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Research paper

Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: In vitro and in vivo evaluation ☆

Ziya Bayrak [a], Cetin Tas [a,*], Umut Tasdemir [b], Halil Erol [b], Cansel Kose Ozkan [a], Ayhan Savaser [a], Yalcin Ozkan [a]

[a] Gulhane Military Medical Academy, Department of Pharmaceutical Sciences, Ankara, Turkey
[b] Lalahan Livestock Central Research Institute, Ankara, Turkey

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ABSTRACT

First-pass metabolism can be overcome by sublingual drug delivery, and quick drug entry into the systemic circulation can be obtained. In certain diseases such as migraine therapy, taking fast pharmacological response is an important criteria. In this study, zolmitriptan sublingual tablets were prepared by direct compression method using different mucoadhesive polymers such as hydroxypropyl methyl cellulose, chitosan and sodium carboxy methyl cellulose at a concentration range of 0.5–5% to reduce flushing action of saliva and provide enough time for drug to be absorbed. Tablets were evaluated for the physical properties, and optimum formulations were chosen for in vivo studies to carry on sheep model. The tablets disintegrated rapidly, and dissolution tests revealed that zolmitriptan was dissolved from the formulation within the compendial limits. This especially showed us that the concentration range of polymers is in acceptable limit. It was also concluded that microcrystalline cellulose, spray-dried lactose and sodium starch glycolate are the appropriate excipient and formulated in good proportions. In vivo studies indicated that formulation containing 5% chitosan has the maximum C_{max} and AUC and minimum t_{max} values ($p < 0.05$). As a result, sublingual tablet administration of zolmitriptan formulated with appropriate excipients and especially with chitosan seems promising alternative to traditional routes.

1. Introduction

Cluster headache is a relatively rare but extremely debilitating disorder that is characterized by the rapid onset of unilateral, periorbital headache that quickly escalates to maximum intensity. Patients routinely report the pain of an attack as being the most severe they have ever experienced. By the definition of the International Headache Society, attacks typically last from 15 to 180 min when left untreated and are accompanied by one more cranial autonomic features such as ipsiletaral conjunctival injection, lacrimation and rhinorrhea or nasal congestion [1]. In this case, a rapid onset of pharmacological effect is an often desired from drugs. This can effectively be achieved by parenteral administration, but this method may not always be convenient for the patient. Therefore, there is growing interest in developing new, non-parenteral, reliable and convenient dosage forms using administration routes where a rapidly dissolved drug is immediately absorbed into the systemic circulation [2,3].

Sublingual administration can offer an attractive alternative route of administration. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation bypassing enzyme degradation in the gut and liver. In addition, the thin sublingual mucosa (about 190 μm compared to 500–800 μm of the buccal mucosa) and the abundance of blood supply at the sublingual region allow excellent drug penetration (absorption) to achieve high plasma drug concentration with a rapid onset of action. A well-established example is nitroglycerin, which is used for the treatment of acute angina [4]. One problem associated with sublingual drug delivery is the fact that the patient does tend to involuntarily swallow liquids greater than 200 μL and rapid elimination of drugs due to the flushing action of saliva. Because of the involuntary swallowing, the drug to be delivered via the sublingual route is removed from the oral cavity and enters the gastrointestinal tract. To ensure a more intimate contact of the dosage form with the sublingual mucosa, there is a need of

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* Corresponding author. Gulhane Military Medical Academy, Department of Pharmaceutical Sciences, 06018 Etlik, Ankara, Turkey. Tel.: +90 312 304 6073; fax: +90 312 304 6091.
E-mail address: ctas@gata.edu.tr (C. Tas).

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Table 1
Composition of the sublingual tablet formulations of zolmitriptan.

Ingredient (mg)	Code of formulations									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
A	5	5	5	5	5	5	5	5	5	5
B	2	2	2	2	2	2	2	2	2	2
C	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
D	0	0.38	1.5	3.75	0	0	0	0	0	0
E	0	0	0	0	0.38	1.5	3.75	0	0	0
F	0	0	0	0	0	0	0	0.38	1.5	3.75
G	6.42	7.09	6.98	6.75	7.09	6.98	6.75	7.09	6.98	6.75
H	57.8	63.8	62.8	60.8	63.8	62.8	60.8	63.8	62.8	60.8

A: Zolmitriptan, B: SSG, C: PEG 3350, D: HPMC, E: Chitosan, F: CMCNa, G: MCC, H: SDL.

adhesion to the moist surface of mucosa and resistance to the flushing action of saliva. To overcome this disadvantage, bioadhesive polymers are used in formulations. Commonly used ones include chitosan, carbopol and cellulose derivatives [5–9].

Zolmitriptan is a second-generation triptan prescribed for patients with migraine attacks, with and without an aura, and cluster headaches. It has a selective action on serotonin receptors and is very effective in reducing migraine symptoms, including pain, nausea and photo- or phonophobia. It is currently available as a conventional tablet, an oral disintegrating tablet and a nasal spray (2.5 mg and 5 mg per dose). The absolute bioavailability of zolmitriptan is up to 40% for both oral and nasal dosage forms [10].

In this study, we have developed zolmitriptan sublingual tablets using with different mucoadhesive polymers like hydroxypropyl methyl cellulose (HPMC), chitosan and sodium carboxy methyl cellulose (CMCNa) to determine the optimum polymer concentration which can be added to sublingual tablet formulations without changing their basic tablet characteristic especially disintegration and dissolution time profiles. For this reason, developed sublingual tablet formulations were evaluated with basic tablet physical tests, in vitro permeation studies and in vivo studies in sheep model.

2. Materials and methods

2.1. Materials

Zolmitriptan was kindly supplied by Fargem (Duzce, Turkey). Chitosan (medium molecular weight), HPMC (Viscosity of 2% aqueous solution 25 °C: 4000 cps.), CMCNa (Viscosity of 4% aqueous solution 25 °C: 50–200 cps.), sodium starch glycolate (SSG) and polyethylene glycol 3350 (PEG 3350) were purchased from Sigma–Aldrich (St. Louis, MO). Microcrystalline cellulose 90 M (MCC) was purchased from Penwest Pharmaceutical Co. (Patterson, New York). Spray-dried alpha-lactose monohydrate FlowLac 100 (SDL) was purchased from Meggle Pharma Excipients & Technology (Wasserburg, Germany). Semi-permeable cellulose dialysis membrane was purchased from Travenol Lab. Inc. (Illinois, USA).

2.2. Formulation of drug-loaded sublingual tablets

Accurate amount of the active ingredient and all additives were homogeneously blended using geometric dilution after passing through 500 μm screen sieve. Then, PEG 3350 added to the mixture. Tablets were directly compressed by a single punch tableting machine (Erweka AR400, Frankfurt, Germany) equipped with 6 mm flat faced punch and die set. The compression force and mass of all tablets were kept constant, and each tablet contained% 6.67 (5 mg) of zolmitriptan. Compositions of each formulation are given in Table 1.

2.3. Determination of physicochemical parameters

2.3.1. Content uniformity, weight variation, thickness, hardness test and friability

Drug content uniformity was determined by dissolving the crushed tablets in distilled water and filtered through 0.45 μm PTFE filter. It was made necessary dilutions and analyzed at 224 nm using a spectrophotometer.

Weight variation test was done by weighing 20 tablets, and individual tablet weights were compared with calculated average weights.

The thickness of the tablets was measured with a micrometer (Torq, China) placed perpendicular to the diameter.

The strength of tablet is expressed as tensile strength (N: Newton). The tablet crushing load is the force required to break a tablet into halves by compression. It was measured using a tablet hardness tester (Pharma Test, Hamburg, Germany).

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Friabilator (Pharma Test, Hamburg, Germany) was used for the purpose. Preweighed sample of tablets was placed in the friabilator, which was then operated 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weigh.

2.3.2. In vitro disintegration

Disintegration test was carried out using a disintegration apparatus (Blue M Type SBG 1070) at 37 ± 0.5 °C in distilled water.

2.3.3. In vitro dissolution

Formulations were studied for drug dissolution, employing a USP apparatus type II (paddle method, Sotax) at a rotating speed 100 rpm according to USP 31. The medium used for these dissolution tests was 900 ml of distilled water maintained at 37 ± 0.5 °C. Samples were collected at predetermined time intervals (2, 5, 8, 15 and 20 min) and analyzed for drug content with a UV spectrophotometer (GBC Cintra 303, Melbourne, Australia) set at 224 nm. All dissolution studies were made six replicates to ensure a high sample power and confidence in the results. The calibration curve for zolmitriptan, in water, was linear from 1 to 8 μg/ml ($r^2 > 0.99$).

2.3.4. In vitro permeation

In vitro permeation studies were carried out with modified horizontal diffusion chambers (Çalışkan cam, Ankara, Turkey). The medium used for these studies was phosphate buffer (pH 7.4), maintained at 37 ± 0.5 °C. Cellulose dialysis membrane was used as a permeation barrier. Samples were collected at predetermined time intervals (0, 5, 8, 15, 20, 30, 45, 60, 90 and 120 min). Samples were analyzed for drug content with a UV spectrophotometer set at 224 nm. All permeation studies were three replicates for each

Table 2
Validation parameters of zolmitriptan HPLC analysis.

Linearity range	2.5–500 ng/mL
Correlation coefficient	0.999
Detection limit	1.00 ng/mL
Quantification limit	2.50 ng/mL
Intra-day precision (RSD%)	0.95
Inter-day precision (RSD%)	1.11

formulation. The calibration curve for zolmitriptan, in phosphate buffer, was linear from 1 to 8 μg/ml (r^2 = 0.99).

The cumulative amount of zolmitriptan permeated per unit area was plotted against time, and the slope of the linear portion of the plot was used as steady state flux (J_{ss}). The permeability coefficient (K_P) was calculated with Eq. (1), in which C_V is the total donor concentration of the formulation

$$K_P = J_{ss}/C_V \quad (1)$$

2.4. In vivo studies

2.4.1. Administration of formulations to sheep

In vivo experiments have been carried out under approval of animal ethic committee from Lalahan Livestock Central Research Institute, Ankara, Turkey. Twenty female sheep (Akkaraman, 50 kg) were divided into five groups. Four sublingual tablet formulations chosen according to in vitro experiments, and one sterile 5 mg/2 ml solution (for subcutaneous application) of zolmitriptan were applied to sheep. Samples were taken jugular vein and collected at predetermined time intervals (0, 8, 15, 20, 30, 45, 60, 90, 120, 180 and 240 min). Then, blood samples were centrifuged 15 min at 4400 rpm for separation of serum.

2.4.2. Preparation of serum samples for HPLC analysis to quantify zolmitriptan level

The sample preparation: 100 μL internal standard of sumatriptan at a concentration of 500 ng/mL was added to 500 μL serum sample in a conical test tube and vortexed for 30 s. After that, 50 μL 10 N NaOH solution was added and vortexed for 30 s. Then, 2 mL diethylether was added and vortexed 30 s. The solution was centrifuged for 15 min, at 4400 rpm. Organic layer was taken and evaporated to dryness under a stream of nitrogen, then reconstituted with 500 μL of mobile phase.

Serum samples were analyzed by HPLC (Agilent 1100, Santa Clara, USA). The mobile phase consisted of a (14.5:64.5:20) mixture at pH 4.8, of acetonitrile, double distillated water and phosphate buffer, set at a flow rate of 1 mL/min. C18, 4.6 × 250 mm, column was used with the fluorescence detector. The detection was performed at 225 nm (excitation) and 360 nm (emission). A 20-μL sample mixture was injected into the column by using the autosampler. Column temperature was adjusted at 37.5 °C. Table 2 shows the calibration and validation parameters of zolmitriptan HPLC analysis.

2.5. Pharmacokinetic data analysis

Pharmacokinetic parameters, including the area under the curve (AUC) of the serum concentration curve and mean zolmitriptan concentration after each administration, were obtained directly from the plasma zolmitriptan concentrations. The AUCs for each administration were calculated by the linear trapeizodal rule. The relative bioavailability of zolmitriptan after each administration was calculated according to the following Eq. (2)

$$F_R = [(\mathrm{AUC}_{\text{sublingual tablet}} \times D_{\text{s.c.}})/(\mathrm{AUC}_{\text{s.c.}} \times D_{\text{sublingual tablet}})]100\% \quad (2)$$

where F_R is the relative bioavailability and D is the administered dose.

2.6. Statistical analysis

Statistical analysis was performed with (repeated measures) variance analysis (SPSS 15.0 for Windows software). Tukey–Kramer's adjustment, which controls the experiment wise error rate at the $\alpha = 0.05$ level, was used to determine significance among all possible pairs of formulations and interactions. At $p \leqslant 0.05$, data were considered to be significant.

3. Results and discussion

3.1. Determination of physicochemical parameters

The comparison of physical properties of the sublingual tablets is shown in Table 3. Drug uniformity results were found to be good among different batches of tablets, and the percentage of drug content was more than 98%. The results also showed acceptable and homogenous distribution of drug in tablets.

The weight and thickness of the formulations ranged from 74.7 to 76.2 mg and from 2.01 to 2.06 mm, respectively. All tablets prepared in this study meet the USP requirements for weight variation of all formulae was less than 2% (USP 31).

In all the formulations, the hardness test indicated good mechanical strength, whereas friability is less than 1%, which indicated that the tablets had a good mechanical resistance. Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the compendial limits (USP 31).

3.2. In vitro disintegration study

The most important parameter that needs to be optimized in the development of sublingual tablets is the disintegration time of tablets. In the present study, all the tablets disintegrated in the range varied from 20.7 ± 4.41 to 41.2 ± 3.06 s (Table 4). In the USP disintegration test for sublingual tablets, the disintegration apparatus for oral tablets is used without the covering plastic disks, and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (<2 min) for sublingual tablets (USP 31). So all of our formulations meet the requirement for disintegration. The rapid and desired disintegration of tablets is due to the presence and good proportion of SDL, MCC and SSG and can be explained with following reasons.

MCC has good wicking and absorbing capacities. Tablets of MCC disintegrated rapidly due to the rapid passage of water into the tablets resulting in the instantaneous rupture of the hydrogen bonds.

Table 3
Physical properties of the sublingual tablets.

Code	CU (%)	WV (mg) (n = 20)	T (mm) (n = 10)	F (%)	H (Newton) (n = 10)
F1	108.2	75.6 ± 1.47	2.06 ± 0.02	0.91	36 ± 3.06
F2	107.6	75.4 ± 1.09	2.05 ± 0.02	0.73	37.4 ± 2.5
F3	100.6	75.6 ± 1.43	2.04 ± 0.01	0.67	43.9 ± 3.87
F4	100.8	74.7 ± 1.31	2.03 ± 0.02	0.54	36.4 ± 4.12
F5	103.8	74.7 ± 1.27	2.02 ± 0.02	0.79	38.9 ± 3.21
F6	98.6	75.4 ± 1.31	2.02 ± 0.01	0.62	43.7 ± 4.11
F7	102.2	75.4 ± 1.18	2.03 ± 0.01	0.51	42.7 ± 2.58
F8	107	75.6 ± 0.76	2.02 ± 0.01	0.65	41.1 ± 3.11
F9	105.2	75.6 ± 1.47	2.01 ± 0.02	0.54	42.8 ± 2.35
F10	99.4	76.2 ± 1.23	2.05 ± 0.02	0.45	35.7 ± 3.2

CU: content uniformity, WV: weight variation, T: thickness, F: friability, H: hardness.

Table 4
Disintegration times of the sublingual tablets ($n = 6$).

Code of formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Mean (s)	20.7	21.8	27	24.3	20.7	22	26.8	22.7	31	41.2
SD (s)	2.34	2.32	4.69	3.72	4.41	3.16	2.14	1.63	4.94	3.06

SD: standard deviation.

The ratio of MCC in tablet formulations changes between 8% and 10% and verifies the findings that the optimum concentration of MCC may be less than 12% [11]. MCC accelerates water penetration into tablets can cause easily swelling of SSG, and this reveals readily superdisintegrant property of SSG. But here, there is another important point that must be taken into consideration that the ratio of SSG in sublingual tablet formulation is very important because it was reported that disintegration time increased with increase in the level of SSG in the tablets. It was shown that the increase in the level of SSG had a negative effect on the disintegration of the tablets. At higher levels, formation of a viscous gel layer by SSG might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. Thus, tablet disintegration is retarded to some extent with tablets containing SSG. So it can be concluded that the use of SSG in sublingual tablet formulations in a ratio of 2.67% gives the tablet desired disintegration time [12,13].

On the other hand, SDL has a highly water-soluble property, and this may leave pores in the tablet matrix after rapid dissolution of it. These pores can accelerate capillary action that may be responsible for penetration of surrounding fluid in the tablet matrix and there after rapid disintegration [14].

The effect of different polymers at different concentrations on disintegration of tablets can be summarized as follows:

Increasing the HPMC content in the sublingual tablet formulations from 0.5% to 2% and 5% ratios increased the disintegration time ($p > 0.05$). Insignificant increase in disintegration time can be explained with lower polymer content below 10%. For the tablets including more than 10% HPMC, it was shown that increasing concentration of HPMC caused an increase in disintegration time of HPMC tablets. When HPMC tablets were exposed to water, HPMC absorbed water rapidly and formed gelatinous layer on the tablet surface. This result in undisintegrated tablet, and erosion became the main pathway for the size reduction of the tablet. When the concentration of HPMC was less than 10%, however, the gel layer of HPMC was not formed and the tablet could disintegrate [15,16].

Disintegration time increased with increase in the level of polymers in the tablets of chitosan and CMCNa. This increase is significant ($p < 0.05$) in the formulations prepared with CMCNa. This indicates that increase in the level of polymer had a negative effect on the disintegration of the tablets. This is an expected result indicates that at higher polymer ratios formation of a viscous gel layer by polymers might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents [17].

The disintegration time is in acceptable limits for all formulations containing polymer with different ratios can be explained with low percentages of them. Also another reason can be explained with the presence of SDL. It may have increased the porosity of the swelling polymer gel matrix. Tablets with relatively high lactose content and low mucoadhesive polymer concentrations can provide desirable disintegration profiles [18].

3.3. In vitro dissolution studies

Fig. 1 and Table 5 show the dissolution profile of zolmitriptan from the formulations. As shown, 5 min after starting the experiment, more than 85% of drug was dissolved in the medium (except

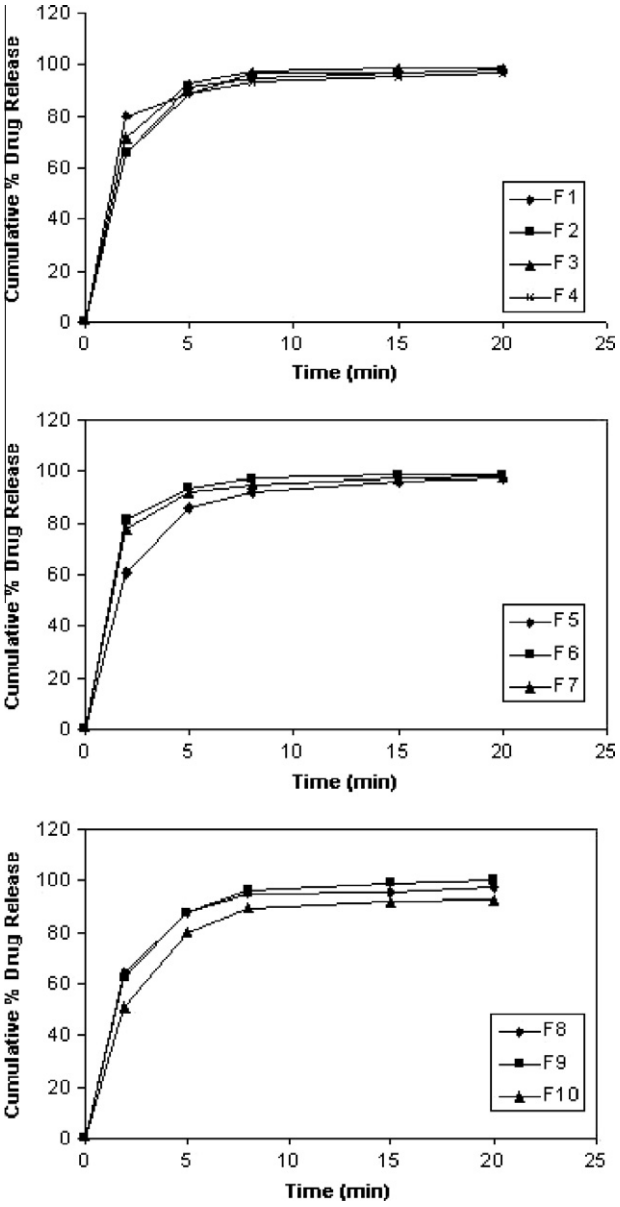

Fig. 1. Dissolution profiles of sublingual tablet formulations ($n = 6$).

F10). According to the literature, the amount of drug dissolved from sublingual tablets must exceed 80% in 15 min [19]. Therefore, the resulted dissolution profile met the above-mentioned requirement. Fast dissolution of the drug from the formulations can be explained with the following comments:

We think that manufacturing method can be one of the most important parameters for the fast dissolution. As it is known, the tablets prepared by direct compression disintegrate into zolmitriptan particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution [20].

Table 5
Dissolution values (%) of sublingual tablet formulations ($n = 6$).

Formulation code	Time (min)				
	2	5	8	15	20
F1	79.77 ± 8.23	88.95 ± 5.11	96.69 ± 5.33	96.57 ± 4.8	97.74 ± 4.78
F2	65.12 ± 5.45	91.45 ± 2.63	95.08 ± 3.71	96.72 ± 4.15	98.03 ± 3.86
F3	71.32 ± 3.78	92.6 ± 2.98	96.98 ± 2.27	98.42 ± 2.58	98.68 ± 2.72
F4	65.17 ± 9.22	88.93 ± 8.19	93.2 ± 7.22	95.42 ± 7.33	96.35 ± 7.88
F5	60.78 ± 4.47	85.96 ± 4.97	91.64 ± 3.95	95.99 ± 4.89	97.01 ± 6.53
F6	80.75 ± 6.67	93.55 ± 6.8	97.33 ± 4.84	98.2 ± 6.29	98.25 ± 6.24
F7	77.51 ± 2.96	91.77 ± 3.01	94.84 ± 3.17	97.24 ± 3.65	97.95 ± 3.52
F8	64.06 ± 7.67	87.89 ± 5.96	94.98 ± 5.5	95.21 ± 5.17	97.31 ± 6.47
F9	62.51 ± 8.02	87.77 ± 8.5	95.77 ± 3.04	98.79 ± 4.31	99.98 ± 4.52
F10	50.97 ± 3.68	79.99 ± 4.25	89.46 ± 3.03	91.59 ± 2.68	92.16 ± 2.89

It is well known that the addition of SDL can improve the flow and bond properties of other excipients during direct compression. In particular, SDL with higher solubility might also facilitate the dissolution of solid dosage forms [21].

When it was compared the dissolution of zolmitriptan particles within two minutes, off all the polymer containing formulation, formulation F6 and F7 containing 2% and 5% chitosan gave the maximum drug dissolution. This can be attributed that chitosan generously engulfs water when in contact with aqueous media and burst due to the pressure exerted by their capillary action thereby impart instantaneous disintegration of the dosage form and resulting in formation of a uniform dispersion in the surrounding media which behave like a true suspension formed inside the body leading to rapid dissolution of drug [22].

On the other hand, there was found no correlation between polymer content of the formulation and dissolution rate of drug for the formulations containing HPMC and chitosan. This can be explained with small concentration range (0.5–5%) of these polymers.

Only for the tablets prepared with CMCNa showed a correlation that increasing polymer content of formulation decreased the dissolution rate of the drug. This can be explained with that high ratio of polymer content in the formulation can increase the diffusional pathway, decreases the water uptake and erosion of the tablets so decrease the drug dissolution [23–25].

When we evaluate all formulations, polymer ratios (0.5–5%) can give us the chance of preparing sublingual tablets without changing their basic tablet characteristic especially disintegration and dissolution profiles.

3.4. In vitro permeation studies

Permeation of drugs from formulations at the end of four hours is between 9.55% and 20.33% (Fig. 2, Table 6). Low and slow release of drug can be attributed to small volume (2 mL) of donor compartment makes tablets swell. Swollen particles have porosity, and drug release occurs by diffusion through the openings created by the porosity of matrix as described by Higuchi square root equation. In in vivo conditions, pressure applied by tongue to the tablet can prevent swelling and enhances disintegration of tablet and dissolution of drug [26].

On the other hand, Chitosan and HPMC formulations exhibited more drug release and higher steady state flux and permeability coefficient values (Table 7) compared to CMCNa formulations. Higher swelling index ratio of CMCNa may cause to extend diffusion pathway of drug in the swollen matrix, and this may decrease the drug release [27].

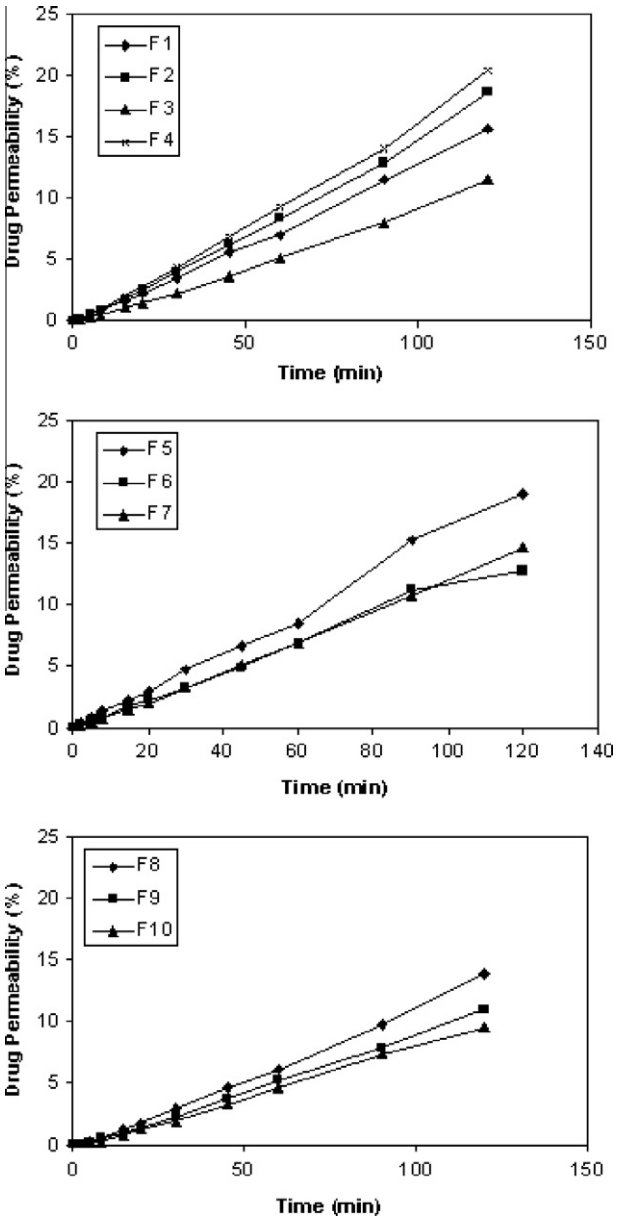

Fig. 2. Permeation profiles of zolmitriptan through cellulose membrane ($n = 3$).

3.5. In vivo studies

The optimum formulations were chosen according to in vitro tests results by means of exhibiting fast disintegration and dissolution profiles. Formulation F1 was directly included in in vivo experiments as a control formulation that does not contain polymer. Sterile solution of zolmitriptan at a concentration of 5 mg/2 mL was used to calculate relative bioavailability.

Table 6
Permeation values (%) of zolmitriptan through cellulose membrane ($n = 3$).

Time (min)	Formulation Code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
2	0.18 ± 0.04	0.08 ± 0.02	0.09 ± 0.03	0.11 ± 0.02	0.39 ± 0.15	0.19 ± 0.12	0.1 ± 0.05	0	0	0
5	0.46 ± 0.12	0.49 ± 0.03	0.38 ± 0.04	0.49 ± 0.07	0.89 ± 0.41	0.41 ± 0.14	0.46 ± 0.05	0.25 ± 0.01	0.13 ± 0.02	0.11 ± 0.03
8	0.85 ± 0.2	0.85 ± 0.13	0.5 ± 0.04	0.9 ± 0.11	1.32 ± 0.66	0.74 ± 0.22	0.77 ± 0.09	0.51 ± 0.05	0.54 ± 0.15	0.28 ± 0.12
15	1.63 ± 0.47	1.81 ± 0.24	1.09 ± 0.13	1.94 ± 0.24	2.27 ± 0.75	1.74 ± 0.54	1.49 ± 0.21	1.26 ± 0.1	0.97 ± 0.09	0.7 ± 0.35
20	2.23 ± 0.64	2.55 ± 0.33	1.44 ± 0.15	2.77 ± 0.33	2.94 ± 0.69	2.31 ± 0.74	2.05 ± 0.27	1.81 ± 0.12	1.39 ± 0.11	1.25 ± 0.64
30	3.48 ± 0.94	3.99 ± 0.49	2.26 ± 0.28	4.33 ± 0.5	4.7 ± 0.66	3.26 ± 1.03	3.29 ± 0.45	2.98 ± 0.28	2.3 ± 0.11	1.93 ± 0.96
45	5.61 ± 1.38	6.22 ± 0.68	3.59 ± 0.49	6.88 ± 0.8	6.58 ± 0.8	4.83 ± 1.89	5.17 ± 0.72	4.63 ± 0.46	3.74 ± 0.15	3.27 ± 1.64
60	7.05 ± 2.1	8.33 ± 0.87	5.07 ± 0.81	9.29 ± 0.82	8.54 ± 0.54	6.92 ± 1.92	6.88 ± 1.1	6.07 ± 0.58	5.25 ± 0.14	4.63 ± 1.17
90	11.44 ± 2.04	12.82 ± 1.27	7.98 ± 1.32	13.95 ± 0.99	15.19 ± 3.98	11.25 ± 3.17	10.75 ± 1.69	9.74 ± 0.92	7.85 ± 0.51	7.42 ± 1.89
120	15.58 ± 4.98	18.63 ± 1.94	11.54 ± 1.54	20.33 ± 0.9	18.95 ± 3.72	12.71 ± 3.74	14.61 ± 2.54	13.83 ± 1.31	10.97 ± 0.57	9.55 ± 1.06

Table 7
Drug release parameters (by using cellulose membrane at the end of a 4-h period) of the formulations ($n = 3$).

Formulation code	Released%	J_{ss} (μg/cm² h)	K_P (cm/h)
F1	15.58 ± 4.98	402.67 ± 91.15	161.07 ± 36.46
F2	18.63 ± 1.94	474.79 ± 42.23	189.92 ± 16.89
F3	11.54 ± 1.54	282.47 ± 29.31	112.99 ± 11.72
F4	20.33 ± 0.9	486.81 ± 32.47	194.72 ± 12.99
F5	18.95 ± 3.72	438.73 ± 84.62	175.49 ± 33.85
F6	12.71 ± 3.74	342.57 ± 87.11	137.03 ± 34.84
F7	14.61 ± 2.54	384.64 ± 72.09	153.86 ± 28.84
F8	13.83 ± 1.31	360.06 ± 14.24	144.02 ± 5.69
F9	10.97 ± 0.57	246.41 ± 11.91	98.56 ± 4.76
F10	9.55 ± 1.06	276.46 ± 114.03	110.58 ± 45.61

J_{ss}: steady state flux, K_P: permeability coefficient.

The mean serum concentration–time data of zolmitriptan following the administration of the sterile solution formula via subcutaneous and sublingual tablet formulations (F1, F4, F7 and F8) is shown in Fig. 3.

C_{max} and AUC values of the sublingual tablet formulation prepared without bioadhesive polymer were found to be lowest ($p < 0.05$) when compared with other sublingual tablet formulations that contain mucoadhesive polymer. This may be the flushing action of saliva that can show its effect on formulation that does not contain any mucoadhesive polymer [5–7,18].

Of all the formulations containing mucoadhesive polymers, F7 coded formulation containing 5% chitosan has the maximum C_{max} and AUC and minimum t_{max} ($p < 0.01$) values (Table 8). Increasing the contact time with the sublingual mucosa with a mucoadhesive polymer improve sublingual bioavailability and result in more predictable plasma levels of the drug, leading to better therapeutic efficacy and reproducibility. Also chitosans are suggested to enhance absorption of drugs through mucoadhesion by binding strongly to negatively charged biological surfaces such as mucous membranes and improved aqueous solubility of a drug [28].

Another mechanism of action of chitosan in improving transport of drugs across mucosal membranes has been reported to be the transient opening of the tight junctions in the cell membrane to allow polar drugs to penetrate, whereas for buccal mucosa it is known that the barrier is not based on tight junctions. Tight junctions are the cell-to-cell junctions that seal adjacent epithelial cells together; they are caused by the attachment of the actin filament system from one cell to that of a neighboring cell, preventing the passage of most dissolved molecules from one side of the epithelial sheet to the other [29].

Chitosan might be increasing the thermodynamic activity of the penetrant which results in enhanced penetration. Research on the permeability of oral mucosa indicated that the majority of compounds pass through the paracellular pathway. However, the major intercellular barrier in oral epithelium consists of organized lipid lamellae in the intercellular regions of the superficial layers of the epithelium. As chitosan has been shown to be capable of disrupting lipid micelles in the intestine, the permeabilizing effect can be attributed to its interference with the lipid organization in the buccal epithelium [6].

Another approach for better absorption of zolmitriptan is its physicochemical properties and anatomical structure of sublingual

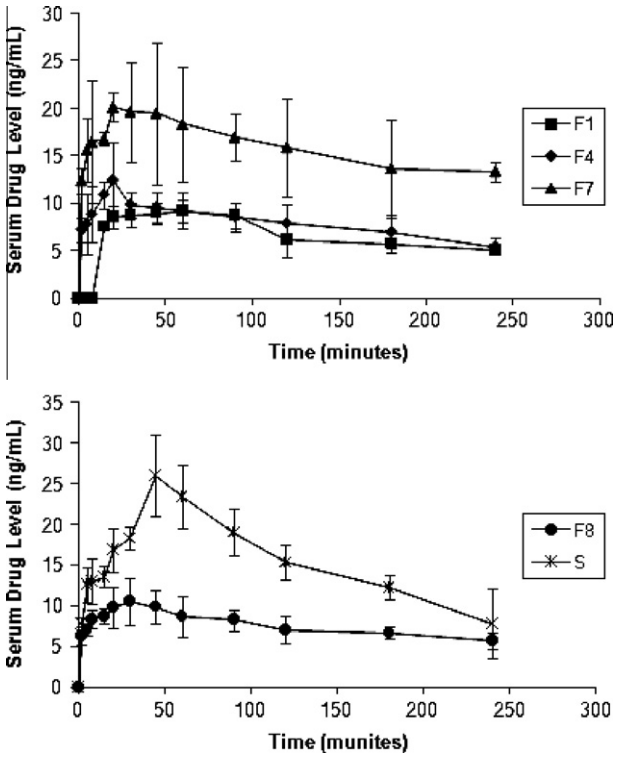

Fig. 3. Serum concentration profiles of zolmitriptan ($n = 4$) after application different delivery routes (F1, F4, F7 and F8 are sublingual administration of tablet formulations; S is subcutaneous administration of solution formulation).

Table 8
Pharmacokinetic parameters after subcutaneous and sublingual administration of zolmitriptan in sheep ($n = 4$).

Delivery route and code of formulation	AUC (ng/mL min)	C_{max} (ng/mL)	t_{max} (min)	F_R (%)
Subcutaneous – S	3705.92 ± 344.9	26.012 ± 5.001	45	100
Sublingual – F1	1586.06 ± 231.9	9.223 ± 1.336	60	42.81
Sublingual – F4	1876.9 ± 139.7	12.394 ± 4.003	20	50.64
Sublingual – F7	3842.02 ± 488.9	20.151 ± 1.490	20	103.67
Sublingual – F8	1814.9 ± 190.9	10.561 ± 2.899	30	48.97

F_R: relative bioavailability.

area. Generally, small molecules, preferably less than 600 Da, and moderate lipophilicity, with a log *P* of 1.6–3.3, are absorbed more rapidly. At high log P values (i.e., highly lipophilic molecules), the permeability is low. This is probably due to accumulation of lipophilic drugs in biological layers because of low aqueous solubility [7,30,31]. Zolmitriptan is a small molecule and has a molecular weight of 287.36. It has a well balance of lipophilic and hydrophilic value which corresponds a log *P* value of 1.644 [32,33]. Normally, saliva is a weak buffer and has a pH typically around neutral. Zolmitriptan has a p*K*a value of 9.52 indicating that it is almost completely ionized in saliva. This provides completely dissolution of zolmitriptan in small volume of saliva (~1 mL) [7,32,34,35]. After dissolution of active substance at the site of absorption, the next step is passing the biological barriers. At this point, the desired physicochemical properties explained above makes zolmitriptan absorbed well. On the other hand, sublingual mucosa is five times thinner than buccal mucosa, and this makes it the most permeable region of oral mucosa [9]. As a result, desired physicochemical properties of active substance and high permeability of sublingual mucosa region make zolmitriptan a good candidate for preparing sublingual tablets.

4. Conclusion

All prepared tablets met the compendial limits in terms of physicochemical parameters, disintegration and dissolution studies. HPMC, chitosan and CMCNa as bioadhesive polymer at the ratio 0.5–5 can be used in sublingual tablet formulations to provide necessary time of active drug to be absorbed and protect it from flushing action of saliva. When given sublingually, zolmitriptan is well absorbed, and its bioavailability by this route is significantly enhanced with the addition of chitosan at the ratio of 5. As a result, sublingual tablet administration of zolmitriptan appeared to be a promising alternative to traditional drug administration routes.

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