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DESIGN AND CHARACTERIZATION OF GASTRORETENTIVE FLOATING TABLETS OF SUMATRIPTAN SUCCINATE

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ABSTRACT

The aim of this study was to formulate and evaluate sumatriptan floating drug delivery system. The floating tablets of Sumatriptan were prepared by using HPMC K15M, HPMCE15LV, Carbopol 940 polymers. The precompression and post compression evaluation were performed as per pharmacopoeial standards. The tablets were prepared by direct compression method. Dissolution measurements were carried out in a (USP) dissolution testing apparatus II. Compatibility study was performed by FTIR. The compatibility study of the prepared Sumatriptan floating tablets confirms that there is no interaction between the drug and polymers used. The cumulative drug release was performed in order of kinetics. The drug release kinetics was observed by Non-fickian diffusion mechanism. The floating lag time were found to be significantly increased with the increasing concentration of the polymers. When compared to the other formulation depends on dissolution profile HPMCE15 shows better effect. The release kinetic data implies that the release mechanism of all the formulations was Non-fickian. It may be used to extended period of drug release for at least 12h, that's way improving the bioavailability and patient compliance.

KEYWORDS

Sumatriptan Gastroretentive, Floating drug delivery and Sustained release.

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INTRODUCTON

The aim of controlled release and sustained release to increase the therapeutic effectiveness of drug by its site of action and reduce the dose and delivery of drug is uniformed¹. The current controlled release technology had made it possible to release drugs at a constant release rate for longer periods of time ranging from days to years². However, this benefit had not satisfied a variety of important drugs that (i) are locally active in the stomach, (ii) have an

absorption window in the stomach or in the upper small intestine, (iii) are unstable in the intestinal or colonic environment, or (iv) exhibit low solubilities at high pH values³. The dosage form significantly prolonged gastric residence and controlled release. Besides being able to continually and sustainably deliver drugs to the small intestinal absorption window, the improvements provided from GRDDS include: achieving a greater and prolonged therapeutic effect and thus reducing the frequency of administration periods, providing a more effective treatment of local stomach disorders, and minimizing both lower-tract inactivation of the drug and drug effects on the lower intestinal flora⁴.

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach based on high density and low density of polymers⁵. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach⁶. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. The gastric content are needed to buoyant of system⁷. Many buoyant systems have been developed based on granules, powders, capsules, tablets, laminated films and hollow microspheres⁸.

Sumatriptan is widely prescribed as an anti-migraine. It is a selective agonist of vascular serotonin ((5-hydroxytryptamine; 5-HT) type 1-like receptors. It is an effective and popular drug for relieve migraine symptoms⁹. Sumatriptan is also used for treatment of relieve headache, pain, and other symptoms. The recommended dose of Sumatriptan is 25 mg orally. As biological half-life shorter it is poor candidate for sustained release drug delivery system¹⁰. Thus a sustained release dosage form of Sumatriptan is desirable, as biological half-life of Sumatriptan is about (2.5 hours). This favors development of sustained release formulation.

Traditional oral sustained formulations have a drawback that it cannot release a drug at specific site. Its absorption window is either in colon or

through the GIT. This leads to poor absorption of drug, and this affects the therapeutic effect of the drug. Sumatriptan is a pro-kinetic drug and it acts mainly on GIT and CNS¹¹. It has more prominent effect on upper part GIT. And sustained release dosage forms are designed to complement the pharmaceutical activity of medicament in order to achieve better selectivity and longer duration of action. So Sumatriptan is chosen for the present study¹².

A serotonin agonist that acts selectively at 5HT1 receptors. It is used in the treatment of migraine disorders. A transdermal patch version of sumatriptan is currently in phase I trials in the U.S. The 5-HT_{1B} and 5-HT_{1D} receptors function as auto receptors, which inhibit the firing of serotonin neurons and a reduction in the synthesis and release of serotonin upon activation. After sumatriptan binds to these receptors, adenylyl cyclase activity is inhibited via regulatory G proteins, increases intracellular calcium, and affects other intracellular events¹³. This results in vasoconstriction and inhibition of sensory nociceptive (trigeminal) nerve firing and vaso-active neuropeptide release¹⁴.

MATERIAL AND METHODS

Material

Sumatriptan was a generous gift from Spectrum Pharma labs Hyderabad, Hydroxyl propyl methyl cellulose, Carbopol 940, Avicel, Sodium bicarbonate, Lactose, Mg-Stearate, Talc, Hydrochloric acid were obtained from S.D fine chemicals, Mumbai.

Methods

Preparation of Sumatriptan floating tablets by compression method

Sumatriptan floating was prepared by direct compression technique using drug and variable concentration of polymers (HPMC K4M, HPMC E 15LV, Carbopol 940, Sodium Bicarbonate, MCC, Lactose, Mg-stearate, and Talc). The respective powders and optional additives were blended thoroughly with a mortar and pestle. The powder blended was then lubricated with Mg-stearate and purified talc and then compressed on a tablet punching machine.

RESULTS AND DISCUSSION

Drug - excipients compatibility studies

The IR spectrum of pure drug was found to be similar to the standard spectrum of Sumatriptan. Compatibility studies were performed through FTIR spectroscopy. The IR spectrum of pure drug and physical mixture of drug and polymer was studied. The characteristic absorption peaks of Sumatriptan obtained were obtained at 4000-500cm⁻¹. It has been observed that there is no chemical interaction between Sumatriptan and polymer's used. It was observed that peak obtained in spectra drug and polymers. Which show there were no interaction between drug and polymers?

Standard calibration curve of Sumatriptan using 0.1 N HCL

100 mg drug was accurately in 100ml volumetric flask. It was dissolved in 0.1N HCL to gives 1000µg/ml. the standard stock solution stock solution was then serially diluted with 0.1 N HCL to get 1 to 10 µg/ml of Sumatriptan. The absorbance was measured against 0.1 N HCL as blank at 225 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Different Drug Release Kinetics Model for Sumatriptan Floating Tablets

Regression coefficients fit to different drug release kinetics models for Sumatriptan floating tablets.

The present study is an attempt to develop floating tablets of Sumatriptan, with different polymers which releases a therapeutic amount of Sumatriptan to the proper site in the body and also to achieve and maintain the desired Sumatriptan concentration. Direct compression method was used for formulation of floating tablets, also different types of polymers like HPMC (HPMC K15M, HPMC E15LV), Carbopol 940 were studied. These polymers were widely used gel forming polymers. The release rate could effectively be modified by varying the “polymer” concentration. By using HPMC E15LV they gave optimum FLT as well as long acting effect. It was found that the tablet formulation retarded the drug release for 12h as desired.

The results of the drug-excipients compatibility by FTIR studies revealed that there was no chemical interaction between the pure drug and excipients. The Precompression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. The final formulation showed acceptable flow properties. The post compression parameters like the thickness, hardness, friability, weight variation, content uniformity, FLT and TFT and *In vitro* release, were carried out and the values were found to be within IP limits. Thus it is summarized and concluded that HPMC E15 LV can be successfully used in formulation of Sumatriptan sustained release gastroretentive floating tablets.

Total weight = 200mg

S.No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	DRUG	25	25	25	25	25	25	25	25	25	25	25	25
2	HPMCE 15 LV				25	30	45	20	20	20			
3	HPMC K15M	25	30	45							20	20	20
4	CARBOPOL 940							10	15	20	10	15	20
5	MCC	65	65	65	65	65	65	65	65	65	65	65	65
6	NAHCO ₃	20	20	20	20	20	20	20	20	20	20	20	20
7	MG -STERATE	2	2	2	2	2	2	2	2	2	2	2	2
8	TALC	3	3	3	3	3	3	3	3	3	3	3	3
9	LACTOSE	60	55	40	60	55	40	55	50	45	55	50	45

Pre-Compression Evaluation of Sumatriptan Floating Tablets

Formulation code	Angle of repose (°) ±SD	Bulk density 3 (gm/cm) ±SD	Tapped density 3 (gm/cm) ±SD	Hausner ratio (HR) ±SD	Carr index (Ic) ±SD
F1	22.46±0.726	0.221±0.010	0.261±0.010	1.180±0.010	15.398±0.596
F2	24.08±0.556	0.223±0.020	0.260±0.010	1.150±0.060	15.794±0.359
F3	22.49±0.471	0.232±0.016	0.270±0.026	1.190±0.010	16.018±0.640
F4	22.64±0.746	0.250±0.010	0.267±0.015	1.127±0.005	11.707±0.514
F5	23.68±0.312	0.232±0.011	0.300±0.010	1.198±0.009	16.678±0.560
F6	22.84±0.665	0.220±0.010	0.262±0.011	1.127±0.006	11.407±0.513
F7	22.26±0.825	0.210±0.010	0.262±0.010	1.180±0.010	15.397±0.593
F8	21.76±0.645	0.230±0.011	0.250±0.010	1.190±0.010	16.016±0.640
F9	21.68±0.346	0.221±0.005	0.281±0.012	1.204±0.004	17.657±0.734
F10	22.79±0.934	0.227±0.010	0.266±0.005	1.175±0.005	15.000±0.329
F11	22.91±0.471	0.230±0.010	0.270±0.010	1.170±0.010	14.828±0.550
F12	22.89±0.520	0.225±0.011	0.260±0.010	1.165±0.030	15.399±0.594

All the values are expressed as mean ± SD. (n=3)

Post Compression Evaluation of Sumatriptan Floating tablets

Formulation code	Weight variation Average wt in (mg)±SD	Hardness (Kg/cm ²) ±SD	Diameter in (mm) ±SD	Thickness in (mm) ±SD	Friability (%) ±SD	Drug content uniformity (%)±SD
F1	199.58± 0.933	4.258± 0.208	9.32± 0.577	2.238± 0.058	0.756± 0.057	99.686±0.613
F2	200.4± 0.882	4.942± 0.115	9.31± 0.577	2.141± 0.067	0.584± 0.055	97.571±0.407
F3	196.6± 0.825	4.856± 0.115	9.64± 0.577	2.231± 0.055	0.757± 0.015	99.040±0.819
F4	200.05± 0.887	5.063± 0.155	9.00± 0.000	2.250± 0.000	0.670± 0.010	99.487±0.147
F5	200.3±0.833	4.800± 0.200	8.66± 0.577	2.271± 0.057	0.769± 0.011	98.590±0.391
F6	200.2± 0.951	4.942± 0.115	8.64± 0.577	2.119± 0.010	0.764± 0.090	97.350±0.306
F7	199.98± 0.887	4.864± 0.115	9.00± 0.000	2.235± 0.049	0.740± 0.060	98.741±0.228
F8	200.2± 0.833	4.464± 0.115	8.65± 0.577	2.874± 0.052	0.767± 0.011	98.148±0.503
F9	200.15± 0.812	4.734± 0.115	8.64± 0.577	2.886± 0.057	0.660± 0.010	98.435±0.119
F10	200.1± 0.852	4.942± 0.115	8.65± 0.577	2.254± 0.000	0.778± 0.017	97.421±0.355
F11	200.14± 0.812	4.643± 0.115	9.00± 0.000	2.200± 0.100	0.660± 0.010	95.514±0.130
F12	200.13± 0.745	4.800± 0.200	8.64± 0.577	2.350± 0.100	0.780± 0.010	96.162±0.678

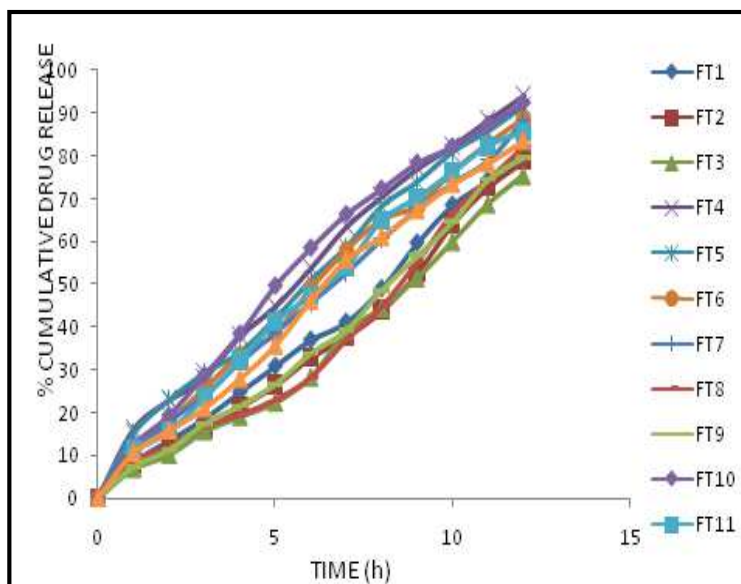
All the values are expressed as mean ± SD. (n=3)

In-Vitro Drug Release Studies

Time	% Cumulative release											
	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10	FT11	FT12
1	9.16	7.10	7.78	14.88	15.16	10.05	11.68	9.78	8.56	11.21	12.24	11.54
2	12.38	11.51	11.21	21.91	22.73	17.87	18.89	10.89	12.42	18.43	14.53	14.73
3	19.44	15.34	16.73	27.18	29.08	25.44	23.08	15.74	16.27	27.81	22.54	22.16
4	23.68	20.32	20.13	38.42	34.02	33.54	30.34	18.36	22.52	37.54	31.24	26.83
5	31.71	27.38	23.52	45.73	42.08	38.61	37.73	22.06	27.56	48.62	42.24	34.74
6	37.85	33.78	29.29	51.54	50.83	49.14	44.74	27.15	34.78	57.64	46.45	45.34
7	42.21	36.61	37.56	62.31	58.52	58.08	51.74	36.17	38.36	67.56	52.14	54.7
8	47.76	44.81	45.54	71.33	68.35	65.21	59.77	43.84	47.57	71.53	63.84	60.3
9	60.53	53.52	52.54	75.81	73.76	68.48	66.52	54.53	55.48	77.61	71.24	66.46
10	69.39	63.31	61.08	83.44	80.85	76.30	72.05	65.73	63.36	81.41	75.33	72.42
11	73.37	71.64	69.75	89.24	85.81	82.14	78.20	73.43	73.41	86.56	81.45	77.54
12	80.40	77.42	74.62	95.08	91.63	88.68	87.49	81.24	78.47	91.63	84.65	82.74

All the values are expressed as mean ± SD. (n=3)

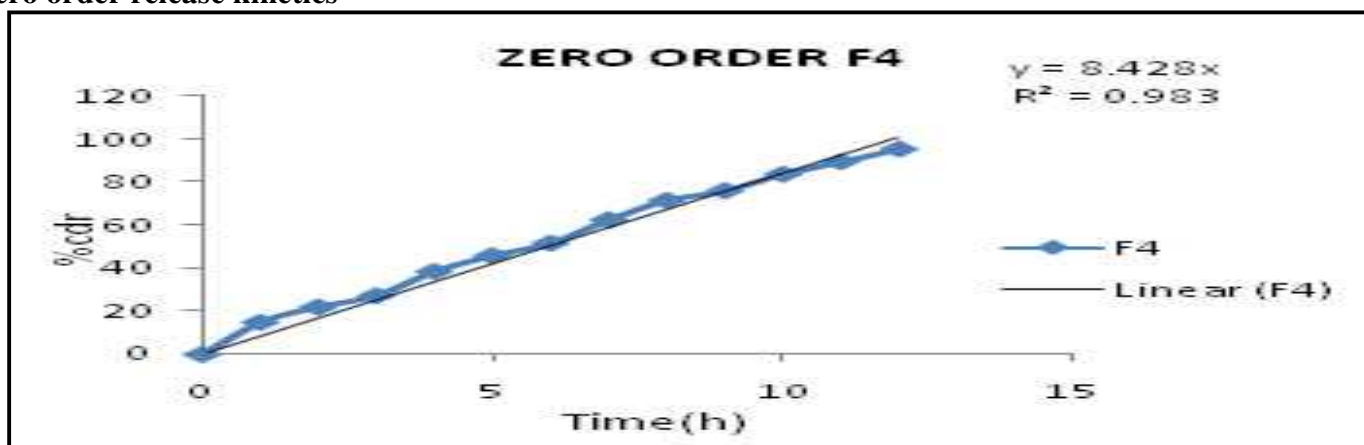
Time (h)	F4
0	0
1	14.886
2	21.914
3	27.188
4	38.424
5	45.731
6	51.542
7	62.312
8	71.331
9	75.814
10	83.443
11	89.242
12	95.089



In-vitro drug release profile of Sumatriptan floating tablets of batches F1 to F12.

Drug Release Kinetics of Sumatriptan F4

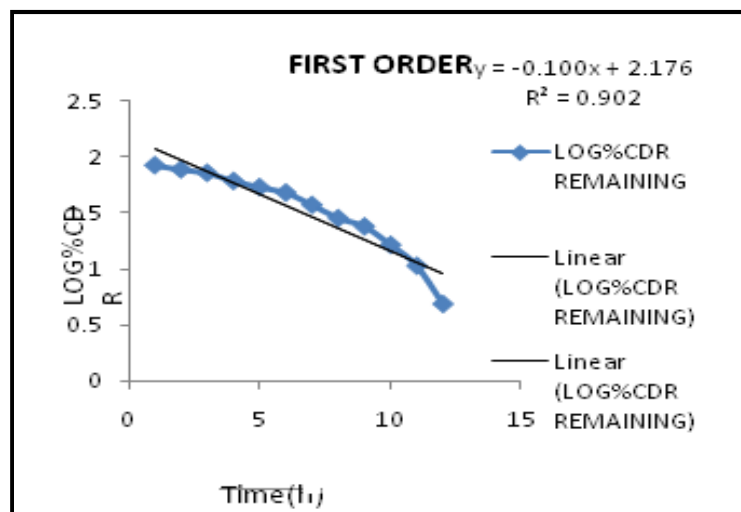
Zero order release kinetics



First order release kinetics data of Sumatriptan floating tablets

First order release kinetics of Sumatriptan F4

Time	Log % cdr remaining
1	1.930001001
2	1.892573176
3	1.86220296
4	1.789411474
5	1.734551819
6	1.685365486
7	1.575972562
8	1.457412545
9	1.383564049
10	1.218981649
11	1.03173154
12	0.691169934



Formulation code	Zero order	First order	Higuchi	Peppas
	r^2	r^2	r^2	r^2
F4	0.983	0.902	0.979	0.987

CONCLUSION

From the compatibility studies, it is concluded that HPMC E15LV, HPMC K15M, Carbopol 940 were compatible with drug Sumatriptan and thus suitable for the formulation of Sumatriptan floating tablets. Sumatriptan tablets were fabricated by direct compression method. *In-vitro* buoyancy studies were performed for all the formulations, F1 to F12 by using 0.1 N HCL solutions at 37°C. Tablet containing HPMC (F4) showed good buoyancy with very short lag time and long floatation time of more than 12 hrs in 0.1 N HCL. *In-Vitro* release study is performed for 12 hrs. Optimized formula containing HPMC E15LV (F4) showed better release compare to other formulations and it followed zero order kinetics. The non-Fickian diffusion was confirmed as the drug release mechanism from this formulation.

From this study, it was concluded that HPMC E15LV can be used in formulation of Sumatriptan sustained release gastro retentive floating drug delivery system. Over all, this study concludes that viscosity of the polymer is a major factor affecting the drug release and floating properties of FDDS.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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