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Research Article

Formulation and Development of Bilayer Tablet Containing Telmisartan and Indapamide

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Abstract

Bilayer tablets of Telmisartan (IR) Indapamide (SR) were formulated for the management of hypertension. In the formulation of immediate release Starch 1500 and Sodium Starch Gycolate were used as super disintegrant. For sustained release portion HPMC polymers were used in granulation stage . Preformulation studies were performed prior to compression. The compressed

bilayer tablets were evaluated for weight variation, dimension, hardness, friability, drug content, disintegration time and invitro drug release using USP dissolution apparatus type 2 (paddle). It was found that the optimized formulation showed 32.1%, 68.%, 82.2%, 96.3% release for Indapamide in 1, 4, 8, 20 hours respectively.However, Telmisartan released 96.7% at the end of 60 minutes.The IR spectrum studies revealed that there is no disturbance in the principal peaks of pure drugs Indapamide and Telmisartan. This further confirms the integrity of pure drugs and no incompatibility of them with excipients. The stability studies were carried out for the optimized batch for three months and it showed acceptable results.

Key words: Bi-layer tablet,Telmisartan, Indapamide.

Introduction

The oral route of drug administration is the most convenient and commonly used method of drug delivery. Layer tablets are composed of two or three layers of granulation compressed together. It makes possible to formulate sustained release preparation as one layer with the immediate release preparation as the second layer. They are preferred for the following reasons: to co-administer two different drugs in the same dosage form,to minimize physical and chemical incompatibilities, for staged drug release, IR and SR in the same tablet,for chronic condition requiring repeated dosing.[1,2]

Hypertension is the most common cardiovascular disease; its prevalence increases with advancing age. Hypertension is the principal cause of stroke, is a major risk factor for coronary artery disease and its complications, and is a major contributor to cardiac failure, renal insufficiency, and dissecting aortic aneurysm. Hypertension is defined as a sustained increase in blood pressure ≥140/90 mm Hg. [3]

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Literature survey shows that, a combination of angiotensin-II receptor antagonist and diuretic agent helps for the improvement in cardiac function after myocardial infarction. Telmisartanl reduces blood pressure (BP) by interfering with the binding of angiotensin II to the angiotensin II AT_1.-receptor by binding reversibly. Indapamide act as a thiazide diuretic.. This combination does not have any pharmacokinetic interaction. A combination of angiotensin-II receptor antagonist and diuretic agent helps for the improvement in cardiac function after myocardial infarction.

Indapamide is Class-II drug and has very short half life i.e. 3-4hrs. So, to Reduce frequency of administration of drug in a day Extended release tablet of Indapamide is formulated.

Telmisartan is Class-II drug and has a longer half life 9-18hrs.[4]

The present work aims to develop a stable and optimized Bilayer dosage form containing one immediate release drug layer and other is sustained release drus layer.

Materials and Methods

Materials

Telmisartan were received from Ami lifesciennce, Indapamide were received from Unichem labs ltd., HPMC K4M, HPMC K 15M, were received from colorcon PVP K 30, Microcrystalline cellulose , Lactose mono hydrate , Starch 1500, Sodium starch glycolate, , Aerosil , Purified talc,Magnesium stearate, mannitol, cross povidon, methanol and Iron oxide red. All chemicals are of analytical grades.

Fourier transforms infrared (FT-IR) spectroscopy

Compatibility studies were carried out to know the possible interactions between Indapamide, Telmisartan and excipients used in the formulation. Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FT-IR spectroscopy. IR spectrum of pure drug and polymers was seen in between 600- 4000 cm^{-1} .

Differential scanning calorimetry (DSC)

To study the compatibility pure drug, physical mixtures of drug and excipients the DSC studies were carried out. The analysis were performed at a standard heating rate of 10 ºC/min over a temperature range of 50 ºC – 200 ºC using a DSC 822 mettler instrument.[5]

Preparation of bilayer tablets

Preparation of Telmisartan immediate release layer:

Mannitol and Starch 1500 and sodium starch glycolate was sifted through sieve 40 #.

Accurately weighed quantity of Sodium Hydroxide pellets was dissolved in methanol (q.s.) followed by addition of Telmisartan under stirring to get clear solution.Now granulate the mixture with granulating solution.The mix were dried until LOD was NMT 1.5%. Add crosspovidon and mix was blended then lubricated with Talc and Magnesium Stearate.

Preparation of Indapamide sustained release layer:

Indapamide, Lactose Monohydrate, MCC PH 101 and half quantity of Methocel (HPMC K4M, HPMC K 15M)were all Sifted through sieve 40 # and Brilliant blue FCF was sifted through sieve 80 #.This mix was granulated with Binder solution (prepared by dissolving accurately weighed quantity of PVP K-30 in IPA under stirring).This mix was dried until LOD was NMT 2% w/w.

The extra granular material i.e. Half quantity of Methocel(HPMC K4M, HPMC K 15M) and Aerosil 200 was sifted through sieve 40 # and blended with dried granules followed by lubrication with magnesium stearate in conta blender.

Weight variation Ten bilayer tablets of each formulation were weighed using an electronic balance and average weight of ten tablets and standard deviation were calculated.

Thickness Thickness of each formulation was measured using vernier calipers. Ten bilayer tablets from batch were used and average values were calculated.

Hardness The hardness of the tablets was determined using Schleuniger hardness tester. It was expressed in Newton (N).

Friability The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). About 20 tablets ($W_{initial}$) were transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were dedusted and weighed again (W_{final}).[6]

Disintegration test It is determined by using USP device which consist of 6 glass tubes that are 3 inches long, open at one end and held against 10 mesh screen at the bottom end of basket rack assembly. To test for disintegration time, one tablet is placed in each tube and the basket arch is positioned in a1 liter beaker of water at 37°C ± 2°C.A standard motor driven device is used to move the basket assembly up and down. To be incompliance with the USP standard, all tablets must disintegrate and all particles must pass through the 10 mesh in the time specified[7]

In vitro dissolution study of Bilayered Tablet The US Pharmacopeia rotating paddle method was used to study the drug release from the Bilayer tablet. The dissolution medium consisted of 500 ml of phosphate buffer pH 6.8 for Indapamide and 0.1N Hydrochloric acid for Telmisartan. The release study was performed at 37^0 C ± 0.5^0 C, with a rotation speed of 50 rpm. The Telmisartan layer releases its content within 60 min, as it is immediate release layer. Indapamide is extended release layer for 20 Hrs, so it releases its content within 20 Hrs. Samples of 5 ml were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.2-µm Whatman filter paper and analyzed after appropriate dilution by HPLC (Merck Hitachi).

Stability Study The optimized formulation was tested for stability of period of 3 Month accelerated study at 40°C ± 75% RH, for their drug content and other parameters.

RESULTS The main aim of this work was to prepare bilayered tablets of Indapamide and Telmisartan, to release the drug at predetermined interval of time i.e. Indapamide within 20hrs and Telmisartan within 60 minutes. HPMC K4M, HPMC K15M, were selected as Release retarding polymers on the basis of their matrix forming properties.

Drug polymer compatibility studies using FTIR

All the characteristic IR peaks related to pure drug, Indapamide and Telmisartan were also appear in the IR spectrum of mixture of Drug-excipients so there was no any chemical incompatibility between drug, polymer and excipients (Fig 1).

Drug polymer compatibility studies using DSC In order to investigate the possible physical interaction between drug and excipients, DSC studies were carried out. The drug exhibited a sharp melting endotherm at 168^0 C and 179^0 Cwhich is the melting point of the Indapamide and,Telmisartan respectively. Similarly the thermograms of the physical mixture of Indapamide and Telmisartan with excipients under study exhibited endothermic peak in the vicinity of its melting point range indicating absence of any drug polymer interactions.

Weight variation and thickness The maximum average weight of the tablets was found to be 545.75 ± 5mg. As none of the formulation shows a deviation (I.P. limit, ± 7.5%) for any of the tablets tested, the prepared formulations comply with the weight variation test (Table 3). The average thickness from all the formulations was found to be 5.0 ± 0.2mm. (Table No.3)

Hardness and Friability Hardness bilayered buccal tablets ranged from 135-150 N.Friability of bilayered tablets was found to be within the limits of conventional

oral tablets stated in the Indian Pharmacopoeia. (Table 3)

Disintegration test Telmisartan layer of 6 Tablets disintegrates within 5-6 minutes (Table No.3)

***In vitro* dissolution studies** Release of drug from the bilayered tablets varied according to the type and ratio of matrix forming polymer. HPMC K15M has excellent release retarding, gelling properties and also helps in sustaining effect. The *in vitro* drug release profile of tablets containing HPMC K15M show cumulative percent drug release for formulation FT_6 & FT_8 were ranging 32.1% & 33.1% during first hour. Also at the end of 4 h, the cumulative percent drug releases were found to vary from 68% & 67.2%. At the end of 8 Hr the cumulative percent drug releases were found to vary from 82.2% & 81%. At the End of 20 Hr the cumulative percent drug releases were found to vary from 96.3% & 95.6%.On physical examination of tablets during dissolution study, it was found that tablets were initially swell and slowly eroded over the period of time (Fig.No.2) (Table No. 4).

Conclusion

The aim of the present study was to develop an optimized formula for bilayer tablet containing Indapamide and Telmisartan for the management of hypertension. Indapamide was planned to design as the sustained release part and Telmisartan as the immediate release part.

After preformulation studies it was decided to prepare Telmisartan and Indapamide by wet granulation method.

For sustained release portion HPMC polymer was used in granulation stage and also extragranularly.In the formulation of immediate release sodium starch glycolate and pregelatinised starch were used as super disintegrant.

Prior to compression the granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio. The compressed bilayer tablets were also evaluated for weight variation, dimension, hardness, friability, drug content, disintegration time and *invitro* drug release.

In the above studies **FT_6** formulation showed promising results. It was further supported by FTIR and DSC analysis which showed that **FT_6** had no interaction with excipients.

The stability studies were carried out for the optimized batch **FT_6** for three months and it showed acceptable results. The kinetic studies of the formulations revealed that diffusion is the predominant mechanism of drug release.

So **FT_6** formulation was considered as the optimized formulation.

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Table 1: Brief summary of formulation of Indapamide

Name of Ingredients	FT_1	FT_2	FT_3	FT_4	FT_5	FT_6	FT_7	FT_8
Indapamide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Lactose Monohydrate	87.03	90	85.32	79.58	77.22	79.31	82	82
MMC PH 101	17.2	20.23	19.11	15.15	17.01	15	17.31	17.31
Iron Oxide Red	0.59	0.59	0.59	0.59	0.59	0.59	0.59	0.59
PVP K-30	6	5	5.8	5.5	6	6	6	6
Methocel K-15M	-	45	80	50	-	90	-	85
Methocel K-4M	80	35	-	40	90	-	85	-
Aerosil 200	0.68	0.68	0.68	0.68	0.68	0.70	0.70	O.70
Magnesium Stearate	2	2	2	2	2	1.90	1.90	1.90
Iso Propyl Alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 2: Brief summary of formulation of Telmisartan

Name of Ingredients	FT_1	FT_2	FT_3	FT_4	FT_5	FT_6	FT_7	FT_8
Telmisartan	40.24	40.24	40.24	40.24	40.24	40.24	40.24	40.24
Mannitol	262.26	262.26	263.26	263.26	262.26	263.26	263.26	261.26
Sodium hydroxide pellets	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50
Methanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Starch 1500	23	-	10	14	-	22	-	24
Sodium Starch Glycolate	-	24	13	9	24	-	22	-
Crosspovidone	8	7	7	7	7	8	8	8
Talc	9	9	9	9	10	10	10	10
Magnesium Stearate	4	4	4	4	3	3	3	3

Table 3: Post Physicochemical Properties Bilayer tablet

Batch No	Av. Wt (mg)	Thickness	Hardness (kg/cm^2)	Disintegration Time	
				Indapamide	Telmisartan
FT_1	545	4.5	135	--	7 min 32 secs
FT_2	545	5.12	140	--	6 min 52 secs
FT_3	545	4.76	135	--	7 min 02 secs
FT_4	545	4.99	138	--	6 min 08 secs
FT_5	545	5.03	138	--	5 min 58 secs
FT_6	545	4.96	142	--	5 min 49 secs
FT_7	545	4.82	148	--	6 min 15 secs
FT_8	545	5.02	145	--	5 min 38 secs

Table 4: dissolution profile of Bilayer tablets containing Indapamide

Batches	Time in Hours			
	1	4	8	20
FT_1	15.3	45.6	58.0	80.7
FT_2	27.0	60.3	77.6	91.0
FT_3	26.2	62.0	79.7	92.7
FT_4	23.0	59.1	75.3	91.4
FT_5	32.6	65.8	80.0	93.1
FT_6	32.1	68.0	82.2	96.3
FT_7	29.0	64.0	78.4	93.7
FT_8	33.1	67.2	81.0	95.6

Table 5: dissolution profile of Bilayer tablets containing Telmisartan

Batches	Time 60 min
FT_1	**92.3**
FT_2	**94.6**
FT_3	**92.4**
FT_4	**93.0**
FT_5	**92.4**
FT_6	**96.7**
FT_7	**93.0**
FT_8	**96.0**

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