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Research Article

FORMULATION OPTIMIZATION AND *IN VIVO* EVALUATION OF ORODISPERSIBLE TABLETS OF ALMOTRIPTAN FOR THE EFFECTIVE TREATMENT OF MIGRAINE

SIRISHA Y*

Department of Pharmaceutics, Mallareddy Institute of Pharmaceutical Sciences, Hyderabad, Telangana, India.
***Corresponding author: Sirisha Y; Email: drsirishayella@gmail.com**

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ABSTRACT

Objectives: The present research work focuses on formulation, optimization, and *in vivo* evaluation of the orodispersible tablets of almotriptan to achieve the desired bioavailability and give a rapid relief from the migraine headache.

Methods: The optimization was done using 3^2 factorial design considering the three superdisintegrants as factors and minimum (0) and maximum 2 levels using response surface methodology, and the formulation was subjected to several *in vitro* evaluation studies. The stability studies were conducted on the optimized formulation for 6 months, the optimized stable formulation of almotriptan was subjected to in-vivo studies using animal models (rabbits) to determine the plasma concentration of the drug within the required time. The pharmacokinetic parameters such as Cmax, Tmax, area under the curve (AUC), and others were calculated. *In vitro–in vivo* correlation was done by deconvolution using Wagner–Nelson method, and the graphs were plotted to report the correlation of drugs.

Results: The almotriptan formulation F16 containing mannitol as diluent and cross-povidone 8 mg as superdisintegrant has shown better release of drug, i.e., 98.87% in 30 min, all the pre- and post-compression parameters were within limits. The optimized formulation has shown 98.27% drug release in 15 min, and the same formulation was taken for an *in vivo* study, which gave greater Cmax, Tmax, and AUC values compared to the marketed formulation. The *in vitro–on vivo* correlation was well established with an R^2 value of 0.9908.

Conclusion: Almotriptan orodispersible tablets have been successfully formulated and evaluated, and show rapid release with enhanced bioavailability.

Keywords: Almotriptan, Mannitol, Cross carmellose sodium, Cross povidone, Sodium starch glycolate, *In vivo* study, *In vitro–in vivo* correlation.

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INTRODUCTION

Oro-dispersible tablets, also called fast-dissolving or mouth-dissolving tablets, are those that show rapid activity by dispersing in the mouth itself without any water requirement. They differ from the compounds that are absorbed from other parts of the gastrointestinal tract. The solubilization of these drugs occurs in saliva itself, which, on further passage into the gastrointestinal facilitates dissolution of the drug [1]. Migraine is a neurological disease which is characterized by mild-to-severe headaches that last from 1 h to several hours, with symptoms affecting the autonomic nervous system. It is a Greek word meaning pain on one side of the head. Pain is caused in a pulsating nature on one side of the head, lasting from 2 to 72 h [2]. Several other symptoms are associated with it such as nausea, vomiting, and sensitivity to sound, light. In general, migraine headache is followed by aura, which is a visual, sensory, or motor disturbance. Triptans are the drugs that are being widely used in the present day to treat migraine, other than analgesics and alkaloids. The above triptan drugs selected were less explored, and very few investigations have been done on them based on the literature survey. Migraine headaches are to be treated immediately to get relief, so the development of oral disintegrating tablets of triptans will be the apt formulation for the treatment of migraine, which shows maximum effect within a short time. These formulations, without the need for water, disintegrate rapidly in the mouth and show faster absorption of the drug through saliva within minutes to treat migraine headaches [3]. Hence, orodispersible tablets of Anti-migraine drugs were formulated using various diluents and superdisintegrants.

METHODS

Almotriptan, Microcrystalline cellulose, Sodium starch Glycolate, Cross Carmellose Sodium, Cross Povidone, Talc, Magnesium Stearate from standard deviation (SD) Fine Chemicals Ltd.

Construction of calibration curve in pH 6.8 phosphate buffer [4]

From stock solution B 2, 4, 6, 8 mL of solutions were pipette out and transferred into 10 mL volumetric flasks, and the volume was made up to 10 mL with phosphate buffer pH 6.8 to get the solutions of concentrations 2, 4, 6 and 8 µg/mL. Their absorbance was measured by ultraviolet spectrophotometer at their maximum wavelength analytically and calibration curve was plotted.

Construction of calibration curves for drugs in biological fluids [5]

A volume of 1 ml of blank plasma and 200 µL of almotriptan at concentrations 30 ng/mL, 60 ng/mL, 90 ng/mL, 150 ng/mL, 250 ng/mL, 300 ng/mL, 400 ng/mL, and 500 ng/mL working standard solutions were transferred separately into a series of centrifugal tubes. To this added 300 µL of internal standard (ISD) (Naratriptan 1000 ng/mL) and 1 mL of Acetonitrile and placed on a cyclomixer for 15 s. Then vertexes for 2 min and finally centrifuged for 5 min at 3200 rpm. After the centrifugation, collected the organic layer in these analytes concentrations to produce 6 ng/mL, 12 ng/mL, 18 ng/mL, 30 ng/mL, 50 ng/mL, 60 ng/mL, 80 ng/mL and 100 ng/mL whereas 150 ng/mL of ISD concentration was directly injected 20 µL into high-performance liquid chromatography (HPLC).

Chromatographic conditions

Mobile phase	:	OPA and Acetonitrile (50:50).
Flow rate	:	1.0 mL/min
Column	:	KROMASIL, C18, 250×4.6 mm, 5 m.
Detector wave length	:	227 nm
Injection volume	:	20 mL
Run time	:	10 min

Table 1: Composition of almotriptan orodispersible tablets formulated using various concentrations of superdisintegrants (n=17)

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17
Almotriptan	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
SSG	4	6	8	10	12	14	16										
CCS								1	2	4	6	8	10				
CP														4	6	8	10
Mannitol	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160
Aspartame	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Aerosil	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mg stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Total weight (mg)	176.5	178.5	180.5	182.5	184.5	186.5	188.5	173.5	174.5	176.5	178.5	180.5	182.5	176.5	178.5	180.5	182.5

CCS: Cross carmellose sodium, CP: Cross povidone, SSG: Sodium starch glycolate

Table 2: Formulation of almotriptan orodispersible tablet for *in-vivo* administration

S. No.	Ingredients	Quantity (mg)
1	Almotriptan	1.605
2	Mannitol	30
3	Sodium starch glycolate	10
4	Aspartame	10
5	Aerosil	2
6	Mg.stearate	4
7	Talc	4
Total wt		61.605

Validation of the bioanalytical method: [6]

Method validation was carried out according to ICH guidelines (24) in rabbit plasma to evaluate the method for selectivity, linearity of response, accuracy, precision, recovery during processing, and stability during storage.

Selectivity

Selectivity was checked by injecting blank plasma samples from six different rabbits to confirm no interfering peaks around the retention time (RT) of both Naratriptan and IS.

Acceptance criteria

The % coefficient of variation (CV) of the RT should be ≤2.00%.

The % CV of the area ratio should be ≤5.00%

Calibration, linearity, and quality control (QC) samples

Calibration curves were obtained daily for 3 days using standards containing eight different concentrations. Curves were constructed by calculating the peak-area ratio of Naratriptan to that of IS. For the preparation of calibration standards, working solutions of Naratriptan (200 µL) and IS (300 µL) were added to blank plasma (1 mL) to obtain final concentrations of 6 ng/mL, 12 ng/mL, 18 ng/mL, 30 ng/mL, 50 ng/mL, 60 ng/mL, 80 ng/mL and100 ng/mL. The QC samples were prepared similarly as the calibration standards at three different levels: 6 ng/mL low QC (LQC), 20 ng/mL medium QC (MQC), and 32 ng/mL high QC (HQC).

Precision and accuracy

The precision and accuracy of the assay were determined using QC samples of known Naratriptan concentrations (i.e., 6, 20, and 32 ng/mL), which were processed each validation day freshly as described for calibration curve standards. Six replicates of each QC were analyzed on 3 days, and the intra- and inter-assay means, SD, and CV were calculated. The recovery of Naratriptan from plasma samples was carried out at three concentration levels (LQC, MQC, and HQC) by analysis of replicate (n=6) samples. The peak area of QC samples in plasma was compared with the peak area of the actual analyte (in mobile phase) at the same final concentrations. The recovery was expressed as a percentage value, and the extent of recovery of Naratriptan and of the IS should be consistent, precise, and reproducible.

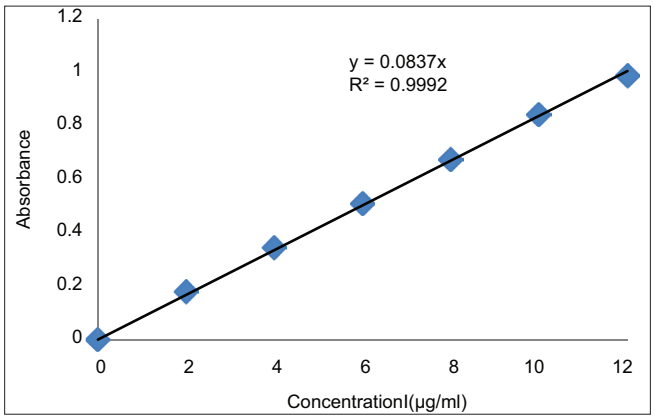


Fig. 1: Standard calibration curve of almotriptan pure drug in pH 6.8 Phosphate buffer

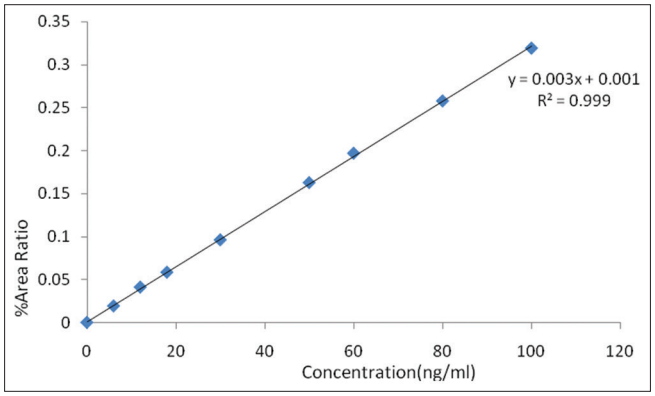


Fig. 2: Standard calibration curve of almotriptan in spiked rabbit plasma

Acceptance criteria

a) CV% <15% except LLOQ for which it is <20%
b) 67% QCs per level shall be 100±15%
c) Mean % Nominal (100±15%)
d) 67% total QCs shall be 100±15% nominal value except LLOQ for which it is <20%.

Ruggedness: The stability of the method for the changes in internal and external conditions of the experiment.

Acceptance criteria

a) CV %< 15% LLOQ for which it is <2
b) 67% QCs per level shall be 100±15%
c) Mean % Nominal (100±15%)
d) 67% total QCs shall be 100±15% nominal value for which it is <20%.

Table 3: Data of post-compression parameters of orodispersible tablets of almotriptan

F code	Average weight	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegration time (s)	% of drug content	Wetting time (s)	Water absorption ratio
F1	176.6±0.034	4.32±0.054	3.76±0.054	0.19±0.075	38±0.061	98.54±0.034	19±0.065	0.18±0.054
F2	179.8±0.051	4.34±0.048	3.78±0.019	0.19±0.065	35±0.019	98.32±0.065	25±0.017	0.193±0.062
F3	180.5±0.068	4.36±0.014	3.79±0.064	0.2±0.081	34±0.038	99.09±0.069	30±0.058	0.201±0.035
F4	182.6±0.078	4.4±0.054	3.8±0.058	0.21±0.033	31±0.041	97.14±0.081	24±0.049	0.211±0.095
F5	184.2±0.092	4.42±0.065	3.81±0.045	0.17±0.021	25±0.022	99.21±0.027	22±0.039	0.22±0.0.58
F6	186.7±0.064	4.43±0.083	3.82±0.097	0.13±0.063	23±0.077	99.82±0.036	20±0.058	0.231±0.024
F7	188.7±0.046	4.45±0.091	3.83±0.087	0.22±0.035	22±0.064	99.86±0.022	18±0.044	0.298±0.048
F8	173.2±0.055	4.46±0.062	3.84±0.027	0.19±0.046	42±0.045	99.79±0.011	29±0.085	0.17±0.057
F9	175.4±0.042	4.49±0.0.033	3.86±0.035	0.21±0.044	40±0.033	99.55±0.054	26±0.069	0.185±0.034
F10	177.1±0.036	4.28±0.0.044	3.74±0.064	0.18±0.088	39±0.086	99.71±0.062	23±0.077	0.216±0.066
F27	179.7±0.058	4.3±0.026	3.75±0.0074	0.19±0.071	37±0.024	98.12±0.086	28±0.055	0.21±0.092
F11	182.4±0.045	4.31±0.0.065	3.75±0.064	0.22±0.062	38±0.051	98.22±0.049	20±0.061	0.24±0.084
F12	181.8±0.024	4.34±0.0.055	3.77±0.038	0.24±0.014	39±0.059	99.07±0.057	25±0.073	0.303±0.057
F13	177.4±0.065	4.31±0.061	3.75±0.022	0.2±0.074	37±0.064	98.42±0.036	22±0.026	0.176±0.021
F14	179.3±0.087	4.34±0.075	3.76±0.021	0.21±0.089	36±0.077	98.14±0.081	19±0.044	0.181±0.066
F15	180.9±0.049	4.36±0.051	3.77±0.054	0.22±0.028	37±0.068	99.17±0.055	24±0.017	0.217±0.054
F16	183.7±0.035	4.4±0.034	3.79±00.2	0.24±0.06	39±0.054	97.89±0.06	21±0.06	0.22±0.025

n=3, mean±standard deviation

Table 4: *In vitro* release kinetics data observed from almotriptan orodispersible formulations

F code	T_{50} (min)	T_{90} (min)	R^2 value Zero order First order	K Value (min-1)	Dissolution effeciency (D.E) 20 min	Absorption ratio
F1	24.31±0.045	35.24±0.026	0.8873	0.9511	0.0285±0.012	50.30±0.162
F2	20.54±0.017	34.55±0.019	0.7812	0.9623	0.0337±0.006	44.56±0.057
F3	15.82±0.062	25.27±0.044	0.6862	0.9512	0.0438±0.006	42.63±0.115
F4	11.12±0.022	24.32±0.036	0.6687	0.9541	0.0623±0.007	40.14±0.066
F5	9.66±0.026	19.54±0.022	0.7423	0.9632	0.0717±0.002	41.05±0.148
F6	9.52±0.087	19.12±0.044	0.8129	0.9762	0.0727±0.004	41.3±0.241
F7	9.51±0.066	19.06±0.052	0.7582	0.9592	0.0728±0.003	41.38±0.062
F8	29.67±0.034	40.58±0.024	0.6944	0.9629	0.0233±0.001	37.36±0.081
F9	29.54±0.011	39.87±0.078	0.6337	0.9539	0.0234±0.002	36.4±0.254
F10	26.88±0.047	39.52±0.022	0.7891	0.9534	0.0257±0.005	37.5±0.068
F11	25.11±0.061	34.66±0.031	0.8048	0.9661	0.02759±0.007	33.94±0.158
F12	19.43±0.033	29.43±0.055	0.6732	0.9683	0.0356±0.003	33.65±0.324
F13	14.79±0.084	29.42±0.042	0.7422	0.9565	0.0468±0.002	34.09±0.245
F14	14.88±0.095	30.05±0.019	0.6892	0.9757	0.0465±0.004	41.12±0.085
F15	14.67±0.067	25.88±0.048	0.8115	0.9683	0.0472±0.006	34.03±0.073
F16	14.56±0.025	25.1±0.028	0.7446	0.9884	0.0476±0.005	34.2±0.142
F17	13.78±0.034	25.07±0.027	0.8552	0.9782	0.0503±0.003	34.3±0.321

n=3, mean±standard deviation

Table 5: Factorial design table of composition for almotriptan with SSG and mannitol

Standard	Run	Factor 1 SSG	Factor 2 Mannitol	Response drug release
4	1	16	160	98.54
3	2	4	160	85.67
1	3	4	100	88.35
2	4	16	100	96.78

SSG: Sodium starch glycolate

Stability

Short-term (on-bench) stability

The QC samples at low, medium, and high concentrations (18, 50, and 80 ng/mL, respectively) of almotriptan were thawed completely unassisted at room temperature and kept on the bench for time required to prepare/extract the samples (~4–6 h). The samples were assayed in one of the validation batches. The measured concentrations were compared with the actual concentrations of these samples.

The overall mean recovery % CV for all QC levels should be ≤20.00%.

Long-term stability

For the determination of long-term stability in rabbit plasma, Almotriptan-spiked QC samples were stored at~ −80°C for 30 days (long enough to cover the time period elapsed from the 1st day of sample collection to the final sample analysis). These samples were thawed on the day of testing and run together with freshly prepared calibration standards. All stability experiments were carried out against freshly spiked calibration standards.

Acceptance criteria

At least 67% (2 out of 3) of samples at each level should be within 85.00–115.00%. At least 80% (5 out of 6) of the matrix lot should be within the acceptance criteria.

The % mean accuracy of back-calculated concentration of LQC and HQC samples prepared from different biological matrix lots should be within 85.00–115.00%.

Drug-excipient compatibility studies By I.R [7]

Drug excipient compatibility studies were conducted to monitor or determine the interactions among the active pharmaceutical ingredients and all the excipients that were employed in various formulations.

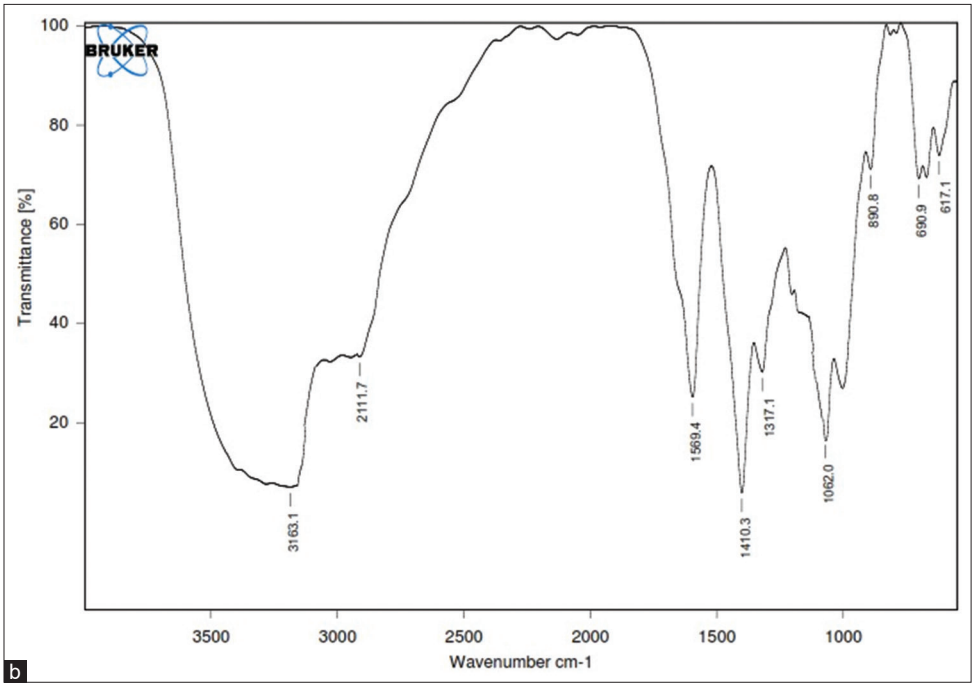


Fig. 3: (a and b) IR spectrum of pure drug and optimized formulation of almotriptan

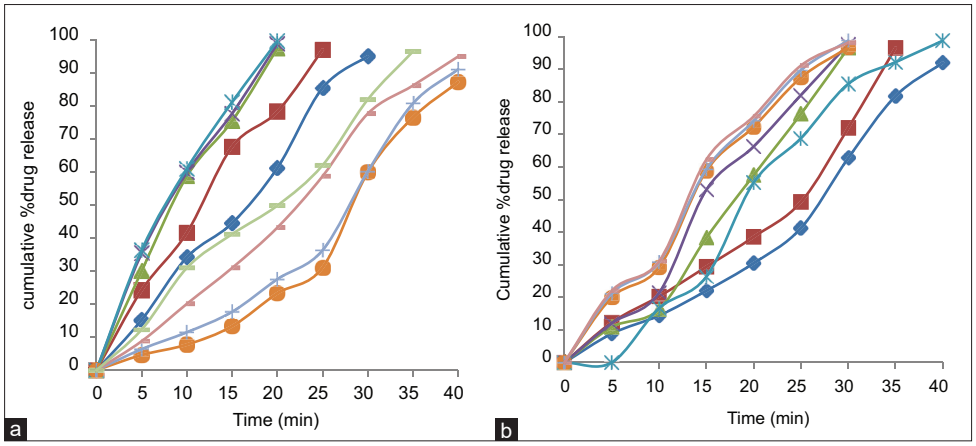


Fig. 4: (a and b) *In-vitro* dissolution data observed from almotriptan orodispersible tablets formulated with various superdisintegrants F1-F17

Wetting time [8]

Wetting time is the time taken for the tablet to completely absorb water to disintegrate rapidly. A petri plate was taken and filled with a certain volume of buffer solution. Filter paper or tissue paper was placed in the petri plate in the buffer solution, and the tablet was placed on it. The time taken for the buffer solution to completely wet the tablet was noted. More the wetting time, results more disintegration time is taken by the tablet, and vice versa.

Water absorption ratio [8]

The tablets were initially weighed, and the weight was noted as W1. Then they were evaluated for wetting time, and the tablet weight after complete wetting was noted as W2. The water absorption ratio is calculated from the formula.

$$R = \frac{W2 - W1}{W1}$$

***In vitro* disintegration studies: [4]**

Disintegration time is the time in which complete tablet to breaks down into finer particles and dissolve into the fluid. This is a specific test for orally disintegrating tablets as they ought to show very less disintegration time. The Electrolab disintegration test apparatus was employed, containing 6 tubes 3 inches long, held by 10 mesh screen and open at the top. 1 tablet was placed in each tube and the basket was moved up and down in a beaker containing 1 L pH 6.8 phosphate buffer at a height of 2.5 cm and the temperature of 37±0.5°C. Then the disintegration time of tablets was noted, and the average was calculated.

Drug content uniformity [4]

The tablets formulated were tested for uniformity in drug content. The percentage of the drug actually present in them compared to the incorporated drug. 20 tablets were weighed accurately and powdered, the powder equivalent to the dose of the drug was transferred to 100 mL of buffer solution, and was dissolved thoroughly by shaking and allowed to stand for 24–48 h. Then a sample was withdrawn, filtered through Whatman filter paper, and diluted suitably. The absorbance was measured from which the amount of drug was calculated. The % drug content was then calculated practically.

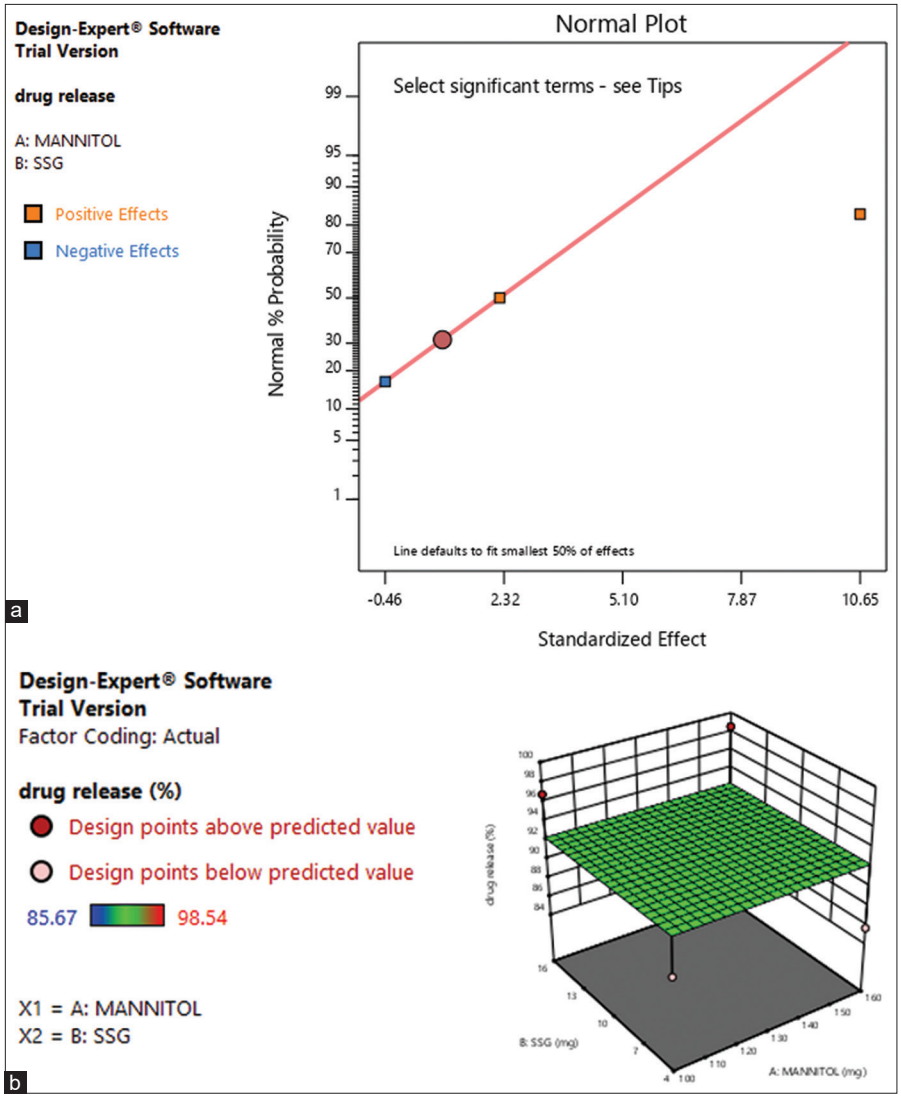
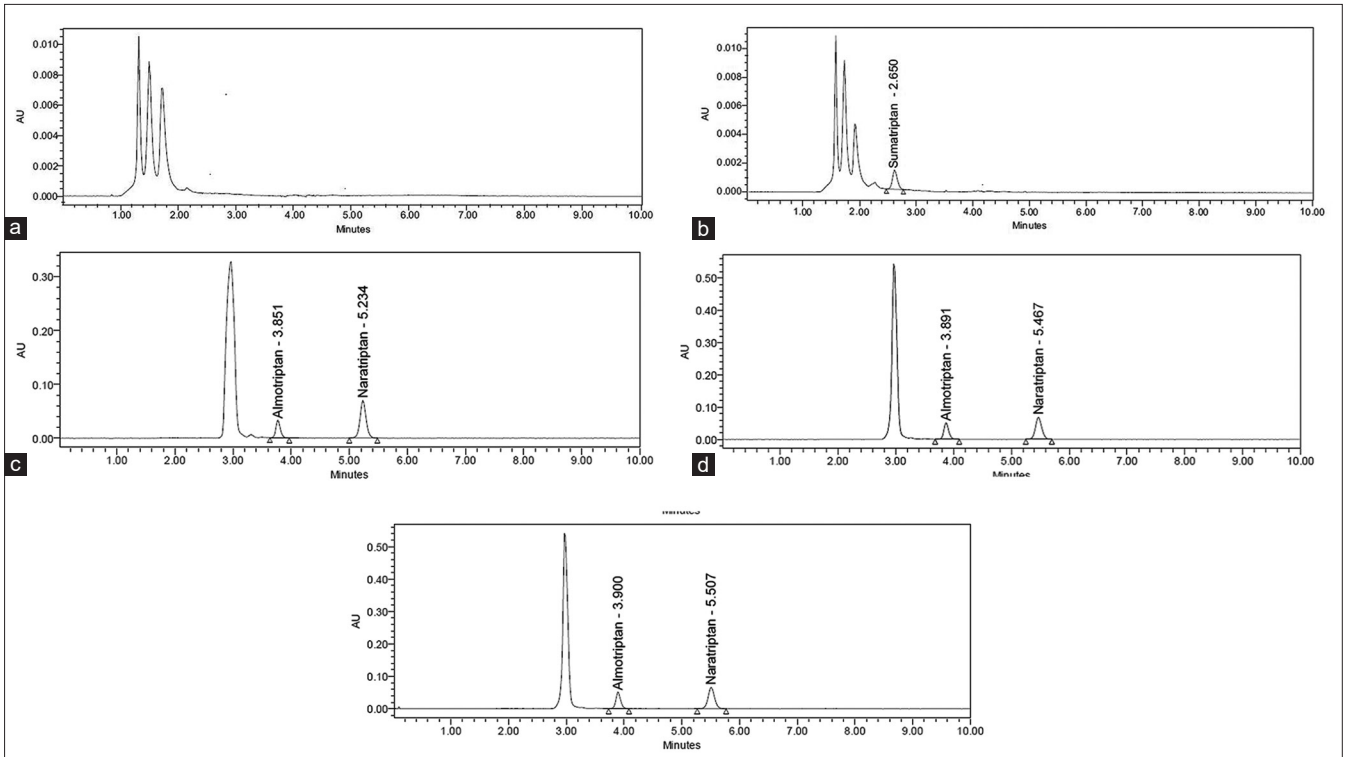


Fig. 5: (a) Normal plot of factorial design of almotriptan formulation with mannitol and sodium starch glycolate (SSG). (b) 3-D surface graph of factorial design of almotriptan formulations of SSG and mannitol

Table 6: Statistical analysis, ANOVA table for selected factorial model

Analysis of variance table (Partial sum of squares - Type III)						
Source	**Sum of squares**	**df**	**Mean square**	**F-value**	**p-value Prob > F**	**Significant**
Model	134.1	1	134.1	21.06	0.0443	
B-CCS	134.1	1	134.1	21.06	0.0443	
Residual	12.73	2	6.37			
Cor total	146.83	3				
Standard deviation		2.52		R-squared		0.9133
Mean		91.89		Adj R-squared		0.8699
C.V. %		2.75		Pred R-squared		0.6531
Press		50.94		adeq precision		6.49
-2 Log Likelihood		15.98		BIC		18.76
			AICc		31.98	
Factor	**Coefficient estimate**	**df**	**Standard error**	**95%CI Low**	**95%CI high**	**Recovery VIF**
Intercept	91.88	1	1.26	86.46	97.31	
B-CCS	5.79	1	1.26	0.36	11.22	1
Final equation in terms of coded factors				**Final equation in terms of actual factors**		
drug release				Drug release		
91.88				82.235		
5.79		*B		0.965		*SSG

p<0.005, CI=95%. CI: Confidence interval, AIC: Akaike information criterion, BIC: Bayesian information criterion, ANOVA: Analysis of variance, SSG: Sodium starch glycolate, CCS: Crosscarmellose sodium



Peak Name: Almotriptan

	Peak Name	RT	Area	USP Plate Count	USP Tailing
1	Almotriptan	3.812	75823	10088	1.21
2	Almotriptan	3.813	99528	11875	0.99
3	Almotriptan	3.815	131543	10228	1.19
4	Almotriptan	3.877	145093	10554	1.17
5	Almotriptan	3.891	130560	10705	1.16
6	Almotriptan	3.887	87616	10598	1.08
7	Almotriptan	3.872	54767	12452	1.11
8	Almotriptan	3.856	31329	10675	1.13
9	Almotriptan	3.847	3931	10426	1.16
10	Almotriptan	3.832	1608	10663	1.16

Peak Name: Naratriptan

	Peak Name	RT	Area	USP Plate Count	USP Tailing	USP Resolution
1	Naratriptan	5.534	529284	10022	1.11	8.0
2	Naratriptan	5.581	547499	12364	1.10	8.7
3	Naratriptan	5.591	529389	10669	1.12	8.1
4	Naratriptan	5.567	538346	12132	1.10	8.8
5	Naratriptan	5.574	538552	12057	1.11	8.8
6	Naratriptan	5.579	543222	12392	1.14	9.1
7	Naratriptan	5.513	536437	12673	1.11	9.1
8	Naratriptan	5.524	536325	12634	1.14	9.0
9	Naratriptan	5.532	539789	12151	1.06	9.0
10	Naratriptan	5.565	530464	12170	1.09	9.3

Fig. 6: (a-e) Chromatograms of *in-vivo* evaluation of almotriptan. (a) Chromatogram of blank plasma for almotriptan *in-vivo* studies by High-performance liquid chromatography (HPLC) method. (b) Chromatogram of internal standard sumatriptan for almotriptan *in-vivo* studies in rabbitplasmaby HPLC method. (c) Chromatogram of linearity data of almotriptan pure drug in rabbit plasma by HPLC for maximum concentration. (d) Chromatogram of optimized formulation of almotriptan in rabbit plasma by HPLC. (e) Chromatogram of marketed formulation of almotriptan in rabbit plasma by HPLC

Dissolution studies [9]

The dissolution/drug release studies were carried out using a paddle-type USP-II dissolution apparatus. pH 6.8 phosphate buffer was employed as dissolution fluid in a volume of 900 mL, the rpm was maintained 50 rpm, temperature was maintained at 37±0.5°C. Aliquots of 5 mL were collected at regular intervals and replaced with an equal volume of fresh buffer to maintain sink conditions. The samples were filtered, suitably diluted, and analyzed by ultraviolet-spectrophotometer at the maximum wavelength of the drugs.

***In vivo* drug release studies**

Animal dose calculation [10,11]

Human equivalent dose (HED) (mg/kg) =Animal dose (mg/kg) X Animal Km factor/Human Km factor.

12.5=A.D. × 37/12=37/12*12.5/60=0.642 mg/kg.

HED

Animal Km factor=12, Human Km factor=37, Wt. of the rabbits=2.5 kg. Hence, the dose of the drugtaken is 1.605 mg.

All the ingredients were weighed accurately, passed through sieve number 22 mixed thoroughly by physical mixing, and compressed into a tablet by direct compression using 5 mm punch. Three marketed tablets were weighed initially and powdered, and then the powder containing the drug dose equivalent to 1.605 mg was accurately and carefully weighed using 1 mg sensitivity balance, collected, and formulated to administer to animals for *in vivo* study.

Pharmacokinetic study

Healthy rabbits (New Zealand Albino) of either sex weighing 2.5 kg were selected and housed with CPCSEA guidelines (Approval No.ARTI/CPCSESA/2016/ARTI19/A), (Reg.No.1722/RO/Ere/S/13/CPCSEA) were fasted overnight and had free access to drinking water.

Experimental design [5]

Animals were separated into two experimental groups, each group consisting of six animals (n=6). The test formulation of batch (Optimized) was compared with (reference/marketed formulation) with the following treatment schedule under fasted condition.

- Group I – Almotriptan marketed formulation
- Group II- Almotriptan optimized formulation used as test.

Table 7: *In vivo* plasma concentration versus time data of almotriptan optimized formulation

Time (h)	Optimized (ng/mL)	Marketed (ng/mL)
0	0	0
1	25.46±1.28	19.18±1.12
1.5	33.42±5.28	25.26±1.22
2	44.17±3.04	35.13±1.16
2.5	48.72±2.11	40.18±1.08
3	43.84±1.24	30.29±1.04
6	29.42±1.10	20.56±1.16
8	22.39±1.56	15.14±1.26
10	18.52±1.08	12.52±1.20
16	11.32±1.84	8.54±1.16
24	7.54±2.26	5.32±1.22

n=3, mean±standard deviation

Table 8: Pharmacokinetic parameters determined by *in vivo* studies on almotriptan optimized and marketed formulation

Parameters	Optimized	Marketed	One paired t-test "p"-value
$C_{max\ (ng/mL)}$	48.72±0.04	40.18±0.24	0.0024
$T_{(max)}$ h	2.5±0.26	2.5±0.02	0.0035
Vd (L)	185.5±0.015	162.93±0.056	0.0047
Clearance (L/h)	56.44±0.234	48.32±0.137	0.0044
AUC (0-∞) ng.h/mL	492.15±0.12	336.22±0.16	0.0018
MRT (h)	6.363±0.278	7.108±0.158	0.0029
K_E (h^{-1})	1.270±0.033	0.926±0.021	0.0016
T_{50} (h)	0.545±0.026	0.748±0.054	0.0036
T_{90} (h)	1.804±0.047	2.07±0.044	0.0027

n=3, mean±standard deviation, *P*<0.005. AUC: Area under the curve, MRT: Mean residence time

The test formulation of almotriptan was formulated into an orodispersible tablet by the direct compression method, taking the animal dose of 1.605 mg into consideration. This is placed in the oral cavity of a rabbit using tweezers and is held until the tablet has completely disintegrated. Blood samples (each of about 1–2 mL from each animal) were withdrawn from the marginal ear vein at regular time intervals after administration. The collected blood samples were immediately centrifuged at 5000 rpm in ultra-cooling centrifuge for 10 min at 4°C. The supernatant plasma sample was separated and stored in a clean screw capped 5 mL polypropylene plasma tubes at −20°C in a deep freezer, until further analysis.

Estimation of drug from rabbit plasma [12]

The stored plasma samples were processed at room temperature, and 250 µL of plasma was added to 500 µL of Acetonitrile to precipitate the proteins. The samples were vortexed on a vortex mixer for 15 min, followed by centrifugation at 10000 rpm for 15 min. The respective samples were injected into the HPLC C_{18} column. The injection volume was 20 µL, and run time is 10 min.

Data analysis [13,14]

The total area under plasma concentration time curve (area under the curve $[AUC]_{0-\infty}$), the maximum plasma concentration (C_{max}), and time to reach the maximum plasma concentration (T_{max}) were selected as parameters for pharmacokinetic evaluation. The C_{max} and T_{max} were obtained directly from the experimental data of plasma concentration versus time. $AUC_{0-\infty}$ was obtained by adding the $AUC_{(0-t)+}$ $AUC_{(0-\infty)}$, which was calculated by the trapezoidal rule. The differences in the average of data were compared by sample analysis of variance (one-way analysis of variance) or independent sample t-test. The significance of the difference was determined at 95% confidence limit (p=0.05).

***In vitro–in vivo* correlation study: [15]**

Deconvolution: Level A correlation is developed by the deconvolution process that converts the output (plasma concentration profile) to the input *in vivo* dissolution of the dosage form.

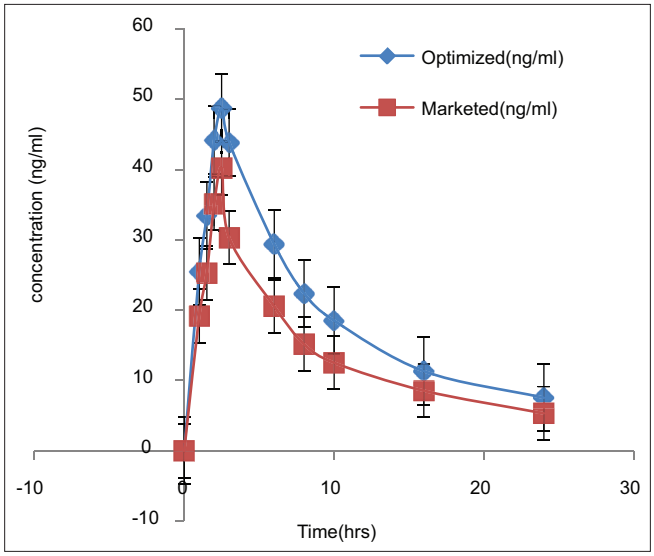


Fig. 7: Comparative plasma concentration versus time curves of almotriptan optimized and marketed orodispersible formulation

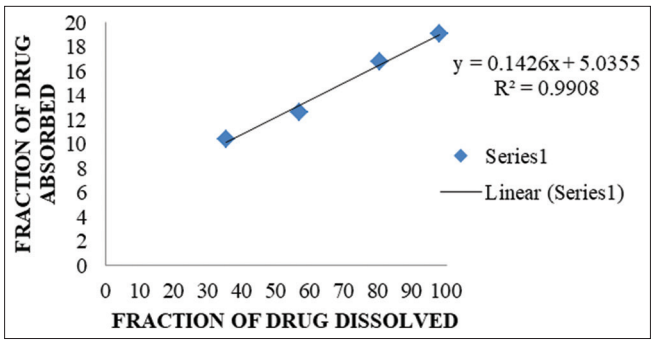


Fig. 8: *In-vitro in-vivo* correlation values of *in-vitro* drug release and fraction of drug absorbed *in-vivo* of almotriptan formulation

The Wagner–Nelson method was employed in the present study for conversion.

This method is used for a one-compartment model and is less complicated. The fraction of drug absorbed at time t (F_t) can be calculated from the formula.

$$F_t = Ct + Ke\int_0^t AUC \,/\, Ke\int_0^\infty AUC \times 100$$

Where; Ct is plasma concentration at time t,
Ke is the elimination rate constant

$\int_0^t AUC$ is area under curve from time zero to time t.

$\int_0^\infty AUC$ is area under curve from time zero to infinite time

RESULTS

Interpretation of IR for pure drug and optimized formulation

O-H – 3186	O-H–3163.1
$C\text{-}H_3$–2912.0	$C\text{-}H_3$–2111.7
Aromatic C=C - 1595.3	Aromatic C=C–1569.4
C-N - 1400.5	C-N–1410.3
$S\text{-}O_2$- 1070.5	$S\text{-}O_2$–1062

The primary functional groups of almotriptan have been interpreted above, and there is no major change in the wavelength of the IR spectra, so there is no interaction found between the pure drug of almotriptan and excipients.

The elimination rate constant is shorter as the half-life of the drug is shorter, and the samples were monitored every 5 min; hence, there is no issue of inconsistency in terminal phase sampling and calculation.

DISCUSSION

Then the calibration curve was constructed in pH 6.8 phosphate buffer and spiked rabbit plasma by using the various dilute concentrations of almotriptan, and the R^2 value was found to be 0.999, which shows that linearity exists between the values. The drug excipient compatibility done by IR spectroscopy shows no alteration in the functional peaks for both pure drug and optimized formulation, and there is no interaction between the drug and excipients used in the formulations. The post-compression parameters were also found to be within IP limits and satisfactory. The drug content uniformity was found to be above 97% for all the formulations, and hence, there is no wastage of drug dose, and the complete dose will be available to the body. The lesser wetting time and higher water absorption ratio also result in rapid uptake of fluid and rapid disintegration of tablets. Among all the formulations containing various superdisintegrants, F16 was found to show the best release of 100% in 20 min and is the optimized formulation, which has mannitol as diluent and SSG (8%) as superdisintegrant. Drug kinetic parameters were determined by all the formulations, such as T50, T90, R^2, KE and dissolution efficiency, and statistical evaluation of analysis of variance and t-test was performed on those parameters where the "p" value was <0.05. It shows that there is no significant variation between the rate constant and dissolution efficiency of the formulation, and the drug release studies conducted were efficient. All the pharmacokinetic parameters determined were better in case of the optimized formulation compared to the marketed formulation, and there was *in vitro–in vivo* correlation found, and hence the bioavailability of almotriptan can be enhanced if it is formulated as an orodispersible tablet.

CONCLUSION

The orodispersible tablets of almotriptan were successfully formulated by employing various superdisintegrants in varying concentrations and evaluated for precompression and post-compression parameters, optimized, and the stable formulation has shown a good *in vivo* profile and correlation.

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AUTHOR'S CONTRIBUTION

The corresponding author, Dr.Y. Sirisha, has done the research work as a part of her Ph.D and is the Research scholar who completely reviewed the literature, selected the drugs and incorporated the methods, and conducted the *in vitro* and *in vivo* study. This is an original research work with complete contribution from the author.

CONFLICT OF INTEREST

There is no conflict of interest as there is only a single author.

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