Pharmaceutical Regulatory Affairs: Open Access

Reddy, Pharmaceut Reg Affairs 2018, 7:2
DOI: 10.4172/2167-7689.1000209

Research Article Open Access

Formulation and *In-vitro* Evaluation of Sumatriptan Succinate Bilayer Tablets

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Abstract

Bilayer tablet is one of the great advanced technologies which contain two different layered formulations with one layer of drug provides immediate release and the other as sustained. Sumatriptan succinate is a triptans class of drug used to treat migraine headaches, which acts selectively at 5-HT1B/1D receptors. The objective is to formulate and evaluate the bilayer tablets of sumatriptan succinate of dose 50 mg. In this case immediate release layer is formulated using sodium starch glycolate, crospovidone and croscarmellose sodium as Super-Disintegrants, Sustained release layer is formulated using hydroxypropyl methylcellulose K15M, ethyl cellulose, xanthan gum and guar gum in various ratios to delay the drug release. FT-IR studies for excipients are tested for compatibility with the drug. Evaluations such as Hardness, Thickness, Friability, Weight variation, Disintegration time and Assay were determined for bilayer tablets. *In vitro* drug release was performed with USP dissolution apparatus type-II (paddle type) using 0.1 N Hydrochloric acid for first hours and later hours with 6.8 pH phosphate buffer by temperature maintaining at 37˚C ± 0.5˚C. Based on results among all formulations F7 formulation containing Xanthan gum and Guar gum in ratio of 1.5:1.5 showed maximum drug release of 97.41%. Thus, drug formulation of F7 has enhanced drug release profile.

Keywords: Bilayer tablet; Layered formulation; Sodium starch glycolate; Crospovidone; Croscarmellose; Hydroxypropyl methylcellulose K15M; Ethyl cellulose; Xanthan gum and Guar gum

Introduction

In the latest occasions, enthusiasm for developing a combination of two or more Active Pharmaceutical Ingredients in a single formulation as bilayer tablet has extended in the pharmaceutical industry, expanding patient compliance and convenience [1,2]. Different reasons in creating bilayer in pharmaceutical for e.g. therapeutic, dose extension, combination, marketing and novel drug delivery systems. Bilayer tablets are combination of two layers with one layer of drug for immediate release while second layer designed to release drug, later, either as second dose or in a sustained or extended release manner. Each layer may contain different agents with change in release profiles, and they are intended for some reasons, for e.g. control the delivery rate of either single or two different APIs and to separate incompatible APIs from each other. With the improvement of pharmaceutical research, dosage form of two or more active ingredients in combination have attracted more importance because they can show synergistic cumulative effect as well as decreased side effects. There additionally few problems exist in the process of preparing such combinations solid dosage forms, for example, incompatibility between API and excipients or between two different APIs. The physical or chemical interaction between two different drug components in same formulation or between the active ingredient and pharmaceutical excipients may frequently occurs which results in no clinical or toxic effects.

Materials

Sumatriptan Succinate (SS), Sodium Starch Glycolate (SSG), Cross Povidone (CP), Croscarmellose Sodium (CCS), HPMC K15 M (HPMC), Ethyl cellulose (EC), Xanthan Gum (XG), Guar Gum (GG), Magnesium stearate (MS), Talc (TC), Starch (ST), Spray Dried Lactose (SDL).

Methods

Preparation of Standard Curve of Sumatriptan Succinate in 0.1N HCl

Weigh accurately about 100 mg of Sumatriptan succinate was dissolved in small quantity of 0.1N HCl and make up to 100 ml [3]. From this above 1 ml was pipette out and was made upto10 ml with 0.1N HCl in 10 ml volumetric flask from this stock, aliquots of 0.2, 0.4, 0.6, 0.8 and 1.0 ml was pipette out and transferred to 10 ml volumetric flasks and final volume was made giving concentrations from 2.0 to 10 µg/ml. The absorbance of these solutions was estimated in UV-Visible spectrometer at 227nm utilizing 0.1N HCl as blank.

Compatible studies with Infrared Spectrum

The infrared spectrum of Sumatriptan succinate was recorded by using FT-IR (Alfa Bruker) instrument. Sumatriptan succinate powder was mixed with various polymers with equal quantity of potassium bromide in the ratio of 1:1 made in the form of pallet and placed in sample cell to record its IR- spectra list may be presented with each item marked by bullets and numbers.

Preparation of tablet blends of Sumatriptan Succinate as immediate release layer

All ingredients (Sodium starch glycolate, Cross povidone, Croscarmellose sodium) were weighed accordingly like below mentioned in ascending order with 25 mg of Sumatriptan and make up to 200 mg SDL and passed through #60 sieve, later magnesium stearate and talc was added [4]. These powders are blended 20 minutes to obtain uniform distribution of the drug. This is prepared for direct compression as first layer. All ingredients (HPMC, Ethyl cellulose, Xanthan Gum, Guar Gum, Starch) were weighed accordingly like below mentioned in ascending order with 25 mg of Sumatriptan and make up to 200 mg SDL and passed through #60 sieve, later magnesium stearate and talc was added. This powder is blended for 20 minutes to obtain uniform distribution of the drug. This is prepared for direct compression as first layer.

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Received November 19, 2018; **Accepted** December 03, 2018; **Published** December 10, 2018

Citation: Reddy BS, Reddy MS, Haq SMFUl (2018) Formulation and *In-vitro* Evaluation of Sumatriptan Succinate Bilayer Tablets. Pharmaceut Reg Affairs 7: 209. doi: 10.4172/2167-7689.1000209

Evaluation

Thickness

The thickness of the tablet might vary without any change in weight of tablet due to the difference in sizes of particles and pressure applied with rotation speed of the tablet machine [5-7]. The thickness of the tablet is determined using Vernier Caliper and measure the individual thickness of tablets and then average of thickness of tablet is calculated.

L=MSR+(VSDx0.1)

Hardness

Hardness is the most important strength to withstand the mechanical shocks during manufacturing, handling, packaging, shipping of tablets. Hardness is tested using hardness tester (Monsanto Hardness tester). The tablet is held in between two jaws and by rotating the knob the tablet fractured at some point of strength. It is noted as hardness of tablet in kg/cm^2.

Friability

Friability is used to measure the tablet strength in combined manner. The number of tablets to combine effects of shock abrasion in closed plastic chamber which rotates 25rpm for 4 mins dropping from 6 inch in each rotation. Tables 1-4 are pre-weighted placed in Roche

Formulations	Immediate release layer			Sustained release layer				Excipients used in both layers			
	SSG	CP	CCS	HPMC	EC	XG	GG	MS	TC	SC	SDL
F1	50 (1:2)					50(1:2)		3.75	10	10	qs
F2							37.5(1:1.5)	3.75	10	10	qs
F3	75 (1:3)			37.5(1:1.5)				3.75	10	10	qs
F4		37.5(1:1.5)			67.5(1:2.5)			3.75	10	10	qs
F5	100(1:4)	62.5(1:2.5)		37.5 (1:1.5:0.5)		12.5 (1:1.5:0.5)		3.75	10	10	qs
F6			25 (1:1)		37.5(1.5:1)			3.75	10	10	qs
F7			37.5(1:1.5)			37.5(1:1.5:1.5)	25(1.5:1)	3.75	10	10	qs
F8		87.5(1:3.5)	62.5(1:2.5)	37.5 (1:1.5:1.5)	37.5 (1:1.5:1.5)			3.75	10	10	qs
F9				25 (1:1.5:0.5:1)	37.5 (1:1.5:0.5:1)	12.5 (1:1.5:0.5:1)	25 (1:1.5:0.5:1)	3.75	10	10	qs
F10								3.75	10	10	qs

Note: 1. Above values are weighed in units of mg 2. The ratios given above are Drug versus Excipient(s)

Table 1: Drug *versus* Excipient.

Wavelength Range	Functional Group
3330-3500	Alkyne
3200-3600	O- H Stretch
2850-3000	C- H alkane
2500-3300	O- H acid
1640-1690	C=O Amide
1400-1600	N- H amide
675-1000	=C- H Bending
1080-1360	C- N Amide
1670-1820	C=O Carbonyl
1340-1370	C- N

Table 2a: Wavelength ranges of Drug -Polymers compatibility Studies.

Formulation	Weight variation%	Friability%	Hardness (kg/cm2)	Disintegration Time	Thickness (mm)
F1	1.25 ± 0.73	0.54 ± 0.14	6.1 ± 0.71	11.2 ± 0.2 mins	4.1 ± 0.42
F2	3.22 ± 0.83	0.65 ± 0.17	6.1 ± 0.71	12.3 ± 0.30 mins	4.3 ± 0.31
F3	1.43 ± 0.71	0.85 ± 0.07	5.7 ± 0.55	10.5 ± 0.6 mins	4.6 ± 0.52
F4	1.87 ± 0.44	1.21 ± 0.13	5.2 ± 0.61	8.5 ± 0.2 mins	4.8 ± 0.32
F5	1.77 ± 0.26	1.43 ± 0.22	5.3 ± 0.45	7.4 ± 0.6 mins	4.6 ± 0.53
F6	0.92 ± 0.68	0.78 ± 0.15	6.2 ± 0.25	10.5 ± 0.5 mins	4.3 ± 0.55
F7	0.87 ± 0.33	0.45 ± 0.07	6.5 ± 0.59	12.1 ± 0.3 mins	4.1 ± 0.51
F8	3.23 ± 0.77	1.10 ± 0.10	5.5 ± 0.45	8.5 ± 0.2 mins	4.6 ± 0.61
F9	3.75 ± 0.53	0.73 ± 0.14	6.2 ± 0.41	10.5 ± 0.3 mins	4.2 ± 0.72
F10	1.76 ± 0.95	0.69 ± 0.21	6.3 ± 0.22	11 ± 0.5 mins	4.2 ± 0.32

Table 2b: Evaluation of Physico-chemical properties of tablets.

Time	F1	F2	F3	F4	F5
0 min	0	0	0	0	0
5 min	15.588 ± 1.30	23.976 ± 1.22	34.038 ± 1.32	35.172 ± 0.78	33.39 ± 1.75
15 min	23.778 ± 2.33	29.772 ± 1.45	37.89 ± 0.61	42.498 ± 1.45	39.852 ± 1.90
30 min	29.97 ± 4.33	36.576 ± 2.65	46.062 ± 1.45	43.398 ± 2.25	48.618 ± 2.53
45 min	40.266 ± 1.43	43.398 ± 2.34	49.572 ± 3.64	48.114 ± 1.76	49.842 ± 1.84
1 h	53.37 ± 2.31	51.768 ± 1.65	53.58 ± 1.77	55.638 ± 1.45	56.916 ± 2.85
2 h	61.416 ± 2.33	67.878 ± 2.87	63.72 ± 0.98	66.078 ± 2.20	68.238 ± 2.88
4 h	74.394 ± 1.32	75.366 ± 1.43	75.45 ± 1.73	74.79 ± 1.55	74.034 ± 1.22
6 h	86.652 ± 3.44	80.568 ± 1.12	80.604 ± 3.87	78.804 ± 2.95	80.298 ± 1.42
8 h	91.278 ± 1.33	85.788 ± 2.20	84.438 ± 2.05	82.998 ± 1.62	84.816 ± 1.66

Table 3: Dissolution profile and % drug release of formulations F1, F2, F3, F4, F5 (In all formulation 25 mg of Sumatriptan is added).

Time	F6	F7	F8	F9	F10
0 min	0	0	0	0	0
5 min	15.156 ± 1.44	20.592 ± 1.05	24.516 ± 2.34	14.76 ± 1.34	42.19 ± 2.32
15 min	25.758 ± 1.89	28.566 ± 2.11	30.816 ± 3.32	21.114 ± 3.54	47.57 ± 1.10
30 min	34.398 ± 2.54	34.038 ± 2.43	38.052 ± 1.45	34.866 ± 1.42	52.16 ± 1.43
45 min	40.464 ± 2.54	48.132 ± 3.22	41.616 ± 3.20	43.848 ± 2.43	61.146 ± 1.55
1 h	45.72 ± 1.43	58.734 ± 2.42	45.18 ± 1.43	47.898 ± 1.43	82.152 ± 1.978
2 h	62.496 ± 1.12	70.452 ± 1.75	58.626 ± 1.32	53.658 ± 2.12	96.768 ± 1.54
4 h	71.172 ± 2.55	83.034 ± 1.22	67.68 ± 2.56	63.396 ± 2.33	97.902 ± 0.90
6 h	77.796 ± 3.02	90.252 ± 0.78	77.778 ± 3.20	78.3 ± 1.35	97.002 ± 1.51
8 h	89.55 ± 2.12	97.416 ± 1.08	88.362 ± 1.53	88.38 ± 1.44	96.498 ± 0.54

Table 4: Dissolution profile and % drug release of formulations F6, F7, F8, F9, F10.

friabilator and it is operated for 100 revolutions and measures the final weight.

% Friability = (Initial Weight-Final weight) /initial weight x 100

Weight variation

Take 20 tablets randomly and weighed individually and weight the complete all 20 tablets and calculate the average. The difference for individual tablet with average weight of tablet is calculated, not more than two should cross the limits.

Deviation % = (Average weight-individual weight)/average weight *100

Disintegration time

Disintegration apparatus consists of 6 tubes with 3-inch length and the bottom of glass tube have #10 mesh the particles should pass through it; each tablet is placed in each tube and tubes are placed in 1 liter of 0.1N HCl. The device is raising and lowering the basket in the immersion fluid at a constant frequency rate of 29 and 32 cycles per minute and is maintained at 37 ± 2˚C. The time taken to disintegrate the tablet is determined when all particles should pass through the #10 mesh in glass tube.

In-vitro dissolution of tablets

Sumatriptan succinate release rate from bilayer tablets was determined using USP Dissolution Testing Apparatus type-II i.e. Paddle apparatus. A sample about 5 ml of the solution was regularly withdrawn from the apparatus and the samples were replaced with fresh buffer medium. It is filtered through 0.45 µ membrane filter and diluted using respective medium. Absorbance was measured at 227 nm using a UV-Visible spectrophotometer. The experiments carried for all formulations.

For sumatriptan succinate IR layer:

Medium: 900 ml of 0.1N Hydrochloric acid

RPM: 75 [8].

Apparatus: Paddle (USP type-II apparatus)

Time: 15, 30, 45, 60, 120 minutes

Wave Length: 227 nm

Temperature: 37˚C ± 0.5˚C

For sumatriptan succinate SR layer:

Medium: 900 ml of 6.8 pH buffer.

RPM: 75

Apparatus: Paddle (USP type-II apparatus)

Time: 1st, 2nd, 4th, 6th, 8th Hours.

Wave Length: 227 nm

Temperature: 37˚ C ± 0.5˚C

Results and Discussion

Calibration curve of sumatriptan succinate by using 0.1N HCl

Result: The Calibration curve of Sumatriptan Succinate plotted at 227 nm and correlation coefficient (R2) of determination was 0.99 (Graphs 1-5).

FTIR spectroscopy of sumatriptan

FTIR spectroscopy of sumatriptan is shown in Graph 2.

FTIR spectroscopy of excipients and sumatriptan

Result: All excipients are compatible with the drug (Graph 3).

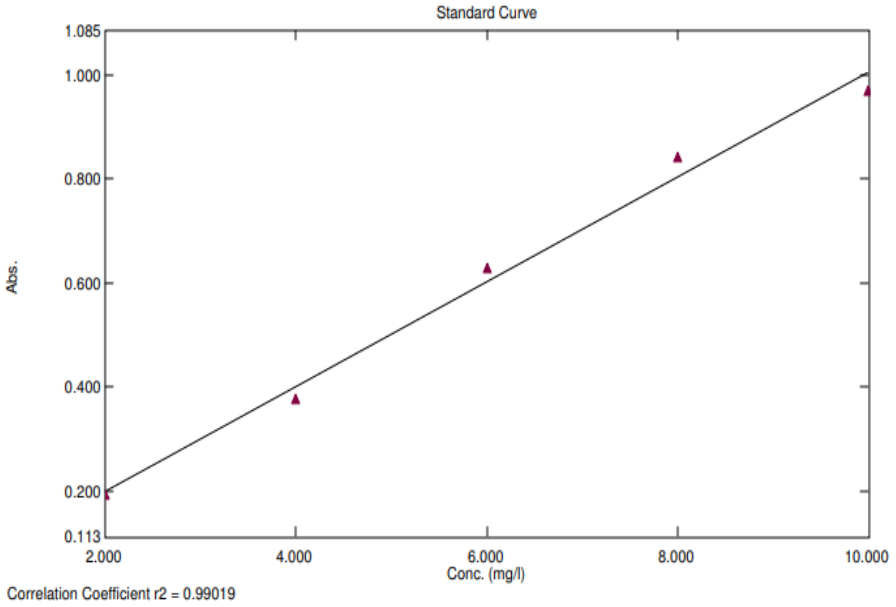
Wavelength ranges of Drug-polymers compatibility studies

Dissolution profile and % drug release of formulations F1, F2, F3, F4, F5

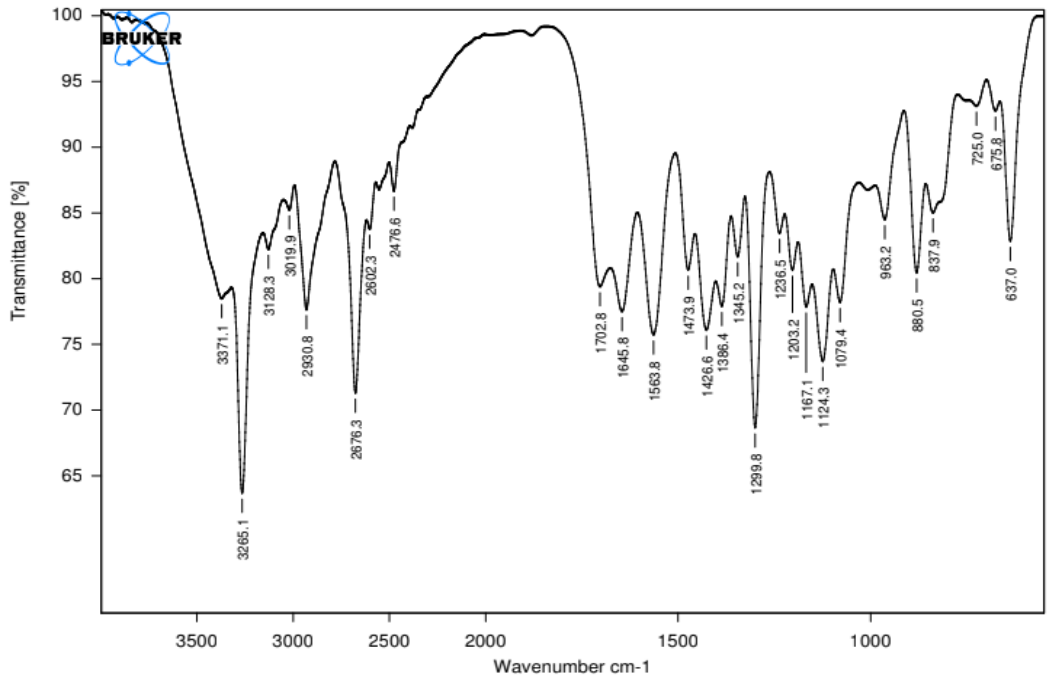
Dissolution profile and % drug release of formulations F6, F7, F8, F9, F10

Summary and Conclusion

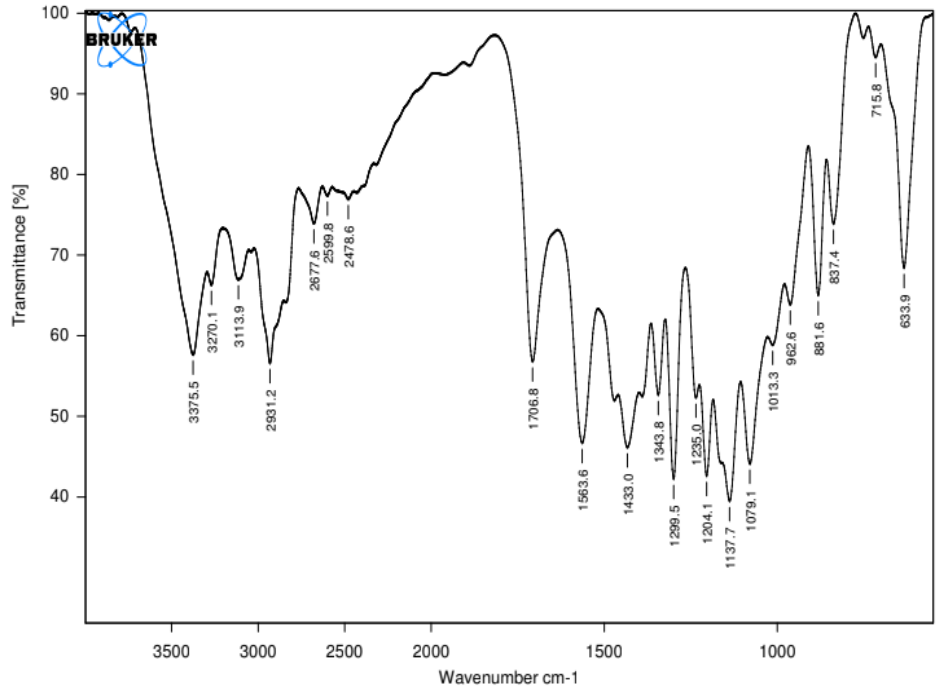
The formulation and *In-vitro* evaluation of bilayer drug of Sumatriptan succinate tablets [9] was performed in the present study. The F7 bilayer tablets containing Xanthan gum and Guar gum in the ratio of 1.5:1.5 were concluded the best formulation among all other formulations and giving the most desired drug release profile. It will be considered as most optimized formulation. The F7 bilayer tablets containing Cross povidone in ratio of 1:1 with drug shows good results in immediate release layer. The formulated bilayer tablets were evaluated for physical characterization like thickness, friability, hardness, weight variation and drug content [10]. These have good results FT-IR studies on drug and polymer interaction has no change in wave peaks in drug



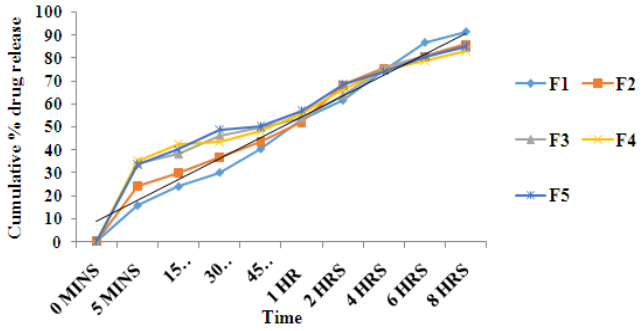
Graph 1: Calibration Curve of Sumatriptan succinate by using 0.1N HCl



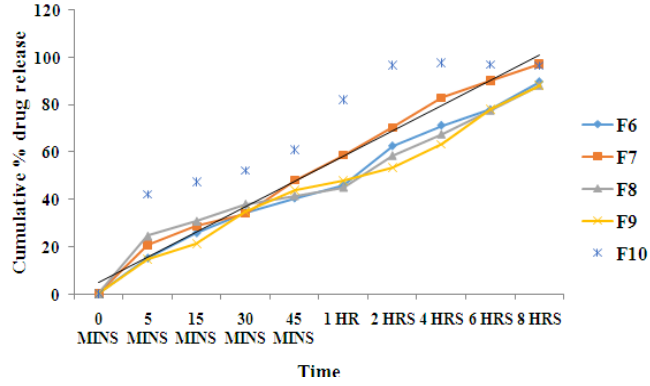
Graph 2: FTIR spectroscopy of Sumatriptan.



Graph 3: FTIR Spectroscopy of Excipients and Sumatriptan.



Graph 4: *In vitro* % drug release Sumatriptan Bilayer tablets (F1-F5).



Graph 5: *In vitro* % drug release Sumatriptan Bilayer Tablets (F6-F10).

band region. The *in-vitro* dissolution studies indicate the formulation F7 was found to be the best with good drug release profile among all formulations. The regression correlation co-efficient value was concluded in most of kinetics modeling, the formulation F7 having R2 value lies below 1.0. Hence it is concluded that formulation F7 following good drug release kinetics. From the stability data results, we can be concluding formulation F7 as highly stable formulation.

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