Original Article

In vitro evaluation of different transnasal formulations of sumatriptan succinate: A comparative analysis

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ABSTRACT: Sumatriptan succinate is an agonist for a vascular 5-hydroxytryptamine (5-HT)$_1$ receptor subtype (probably a member of the 5-HT$_{1D}$ family). It does not have significant affinity for the remaining 5-HT receptors. It does not have affinity for alpha$_1$, alpha$_2$ or beta-adrenergic, dopamine$_1$, dopamine$_2$, muscarinic or benzodiazepine receptors. The objective of the study was to evaluate the *in vitro* transnasal absorption of sumatriptan succinate through sheep nasal mucosa and to determine its *in vitro* permeation behavior from various formulations containing penetration enhancers. In this study four different thermoreversible gel formulations designed for nasal delivery of sumatriptan succinate were formulated. The formulations were prepared by using a poly(oxythylene) poly(oxypropylene) block copolymer (Pluronic F 127) based gel along with different permeation enhancers and a pluronic lecithin organogel base. The effect of different concentrations of sodium glycocolate, EDTA and transcutol on *in vitro* nasal diffusion of sumatriptan succinate was studied. The best permeation profile was obtained with a formulation containing transcutol at a concentration of 0.005% w/w. Pluronic lecithin organogel showed good gelling properties at a concentration in the 20% range.

Keywords: Sumatriptan succinate, Pluronic F 127, transcutol, sodium glycocolate, EDTA, pluronic lecithin organogel

1. Introduction

Migraine is currently thought to be a primary neural process. In the milieu of a hyperexcitable cortex, various stimuli probably produce disturbances in neuronal ion channel activity, resulting in a lowered threshold for external or internal factors to trigger "cortical spreading dysfunction (CSD)". This slowly propagating wave of neuronal depolarisation is most likely responsible for the migraine aura and activation of the trigemino-vascular system (*1*). Migraine treatment has evolved into the scientific arena, but opinions differ on whether migraine is primarily a vascular or a neurological dysfunction (*2*,*3*). Sumatriptan succinate (SS) is a potent and selective vascular 5-hydroxytryptamine1-receptor agonist effective for the treatment of migraine. It is rapidly but incompletely absorbed following oral administration and undergoes first-pass metabolism, resulting in a low absolute bioavailability of 14% in humans (*4*). In adults, intranasal SS is well absorbed and tolerated (*5*). For more than a decade intranasal SS has been a widely used drug for the treatment of acute migraine and has an excellent safety record (*6*,*7*). However, the problem associated with nasal delivery of SS solution is lower retention time in the nasal cavity (15 min) resulting in lower bioavailability as well as lower transfer of SS directly to the brain through the olfactory pathway. After 15 min, SS solution is swallowed and it enters the gastrointestinal tract (GIT), where the remaining dose is absorbed. Although SS nasal spray provides a faster onset effect than the tablet, it produces a similar headache response at 2 h (*8*).

The purpose of this work was to increase the nasal absorption of SS by increasing the residence time and increasing the absorption by using various penetration enhancers. We have formulated in situ gels using Pluronic F 127 (PF 127) and pluronic lecithin organogels (PLO) that can serve to improve drug delivery *via* the transnasal route. Different concentrations of absorption enhancers including: transcutol, sodium glycocolate, and EDTA were optimized. PLO is composed of isopropylpalmitate (or less commonly myristate), soya lecithin, water and PF 127.

2. Materials and Methods

2.1. *Materials*

Sumatriptan succinate was a gift sample from Dr. Reddys Lab. (Hydrabad, India). Transcutol and PF 127 was from ICPA Ltd. (Ankeleshwar, Gujarat, India).

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EDTA, sodium glycocolate, benzalkonium chloride, lecithin, and isopropyl palmitate chemicals were of analytical grade.

2.2. *Preparation of transnasal gels*

2.2.1. *Preparation of thermoreversible SS gel*

Preparation of thermoreversible gels was excellently reviewed by Karmarkar *et al.* (*9*). Thermoreversible gels were prepared using cold technique (*10*). PF 127 and SS were solubilized in distilled water containing PEG 4000, propylene glycol and benzalkonium chloride (BAC) in required quantities. The liquid was kept at 4°C until a clear solution was obtained to get a gelation temperature in the range of 36-37°C. Different thermoreversible gels containing permeation enhancers such as transcutol (0.01% w/w, 0.03% w/w, and 0.05% w/w concentrations), EDTA and sodium glycocolate (0.1% w/w, 0.3% w/w, and 0.5% w/w concentrations) were prepared. The concentration of EDTA (when a chelating agent is used, preferably, it is present in an amount within a range from about 0.005% to about 1% of the total weight of the composition, more preferably, from 0.01% to 0.5%, still more preferably, from about 0.05% to about 0.2% of the composition) (*11*) and sodium glycocolate was kept at 0.5% (1% SG was tried in humans for 60 mg/mL of gentamycin solution in saline) (*12*). The concentration of transcutol was reduced to 0.05% w/w because it was reported to be a non-irritant at the concentrations studied (0.005-0.03% w/w), while it produced slight irritation in rabbit eyes at a concentration of 0.05% w/w (*13*). To achieve the gelation temperature in the range of 35-37°C, optimization of the formulation was done by using different concentrations and PEG 4000 as shown in Tables 1-4 (formulation A3, A2, A1, A, B2, B1, B, C2, C1, C, D2, D1, and D).

2.2.2. *Preparation of sumatriptan pluronic lecithin organogel (PLO)*

Formulations were prepared by using factorial design. Twenty-seven batches of sumatriptan succinate PLO gel were prepared by dissolving SS in purified water, adding to it PF 127 and mixed. We incorporated the soya lecithin: isopropyl palmitate solution and mixed well. Sufficient water with mixing was added to get the final weight (*14*). The final weight of all formulations was adjusted to 10 g. The batches were prepared as shown in Tables 5 and 6. The batch of PLO with gelation near 37°C was considered for further evaluation. The batch containing P407 20%, soyalicithin 8%, isopropyl palmitate 5% along with drug 10% w/w and BAC 0.001% w/w had gelation at 35°C (Formulation IV-E). This was considered for further evaluation.

Table 1. Batches of PF 127 gel formulations containing SS

Formulation ingredients	A3	A2	A1	A
SS (% w/w)	10	10	10	10
PF 127 (% w/w)	20	20	20	20
PEG 4000 (% w/w)	1	1	2	2
PG (% w/w)	0.1	0.2	0.1	0.2
BAC (% w/w)	0.001	0.001	0.001	0.001
2 M NaOH	q.s.*	q.s.	q.s	q.s.
Distilled water	q.s.	q.s.	q.s	q.s.

* q.s., quantum sufficiat.

Table 2. Batches of PF 127 gel formulations containing SS with different concentrations of EDTA

Formulation ingredients	B2	B1	B
SS (% w/w)	10	10	10
PF 127 (% w/w)	20	20	20
PEG 4000 (% w/w)	2	2	2
PG (% w/w)	0.2	0.2	0.2
EDTA (% w/w)	0.1	0.3	0.5
BAC (% w/w)	0.001	0.001	0.001
2 M NaOH	q.s.*	q.s.	q.s
Distilled water	q.s.	q.s.	q.s

* q.s., quantum sufficiat.

Table 3. Batches of PF 127 gel formulations containing SS with different concentrations of SG

Formulation ingredients	C2	C1	C
SS (% w/w)	10	10	10
PF 127 (% w/w)	20	20	20
PEG 4000 (% w/w)	1	1	1
PG (% w/w)	0.2	0.2	0.2
SG (% w/w)	0.1	0.3	0.5
BAC (% w/w)	0.001	0.001	0.001
2 M NaOH	q.s.*	q.s.	q.s
Distilled water	q.s.	q.s.	q.s

* q.s., quantum sufficiat.

Table 4. Batches of PF 127 gel formulations containing SS with different concentrations of TC

Formulation ingredients	D2	D1	D
SS (% w/w)	10	10	10
PF 127 (% w/w)	20	20	20
PEG 4000 (% w/w)	2	2	2
PG (% w/w)	0.2	0.2	0.2
TC (% w/w)	0.01	0.03	0.05
BAC (% w/w)	0.001	0.001	0.001
2 M NaOH	q.s.*	q.s.	q.s
Distilled water	q.s.	q.s.	q.s

* q.s., quantum sufficiat.

2.3. *Evaluation of transnasal gels*

2.3.1. *Gelation temperature*

Gelation temperatures of the gels were measured according to the method described by Gilbert *et al.* (*15*). Two milliliter aliquots of the gel were transferred to test tubes sealed with parafilm and immersed in a water bath at 4°C. The temperature of the bath was increased in increments of 1°C and left to equilibrate for 15 min at each new setting. The samples were examined for gelation, which was said to have occurred when the meniscus would no longer

Table 5. Factorial design of PLO gel formulations containing SS

Coded levels	Values of variables		
	PF 127	SL	IIP
Low (-1)	10%	2%	4%
Medium (0)	20%	4%	5%
High (+1)	30%	8%	6%

Table 6. Formulation compositions of PLO gels using 3^3 factorial design

Batch Number	Values of variables			PF 127 (% w/w)	SL (% w/w)	IIP (% w/w)
1PLO	-1	-1	-1	10	2	4
2 PLO	-1	-1	-1	10	2	5
3 PLO	-1	-1	-1	10	2	6
4 PLO	-1	-1	-1	10	4	4
5 PLO	-1	-1	-1	10	4	5
6 PLO	-1	-1	-1	10	4	6
7 PLO	-1	-1	-1	10	8	4
8 PLO	-1	-1	-1	10	8	5
9 PLO	-1	-1	-1	10	8	6
10 PLO	0	0	0	20	2	4
11 PLO	0	0	0	20	2	5
12 PLO	0	0	0	20	2	6
13 PLO	0	0	0	20	4	4
14 PLO	0	0	0	20	4	5
15 PLO	0	0	0	20	4	6
16 PLO	0	0	0	20	8	4
17 PLO	0	0	0	20	8	5
18 PLO	0	0	0	20	8	6
19 PLO	1	1	1	30	2	4
20 PLO	1	1	1	30	2	5
21 PLO	1	1	1	30	2	6
22 PLO	1	1	1	30	4	4
23 PLO	1	1	1	30	4	5
24 PLO	1	1	1	30	4	6
25 PLO	1	1	1	30	8	4
26 PLO	1	1	1	30	8	5
27 PLO	1	1	1	30	8	6

To the above compositions, SS in a concentration of 10% w/w and BAC 0.001% w/w were added.

move when tilted through 90°. All measurements were performed in triplicate (n = 3).

2.3.2. *Content uniformity*

All optimized batches were checked for content uniformity. Weight of the gel equivalent to theoretical weight (Dose of drug *i.e.*, 20 mg) of the drug was taken and dissolved in water. The drug content was determined at 282 nm, using a Shimadzu 1700UV-VIS spectrophotometer (*16*) (Linearity range, 20 µg/mL to 100 µg/mL; Slope, 69.45; Intercept, -0.3692; R value, 0.9998).

2.3.3. *Measurement of gel strength*

A sample of 50 g of gel was placed in a 100 mL graduated cylinder and gelled in a thermostat at 37°C. The apparatus for measuring gel strength given by Choi *et al.* (*17*) was allowed to penetrate the gel. Gel strength *i.e.* the viscosity of the gels at physiological temperature was determined as the time (in seconds) for the apparatus to sink 5 cm through the prepared gel. All measurements were performed in triplicate (n = 3).

2.3.4. *Determination of bioadhesive force*

The bioadhesive force of all batches was determined by the method given by Choi *et al.* (*17*). A section of nasal mucosa was cut from the sheep nasal cavity and instantly fixed with mucosal side out onto each glass vial using a rubber band. The vials with nasal mucosa were stored at 37°C for 5 min. The next vial with a section of mucosa was connected to the balance in inverted position while the first vial was placed on a height adjustable pan. Nasal gel was added to the nasal mucosa of the first vial. The height of the second vial was adjusted so that the mucosal surfaces of both vials came into intimate contact. Two minutes of contact was allowed. Weight kept rising in the pan until the vials detached. Bioadhesive force was the minimum weight required to detach two vials. Nasal mucosa was changed for each measurement.

2.3.5. *Diffusion across nasal mucosa*

Noses of healthy sheep were obtained from the local slaughterhouse. It was cleaned and the mucosa was removed from the anterior nasal cavity. The mucosa was stored in normal saline with a few drops of gentamycin sulphate injection, to avoid bacterial growth. Phosphate buffer pH 7.4 was used as diffusion medium. *In vitro* diffusion studies were carried out in the nasal diffusion cell by the method of Pisal *et al.* (*18*). The outlet of the reservoir was maintained at 37 ± 0.5°C. About 1 mL of sample was withdrawn at a time interval of one hour from sampling port of receptor compartment and the same volume was then replaced with receptor fluid solution in order to maintain skin condition. The samples were appropriately diluted and the absorbance was measured at 282 nm using a Shimadzu 1700UV-VIS spectrophotometer.

3. Results and Discussion

3.1. *Gelation temperature*

It was previously proved that pluronics undergo thermal gelation or sol-gel transition at a temperature of about 25 to 35°C. Below the transition temperature pluronic solutions allow a comfortable and precise delivery in the nasal cavity where thermogelation occurs. Immediate gelling increases residence time and enhances bioavailability of drug (*19*). The gelation temperature of all batches is shown in Tables 7 and 8. All gel formulations containing PF 127 showed good gelling properties. Absorption enhancers have increased the gelation temperature of PF 127 base. For PLO

gels, the batches containing 10% PF 127 showed no gelation. Batches with 20% PF 127 indicated gelation in the range of 24-37°C whereas batches with 30% PF 127 concentrations did not have liquid consistency. At temperatures below 10°C batches containing 10% and 20% PF 127 exhibited a two-phase system. Increasing concentrations of soya lecithin decreased the gelation point in batches containing 20% PF 127. Batches containing 20% PF 127, 8% soya lecithin, and 5% isopropyl palmitate along with drug and BAC gelled at 35°C (Formulation E). This was considered for further evaluation.

Table 7. Gelation temperature of PF 127 gel formulations under various conditions

Sr. No.	Formulation*	Gelation temperature (°C)
1	A3	30.36 ± 0.15
2	A2	30.56 ± 0.05
3	A1	32.26 ± 0.20
4	A	34.50 ± 0.28
5	B2	35.23 ± 0.11
6	B1	35.36 ± 0.05
7	B	35.61 ± 0.10
8	C2	36.10 ± 0.20
9	C1	37.16 ± 0.40
10	C	37.60 ± 0.05
11	D2	36.80 ± 0.10
12	D1	37.20 ± 0.20
13	D	37.40 ± 0.17

* A3, A2, A1, and A, PF 127 gel formulations containing SS; B2, B1, and B, PF 127 gel formulations containing SS with different concentrations of EDTA; C2, C1, and C, PF 127 gel formulations containing SS with different concentrations of SG; D2, D1, and D, PF 127 gel formulations containing SS with different concentrations of TC in different concentrations. See Tables 1-4 for the composition of each formulation.

Table 8. Gelation temperature of formulations of SS in PLO gel

Batch No. of PLO*	Two phase	One phase	Gelation	Gel melting
1	< 10°C	15°C	No gelation	–
2	< 10°C	15°C	No gelation	–
3**	< 10°C	18°C	No gelation	–
4**	< 10°C	18°C	No gelation	–
5**	< 10°C	12°C	No gelation	–
6**	< 10°C	18°C	No gelation	–
7	< 10°C	19-20°C	No gelation	–
8	< 10°C	21°C	No gelation	–
9***	< 10°C	21°C	No gelation	–
10	< 10°C	21°C	27°C	90°C
11	< 10°C	16°C	25°C	75°C
12	< 10°C	21°C	25°C	90°C
13	< 10°C	20°C	25°C	90°C
14	< 10°C	18°C	25°C	90°C
15	< 10°C	19°C	25°C	90°C
16	< 10°C	25°C	38°C	90°C
17	< 10°C	22°C	35°C	91°C
18	< 10°C	25°C	30°C	90°C
19****			5°C	> 100°C
20****			5°C	> 100°C
21****			5°C	> 100°C
22****			5°C	> 100°C
23****			5°C	> 100°C
24****			5°C	> 100°C
25****			5°C	> 100°C
26****			5°C	> 100°C
27****			5°C	> 100°C

* See Table 6 for the formulation composition of each PLO batch; ** Batch numbers 3 to 6 of PLO became very viscous in the range of 25-35°C and gave very homogeneous mixtures at 40°C; *** Batch numbers 3 to 6 of PLO became very viscous in the range of 25-35°C; **** All the systems are in one phase. Gel at 5°C. Gel melting is above 100°C.

3.2. *Content uniformity*

Content uniformity of various formulations is summarized in Table 9.

3.3. *Measurement of gel strength*

Gel strength providing an indication of viscosity of gel formulations (*17*) was measured as described in "Materials and Methods". Results are shown in Table 9.

3.4. *Determination of bioadhesive force (detachment stress)*

The detachment stress and gel strength of PF 127 gel of SS was slightly decreased with the addition of absorption enhancers (effect seen at high concentrations). An increase in detachment stress was observed with PLO gel. PLO gel is Pluronic Lecithin Organogel. PLO was compounded from an aqueous phase, PF 127 and a lipid phase, lecithin and isopropyl palmitate. As the lipid content is increased in PLO the detachment stress of PLO gel is high. Results are shown in Table 9.

3.5. *Diffusion across nasal mucosa*

The percentage of drug diffusion of various formulations through nasal mucosa over a period of 8 h for formulations is shown in Figures 1-4.

In the initial phase, the rate of diffusion of SS from all batches containing EDTA was nearly the same. However, in the latter phase (time period more than 60 to 90 min), the amount of drug diffusion from the formulations containing higher concentrations of EDTA was greater and the cumulative amount of drug released was also greater. Thus, until a time period from 60 to

Table 9. Content uniformity, bioadhesion and gel strength of gel formulations

Formulation	Content uniformity	Detachment stress (dynes/cm^2)	Gel strength (sec)
A	99.9%	3792.41	118
B2	99.7%	3754.10	114
B1	99.8%	3734.95	115
B	99.9%	3723.46	115
C2	99.8%	3727.29	114
C1	99.9%	3719.63	115
C	100.1%	3715.80	116
D2	100.2%	3784.75	118
D1	99.8%	3773.26	117
D	99.8%	3769.43	117
E	100.2%	4290.40	131

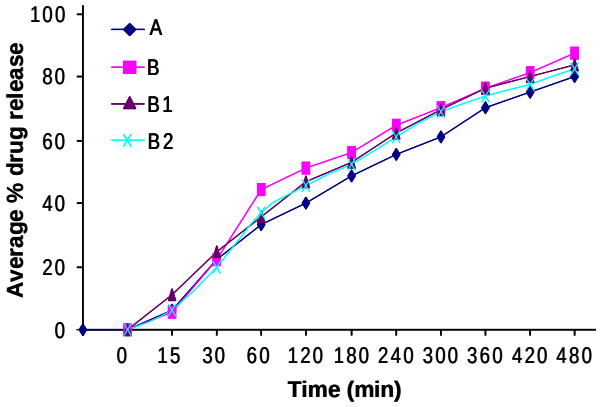

Figure 1. Plot of *in vitro* drug (SS) diffusion of various formulations (gels) containing PF 127 along with EDTA at different concentrations. See Tables 1 and 2 for composition of formulations A, B, B1, and B2.

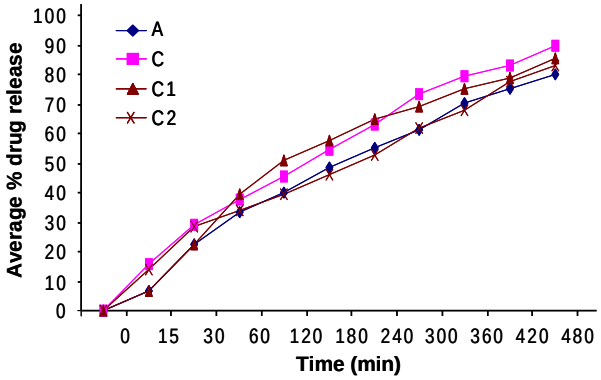

Figure 2. Plot of *in vitro* drug (SS) diffusion of various formulations (gels) containing PF 127 along with SG at different concentrations. See Tables 1 and 3 for the composition of formulations A, C, C1, and C2.

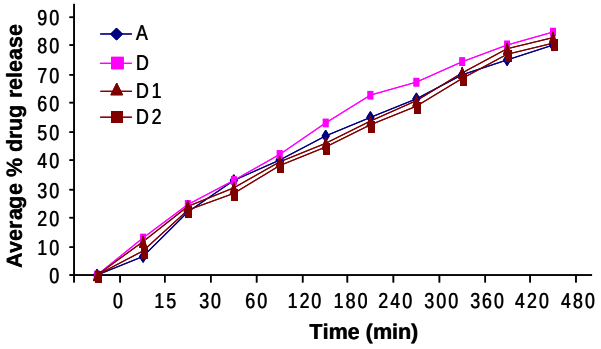

Figure 3. Plot of *in vitro* drug (SS) diffusion of various formulations (gels) containing PF 127 along with TC at different concentrations. See Tables 1 and 4 for the composition of formulations A, D, D1, and D2.

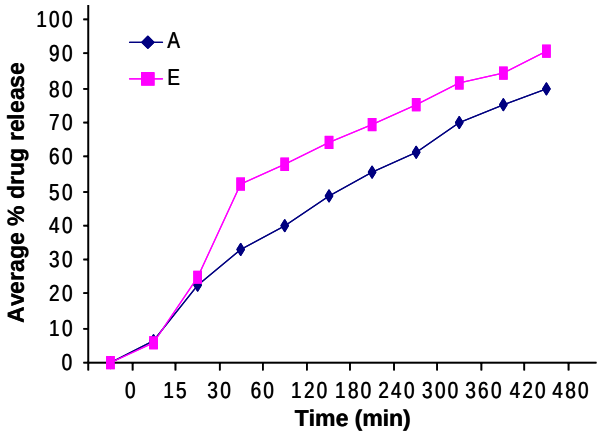

Figure 4. Plot of *in vitro* drug (SS) diffusion from PLO (Formulation E).

90 min EDTA fails to show a penetration enhancement effect. All the batches of SS in PF 127 gel along with the penetration enhancers followed a matrix model as the best-fit model for the release of drug. As compaired to EDTA, SG showed an increase in cumulative release of SS. The effect of penetration enhancement is concentration dependent. TC has also shown an increase in cumulative drug release from the formulations. This observed effect was also concentration dependent. This might be due to the hydrophilic nature of SS.

To our knowledge, no report has described the use of PLO gel as a penetration enhancer for a nasal drug delivery system. The aim of this study was to explore the use of PLO gel in a nasal drug delivery system. The *in vitro* diffusion of SS from PLO reveals that the *in vitro* transnasal transport of SS is greater than plain gel. The hypothesis that lecithin can increase mucosal drug transport was successfully evaluated for transnasal formulations from the above studies. Similar transnasal drug delivery of PLO gels with a suitable model drug can be further carried out to obtain desirable nasal drug delivery formulations.

The highest flux was shown by PLO gel formulations. The order of decreasing flux with different enhancers is as follows, PLO gel (63.25%) > 0.5% SG formulation (55.95%) > 0.5% EDTA (55.47%) > Plain PF 127 gel (53.14%) > 0.01% TC (46.33%).

4. Conclusion

The effect of different concentrations of sodium glycocolate, EDTA and transcutol on *in vitro* nasal diffusion of SS was studied. The effect of these absorption enhancers was found to be concentration dependent. The order of increasing absorption of SS caused by the enhancers was sodium glycocolate > EDTA at a concentration of 0.5%. Transcutol showed significant diffusion at concentration of 0.05%. Pluronic lecithin organogel showed good gelling properties with a concentration in the range of 20%. The pluronic lecithin organogel showed the highest release among all the formulations.

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