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Formulation and Evaluation of Oral Elementary Osmotic Pump Tablets of Sumatriptan Succinate

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Authors' contributions

This work was carried out in collaboration between all authors. Authors JKP and SP designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors YMR and YSK managed the analyses of the study, author AV managed the literature searches. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aim: In the present study, Sumatriptan succinate was formulated as oral elementary osmotic pump with a zero-order drug release profile.
Methodology: The effect of different formulation variables i.e. different types of osmogens, concentrations of osmogen and concentration of coating solution were studied. The *in vitro* evaluation was carried out in different release media.
Result: Highest percentage of drug release was observed at high concentration of mannitol i.e., 1:3 (drug: mannitol). Osmogen with low osmotic pressure (38 atm) showed 71.01% zero-order drug release for 12 hours when compared to that of the osmogen with high osmotic pressure (356 atm) which showed 67.38% of release by zero order.
Conclusion: Elementary osmotic pump tablets of Sumatriptan succinate were able to deliver zero-order release up to 12 hours independent of pH of dissolution media and have overcome the problem of chronotherapeutic effect.

Keywords: Sumatriptan succinate; osmogens; elementary osmotic pump; controlled release.

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1. INTRODUCTION

Sumatriptan succinate (SS) is a selective serotonin agonist and a vasoconstrictor agent, which must be administered daily 100 mg with a time interval of 2 hours. To reduce this dosing frequency a controlled release formulation is necessary. It also has chronotherapeutic action, so to overcome this problem controlled release formulation has been designed. By optimizing formulation and processing factors, it is possible to develop osmotic drug delivery system to deliver drug of diverse nature at a pre-programmed rate. A high degree *In-vitro-In-vivo* correlation can be obtained from the osmotic pumps. Out of different osmotic pumps which were developed, Elementary Osmotic pumps (EOP) is the simplest osmotic pump [1]. It is like a coated tablet with an aperture on its surface for the release of drug. EOP systems are expected to release the drug (60-80%) in zero-order fashion [2,3]. The drug release follows a constant rate, until there is osmotic pressure inside the tablet.

2. MATERIALS AND METHODS

2.1 MATERIALS

SS was obtained as a gift sample from NATCO Pharmaceuticals Limited, Cellulose acetate (39.8% acetylation) (CA) from Loba chemicals, Sodium chloride (NaCl), Mannitol, Microcrystalline cellulose (MCC- pH 101 grade), Dibutylphthalate (DBP), Magnesium stearate, Acetone, Polyethylene glycol – 400 were procured from Finar chemicals, Talc was obtained from Qualikem reagents.

2.2 Methods

2.2.1 Preformulation studies

Preformulation studies were primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

2.2.1.1 Drug- excipient compatibility study

Sumatriptan succinate was mixed in different proportions with all excipients, which were used in the formulation, in different ratios and kept at 40°C/75% RH conditions for two months. The physical properties (colour change) were monitored regularly. The change in colour of any mixture was considered as incompatibility and the excipient blend was discarded from study.

2.2.1.2 FT-IR

A Fourier Transform – Infra Red spectrophotometer (spectrum BX series, 51658, Perkin Elmer BX, UK) equipped with spectrum v2.19 software by KBr pellet method was used to study the non-thermal analysis of drug-excipient (binary mixture of drug: excipient in 1:1 ratio) compatibility. The spectrum for each sample was recorded over the 400-4000 cm^{-1} special region with a resolution of 4 cm^{-1}.

2.2.1.3 Determination of flow properties of powder

Various properties of powders such as bulk density, tapped density, Carr's Index, Hausner's ratio and angle of repose were determined.

2.2.1.4 Standard graph of Sumatriptan succinate

Standard graph of Sumatriptan succinate in distilled water, 0.1N HCl, phosphate buffer (PB) of pH 7.0 and pH 6.8 were drawn [4,5].

2.2.2 Preparation of core tablets

Required amounts of SS and other excipients were weighed and passed through 40 mesh sieve, sodium chloride and potassium chloride which were used as osmogens were passed through 100 sieve [6]. Core tablets of SS were prepared using 8 mm deep concave punches by direct compression method using rotary compression machine (Cemach). Composition of core tablets was shown (Table 1).

Table 1. Composition of core tablets of SS (Total weight of tablet = 300mg)

Ingredients	FT1 (mg)	FT2 (mg)	FT3 (mg)	FT4 (mg)	FT5 (mg)	FT6 (mg)	FT7 (mg)	FT8 (mg)	FT9 (mg)	FT10 (mg)
Sumatriptan succinate	50	50	50	50	50	50	50	50	50	50
NaCl	-	50	100	150	-	-	-	50	50	50
Mannitol	-	-	-	-	50	100	150	50	100	150
MCC pH 101	240	190	140	90	190	140	90	140	90	40
Talc	5	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5	5
Total weight	300	300	300	300	300	300	300	300	300	300

2.2.3 Coating of core tablets

The core tablets of SS were coated in R & D coating pan (VJ instruments, India). The composition of coating solution used for coating [7] of SS was given (Table 2). The formulation variables and the pan coating specifications used in the present work are as shown (Tables 3, 4 respectively).

Table 2. Composition of coating solution

Ingredients	A	B	C	D
Cellulose acetate (CA)	2 gm	2 gm	2 gm	2 gm
PEG 400	0.6 mL	0.4 mL	-	-
DBP	-	-	0.4 mL	0.6 mL
Acetone	97.4 mL	97.6 mL	97.6 mL	97.4 mL

Table 3. Formulation variables used in the preparation of Sumatriptan succinate EOP

Nature Of Semi-Permeable Membrane	Cellulose Acetate
Plasticizer	PEG- 400, Dibutyl Phthalate
Coating Solution	Cellulose Acetate
Osmogens	Sodium Chloride, Mannitol
Ph	0.1N HCl, 6.8 pH & 7.0 pH Phosphate Buffer

Table 4. Pan coating specifications

Pan Rotational Speed	23-27 rpm
Inlet Air Temperature	50-55°C
Outlet Air Temperature	23-27°C
Flow Rate	2 mL/min
Atomization Pressure	1 kg/cm^2
Gun To Bed Distance	8cm

2.2.4 Drilling of coated tablets

A small orifice was drilled through one side of coated tablets using syringe needle of 30 guage (ranging from 480 to 700 µm) [8].

2.2.5 Dissolution studies

Dissolution studies were carried out using USP II apparatus under following conditions:

Dissolution medium: 900 mL of 0.1N HCl and 6.8 pH phosphate buffer
Temperature: 37+0.5ºC
Rotating speed of the paddle: 50 rpm
Sample time intervals: 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 hours
Detection: UV-Visible spectrophotometer at λ_{max} 228 nm

3. RESULTS AND DISCUSSION

3.1 Preformulation Studies

3.1.1 Drug – excipient compatibility studies by physical observation

Sumatriptan succinate mixed with various proportions of excipients did not show any change in the colour at the end of two months, showing no drug-excipient interactions.

3.1.2 FTIR studies

Drug polymer interactions were studied by FTIR. From the spectra it was observed that there was no interaction between the drug and excipients (Figs. 1, 2) as the characteristic peaks remained as such. The C-H stretching, C-H bending, C=C stretching are in the specified values and the FTIR peak values and the structure of Sumatriptan succinate is shown. (Tables 5 and Fig. 3)

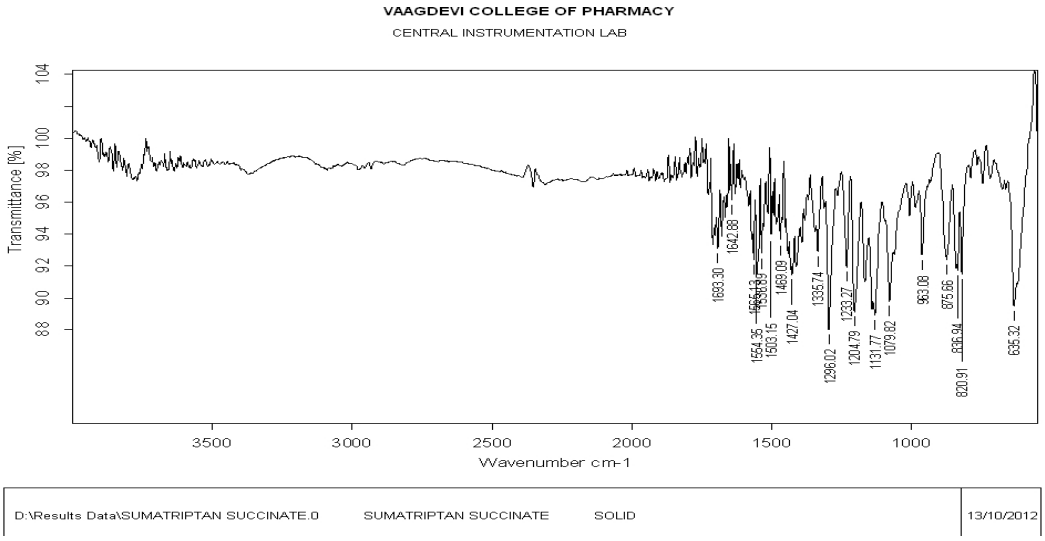

Fig. 1. FT-IR spectra of Sumatriptan succinate

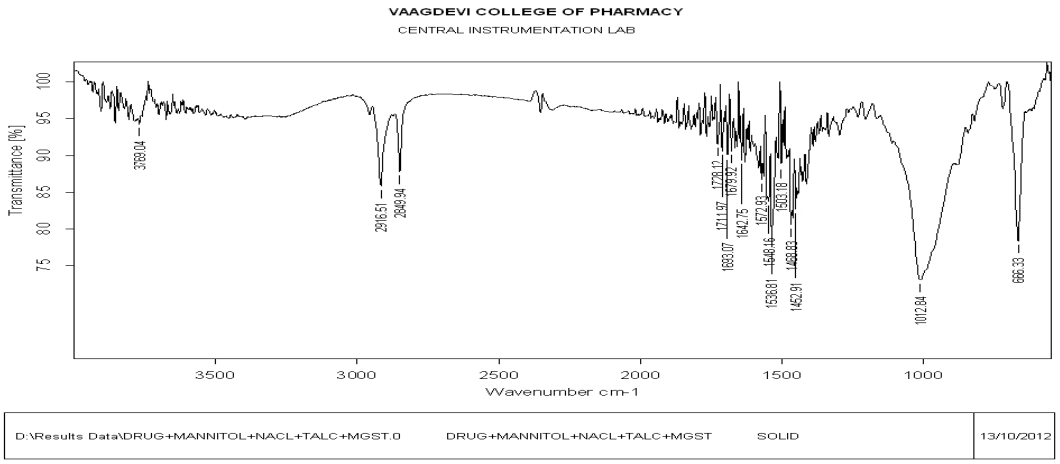

Fig. 2. FTIR spectra of drug + all excipients

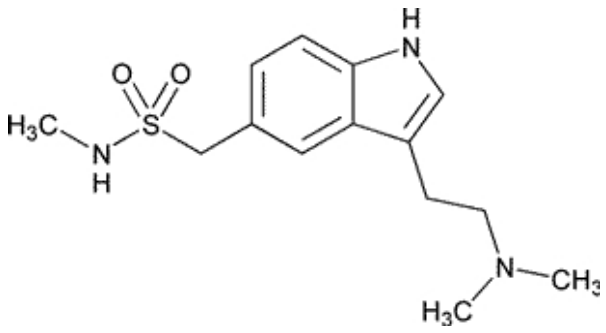

Fig. 3. Chemical Structure of Sumatriptan succinate

3.2 Evaluation of Post- Compression Parameters

The results of the physical tests of the formulations were within the limits and complied with the standards [9]. The weight of the tablets ranged from 247 mg to 305 mg and was within ±5% of the average weight. The thickness was found to be in the range 3.36 mm to 4.23 mm. Hardness of the tablets was in the range of 3.6 kg/cm^2 to 4.6 kg/cm^2 and the friability was in the range 0.09% to 0.16%, indicating that the tablets were hard enough to withstand the tumbling action in the coating pan. The drug content on an average was found to be 98.24%. All these parameters were within acceptable limits which are shown (Table 6).

3.3 EFFECT OF FORMULATION VARIABLES ON *IN VITRO* DRUG RELEASE

3.3.1 Effect of nature and type of semi-permeable membrane forming polymer

Cellulose acetate (CA) films are insoluble, yet semi-permeable to allow water to pass through the tablet coating. The water permeability of CA is relatively high and can be easily adjusted by varying the degree of acetylation [10]. The permeability of CA film can be further increased by the addition of hydrophilic flux enhancer (necessary in case of poorly water soluble drugs). Incorporation of a plasticizer in CA coating formulation generally lowers the glass transition temperature, increases the polymer-chain mobility, enhances the flexibility and affects the permeability of the film [11]. The semi permeable membrane formed from CA possess sufficient wet strength and wet modulus so as to retain its dimensional integrity during the operation and the reflection coefficient (σ), leakiness of the membrane i.e., leakage of solute through the membrane is near to 1 which was desired [12]. The polymer was also biocompatible.

The weight of coating film ranged from 265.61 mg to 334.23 mg. The increase in weight and thickness due to coating are presented (Table 6).

Cellulose acetate coating remained intact even after 24 hours of dissolution. The 2% w/w of CA in acetone had excellent spray properties. CA coating improved the elegance of osmotic pump along with controlling the release of the drug from the core formulation. The thickness of the coating for various formulations ranged from 4.21 mm to 5.28 mm.

3.3.2 Effect of nature and amount of plasticizer

The coated tablets containing PEG-400 were found to release the drug by diffusion. As PEG-400 is a hydrophilic plasticizer, it could be leached easily and leave behind an entirely porous structure, which increases membrane permeability and drug release was rapid.

In contrast, as dibutylphthlate (DBP) is insoluble in water, it is difficult to leach. Because of its hydrophobic nature the residual DBP would resist water diffusion and as a consequence the drug release was controlled [13]. The more DBP incorporated into the membrane, the more difficult it was to leach and in turn the lower the permeability of the membrane and lower the drug release rate was obtained. DBP at the concentration of 10% of CA in the coating solution form coating which was brittle. DBP at concentration of 15% w/w of the polymer was found to form a film with good flexibility, elegant appearance, controlling the imbibition of water from the dissolution media and thus the drug release. Further increase in plasticizer did not result in any improvement.

Table 5. FTIR spectra values

IR Spectra	Peak of Functional groups [Wave length (cm^{-1})]					
	C-H Stretching (alkane)	C-H Bending (aromatic)	N-H Stretching (Amine)	S=O Stretching (Sulphide)	C=C Stretching (Aromatic)	N-H Stretching (Aromatic)
Sumatriptan	1469	963	1642	1296	875	1642
Sumatriptan+ NaCl	1482	875	1633	1233	1554	1565
Sumatriptan + Mannitol	1484	750	1656	1079	1536	875
Sumatriptan + NaCl + Mannitol	1452	1885	1642	1296	1642	3768
Sumatriptan optimised tablet	2916	2849	1548	1012	1548	666

Table 6. Weight variation and thickness before and after coating

Formulation	Weight variation (mg) (Before coating)	Weight variation (mg) (After coating)	Thickness (mm) (Before coating)	Thickness (mm) (After coating)	Content uniformity (%)
FT1	248.8±1.38	265.61±1.28	3.36 ±0.03	4.32±0.01	97.39
FT2	249.4±0.52	269.34±0.43	3.41±0.03	4.56±0.02	98.35
FT3	247.6±0.41	269.51±0.51	3.49 ±0.05	4.23 ±0.04	99.37
FT4	250.3±1.20	270.5±1.09	3.55±0.04	4.35±0.03	99.55
FT5	249.6±1.04	269.46±0.89	3.45 ±0.08	4.63±0.08	97.45
FT6	250.2±0.73	270.31±0.52	3.53±0.05	4.21±0.03	99.52
FT7	250.5±0.65	270.72±0.56	3.54±0.06	4.48±0.05	97.01
FT8	301.0±0.33	334.15±0.28	4.23 ±0.04	5.37 ±0.04	96.21
FT9	298.5±0.70	312.27±0.93	4.15 ±0.06	5.24 ±0.03	98.24
FT10	305.3±0.73	324.23±0.81	4.03± 0.05	5.28± 0.02	99.32

3.3.3 Effect of type and amount of osmogen

Sumatriptan succinate being water soluble does not contribute much to the osmotic pressure of the core along with the osmogens. The formulation (FT1) without osmogen showed drug release by diffusion rather than by zero-order and also the drug release was incomplete. Sodium chloride was chosen as osmotic agent having a high osmotic pressure of 356 atm. From the results it is clear that the higher osmotic pressure resulting from solubilization of sodium chloride leads to faster drug release with a zero order only for a period of 3 hours. Mannitol with osmotic pressure of 38 atm (nearly 10 times less than sodium chloride) was chosen as an osmogen. Formulations containing both the osmogens showed zero-order release for a period of 6 hours.

Sodium chloride, mannitol and a combination of sodium chloride and mannitol were used in various drug:osmogen ratio. Zero-order drug release was not shown until the drug:osmogen ratio was 1:3 with both individual and osmogen combination. Formulations FT2, FT3, FT4 have released 75.56%, 72.28% and 67.38% of drug respectively for a period of 3 hours. Formulations FT2, FT3 and FT4 released 95.65% 96.29% and 97.36% of drug respectively in controlled pattern in 24 hours.

Mannitol when used alone as osmogen i.e FT5, FT6, FT7 formulations have released 82.41%, 70.11% and 71.01% of drug respectively in 12 hours and 92.34%, 96.23% and 98.43% respectively in 24 hours.

FT8, FT9 and FT10 have released 58.18%, 59.43% and 59.57% of drug in 3, 4 and 6 hours respectively. It is evident from the drug release that the formulations without osmogen (FT1) was incomplete with about 85.32% of drug released in 24 hours of *in-vitro* drug dissolution.

FT8, FT9 and FT10 formulations were formulated with combination of sodium chloride and mannitol as osmogens and found to release 88.32%, 94.24% and 97.28% of drug respectively in 24 hours.

3.3.4 Effect of size of the aperture

The size of the orifice is about 500 µm which was observed from Scanning Electron Microscopy (SEM) (Fig. 4). If size of the orifice is increased the drug release also increases but does not give a controlled release formulation so an optimum size of the orifice should be drilled in order decrease the rapid release of drug through the aperture [14]. In our studies 500 µm is suitable.

3.4 Chronotherapeutic Action of the Drug

As the drug has chronotherapeutic action, this controlled release formulation helps in avoiding the chronotherapeutic action. This is the major advantage of the Sumatriptan succinate EOP tablets and with this delivery system we can also reduce the dosing frequency of the tablet.

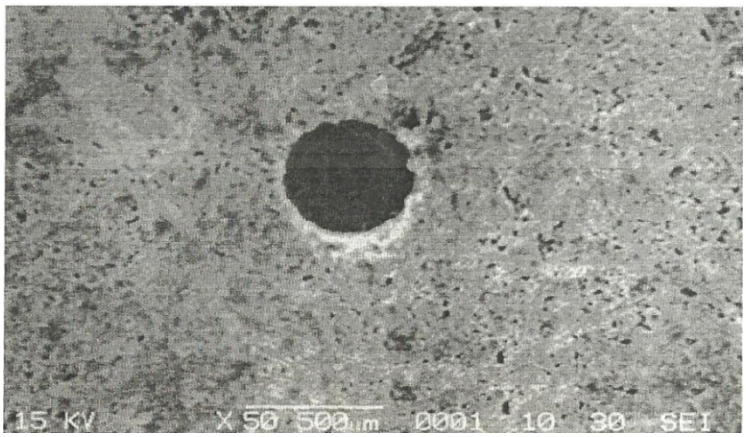

Fig. 4. Scanning Electron Microscopy (SEM) picture of SS EOPT showing mechanically drilled orifice

3.5 Dissolution Profile Modeling

From *in vitro* drug release profile and R^2 values, it was found that the drug release from formulations without osmogen (FT1) was incomplete and was released by Higuchi kinetics governed by non-fickian diffusion with an 'n' value of 0.68. Formulation containing NaCl as osmogen with a drug:osmogen ratio of 1:1 (FT2) showed drug release by Higuchi release kinetics, rather than by zero-order kinetics governed by fickian diffusion with 'n' value of 0.43. Formulation containing drug:osmogen in the ratio of 1:2 (FA3) showed drug release by Korsemeyer and Peppas kinetics with the major mechanism of drug release being non-fickian diffusion (n= 0.67). The formulation with drug:osmogen in the ratio of 1:3 (FT4) released 67.38% of drug in zero-order for a period of 3 hours by non-fickian diffusion mechanism having 'n' value of 0.62.

Formulations with FT5, FT6, FT7 containing 1:1, 1:2 and 1:3 ratio of drug:mannitol ratio released 82.41%, 70.11% and 71.01% and 'n' value was 0.51, 0.54 and 0.42 respectively (Table 7). From 'n' value we can conclude that FT7 the release mechanism involved was fickian diffusion mechanism and the drug release followed zero order kinetics for a period of 12 hours.

FT8 released 58.18% of drug for a period of 3 hours with Korsemeyer and Peppas kinetics mainly by combination of supercase II transport mechanism with an 'n' value of 1.13. Formulations FT9 and FT10 least 59.43% and 59.57% of drug respectively for a period of 4 hours and 6 hours by zero order release kinetics by non-fickian diffusion mechanism governed by 'n' values of 0.52 and 0.53.

Table 7. Effect of type and concentration of osmogen on *in vitro* drug release

Formulation	% Drug release	Time (hrs)	R^2 Value				n value
			Zero order	First order	Higuchi	Korsemeyer - peppas	
FT5	82.41	12	0.97	0.97	0.98	0.96	0.51
FT6	70.11	12	0.97	0.98	0.96	0.95	0.49
FT7	71.01	12	0.98	0.91	0.99	0.97	0.42

4. CONCLUSION

EOP tablets of Sumatriptan succinate were successfully prepared using NaCl and mannitol as osmogens. EOP tablets with mannitol as osmogen, coated with cellulose acetate containing dibutylpthlate were able to deliver zero-order release up to 12 hours independent of pH of dissolution media. It was found that the formulation containing drug: osmogen (mannitol) in the ratio of 1:3 showed R^2 of zero order kinetics with 'n' value of 0.42 indicating drug release followed fickian diffusion.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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