER TABLETS

The compressed bilayer tablets were evaluated for the following parameters and the values are given in table 35

Post Compression Study Of Bilayer Tablets

Parameters	Bilayer Tablet
Uniformity of Weight(g)*	220.83± 0.76
Thickness(mm)*	3.23 ±0.0067
Diameter(mm)*	8.01 ±0.0630
Hardness(kg/cm^2)*	5.85 ±0.3600
Friability(%)**	0.287 ±0.0120
Drug content Lisinopril % w/w Simvastatin %w/w	99.23% ±0.3600 98.71 %± 0.1400

* Mean SD (n=5) , ** mean SD (n=3)

CONCLUSION

- Success of the *in-vitro* drug release studies recommends the product for further *in-vitro*studies , which may improve patient compliance[42].
- From the literature, it is seen that Lisinopril as an individual dosage form is used in the management of hypertension in patients with dyslipidemia and Simvastatin is used alone or in combination with other antihypertensives[43].
- Combination of Lisinopril as an immediate release layer and Simvastatin as a sustained release layer reduces polytherapy to mono therapy and improves the patient compliance.
- From the results, formulated bilayer tablet provides better *in-vitro* release from the immediate release layer as well as sustained release layer[44].
- The data obtained from the *in-vitro* study for sustained release layer were fitted to various mathematical model like zero order , first order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that, the best fit model was zero order .thus the release of the drug from the dosage form was found to be by diffusion and non-fickian release.
- The stability studies indicated that the bilayer tablets are stable and does not show any significant changes[45].

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