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Research

Formulation Development And Evaluations Of Eletriptan Hydrobromide Immediate Release Tablets

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Abstract

This dissertation work was done with an aim to design an porous oral dosage of Elitriptanhydrobromide and evaluation of the tablets for various parameters including in vitro drug release studies. Elitriptanhydrobromide tablets were formulated by using microcrystalline cellulose as filler, camphor and menthol as subliming agents, crospovidone, SSG and CCS as super disintegrant, and magnesium stearate as lubricant.The powdered blend were compressed into tablets and were analyzed for the parameters such as average weight, disintegration time, thickness, weight variation, hardness and drug content. The formulation F6 containing 8% of CCS and 10% of menthol showed disintegration time of 18seconds after drying. menthol as subliming agent was found to be most effective of all other subliming agents as it had showed drastic effect on the drug release. All other parameters viz: Hardness, Thickness, Weight variation and drug content were also found to be within limits.The formulation F6 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective and precise and also yields reproducible good results for manufacturing the tablets.

Keywords: Elitriptanhydrobromide,

INTRODUCTION

Drug delivery system [1]

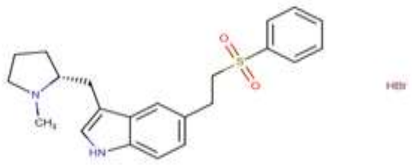
Dosage forms are also referred to as “Drug Delivery Systems” or “Finished Drug Products”. A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and site of release of drugs in the body. The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. That is, the drug delivery system should deliver drug at a rate dedicated by the needs of the body over a specified period of treatment. Oral route of drug administration is most appealing route for delivery of drugs for various dosage forms. The tablet is one of the most preferred dosage forms, because of its ease of administration, accurate dosing and stability as compared to oral liquid dosage forms.

Tablets may be defined as solid unit pharmaceutical dosage forms containing drug substance with or without suitable excipients and prepared by either compression or molding methods.

The first step in the development of dosage form is preformulation, which can be defined as investigation of physiochemical properties of drug substances alone and when combined with excipients. The main objective of preformulation studies, is to develop stable and bioavailable dosage form and study of factors affecting such as stability, bioavailability and to optimize so as to formulate the best dosage form. Here, optimization of formulation means finding the best possible composition (Ansel H.et al., 2004). Compressed tablets are formed by applying pressure, for which compression machines (tablet presses) are used and they are made from powdered crystalline or granular material, alone or in combination with binder, disintegrants, release polymers, lubricants and diluents and in some cases with colorant.

Drug profile

- **General Description:**
- **Name** :EletriptanHydrobromide
- **Structure:EletriptanHydrobromide**



IUPAC name :5-[2-(benzenesulfonyl)ethyl]-3-{[(2R)-1methyl pyrrolidin-2-yl]methyl}-1H-indole
Brand names : Relpax
Categories :Tryptamines and Derivatives
Molecular formula: $C_{22}H_{26}N_2O_2S$
Molecular weight:382.519.

Physico chemical properties

Nature	:	White, odorless powder
Solubility	:	freely soluble in water
BCS class	:	III
Melting point	:	349.94^0c
PKa (strongest acid)	:	17.11
Pka (Strongest Base)	:	8.37
Log p	:	3.9

Materials and equipments

List of materials used

Table 1: Materials Used

S.No.	Materials	Supplier
1	Eletriptanhydrobromide	Provided by Chandra labs, Hyd.
2	Menthol	ESSEL fine chem. Mumbai
3	Camphor	ESSEL fine chem. Mumbai
4	Croscarmelose sodium	ESSEL fine chem. Mumbai
5	Crospovidone	ESSEL fine chem. Mumbai
6	SSG	ESSEL fine chem. Mumbai
7	Micro crystalline cellulose	ESSEL fine chem. Mumbai
8	Magnesium stearate	ESSEL fine chem. Mumbai

List of equipments used

Table 2: Equipments Used

S.No.	Equipments	Manufacturer
1.	Electronic Weighing Balance	Sartorious BSA 224S – CW.
2.	Hardness Tester	CINTEX Mosanto tester, Mumbai.
3.	UV- Spectrophotometer	Shimadzu, Model No. UV-2450.

4.	Friability Test Apparatus	Electrolab EF-2.
5.	Hot air oven	Bio-tech India.
6.	Bulk Density Apparatus	Electro lab
7.	Tablet Compression Machine	CADMACH.
8.	Tablet Dissolution Tester	TDT-08L (USP), Electro lab.
9.	Ultra sonicator bath	Bio-tech India.
10.	Digital pH meter	Microprocessor pH stat/Analyser.
11.	FTIR Spectrophotometer	IR Affinity-1, Shimadzu.

Formulation development
Preformulation studies
Api characterization
Organoleptic evaluation
Organoleptic characters like color, odor, and taste of drug were observed and recorded using descriptive terminology.
Description: Elitriptanhydrobromide is a white colour crystalline powder. It was found to be freely soluble in water, methanol.
Solubility: Elitriptanhydrobromide is freely soluble in water and methanol.
Melting point: The melting point ofElitriptanhydrobromide was found out by capillary method using programmable melting point apparatus.

Analytical evaluation
UV Absorption Maxima (λ_{max}) of drug sample in phosphate buffer pH 6.8
Stock II: One ml of the above solution was then further diluted to 100 ml with phosphate buffer pH 6.8to get a stock solution of 10µg/ml. UVscanning was done for 10 µg/ml drug solution from 200-400 nm using phosphate buffer pH 6.8as a blank in schimadzu, UV 2450 spectrophotometer. The wavelength maximum was found to be at 222 nm.

FT-1R Studies
The IR absorption spectra of the Elitriptanhydrobromide drug and with different superdisintegrants, natural gums and excipients were taken in the range of 4000-450 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powered and dried potassium bromide.

Formulation Development
❖ **Formulation Of ElitriptanHydrobromide Porous Tablets**

By using Direct Compression method
Porous tablets of Elitriptanhydrobromide were prepared by direct compression method employing camphor and menthnol as sublimating agents. The concentrations of the above ingredients were optimized as shown in below table on the basis of trial preparation of the tablets. All the ingredients were weighed accurately. The drug was mixed with the release rate enhancing disintegrants and other excipients, except magnesium stearate, in ascending order of their weight. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then, magnesium stearate was added and mixed for not more than 1 min (to ensure good lubrication.) About 200 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed using 8 mm flat- surface punches. The hardness of the tablets was adjusted at 4-6 kg/cm^2 using a Monsanto hardness tester.

Compression parameters
The lubricated blend was compressed using following parameters
Tooling: 8mm round punch.
Average weight: 200mg.

Table 3: Formulation design of ElitriptanHydrobromide Porous tablets

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Elitriptanhydrobromide	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg
Menthol	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	20mg	-
Camphor										20mg

MCC	150	146	142	150	146	142	150	146	142	142
SSG	8mg	12mg	16mg	-	-	-	-	-	-	-
CCS	-	-	-	8mg	12mg	16mg	-	-	-	16mg
CP	-	-	-	-	-	-	8mg	12mg	16mg	-
Mg.stearate	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg	2mg
Total weight	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg

RESULT AND DISCUSSION

Preformulation Studies

Table 4: Table showing the description of Elitriptanhydrobromide (API)

Test	Description
Colour	A white to off white colour crystalline powder
Odour	Odourless

Solubility

Table 5: Elitriptanhydrobromide(API) in various solvents.

Solvents	Solubility
0.1N HCL	Freely soluble
Water	Freely soluble
pH6.8Phosphate buffer	Soluble
Methanol	Freely soluble
Ethanol	Slightly soluble

Melting Point

Table 6: Melting point of API's

Material	Melting Point	Melting Point Range
Elitriptanhydrobromide	170^0c	169-172^0c

The Result was found to be within limit.

Spectrophotometric Determination of ElitriptanHydrobromide

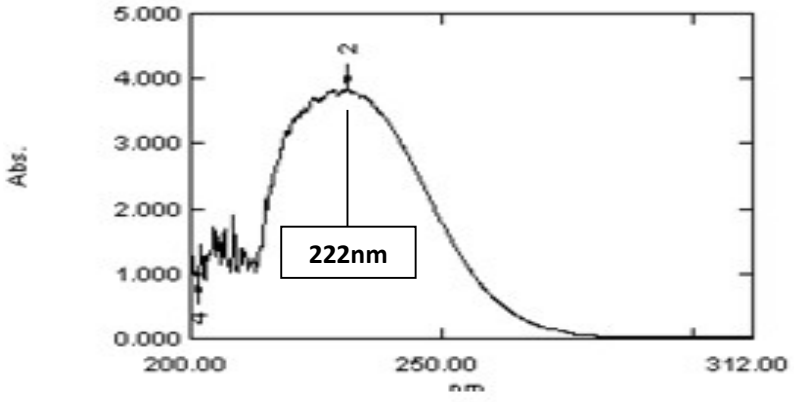


Fig 1: Spectrum of Elitriptanhydrobromide

Standard Graph For ElitriptanHydrobromide In phosphate buffer pH 6.8 At 222nm

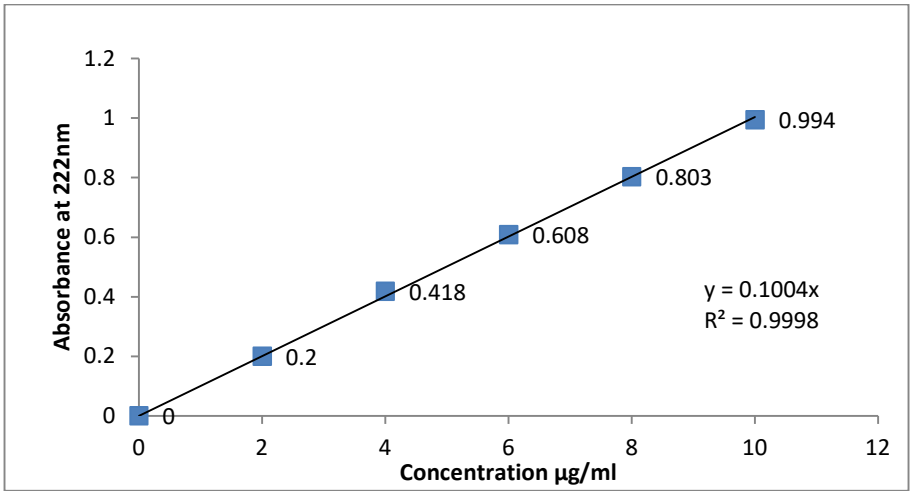


Fig 2: standard graph of Elitriptanhydrobromide

Evaluation of tablet blend

Table 7: Evaluation of tablet blend for formulations (F1 – F10)

Formulation	Bulk Density (g/cc)	Tapped Density(g/cc)	Hausner ratio	Compressibility index (%)	Angle of repose
F1	0.464	0.574	1.23	19.1	29.47
F2	0.423	0.501	1.16	15.5	27.63
F3	0.456	0.542	1.22	15.8	25.54
F4	0.467	0.559	1.25	16.4	26.23
F5	0.485	0.593	1.10	18.2	27.21
F6	0.460	0.556	1.21	17.2	30.38
F7	0.478	0.575	1.24	16.8	28.46
F8	0.450	0.554	1.28	18.7	25.71
F9	0.442	0.537	1.27	17.6	31.82
F10	0.467	0.559	1.25	16.4	26.23

Evaluation Of Tablets
Before Drying

Table 8: Evaluation of porous Tablets For Formulations (F1 – F10) Before Drying

Formulation	Hardness[a] (kg/cm2)	Weight[b] (mg)	Thickness[a] (mm)	Disintegration time[a] (min)	Drug content[c](%)
F1	6.0±0.17	201±0.59	2.4±0.05	6	98.2±0.62
F2	6.1±0.20	198±0.63	2.4±0.02	5min 24sec	98.72±0.23
F3	6.2±0.18	201±0.45	2.6±0.07	4min	98.4±0.34
F4	6.0±0.15	202±0.88	2.5±0.10	5min 45sec	98±0.56
F5	6.2±0.16	203±0.56	2.4±0.03	4min 34sec	98.44±0.49
F6	6.1±0.22	198±0.74	2.45±0.06	2min 21sec	100.8±0.27
F7	6.2±0.24	201±0.67	2.5±0.15	5min 32sec	98.2±0.63
F8	6.0±0.22	201±0.77	2.5±0.03	4min	98.4±0.56
F9	6.1±0.16	203±0.86	2.4±0.01	2 min17sec	99.32±0.37
F10	6.1±0.12	198±0.54	2.4±0.05	2min 28sec	98±0.56

a = 6 tablets, b = 20, c=10

After Drying

Table 9:Evaluation of porous Tablets For Formulations (F1 – F10) After Drying

Formulation	Hardness[a] (kg/cm2)	Weight[b](mg)	Thickness[a] (mm)	Disintegration time[a] (sec)	Drug content[c](%)
F1	3.5.0±0.11	181±0.39	2.4±0.03	1min 14sec	98.2±0.62
F2	3.7±0.13	179±0.43	2.4±0.05	47sec	98.72±0.23
F3	3.9±0.15	182±0.47	2.6±0.06	38sec	98.4±0.34
F4	3.8±0.12	183±0.78	2.5±0.09	1min	98±0.56
F5	3.7±0.12	184±0.43	2.4±0.05	42sec	98.44±0.49
F6	3.6±0.19	183±0.51	2.45±0.08	18sec	100.8±0.27
F7	3.6±0.21	181±0.55	2.5±0.12	45sec	98.2±0.63
F8	3.9±0.25	183±0.57	2.5±0.06	28sec	98.4±0.56
F9	3.8±0.19	184±0.56	2.4±0.07	19sec	99.32±0.37
F10	3.7±0.16	183±0.31	2.4±0.08	22sec	98±0.56

a = 6 tablets, b= 20, c=10

Results Of In-Vitro Release Profile

Table 10:In-Vitro Release Profile of Elitriptanhydrobromide from formulations F1-F10

Time (min)	Cumulative % drug release									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
5	13±0.0021	17±0.011	24±0.023	17±0.023	20±0.019	37±0.011	13±0.017	17±0.021	23±0.011	32±0.021
10	23±0.019	27±0.014	38±0.025	32±0.019	38±0.014	55±0.017	27±0.021	31±0.025	37±0.009	53±0.019
15	35±0.011	42±0.025	54±0.019	45±0.021	57±0.017	70±0.021	38±0.025	45±0.023	53±0.008	68±0.001
20	56±0.016	59±0.021	67±0.023	56±0.025	65±0.018	86±0.022	51±0.019	57±0.026	68±0.012	82±0.007
25	62±0.011	70±0.017	78±0.021	69±0.022	76±0.021	99±0.023	64±0.017	76±0.023	78±0.017	91±0.011
30	77±0.021	83±0.022	91±0.017	86±0.021	93±0.023	102±0.027	79±0.016	84±0.021	97±0.019	99±0.021
35	89±0.014	92±0.017	99±0.021	93±0.021	99±0.025	--	92±0.018	99±0.019	101±0.021	102±0.021
40	101±0.013	98±0.021	--	101±0.018	--	--	99±0.021	102±0.017	--	--

n=3

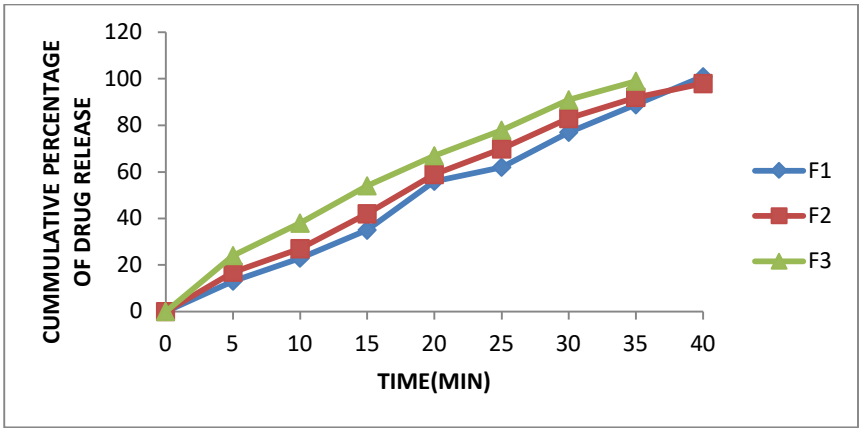


Fig 3: Linear graph comparison between cumulative % drug releases for formulations (F1- F3)

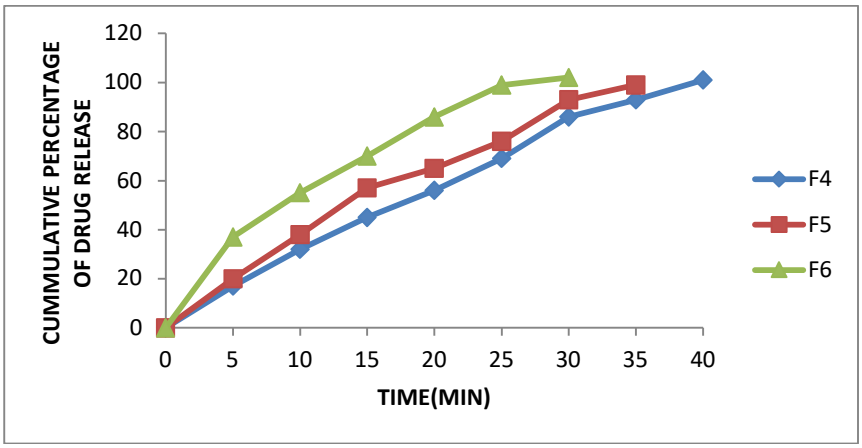


Fig 4: Linear graph comparison between cumulative % drug releases for formulations (F4 - F6)

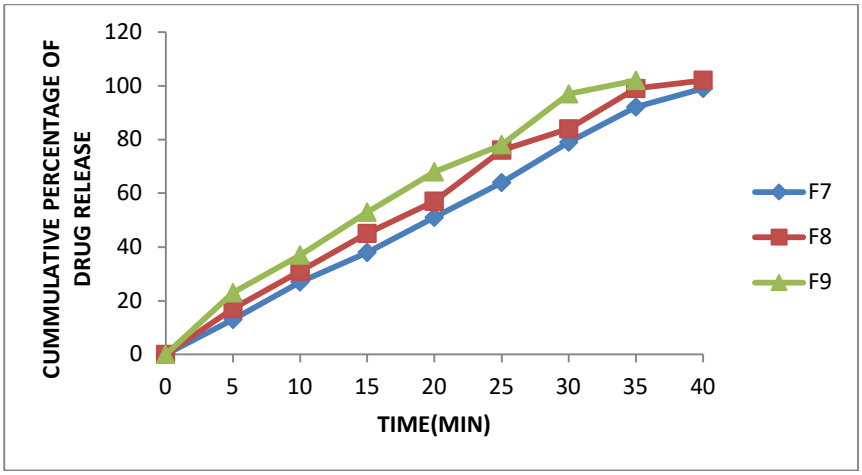


Fig 5: Linear graph comparison between cumulative % drug releases for formulations (F7- F9)

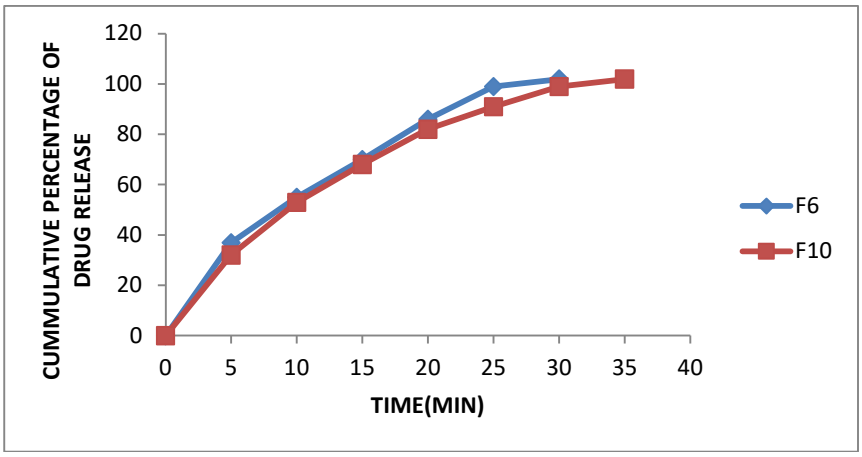


Fig 6: Linear graph comparison between cumulative % drug releases for formulations (F6 & F10)

Summary

This dissertation work was done with an aim to design an porous oral dosage of Elitriptanhydrobromide and evaluation of the tablets for various parameters including in vitro drug release studies.

Elitriptanhydrobromide tablets were formulated by using microcrystalline cellulose as filler, camphor and menthol as subliming agents, crospovidone, SSG and CCS as super disintegrant, and magnesium stearate as lubricant.

The powdered blend were compressed into tablets and were analyzed for the parameters such as average weight, disintegration time, thickness, weight variation, hardness and drug content.

The formulation F6 containing 8% of CCS and 10% of menthol showed disintegration time of 18seconds after drying. menthol as subliming agent was found to be most effective of all other subliming agents as it had showed drastic effect on the drug release. All other parameters viz: Hardness, Thickness, Weight variation and drug content were also found to be within limits.

The formulation F6 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective and precise and also yields reproducible good results for manufacturing the tablets.

CONCLUSION

The above results suggest that the formulated porous tablets of eletriptan exhibited good physical parameters and rapidly disintegrating without affecting the release profile. The overall results indicated that formulation with cross caramellose sodium (8%) as super disintegrant and menthol (10%) as sublimating agent had a higher edge compared to other formulations. This direct compression process is simple, reproducible and robust to prepare immediate release tablets of eletriptan and other anti-migraine drugs.

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