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Formulation and Evaluation of Immediate Release Bilayer Tablets of Telmisartan and Hydrochlorothiazide

R.Natarajan*, Nimesh Patel, and N.N.Rajendran,

Swamy Vivekanandha College of Pharmacy, Elayampalayam,Tiruchengode, Tamil Nadu state, India.

Address for correspondence: Prof R.Natarajan,M.Pharm, (Phd). Email ID: nandhinatty@rediffmail.com Mobile No. 09443316550.

Current state of art is witnessing a revolution in new techniques for drug delivery. Nevertheless, convenience of manufacturing and patient compliance has maintained their significant importance in the design of drug delivery systems. The primary aim of this development was to have a stable formulation of Antihypertensive drugs of the Telmisartan and Hydrochlorothiazide immediate release Bilayer tablet, and to study the dissolution profile with the reference product. The Formulation development work was initiated with Wet granulation. Telmisartan is converted to its sodium salt by dissolving in aqueous solution of Sodium Hydroxide, in order to improve solubility and drug release. Lactose Monohydrate and Microcrystalline Cellulose are used as diluents. Starch paste is prepared in Purified Water and is used as the binder. Sodium Starch Glycolate is added as a disintegrating agent. Magnesium Stearate is used as the lubricant. The prepared granules are compressed into Double layer compression machine. The tablets thus formulated with higher proportion of sodium starch glycolate showed satisfactory physical parameters, and it was found to be stable and in-vitro release studies are shown that formulation (F-T5H5) was 101.11% and 99.89% respectively. And the formulation T5H5 is further selected and compared with the release profile of innovator product, it was found to be similar (f_2 factor) to that of marketed product.

Keywords: Bi-layer tablets; Telmisartan; Hydrochlorothiazide; Super Disintegrant

Introduction

The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration (R.Nagaraju et al, 2009). Oral route of drug administration is perhaps the most appealing route for the delivery of drug. The various dosage forms administered orally, the tablet is one of the most preferred dosage forms because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids, and because it is more tamperproof than capsules. The oral bioavailability of drug is dependent on disintegration, dissolution and various physiological factors. In recent years, scientists have focused their attention on the formulation of quickly disintegrating tablets. The task of developing rapidly disintegrating tablets is accomplished by using a suitable diluents and super disintegrant (Sharma Shailesh et al, 2010).

Bi-layer tablets are prepared for both immediate release while second layer designed to release the drug immediately. Bi-layer tablet is suitable for sequential release of two drug in combination and separate two incompatible substances (Bhavesh Shiyani et al, 2008).

Now a day's various developed and developing countries move towards combination therapy for treatment of various diseases and disorders requiring long term therapy such as hypertension and diabetes. Combination therapies have various advantages over monotherapy such as problem of dose dependent side effects minimized. A low-dose combination of two different agents reduces the dose-related risk, the addition of one agent may counteract some deleterious effects of the other. Using low dosage of two different agents minimizes the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet and thus dosage of the single component can be reduced (Ramya P.N et al, 2010).

Hypertension and angina pectoris, the most common cardiovascular diseases, require constant monitoring. Hypertension means high pressure in the arteries. High blood pressure is one of the most important modifiable risk factors for cardiovascular disease. Hypertension is designated as either primary hypertension or secondary Hypertension (AR Mullaicharam et al, 2010).

Telmisartan is used to treat high blood pressure (hypertension) by blocking the hormone angiotensin thereby relaxing blood vessels, causing them to widen. High blood pressure reduction helps prevent strokes, heart attacks, and kidney problems. Telmisartan is an Angiotensin Receptor Blocker (ARB) shows high affinity for the angiotensin II type 1 (AT1) receptors, has a long duration of action, and has the longest half-life of any ARB (24 hours). The Bioavailability of Telmisartan is Poor About 45%, which due to Extensive First Pass hepatic metabolism (S.Ashutoshkumar et al, 2010).

Hydrochlorothiazide is the diuretics of the benzothiadiazine group and has proved very important in the management of mild to moderate hypertension. It inhibits sodium reabsorption in the distal tubules causing increased excretion of sodium and water as well as potassium and hydrogen ions. Hydrochlorhiazide is poorly water soluble drug having plasma half life of 6-8 hrs (Uday Rangole et al, 2008).

Fixed-dose combinations of ARBs with Hydrochlorothiazide are rapidly going acceptance with physician as an effective treatment option for Hypertension. ARBs plus Hydrochlorothiazide provide an effective antihypertensive therapy while promoting patient compliance with the convenience of once-daily dose (Peter.A.Heredith et al, 2008).

The aim of the current research work is to study the release characteristics of a Bilayer tablet containing Telmisartan and Hydrochlorothiazide in the form of immediate tablets, using a Sodium Starch Glycolate A, by wet granulation method.

Materials and Methods

Materials

Telmisartan was obtained as a gift sample from Glenmark pharmaceuticals Ltd, India and Hydrochlorothiazide from IPCA laboratory Ltd, India, Sodium starch glycholate Type A was gifted by Maruti chemicals, Gujarat, India. Povidone K30 was purchased from ISP Technologies, Ahmedabad, India. Light Magnesium Oxide was purchased from Vasa Pharmachem, Gujarat, India. Meglumine was purchased from Merck Pharmaceuticals, India. Sodium Hydroxide pellet was purchased from RFCL Ltd, India. Magnesium Stearate was purchased from Mallinckodt backer, Gujarat, India. Microcrystalline Cellulose was purchased from Gujarat microwax, Ahmedabad, India. Lactose Monohydrate was purchased from DMV International, India.

Methods

Preparation of Bilayer tablets

Granulation of Telmisartan Blend-1

Composition of different trial formulations for the bland-1 is given in **Table-1**

	Ingredients	T1	T2	T3	T4	T5
		Qty(mg)/Tab				
Blend 1						
Dry Mixing						
1	Microcrystalline Cellulose	233	232.1	139.2	135.8	134.1
2	Maize Starch	0	0	92.3	92.3	92.3
3	Sodium Starch Glycolate Type A	6.8	0	3.4	5.1	5.1
4	Povidone K30	17	17	17	17	17
5	Light Magnesium Oxide	0	1.2	1.2	1.2	1.2
Binder Solution						
6	Telmisartan	80	80	80	80	80
7	ium Hydroxide Pellets	1.2	1.2	1.2	1.2	1.2
8	Meglumine	1.2	0	0	0	0
9	Purified Water	Qs	Qs	qs	Qs	Qs
Blending						
10	Sodium Starch Glycolate Type A	0	6.8	3.4	5.1	6.8
11	Magnesium Stearate	2	1.7	2.3	2.3	2.3
	Total Weight	**340**	**340**	**340**	**340**	**340**

Table 1 Composition of Telmisartan formulations

.MCC, Maize starch, SSG, Povidone K30, Light MgO were sifted through Sieve 40 # & mixed well in a Rapid Mixture Granulator for 10 minutes in Dry mixing. Sodium hydroxide pellets were dissolved in purified water**.** Telmisartan was added slowly to it with stirring till clear thick solution was obtained using a mechanical stirrer. (Meglumine was added and dissolved in it only in BatchT1) additional purified water was added as required. Wet mass was dried in a rapid dryer at 55˚ C ± 2˚ C Dried granules were passed through 1.0 mm screen using a multimill. SSG & Magnesium stearate were passed through 40# & mixed with sized granules in a Double cone blender.

Time (minute)	Innovator	T1	T2	T3	T4	T5
10	67.4	25.26%	39.06%	50.83%	55.87%	72.64%
15	86.6	41.33%	54.705	66.23%	70.56%	90.54%
20	95.1	53.93%	69.56%	70.86%	89.52%	95.25%
30	97.5	68.93%	77.60%	89.70%	93.14%	97.13%
45	98.8	74.20%	85.76%	92.03%	96.01%	99.17%
60	102.2	83.10%	90.43%	94.29%	99.94%	101.11%
f2 factor		**30.35**	**39.35**	**47.83**	**60.36**	**83.32**

Table 4 Percentage drug release of Telmisartan formulations

Granulation of Hydrochlorothiazide Blend-2

Composition of different trial formulations for the bland-2 is given in **Table-2**.

Sl No.	Ingredients	H1	H2	H3	H4	H5
		Qty(mg)/Tab				
Blend 2						
Dry Mixing						
1	Hydrochlorothiazide	25	25	25	25	25
2	Lactose Monohydrate	0	0	115.2	115.2	115.2
3	Microcrystalline Cellulose	289.2	289.5	173.7	172	172
4	Povidone K 30	17	0	0	0	0
5	Sodium Starch Glycolate Type A	6.8	0	3.4	4.25	4.25
6	Ferric oxide yellow	Qs	Qs	Qs	Qs	Qs
Binder Solution						
7	Maize starch	0	17	17	17	17
8	Purified Water	**0**	Qs	Qs	Qs	Qs
Blending						
9	Sodium Starch Glycolate Type A	0	6.8	3.4	4.25	4.25
10	Magnesium Stearate	2	1.7	2.3	2.3	2.3

	Total Weight	**340**	**340**	**340**	**340**	**340**

Ferric oxide Yellow was passed through sieve 80 # with a little amount of Lactose. Hydrochlorothiazide, Lactose & Microcrystalline Cellulose were passed through sieve 40 # & mixed with colour in RMG for 15 minutes at slow impeller speed for Dry mixing. Purified water was boiled. Maize Starch was dispersed in purified water and this starch slurry was added slowly to boiling water, stirred till translucent Starch paste was obtained. Wet mass were dried at 55˚ C ± 2˚ C in a rapid dryer. Dried granules were passed through 1.0 mm screen using a multimill. SSG & mg. stearate were passed through sieve 40 # & mixed with sized granules in a Double cone blender.**Compression of Bilayer Tablets**
Granules of Telmisartan and Hydrochlorothiazide layer were filled separately in two different hopper and compressed using 16.2×7.9 mm, D Tolling, oval shape, having plane surface on both side in Double Layer Compression machine.

Physicochemical properties of prepared tablets
The weight variation of the tablets was carried out with 20 tablets using an electronic balance (Mettler Toledo). Friability was determined using 10 tablets in a Roche friabilator (Pharma lab, Ahmedabad, India) for 4 minutes at a speed of 100 rpm. For each formulation, the hardness of 10 tablets was also evaluated using a Dr.Scheleuniger hardness tester. The thickness of the each 10 tablets was measured with a Vernier Caliper.
Drug Content
Weigh and powder 20 tablets. Transfer an accurately weighed quantity of tablet powder equivalent to 80.0 mg of Telmisartan and 25.0 mg of Hydrochlorothiazide into a 50 ml volumetric flask. Added 25 ml of methanol and shaken for ten minutes, the volume was then adjusted to mark with methanol and mixed. The solution was filtered through Whatman filter paper number 41 and the filtrate was then appropriately diluted with mobile phase to get a final concentration. Drug Content was analyzed by HPLC method (Wankhede S.B. et al., 2007) .
***In-Vitro* Dissolution Studies**
Dissolution Studies were carried out as per USP, Using USP dissolution apparatus type 2 with 900 ml of phosphate buffer pH 7.5 and maintained at 37 ± 0.5˚ C at a rotational speed of 75 rpm for 10, 15, 20, 30, 45, 60 minutes.
Analysis
Telmisartan was estimated by 296 nm and Hydrochlorothiazide was estimated by 273 nm by using UV Spectrophotometer.
FT-IR Study
Infrared spectrum was taken (FT-IR, Spectrum RXI, Perkin Elmer, Switzerland) by scanning the sample in Potassium bromide. The samples of pure drug and excipients were scanned.

Results and Discussion
The FT-IR spectrum of Telmisartan and Hydrochlorothiazide with excipients was shown in figure 1 and 2.

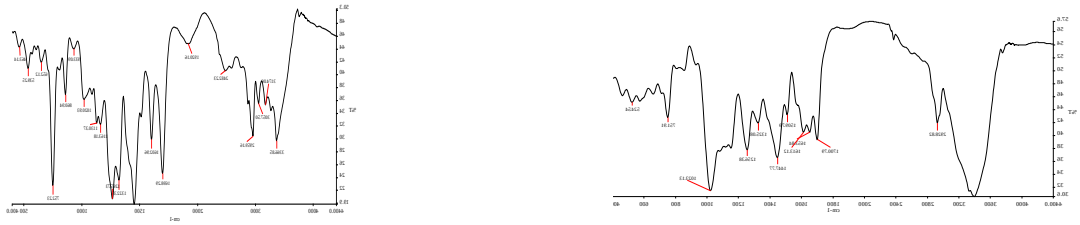

Figure 1 FT-IR Spectrum of a) telmisartan pure b) drug+ excipient

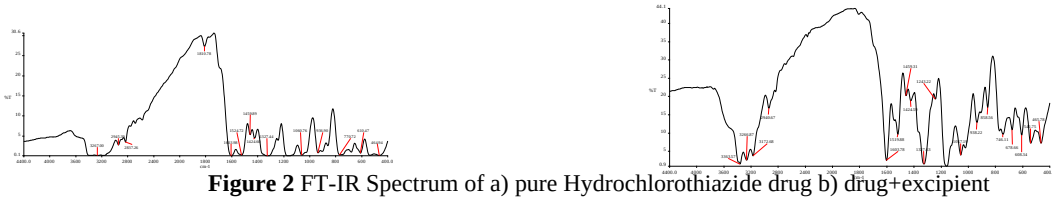

Figure 2 FT-IR Spectrum of a) pure Hydrochlorothiazide drug b) drug+excipient

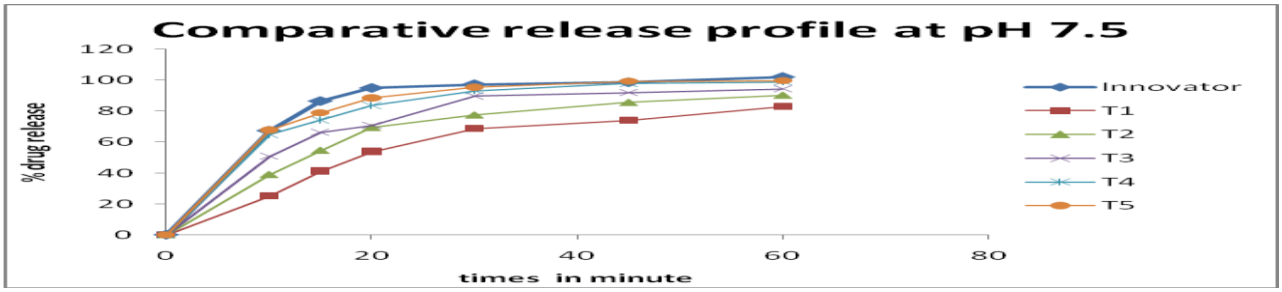

Figure 3 percentage drug release of telmisartan formula (T1-T5)

The spectra revealed the presence of peak at 1698.29 cm^{-1} and 1327.44 cm^{-1} respectively, indicating that there was no interaction between the drug-excipients used in the study.
Tablet Characteristics
Telmisartan was converted to its sodium salt by dissolving in aqueous solution of Sodium Hydroxide, in order to improve solubility and drug release of Telmisartan from the formulation. Hydrochlorothiazide is a yellow colour. Microcrystalline Cellulose, Lactose Monohydrate and Maize Starch are used as diluents. Sodium Starch Glycolate Type A is added as a disintegrating agent. Povidone K30 is used as binder. Light Magnesium Oxide is used as alkalizing agent. Magnesium Stearate is used as the lubricant. The tablet of different formulation was subjected to

various evaluation tests such as weight variation, hardness, thickness, friability, and drug content. The results of these parameters are given in **Table 3.** The Physico-chemical properties have been studies. Based on the result obtained, all the formulations (T1H1-T5H5) were having properties with in the standard limits

S. no	Formulations	Tablet weight (mg)	Hardness (neutons)	Thickness (mm)	Friability (%)	Disintegration (seconds)	Drug Content (%)
1	T1H1	679.63	180.0	7.06	0.15	150.0	T1-98.53 H1-97.39
2	T2H2	680.60	162.0	6.84	0.13	120.0	T2-97.91 H2-97.45
3	T3H3	680.20	159.3	6.73	0.12	90.0	T3-97.45 H3-99.03
4	T4H4	680.30	156.6	6.24	0.11	60.0	T4-98.01 H4-99.11
5	T5H5	680.0	152.67	6.10	0.10	50.0	T5-99.10 H5-99.37

Table 2 Composition of Hydrochlorothiazide formulation

Table 5

	Innovator	H1	H2	H3	H4	H5
10	77.9	20.89%	38.27%	42.36%	81.85%	81.85%
15	82.4	28.86%	56.73%	60.66%	85.2%	85.20%
20	86.9	36.87%	65.52%	71.41%	91.51%	91.51%
30	90.5	51.89%	77.62%	78.50%	92.8%	92.80%
45	97.2	69.89%	83.77%	85.93%	96.74%	96.74%
60	100.3	75.15%	87.38%	90.47%	99.89%	99.89%
f2 factor		**25.52**	**39.47**	**42.82**	**81.82**	**81.82**

Table 5 Percentage drug release of Hydrochlorothiazide formula (H1-H5)

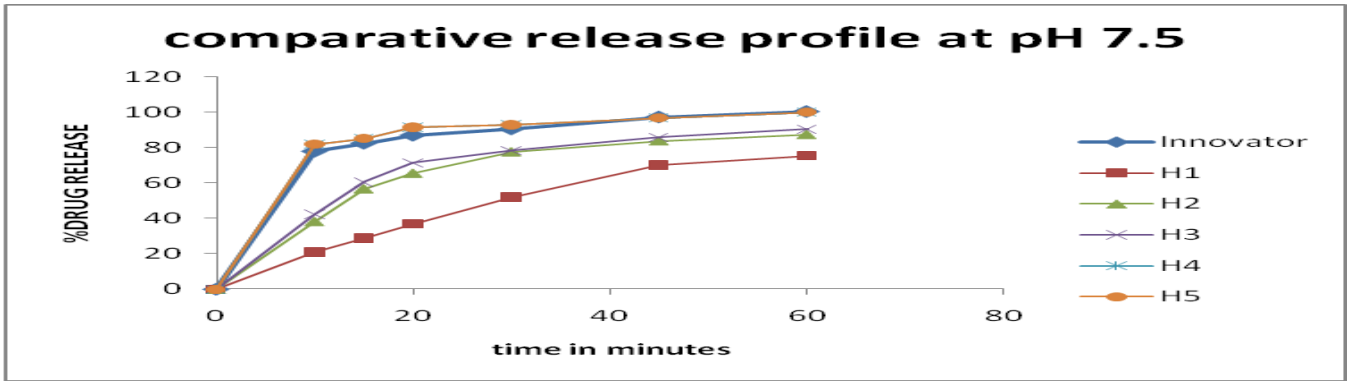

Figure 4 Percentage drug release of Hydrochlorothiazide formulations (H1-H5)

***In Vitro* Dissolution Studies**

Dissolution sample were analyzed by UV Spectrophotometer method. For Telmisartan, the concentration range was 4-24 µg/ml and the correlation coefficient was 0.99. For Hydrochlorothiazide, the concentration range was 4-24 µg/ml and the correlation coefficient was 0.99. The percentage *in vitro* drug release from formulation T1H1-T4H4 was not satisfactory. But in the formulation T5H5 (i.e T5-101.11%, H5-99.89%) it was observed that dissolution release pattern was similar to that by the marketed product.

Drug Content

The formulation (T5H5) shows the maximum Drug Content (i.e.T5-99.10% and H5- 99.37%).

Conclusion

In the present study we can conclude that immediate release Bilayer tablets of Telmisartan & Hydrochlorothiazide (80+25) mg were successfully prepared by wet granulation method and Superdisintegrant using sodium Starch Glycolate Type A and their evaluation were carried out. Drug release from the developed formulations matched with Innovator and also found to be stable formula and f_2 (similarity factor) value are similar.

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