ORIGINAL PAPERS

Polim. Med. 2016, **46**, 1, 5–15
DOI: 10.17219/pim/62511

ISSN 0370-0747

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Development of Bilayer Tablets with Modified Release of Selected Incompatible Drugs

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Abstract

Background. The oral route is considered to be the most convenient and commonly-employed route for drug delivery. When two incompatible drugs need to be administered at the same time and in a single formulation, bilayer tablets are the most appropriate dosage form to administer such incompatible drugs in a single dose.
Objectives. The aim of the present investigation was to develop bilayered tablets of two incompatible drugs; telmisartan and simvastatin.
Material and Methods. The bilayer tablets were prepared containing telmisartan in a conventional release layer using croscarmellose sodium as a super disintegrant and simvastatin in a slow-release layer using HPMC K15M, Carbopol 934P and PVP K 30 as matrix forming polymers. The tablets were evaluated for various physical properties, drug-excipient interactions using FTIR spectroscopy and in vitro drug release using 0.1M HCl (pH 1.2) for the first hour and phosphate buffer (pH 6.8) for the remaining period of time. The release kinetics of simvastatin from the slow release layer were evaluated using the zero order, first order, Higuchi equation and Peppas equation.
Results. All the physical parameters (such as hardness, thickness, disintegration, friability and layer separation tests) were found to be satisfactory. The FTIR studies indicated the absence of interactions between the components within the individual layers, suggesting drug-excipient compatibility in all the formulations. No drug release from the slow-release layer was observed during the first hour of the dissolution study in 0.1M HCl. The release-controlling polymers had a significant effect on the release of simvastatin from the slow-release layer. Thus, the formulated bilayer tablets avoided incompatibility issues and proved the conventional release of telmisartan (85% in 45 min) and slow release of simvastatin (80% in 8 h).
Conclusions. Stable and compatible bilayer tablets containing telmisartan and simvastatin were developed with better patient compliance as an alternative to existing conventional dosage forms **(Polim. Med. 2016, 46, 1, 5–15).**

Key words: sustained release, release kinetics, bilayer tablet, incompatible, conventional release.

For the treatment of diseased conditions, drugs can be administered through various routes such as oral, submucosal, percutaneous, pulmonary, parenteral, etc. The oral route is considered to be the most convenient and commonly-employed route for drug delivery [1, 2]. Tablets are the most preferred and traditional dosage form. Conventional tablets are not suitable where multiple drugs are mandatory for the treatment of chronic disease conditions and the drugs used are incompatible with each other. In such situations, bilayer tablets are the most suitable dosage form to administer incompatible drugs in a single dose [3, 4]. Therapeutic strategies based on bilayer tablets are more popular due to improved patient compliance because of the reduced number of dose administrations [5, 6]. Bilayer tablet technology is a new era for successful modified drug delivery, loading a dose from the conventional/fast-release layer and a maintenance dose from the slow release layer [7–9]. Bilayer tablets have demonstrated their applicability for dosing regimens where a simple

conventional or sustained release of drugs does not entirely satisfy the therapeutic objective.

Hypertension may increase the lipid level of a patient characterized as hypercholesterolemic. In such situations, a combination therapy is recommended to decrease the blood pressure and control lipid level. Combination therapy for the treatment of such a condition generally refers to either the simultaneous administration of two or more drugs or to the combination of different types of therapies. Telmisartan (TSM) is an angiotensin II receptor antagonist (angiotensin receptor blocker) used in the management of hypertension. It works by relaxing the blood vessels, which helps to lower blood pressure. Simvastatin (SVT) is used in the treatment of primary hypercholesterolemia and is effective in reducing total and LDL-cholesterol as well as plasma triglycerides and apolipoprotein B. These drugs are reported to have compatibility problems [10].

Therefore, after considering the above facts, the present project was designed to develop a bilayer tablet system using TSM and SVT as model drugs for conventional and slow-release layers, respectively. The tablets are formulated in such a way that, during the first hour of dissolution, all of the TMS is intended to be released without releasing the SVT, and the SVT will release later as a modified release.

Materials and Methods

Materials

The TMS was received as a gift sample from Medley Pharmaceuticals Ltd., Daman, India. The SVT was received as a gift sample from Lincoln Pharmaceuticals Ltd., Ahmedabad, India. Croscarmellose sodium and HPMC K15 M were purchased from SD Fine Chem. Ltd., Mumbai, India. PVP K 30 was purchased from Central Drug House (P) Ltd., Mumbai. Microcrystalline cellulose, lactose and Carbopol 934P were purchased from Yarrow Chem Products, Mumbai, India.

Pre-Formulation Studies

Various pre-formulation parameters were evaluated and considered before focusing on the formulation development with TMS and SVT.

The melting point apparatus, calibrated using L-ascorbic acid AR and sodium bicarbonate AR, was used for the determination of the melting point of TMS and SVT using the capillary fusion method. The melting points of both the drugs were recorded and compared with literature values.

The λ_{max} of both drugs was determined using a UV spectrophotometer (UV 3000$^+$, Labindia Instruments, Mumbai, India). The TMS (100 mg) and SVT (100 mg) were accurately weighed and transferred separately to 100 mL volumetric flasks. The TMS was dissolved and diluted up to 100 mL with 0.1M HCl (pH 1.2) and the SVT was dissolved and diluted up to 100 mL with a phosphate buffer (pH 6.8) to obtain 1000 μg/mL concentrations. From this solution, 1 mL was taken and diluted up to 10 mL and scanned for λ_{max} at a range of 200–400 nm.

The Fourier transform infrared spectroscopy (FTIR) method was used to examine the interactions, if any. The FTIR spectral analysis of TMS, SVT, the SVT layer, the TMS layer, and a physical mixture of the TMS and SVT layers were carried out using the KBr disc method using FTIR spectroscopy (IR affinity-1, Shimadzu Corporation, Japan). The sample disc was scanned from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}.

Preparation of Granules

For the preparation of granules, all the powder materials were passed through a #80 sieve. The finely sifted materials were dry mixed using a mortar and pestle. The granules for the SVT layer were prepared using starch paste or starch powder as a binder. The TMS layer granules were prepared using isopropyl alcohol. The granulated mass of both the layers was separately passed through a #16 sieve and dried in a hot air oven at 35–40°C. The dried granules were passed through a #22 sieve.

Evaluation of Granules

The purpose of the granule evaluation was to investigate the effects of granule size distribution on the mechanical properties of the prepared bilayer tablets. The resulting granules were evaluated for their micromeritic characterization such as bulk density, tapped density, Hausner ratio, Carr's index and angle of repose.

Determination of Bulk Density and Tapped Density

Different fractions of the granules of both layers were taken into a 10 mL graduated measuring cylinder separately and the volume was noted down. The graduated measuring cylinder was tapped 50 times using USP bulk density apparatus (ETD 1020, Electrolab, Mumbai, India). The bulk density and tapped density were determined using the following formula [11]:

$$\text{Bulk density} = \text{Weight of the granules} \times \text{Initial volume}$$

$$\text{Tapped density} = \text{Weight of the granules} \times \text{Final volume after tapping}$$

Determination of Hausner Ratio

The density measurements were used to determine the Hausner ratio using the following formula:

$$\text{Hausner ratio} = \text{Tapped density} \times \text{Bulk density}$$

Carr's Index

Carr's index is 100 times the ratio of tapped density minus bulk density to tapped density. The density measurements were used to determine Carr's index using the following formula:

$$\text{Carr's Index} = \text{Tapped density} - \text{Bulk density/Tapped density} \times 100$$

Angle of Repose

For the determination of angle of repose, the granules of both the layers were poured through a funnel, which was fixed at a position such that its lower tip was at a height of 2 cm above the surface. The granules of both the layers were poured separately until the tip of the granule pile surface touched the funnel. The $\tan^{-1}$ of the ratio of the height of the pile and the radius of its base gave the angle of repose. The angle of repose was determined using the following formula:

$$\theta = \tan^{-1}h/r$$

Where h is the height of the pile, and r is the radius of the base of the pile.

Preparation of Bilayer Tablets

The conventional release layers contained TMS and the slow-release layer contained SVT as the model drug, respectively. The composition of the TMS and SVT layers are presented in Table 1 and Table 2, respectively. The granules were compressed using a 10 station rotary tablet compression machine (M26 A12, Karnavati Engineering Limited, Ahmedabad, India) using 6 mm round, flat-faced punches. The bilayer tablets were prepared using a double compressing procedure. The compressed tablets were evaluated for various parameters.

Table 1. Composition of various trial formulations for the TMS layer containing telmisartan

Formulation code	Ingredients				
	telmisartan (mg)	croscarmellose sodium (mg)	microcrystalline cellulose (mg)	lactose (mg)	aerosil (mg)
F_1	12	0	20.5	66	1.5
F_2	12	3	17.5	66	1.5
F_3	12	6	14.5	66	1.5
F_4	12	9	11.5	66	1.5
F_5	12	3	17.5	66	1.5
F_6	12	3	17.5	66	1.5
F_7	12	3	17.5	66	1.5
F_8	12	3	17.5	66	1.5

Table 2. Composition of various trial formulations for the SVT layer containing simvastatin

Formulation code	Ingredients						
	simvastatin (mg)	HPMC K15 M (mg)	carbopol 934P (mg)	PVP K 30 (mg)	croscarmellose sodium (mg)	DCP (mg)	binder
F_1	8	57	56	26	–	–	starch paste (5% w/v)
F_2	8	57	56	26	–	–	starch paste (3% w/v)
F_3	8	57	56	26	–	–	starch paste (2% w/v)
F_4	8	57	56	26	–	–	starch powder
F_5	8	57	55	26	1	–	starch paste (5% w/v)
F_6	8	57	55	26	–	1	starch paste (5% w/v)
F_7	8	56	55	26	2	–	starch paste (5% w/v)
F_8	8	56	55	26	–	2	starch paste (5% w/v)

Evaluation of Bilayer Tablets

Appearance

The tablets were evaluated for cracks, surface irregularities, shape and size.

Hardness

The hardness of a tablet is defined as force applied across the diameter of the tablet in order to break the tablet. The hardness of the tablets (20 tablets from each batch) was measured using a Monsanto hardness tester (Cadmach, Ahmedabad, India).

Thickness

The thickness of the tablets (20 tablets from each batch) was determined using Vernier calipers (Mitutoyo, Japan).

Weight Variation

The weight variation test was carried by selecting 20 tablets randomly from each batch and the average weight was calculated. The deviations (as per USP, ± 7.5% limit for 130 to 324 mg tablets) of individual weight from the average weight were calculated [12].

Friability

Twenty tablets were placed in Roche tablet friabilator (EF–2, Electrolab, India), and the friabilator was operated for 4 min at 25 rpm. The tablets were dedusted and the loss in weight caused by fractures or abrasion was recorded as the percentage friability using the following formula:

$$\text{Friability \%} = \text{Initial weight} - \text{Final weight/Initial weight} \times 100$$

Layer Separation Test

A friability test was performed to investigate the layer adhesion integrity and layer separation risk in the bilayer tablets.

Disintegration Test

Disintegration is the process of the tablet breaking into smaller particles. USP tablet disintegration test apparatus (EF2, Electrolab, Mumbai, India) was used to evaluate the tablet disintegration time. One tablet was placed in each cylindrical tube; a basket rack was positioned in a 1 L beaker containing 900 mL of phosphate buffer, pH 6.8 at 37 ± 0.5°C.

Drug Content

Ten tablets were individually weighed and crushed using a mortar and pestle. A quantity equivalent to the mass of 100 mg of the drug was dissolved in 100 mL of 0.1M HCl (pH 1.2) for the TMS layer and 100 mg of SVT was dissolved in 100 mL of a phosphate buffer (pH 6.8) for the SVT layer. The solution was filtered through Whatman filter paper. The drug content was determined by UV visible-spectroscopy at wavelengths 290 nm and 237 nm for the TMS and SVT layers, respectively.

In Vitro Dissolution Test

In order to simulate the pH changes, two dissolution media, 0.1M HCl (pH 1.2) and phosphate buffer (pH 6.8), were sequentially used. For the first hour, the 0.1M HCl (pH 1.2) was used and then the medium was replaced with the phosphate buffer (pH 6.8) for the next 7 h. *In vitro* drug release studies were carried out using USP dissolution test apparatus II (DS 8000, Labindia, Mumbai, India) containing 900 mL of dissolution medium operated at 100 rpm, 37 ± 0.5°C. At different time intervals, 5 mL of the samples were withdrawn and replaced with 5 mL of fresh dissolution medium to maintain the sink conditions. The samples were analyzed by UV spectrophotometer (UV 3000$^+$, Labindia Instruments, Mumbai, India) using a multi-component mode of analysis.

The drug release data was statistically analyzed by two-way ANOVA followed by Bonferroni post-tests to verify the applicability of the various models using Graph Pad Prism v5.1 software (Graph Pad Prism Software, Inc., San Diego, California). The p value of < 0.0001 was considered statistically significant.

The drug release data of the SVT layer underwent kinetic analysis using the zero and first order equations to determine the drug release kinetics. For further confirmation of the order of release, the dissolution data was plotted according to the Higuchi equation, which gives steady-state drug release:

$$Q = (D\,\varepsilon/\tau)\,(2C_{tot} - C_s)\,C_s\,t_{1/2}$$

Where Q is the amount of drug released per unit area exposed to the solvent, D is the diffusion coefficient of the drug in the permeating fluid, ε Is the porosity of the matrix, τ is the tortuosity of the matrix, C_{tot} is the concentration of the solid drug in the dissolution medium, C_s is the saturation drug and t is the time. Assuming that the diffusion coefficient and other parameters remain constant during the release, the above equation reduces to:

$$Q = Kt_{1/2}$$

Thus, for a diffusion-controlled release mechanism, a plot of the cumulative percentage of the drug released vs. square root of time should be linear. The linearity of the plots was confirmed by the calculation of the correlation coefficient.

To find out the mechanism of drug release, and also to verify whether the diffusion is Fickian or non-Fickian, the *in vitro* dissolution data of all the batches was plotted according to the Peppas equation, in which log cumulative percentage of drug release was plotted against log time.

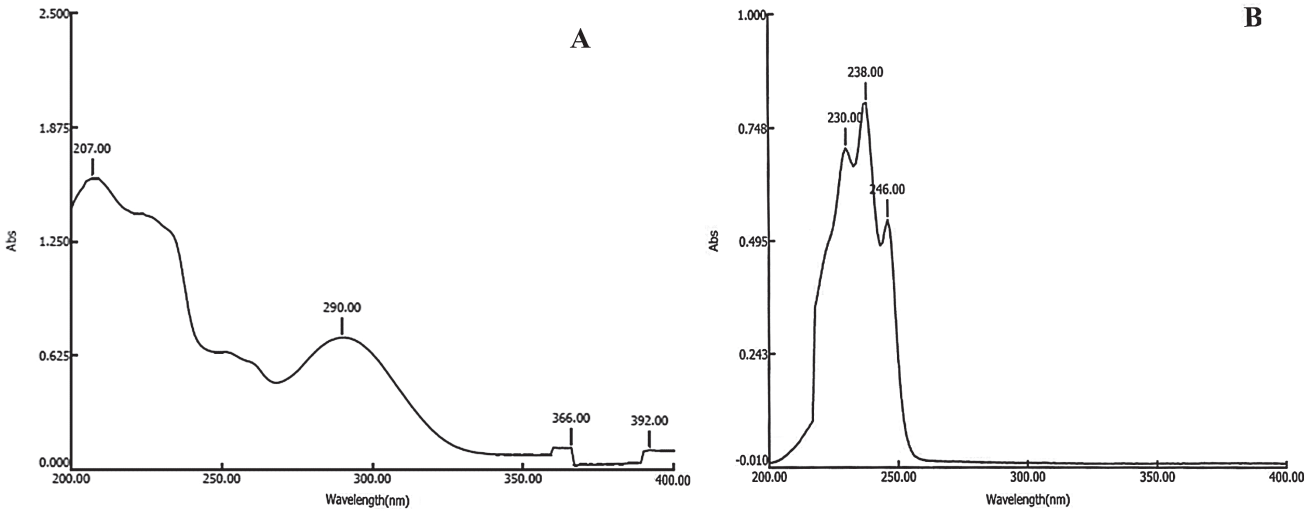

Fig. 1. UV scan spectrum of TMS in 0.1M HCl, pH 1.2 (A), and SVT in methanol (B)

Results and Discussion

Pre-Formulation Studies

It was observed that the TMS used for the development of the bilayer tablet was an odorless, white to pale-yellow crystalline powder while the SVT was a white, non-hygroscopic, crystalline powder.

On calibration of the melting point apparatus with L-ascorbic acid AR (observed melting point 141°C, reported melting point 142–145°C) and sodium bicarbonate AR (observed melting point 271°C, reported melting point 270°C), a correction factor of –1°C was documented. The observed melting points of TMS and SVT were 264°C and 137°C, respectively, which correspond to the literature values of 261–263°C for TMS [13] and 135–138°C for SVT [14], and proves the identity and purity of both the drugs used.

The solutions of TMS and SVT with a concentration of 8 μg/mL in 0.1M HCl (pH 1.2) and phosphate buffer (pH 6.8), respectively, were scanned for λ_{max} in 200–400 nm in the spectrum basic mode. The recorded λ_{max} values for TMS and SVT were 290 and 238 nm, respectively. The scan spectra of TMS and SVT in different selected media are shown in Figure 1.

The purity, identification of the drugs and drug-excipient compatibility were confirmed on the basis of the results of the FTIR spectroscopy study. The FTIR spectrum of SVT, TMS, the SVT layer, the TMS layer and the mixture of both the layers of the bilayer tablet are shown in Figure 2. The major spectral bands of the SVT and TMS are presented in Table 3. All the peaks of SVT were present in the FTIR spectrum of the layer containing SVT, which confirms that there was no chemical interaction between the drug and excipients of the corresponding layer. Similarly, from the FTIR spectrum of the layer containing TMS, it is evident that there was no chemical interaction between the TMS and excipients of the corresponding layer, as all the principal peaks of the drug are present in the spectrum of the tablet layer. No significant shift or reduction in drug peak intensity was observed in the case of both layers separately. A significant reduction in peak intensity, shifting in peak positions and disappearance of drug peaks was observed when the FTIR spectrum of the physical mixture of both layers was examined, indicating an incompatibility problem of the selected drugs.

Table 3. Assignment of bands in FTIR spectrum for telmisartan and simvastatin

Peak positions		Vibration
Telmisartan	1772	C=O stretching vibration
	3132	O-H stretching vibration
	3647	O-H stretching vibration
	1697	C=O stretching vibration
	1352	C-N stretching vibration
	1296	C-N stretching vibration
	1153	C-N stretching vibration
	1481	CH_3 bending vibration
	1382	CH_3 bending vibration
Simvastatin	3550	Free O-H stretching vibrations
	1309	C-H stretching vibrations
	2929	C-H stretching vibrations
	1269	Stretching vibrations of ester
	1165	Stretching vibrations of lactones carbonyl functional groups
	3749	O-H stretch
	2968	C-H stretch vibrations
	1165	Stretch vibrations of C-O and –C=O carbonyl functional group

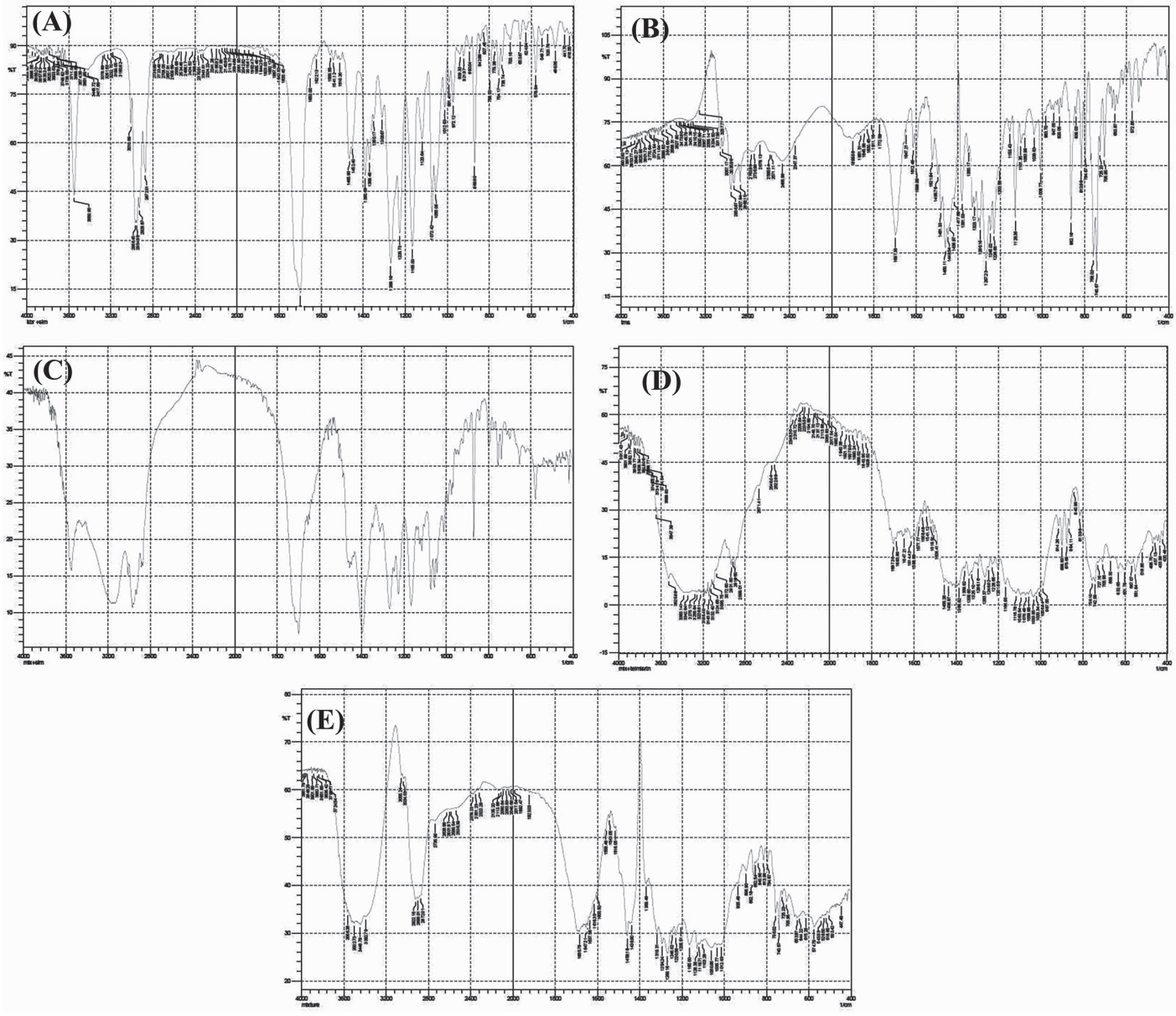

Fig. 2. FTIR spectrum of SVT (A), TMS (B), SVT layer (C), TMS layer (D) and physical mixture of SVT and TMS layers containing telmisartan and simvastatin (E)

Evaluation of Granules

Bulk Density and Tapped Density

The results of bulk density and tapped density are represented in Tables 4 and 5. The bulk density of the blends of all the batches ranges from 0.489 ± 0.011 gmmL^{-1} to 0.903 ± 0.012 gmmL^{-1} and from 0.631 ± 0.005 gmmL^{-1} to 1.061 ± 0.017 gmmL^{-1}, respectively, for the TMS and SVT layers. The tapped density of all the batches ranges from 0.471 ± 0.014 gmmL^{-1} to 0.543 ± 0.020 gmmL^{-1} and from 0.627 ± 0.010 gmmL^{-1} to 0.663 ± 0.006 gmmL^{-1}, respectively, for the TMS and SVT layers. The differences in the values of bulk density and tapped density indicate that the change in volume is very low, even after tapping, and had nearly the same flow properties.

Angle of Repose (θ)

The flow property of all the blends was studied by calculating angle of repose (θ) and Carr's index. The values of angle of repose (θ) for the blends of the TMS layer and SVT layer ranges between 28.39–33.69° and 25.43–31.48°, respectively, (Tables 4 and 5) indicating reasonable or good flow potential of the blends.

Carr's Index

The compressibility index is an indication of the cohesiveness of the particles. A percent compressibility (Carr's index) between 5–15% and 15–20% indicates excellent and good flowability, respectively. However, a value > 30% indicates poor flow. The Carr's index results of the granules of the TMS layer and the SVT layer were within the range of from $14.51 \pm 0.20\%$ to

Table 4. Results of various micromeritic parameters of granules of the TMS layer

Formulation code	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner ratio	Angle of repose (θ)
F_1	0.827 ± 0.010	1.022 ± 0.016	19.11 ± 1.17	1.236 ± 0.017	29.74
F_2	0.612 ± 0.030	0.748 ± 0.040	18.18 ± 0.47	1.22 ± 0.170	31.21
F_3	0.821 ± 0.010	1.032 ± 0.016	20.43 ± 1.15	1.257 ± 0.018	29.05
F_4	0.489 ± 0.011	0.631 ± 0.005	22.53 ± 1.20	1.290 ± 0.020	33.69
F_5	0.755 ± 0.023	0.970 ± 0.038	22.16 ± 0.68	1.284 ± 0.011	32.82
F_6	0.903 ± 0.012	1.061 ± 0.017	14.51 ± 0.20	1.169 ± 0.002	32.59
F_7	0.618 ± 0.020	0.756 ± 0.030	18.25 ± 0.56	1.220 ± 0.242	28.39
F_8	0.707 ± 0.013	0.872 ± 0.020	18.82 ± 3.41	1.233 ± 0.051	30.46

Table 5. Results of various micromeritic parameters of granules of the SVT layer

Formulation code	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner ratio	Angle of repose (θ)
F_1	0.515 ± 0.150	0.662 ± 0.012	22.16 ± 0.862	1.283 ± 0.014	25.43
F_2	0.491 ± 0.010	0.639 ± 0.005	23.20 ± 1.580	1.301 ± 0.027	28.67
F_3	0.543 ± 0.020	0.659 ± 0.006	17.63 ± 2.450	1.213 ± 0.035	27.54
F_4	0.520 ± 0.016	0.635 ± 0.005	18.16 ± 1.950	1.221 ± 0.029	30.72
F_5	0.531 ± 0.010	0.663 ± 0.006	19.90 ± 1.320	1.247 ± 0.021	31.48
F_6	0.507 ± 0.016	0.637 ± 0.005	20.53 ± 1.920	1.257 ± 0.030	29.53
F_7	0.498 ± 0.011	0.633 ± 0.009	21.36 ± 0.650	1.270 ± 0.010	28.95
F_8	0.471 ± 0.014	0.627 ± 0.010	24.90 ± 1.100	1.330 ± 0.020	30.56

22.53 ± 1.200% and from 17.63 ± 2.450% to 24.90 ± ± 1.100%, respectively (Tables 4 and 5). The granules of each layer exhibited Carr's index < 30%, indicating reasonable or good flow properties.

Hausner Ratio

The Hausner ratio is also indicative of the flow property of the powdered blend. The Hausner ratio of all the batches was from 1.220 ± 0.242 to 1.290 ± 0.020 and from 1.213 ± 0.035 to 1.330 ± 0.020, respectively, in the case of the TMS and SVT layers (Tables 4 and 5), which indicated reasonable or good flow properties of all the powder blends of all the batches.

Fig. 3. General appearance of the prepared bilayer tablet

Evaluation of Bilayer Tablets

The color of the TMS layer was white, whereas the SVT layer was off-white (Figure 3). The tablets were free of cracks and depressions. Both of the layers were adhered properly to each other. Both of the layers were distinguishable due to the color difference. Any significant variation in tablet weight may lead to either under- or over-medication. Similarly, layer separation is one of the major tablet defects which can be observed during the compression and transportation of bilayered tablets. Both the parameters were checked regularly during tablet preparation. No layer separation was observed in the prepared tablets. The effect of binder concentration or type on tablet properties in terms of friability, hardness, disintegration and layer separation is shown in Table 6. Friability and layer separation decreased as binder concentration increased. This might be due to the formation of stronger interparticular bonds between the granules during the compression stage.

Hardness

The hardness of the tablet is an indication of its strength. The effect of binder type and/or binder concentration on tablet hardness is shown in Table 6. An increase in tablet hardness was observed with

Table 6. Results of various tablet evaluation tests

Formulation code	Hardness (kg/cm^2)	Friability (%)	Layer separation test	Disintegration test (min)	
				TMS layer	SVT layer
F_1	7.2 ± 0.16	0.619 ± 0.15	–	15 ± 1	*
F_2	6.1 ± 0.29	0.782 ± 0.11	–	8 ± 1	*
F_3	6.5 ± 0.47	0.632 ± 0.21	–	5 ± 2	*
F_4	5.3 ± 0.35	0.667 ± 0.16	+	4 ± 1	*
F_5	5.8 ± 0.16	0.587 ± 0.22	–	8 ± 1	*
F_6	7.5 ± 0.23	0.612 ± 0.17	–	8 ± 1	*
F_7	6.8 ± 0.64	0.724 ± 0.16	–	7 ± 1	*
F_8	7.9 ± 0.72	0.531 ± 0.19	–	7 ± 2	*

– no layer separation; + layer separation in some tablets; * not disintegrated completely till the end of 2 h.

Table 7. Results of weight variation and thickness test

Formulation code	Average weight of tablet (mean ± SD, n= 10)	Average thickness of bilayer tablet (mm) (mean ± SD, n= 10)
F_1	249.0 ± 0.47	4.12 ± 0.18
F_2	251.2 ± 0.72	4.15 ± 0.06
F_3	250.5 ± 0.52	4.20 ± 0.14
F_4	250.4 ± 0.34	4.11 ± 0.17
F_5	250.8 ± 0.51	4.22 ± 0.02
F_6	251.5 ± 0.34	4.17 ± 0.07
F_7	251.7 ± 0.37	4.10 ± 0.08
F_8	252.0 ± 0.22	4.14 ± 0.15

an increase in binder concentration. During the hardness test, it was observed that the TMS layer breaks first, followed by the breaking of the SVT layer.

Uniformity of Tablet Weight and Tablet Thickness

The average weight of the tablets was found to be from 249.0 ± 0.47 mg to 252.0 ± 0.22 mg (Table 7). The prepared tablets comply with the weight variation test, as none of the formulations show a deviation of more than ± 7.5%. The average thickness of the bilayer tablet from all the formulations was found to be from 4.10 ± 0.08 to 4.22 ± 0.02 mm (Table 7). The percent deviation in tablet thickness was found to be 0.02 to 0.18, which is within permissible limits.

Content Uniformity

The maximum percent drug content for all the formulations was found to be 100.08% and 100.42%, respectively for TMS and SVT. The minimum percent drug content for all the formulations was found to be 96.08% and 96.77%, respectively for TMS and SVT, which is within the USP specifications (Table 8).

In Vitro Drug Release

To qualify the dissolution test from the conventional release tablets, the amount of drug dissolved in 45 minutes should be > 80% [15]. Considering gastric pH, the dissolution study for the first hour was performed in 0.1M HCl (pH 1.2). Further, in order to simulate gastric conditions and to investigate the effects of dis-

Table 8. Results of content uniformity test

Formulation code	Telmisartan		Simvastatin	
	amount of telmisartan (mg/tablet)	drug content (%)	amount of simvastatin (mg/tablet)	drug content (%)
F_1	11.53 ± 0.16	96.08	8.01 ± 0.89	99.82
F_2	11.68 ± 0.34	97.56	7.82 ± 0.67	97.82
F_3	11.57 ± 0.81	97.35	7.94 ± 0.84	98.16
F_4	11.67 ± 0.65	97.40	7.53 ± 0.95	96.87
F_5	10.70 ± 0.10	96.72	7.81 ± 0.37	96.77
F_6	12.02 ± 0.17	100.08	7.98 ± 0.29	97.38
F_7	11.36 ± 0.43	97.15	7.92 ± 0.45	97.84
F_8	11.96 ± 0.72	97.93	8.03 ± 0.58	100.42

The values are expressed as mean ± SD, n = 3.

solution medium pH on the dissolution behavior of the SVT layer, the dissolution studies were continued with a sequential change of the dissolution medium (phosphate buffer, pH 6.8). The SVT layer was intact during the first hour of the dissolution study in 0.1M HCl, but dissolved slowly thereafter at the higher pH (phosphate buffer, pH 6.8). There was absolutely no drug release from the SVT layer in the acidic medium, indicating the sequential drug release of both drugs. The presence of rate-controlling polymers and increased hardness of the SVT layer due to double compression are responsible for retarding the disintegration and dissolution rates. The drug release from the TMS layer was significantly increased with an increase in the concentration of croscarmellose. The highest drug release was found in the case of formulation F_4 (93.84 ± 0.99%) after 1 h. Binder type and concentration had a negative effect on drug release. The release rate decreased with an increase in binder concentration. Starch paste was found to be more effective for retarding the drug release as compared to starch powder. Drug release was found to increase with an increase in the concentration of the superdisintegrant. A high release rate was observed in the formulations containing croscarmellose sodium (Ac-Di-Sol) as the superdisintegrant, when compared to dicalcium phosphate (DCP). This might be due to the hydrophobic nature of DCP. At the end of 8 h, the cumulative percent release of SVT was found to increase from 44.15 ± 1.51% to 80.69 ± 0.70% (Figure 5). On physical examination of the tablets during the dissolution study, it was found that initially the TMS layer was eroded followed by swelling of the SVT layer.

From the kinetic data, it was evident that the drug release follows first order kinetics. Further, the drug release data followed Higuchi's model for all the formulations, indicating diffusion-controlled drug release as a mechanism. The calculated slope values of the Peppas equations gave a value between 0.5 and 1, which confirmed that the release mechanism of simvastatin from the SVT layer was Fickian diffusion with swelling. The Higuchi plots were linear and had correlation coefficients ranging between 0.904 and 0.918, which indicates a diffusion-controlled drug release. The linearity of plots was confirmed by the calculation of correlation coefficients (Table 9).

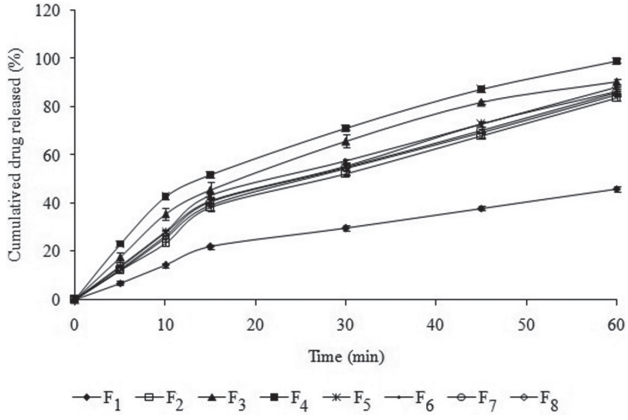

Fig. 4. *In vitro* release profile of TMS from the TMS layer of the bilayer tablet (mean ± SD, n = 3)

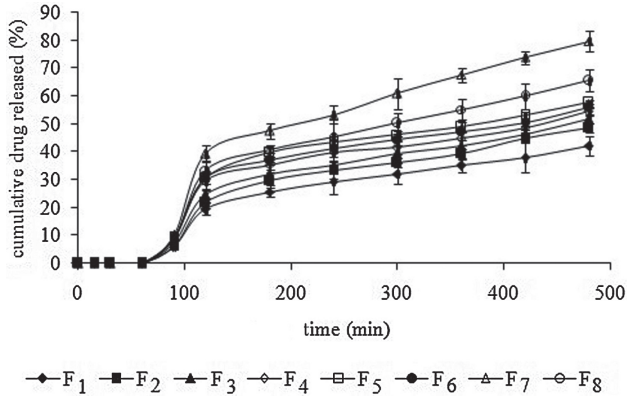

Fig. 5. *In vitro* release profile of SVT from the SVT layer of the bilayer tablet (mean ± SD, n = 3)

On application of two-way ANOVA followed by Bonferroni post-tests on the dissolution data of SVT from the slow release layer, a significant difference was

Table 9. Data of release kinetic studies of SVT layer

Formulation code	Zero order (r^2)	First order (r^2)	Higuchi model (r^2)	Peppas model	
				(r^2)	(n)
F_1	0.920	0.937	0.918	0.798	0.938
F_2	0.924	0.955	0.917	0.789	0.986
F_3	0.916	0.929	0.916	0.782	0.929
F_4	0.886	0.929	0.905	0.744	0.823
F_5	0.884	0.930	0.904	0.745	0.855
F_6	0.883	0.930	0.904	0.739	0.833
F_7	0.920	0.978	0.915	0.766	0.975
F_8	0.907	0.958	0.911	0.751	0.934

Table 10. Results of two way ANOVA followed by Bonferroni post-tests, on simvastatin release profiles of the SVT layer (formulations F_1 – F_8)

Source of variation	Sum of square	Degree of freedom	Mean square	Calculated F	Tabulated F
CSS	2343	7	334.7	14.71	1.91
RSS	45830	11	4166	183.0	1.96
ESS	1752	77	22.76		

CSS – column sum of squares, RSS – raw sum of squares, ESS – error sum of squares.

observed in the *in vitro* drug release profiles among the formulations (F_1–F_8) at a 95% confidence interval ($p < 0.0001$). Since, the calculated F value is much larger than the table value, the null hypothesis of equal population means was rejected and led to the conclusion that there is a statistically significant difference between the dissolution profiles. This supports the role of the polymer in controlling the drug release (Table 10).

Conclusions

In hypertension conditions, there is a chance of an increase in body lipid levels characterized by hypercholesterolemia. Consequently, a combination therapy is needed to decrease blood pressure and simultaneously control the lipid level during hypertension conditions. Considering these factors, modified-release bilayer tablets for the selected incompatible drugs, telmisartan and simvastatin, were developed in a single tablet. Such a treatment can significantly reduce the frequency of pills taken, and thus may increase patient compliance and have a better therapeutic effect. The highest drug release from TMS was obtained when croscarmellose sodium was used at its highest concentration (formulation F_4). The SVT layer needed a superdisintegrant to control the dissolution rates, due to the increased hardness during the compression of granules of the TMS layer. The increased compression force was required to prevent layer separation and this was balanced by adding superdisintegrants. Based on the results obtained, formulation F_4 was determined to be the best formulation, with 85% drug release after 45 min from the TMS layer and 80% drug release after 8 h from the SVT layer. The drug release from the SVT layer was diffusion controlled with swelling. In conclusion, a bilayer tablet of SVT and TMS may be a more effective and patient compliant option in the management of hypertension.

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Conflict of interest: None declared

Received: 24.10.2015
Revised: 31.03.2016
Accepted: 5.04.2016