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Fast Dissolving Sublingual Strips: A Novel Approach for the Delivery of Isosorbide Dinitrate

Marzieh Fathei[1] , Mitra Alami-Milani[2,3], Sara Salatin[1,3], Sharahm Sattari[4] , Hassan Montazam[5] , Farhad Fekrat[3] , Mitra Jelvehgari[2,6]*

[1] Research Center for Pharmaceutical Nanotechnology, Tabriz University of Medical Sciences, Tabriz, Iran

[2] Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.

[3] Student Research committee, Tabriz University of Medical Sciences, Tabriz, Iran.

[4] Nikookari Ophtalmology Center, Tabriz University of Medical Sciences, Tabriz, Iran

[5] Islamic Azad University of Bonab Unit, Bonab, Iran. 6 Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

Abstract

Background and Objective: Isosorbide dinitrate (ISDN) is used for treating the angina attacks. In addition, oral ISDN is available in immediate and sustained release formulations and the bioavailability of ISDN is about 20-25% when taken orally. Further, the ISDN films are developed for sublingual drug delivery by improving drug bioavailability. The present study aimed to design and evaluate the physicochemical properties of the film formulation for sublingual delivery of ISDN.

Methods: In the present study, sublingual films were prepared by the solvent casting technique using the hydroxypropyl methylcellulose (HPMC) polymers (i.e., 100, 150, & 200 mg) with a different drug to polymer ratios (i.e., 1:5, 1:7.5, & 1:10). Then, ISDN was evaluated for the film appearance, drug content, surface pH, mucoadhesion force, differential scanning calorimetry (DSC), *in vitro* drug release, and *ex vivo* permeability.

Results: Based on the results, F3 formulation (1:10 ISDN to HPMC ratio) showed acceptable thickness (0.93 mm), weight (11.14 mg), surface pH (7.82), moisture absorption capacity (6.08%), elasticity (>200), mucoadhesion force (18.05 N/cm^2), and drug content (6.22%). Furthermore, the results demonstrated that HPMC polymer improved the characteristics of the

films, modified the bioadhesiveness, and finally, enhanced elasticity. However, DSC thermogram failed to show any crystalline drug substance in the films except for F1 (immediate release) and the endothermic peak of ISDN was absent in F2 and F3 films. Therefore, the drug which entrapped into the film was in an amorphous or disturbed-crystalline phase of the molecular dispersion or dissolved in the melted polymer in the polymeric matrix. Moreover, the drug release from the films was faster compared to the tablet® (P<0.05).

Conclusions: In general, the formulation of F_1 was observed to be an appropriate candidate for developing the sublingual film for the remedial use.

Key words: Film, Sublingual, Isosorbide dinitrate, Hydroxypropyl methylcellulose, Mucoadhesion

Introduction

Fast dissolving drug delivery systems (FDDSs) serve as a real benefit over the traditional dosage forms where the drug gets quickly degraded and resolves in the salivation without using water.[1]

Accordingly, a fast dissolving film may be located in order to resolve the problems of a fast dissolving tablet. This type of film is very similar to the very elegant strip of plastic adhesive tapes in their form, size, and thickness. In addition, fast dissolving film is readily placed on the tongue of the patient or any oromucosal tissue, which is immediately soaked with the saliva and quickly hydrated and stuck to the seat of the utilization. Afterward, it is quickly degraded and dissolved to release the drug for oromucosal sorption. FDDS fits the drugs which undertake a high first-pass metabolism and is applied for improving the bioavailability, along with reducing the multiplication of drug dosage to mouth plasma peak levels, which itself decreases unfavorable efficacy and makes FDDS cost-effective.[2]

Oral drug delivery arises several complications as hepatic first-pass metabolism and enzymatic disintegration in the gastrointestinal tract.[3] These troubles may be dominant for some categories of drugs, with their utilization by the sublingual tissue. Salivary glands are available on the floor of the mouth under the tongue and produce salivary mucin.

The absorption is defined as the transfer of the drug from its site of administration into the systemic circulation, therefore, it may be claimed that the absorption is regarded as the immediate proportional layer thickness (sublingual > buccal). The sublingual path may make the quick start of the function owing to high permeability and rich blood provision, thus, the drug with a short delivery period can be carried and the dose regimen in this regard would be frequentative.[4]

Upon sublingual administration, the drug immediately arrives at the blood flow by the ventral surface of the tongue and the floor of the mouth. The major mechanism for absorbing the drug in the oral mucosa is inactive diffusion toward the lipoidal membrane. Further, the absorption of the drug by the sublingual path is 3-10 times larger than the oral path and it alone exceeds through the hypodermic injection.[5] Basically, thin films are great candidates for targeting the responsive site that cannot be likely targeted by the tablets or liquid formulations. Furthermore, these films have demonstrated the ability to improve the beginning of the drug function, and the drug effect while decreasing the dose repetition.[6] Likewise, thin films can be beneficial for removing the adverse effects of a drug and decreasing wide metabolism induced by proteolytic enzymes. Moreover, the desired thin films require displaying favorable aspects including enough drug loading capacity, quick dissolution rate or long residence time at the place of dispersion, and approvable formulation stability. Therefore, they should be nontoxic, biocompatible, and biodegradable.[7]

The main limitation of FDDSs is related to the mechanical strength of the tablets, high friability, and the dryness of the mouth due to the decreased saliva production and thus requires a specialized package for physical integrity (under normal condition) and stability.

~~The fast disintegrating film of loratadine with hydroxypropyl methylcellulose has shown to have good physicochemical properties and solvent casting method can be successfully adopted for preparing the films. The first oral strips, developed by Pfizer who named it as Listerine®, were used for mouth freshening. Chloraseptic® relief strips were the first oral thin films which contained benzocaine and were used for the treatment of sore throat.~~

The fast disintegrating film of loratadine with hydroxypropyl methylcellulose has shown to have good physicochemical properties and solvent casting method can be pursued with success for preparing the formulations. The first oral strips, developed by Pfizer who named it as Listerine®, were used for mouth freshening. Also, Chloraseptic® relief strips were a thin oral film containing benzocaine that was applied to treat sore throat.

In the solvent casting method, different natural and hydrophilic polymers containing cellulose or cellulose derivatives are dissolved in a solvent and the drug is dissolved in an appropriate solvent with another material in order to produce fast dissolving films. Next, both of the mixtures are admixed, shocked, and eventually, cast over the Petri plate, dried, and cut into similar dimensions.[8]

Isosorbide dinitrate (ISDN) is an intermediate-acting nitrate accepted for the inhibition of angina pectoris by the Food and Drug Administration. ISDN has only 20-25% bioavailability in oral intake and is exposed to considerable first-pass metabolism. Additionally, the half-life of ISDN is within the range of one hour and the usual dose is 5-80 mg. In addition, ISDN sublingual and chewable tablets are present for the remedy of angina attacks.[9]

The current study sought to design and assess physicochemical properties of the film formulation for sublingual delivery of ISDN.

Materials and Methods

Materials

ISDN and Hydroxypropyl methylcellulose (HPMC) E15 were purchased from Toliddaru Company (Iran) and Sigma-Aldrich Company (USA), respectively. Then, propylene glycol, dichloromethane, acetone, ethanol, sodium chloride, aluminium chloride, potassium chloride, sodium sulfate, ammonium acetate, urea, and lactic acid were supplied from Merck Company (Darmstadt, Germany). All the reagents were of analytical grade.

3.2. ISDN film preparation method

Sublingual films of isosorbide dinitrate (ISDN) were prepared by a solvent casting method using a film forming a mucoadhesive polymer. Further, HPMC was exactly weighed (i.e., 100, 150, & 200 mg) and dissolved in 2.5 mL of ethanol and 2.5 mL of dichloromethane and then was shocked. Next, one droplet of propylene glycol (30 mg) was poured into the polymer solution. At first, ISDN drug was exactly weighed (20 mg) and next dissolved in 1.7 mL of acetone and 0.3 mL of water in another beaker (Table 1). Afterward, both of the polymer and drug solutions were completely admixed together by a magnetic agitator.

Table 1. The composition of various formulations of isosorbide dinitrate prepared by solvent-based film casting method

Analytical methods

Physicochemical properties of films

The physicochemical properties of the prepared films were determined in the following order:

Assessment of thickness and drug content

Six films were randomly selected from each formulation and their weight, thickness, and mean drug content were evaluated. The thickness of the films was measured with the caliper. Furthermore, the films (1x1 cm^2) were dissolved in ethanol and the drug content was analyzed using a UV spectrophotometer at 269.2 nm.

Swelling study

The films including the ISDN were permitted to swell in the glass plate containing 5 mL of phosphate buffer (pH=6.8) at 37°C. Moreover, the difference in the primary and the ultimate diameters was measured at prearranged intervals (i.e., 15, 30, 60, 90, & 120 minutes). Additionally, the excess of phosphate buffer was taken away using the filter paper. Finally, the swelling index was computed using equation A.[10]

$$\text{Swelling index (\%)} = \frac{Dt - D0}{D0} \times 100 \qquad \text{Equation A}$$

where, swelling index denotes the swelling percentage. In addition, $D0$ and Dt demonstrate the primary diameter at time t=0 and the diameter at time t=t, respectively.

Surface pH

The surface pH was computed after putting the selected film in the glass plate containing 5 mL of phosphate buffer (pH=6.8). The film remained for 2 hours in order to swell and the pH was measured by locating the top of the pH-meter (Corning pH-meter 120, USA) in the phosphate buffer for one minute.[11]

Ex vivo mucoadhesion time

The *ex vivo* mucoadhesion was investigated using the sheep sublingual tissue. The sheep sublingual mucosa was placed in the vial. Further, the films were moistened with one or two droplets of the simulated saliva liquid (50-100 µL) and pressed on the mucosa by a force with a finger for 2 minutes. Then, 800 mL of phosphate buffered saline (pH=6.8) was applied to accumulate and hold at 37^{o}C with 100 rpm for 2 hours in order to determine the film adhesive strength. The recently isolated sublingual tissue of the sheep was supplied from the slaughterhouse. The time span required for the film to detach from the mucosa was recorded as the adhesion time.[12]

Differential Scanning Calorimetry

The physical state of the drug in the film was analyzed by ***Differential Scanning Calorimetry (***DSC) (Shimadzu, Japan). Furthermore, the thermograms were obtained at a scanning rate of 10°C/min conducted over a temperature range of 25-300°C.

In Vitro Release Study

In vitro release was evaluated employing 50 mL of phosphate buffered saline, with a pH of 6.8, as the dissolution medium at 50 rpm at 37˚C in a beaker which was put into the incubator shaker. The films were pasted on the glass slides using the cyanoacrylate adhesive.[13] Moreover, a quantity of one mL was removed at 5, 15, 30, 60, 90, 120, 180, 240, 300, 360, and 480 minutes intervals, exchanged by the fresh phosphate buffered saline, with a pH of 6.8, and analyzed spectrophotometrically at 207 nm. Finally, the concentration was computed using the calibration curve of ISDN in this medium.

Permeation studies

The films displaying the best *in vitro* release were selected for the permeation investigation. Then, freshly provided sublingual mucosa of the sheep was placed between the donor and receptor sections in such a way that the smooth surface of the mucosa faced the donor section.[14] Next, the films were put on the mucosa and the sections were firmed altogether. Afterward, the donor section was fed with 3 mL of simulated saliva solution (i.e., sodium chloride 4.50 g, potassium chloride 0.30 g, sodium sulfate 0.30 g, ammonium acetate 0.40 g, urea 0.20 g, lactic acid 3 g, and purified water up to 1000 mL) and the pH of the solution was regulated to 6.8 by one M NaOH solution. Additionally, the receptor section was fed with 24 mL phosphate

buffered saline, with a pH of 6.8, and magnetically shocked at 700 rpm. Eventually, one mL of solution was removed at prearranged time intervals and measured at 207 nm.

Statistical analysis

Where appropriate, the release outcomes were determined using the SPSS software, version 18.0. One-way ANOVA was used to determine whether there were any statistically significant differences. $P<0.05$ was considered as the level of significance.

Results

Physicochemical properties of films

Evaluation of loading efficiency and production yield

The morphology of the film should show homogeneous and integrated properties in order to assure the invariable dispersion of the drug all over the polymeric admixture (Figure 1).

The flexibility of the thin film is significant when they may be administered without any breakage.[15]

Figure 1. The optical microscopic photograph of the sublingual film of the isosorbide dinitrate

In addition, a desirable sublingual film should be smooth, flexible, extensible, and strong enough to resist the cracking due to the stress from the functions in the buccal. Further, such a film must have nice bioadhesive strength so that it can be maintained constant in the range of 0.52-11.14 g. The film thicknesses are demonstrated in the limit of 0.69-0.93 mm in the mouth for the favored period 24.

Furthermore, the thickness should be determined at five various positions (i.e., in the four corners and one center) and it is necessary to indicate the homogeneity in the thickness of the strip since it is directly associated with the precision of the dose dispersal in the strip.[16]

The folding endurance provides the fragility of a film. It was found to be the largest for F_2 and F_3 (up to 200 times) while it was the smallest for F_1 (up to 200 times). Moreover, the folding endurance was practically determined by frequently folding the film at a spot until their fracture. Additionally, the fractured time was evaluated as the terminal spot. The procedure for evaluating the endurance value was as follows.

The film samples (1×1 cm^2) were frequently folded at a similar site until it fractured or a visual crack was found, which was considered as the determination of elasticity. In addition, based on the results of F_2 and F_3, it was displayed as the ideal flexibility for the film formulation.

Further, as shown in Table 2, the surface pH values of all the films are demonstrated to be approximately neutral (7.80-7.83).

Table 2. The Effect of the Drug to Polymer Ratio on Physicomechanical Properties and Mucoadhesive Films

Furthermore, all the swelling indices of the films are represented in the limit of 11.91-19.05% and the value is extremely high in F_1. Studying the physical stableness of the film at the highly moist situation and the entirety of the film at waterless states, their percent moisture absorption (PMA) and percent moisture loss (PML) were determined. As demonstrated in Table 2, the displayed PMA and PML are as F1>F2>F3 and PML is insignificant in F_1, F_2, and F_3.

Evaluation of the drug content

The estimation of the drug by weight while not by casting the region is considered the most recent procedure for analyzing the content. Based on the results of Table 2, the drug content in all the films (1×1 cm^2 and the total) is in the range of 0.14-0.31 (mg/cm^2) and 3.73-6.22% (total film), respectively.

Ex vivo mucoadhesive properties

Bioadhesion force

Moreover, the folding endurance of the produced film is determined to be 200 times and the mucoadhesive force is known to be arranged between 12.85 N/cm^2 and 18.05 N/cm^2 (Table 2).

Mucoadhesion time and swelling study

Table 2 further represents the swelling property of the utilized polymer. Briefly, after the onset of the swelling test (24.3-45 minutes), the applied polymer is swollen indicating that F1 film catches the least time for swelling.

Differential Scanning Calorimetry analysis

Crystalline or amorphous structure of the drug molecule and therefore the thermal status of the polymers were analyzed using differential scanning calorimetry investigation. As illustrated in Figure 2, the ISDN reveals a sharp endothermic peak at 70˚C (melting point of the drug), as well as a wide partly peak at 127.95˚C (the loss of water molecule) and 201.4˚C (the destruction of lactose). The first endothermic peak is related to its ISDN melting point and two endothermic peaks are described with lactose monohydrate (i.e., ISDN is diluted with 60% lactose), respectively. Additionally, hydroxypropyl methylcellulose (HPMC) indicates a wide endothermic peak nearly at 65.84˚C which is related to its Tg, that is, the glass transition temperature.[17]

As shown, the melting peak of the drug disappears in the film formulations. Therefore, the polymer peak shows a complete overlap with the drug melting peak. In addition, dehydration endothermic peak of the lactose is demonstrated with a very low intensity in the film F1 (144˚C) while not appearing in F2 and F3 formulations.

Further, in the physical mixture of the F1, the melting endothermic peak of the ISDN is observed at 70˚C and two peaks are shown with low intensities about the loss of water molecule and destruction of lactose compared to the pure sample, respectively.

Figure 2. Differential scanning calorimetry thermogram of hydroxypropyl methylcellulose (a), isosorbide dinitrate (b), lactose monohydrate (c), the physical mixture of F1 (d), F1 (e), F2 (f), and F3 (g)

In vitro release study

As illustrated in Figure 3, by *in vitro* release, different strips are studied using phosphate buffered saline, with a pH of 6.8, as dissolution medium, and the drug concentration is analyzed spectrophotometrically at 207 nm.

Figure 3. The cumulative release of the isosorbide dinitrate from the films prepared with a different drug to polymer ratios and ISDN tablet commercial

Furthermore, a significant difference is shown in the release of ISDN films containing HPMC (Figure 3).

Table 3. The Comparison of Different Release Properties of Isosorbide Dinitrate From Various Films, Commercial® Tablet, and Isosorbide Powder

In vitro permeation research

The experimental method generally includes using a diffusion cell. Accordingly, for each cell, a donor section is isolated from a receptor section using a layer of the epithelium of sublingual working as the mucosa model. In the present study, indices such as temperature, a combination of the receptor and donor medium, pH, the cell sizes, and hydrodynamic situations were ordinarily regulated. It was found that permeation by the sublingual epithelium happened either by the transcellular or paracellular path as earlier explained, though all the procedures may be normally investigated to be controlled by the inactive diffusion and modeled by Fick's first law of diffusion.[18] In Equation B:

$J_{ss} = P_{app}.C_D$ Equation B

$P_{app} = (V_A/\text{area} \times \text{time}) \times ([\text{drug}_{\text{receptor}}] / [\text{drug}_{\text{donor}}])$

$J_{ss} = Q/A.t$

$K_p = Q/[A.T(C_0-C_i)]$

where, the steady-state flux (J_{ss}) is evaluated by permeability coefficient (P_{app}) or permeability constant (K_p) of the drug in the sublingual mucosa, the area (A) of sublingual mucosa and the donor chamber solution, the time (t) of 240 minutes, the concentration of drug in the donor compartment (C_D), and the quantity of drug transported through the mucosa in time t (Q). Moreover, the slopes of the linear part of the release profiles were computed, which describe the release rate or the flux of various films (Table 3).

Discussion

Fast dissolving tablets are considered as the solid unit dosage form which quickly decomposes in the mouth without a need for taking water. However, some problems are associated with the orally fast dissolving tablets such as occasional problems with their transport, accumulation, and application (i.e., friability and fragility) and these tablets are manufactured using the expensive lyophilization technique.[19]

To overcome these difficulties, oral films were expanded, which are very popular nowadays. Orally fast dissolving film is regarded as a novel drug delivery system for the oral delivery of the drug. It was expanded based on the foundation of the technology of the transdermal route.[20] The delivery system contains an extremely thin oral film, which is easily placed on the patient's tongue or any oral mucosa and immediately moistened with the saliva. Then, the film quickly hydrates and sticks onto the place of utilization.[21]

Hence, a fast dissolving film of the drug rapidly decomposes in the mouth without requiring any water since a dosage form would increase the patient compliance, particularly during the trip or in conditions where the water is simply unavailable. Thus, there is a primary requirement for improving fast dissolving film to dominate the non-acceptability of the patient.[22]

Sublingual administration has some benefits over oral administration. In addition, having a direct route, sublingual administration is mostly quicker and guarantees the decomposition of material only through salivary enzymes before going into the bloodstream while the administered drugs through the mouth should pass through the gastrointestinal tract, which threatens to degrade such drugs either by gastric acid, bile, or by its very enzymes like the monoamine oxidase.

Accordingly, sublingual medication administration is quicker and more impressible compared to the easily administered oral medication.[23]

The thin and extremely permeable membrane of the sublingual mucosa is an appropriate target if a rapid start is favored. Additionally, significant surface area and upper blood flow at this area provide fast availability to the systemic circulation. In addition, the sublingual area is simply available and usually well-admitted by the patient.[24]

~~Further, the interaction between the drug and polymer, as well as the crystalline nature of the drug may lead to the formation of the rough surface in the films. Therefore, assessing the surface morphology and texture is crucial to assure the uniform distribution of the drug without any interaction with the polymer in the film formulation.~~

Further, the interaction between the drug and polymer, as well as the rough surfaces formed in the films may be related to the crystalline nature of the drug. Therefore, the

assessment of morphology and integrity of the surface is essential to ensure the uniform distribution of the drug without any interaction with the polymer in the formulation of the films prepared.[25]

~~Furthermore, variation in pH may cause an increase or decrease in the erosion or dissolution rates of the polymers.~~

Alteration in the pH may result in an increase or decrease in the rate of erosion or dissolution of polymers.[26] ~~Upon contact with the biological fluids, the polymeric film starts to swell following the polymer chain relaxes, which can cause drug diffusion.~~ After contact with biological fluids, the polymeric film begins to swell next the polymer chain relaxes which can lead to diffusion of the drug.[27]

Moreover, hydration is needed for a bioadhesive polymer to develop and form a desirable macromolecule with appropriate size and stimulate the polymer chains in order to increase the mutual contact between the polymer and mucin. Hydroxypropyl methylcellulose, as a mucoadhesive polymer, is water-insoluble, derived from natural or synthetic sources, and able to form several hydrogen bonds due to the presence of carboxyl or hydroxyl functional groups. The swelling test is performed to measure polymer hydration. Hydrophilic polymers with different structures possess a varying degree of swelling based on the relative resistance of matrix network structure against water molecule movement.

~~Measuring the swelling or the degree of hydration of the polymeric film plays an important role in providing the key information on the mucoadhesive strength. As it is known, the hydration of polymers is the reason for the relaxation and interpenetration of the polymeric chain. However, the overhydration leads to a decrease in mucoadhesion properties due to the formation of slippery mucilage.~~

Measuring the swelling or degree of hydration of polymeric films displays the main role in mucoadhesive strength of formulations prepared. It is also known that due to the relaxation and water penetration in polymeric chains, hydration is created in polymers. Whereas, excessive hydration may lead to reducing in the characteristics of mucoadhesion associated with the creation of slippery mucilage.[2]

In many cases, the degree and rate of swelling noticeably contribute to controlling the release of the drug. Therefore, these parameters can be considered as the indicator of bioadhesive or mucoadhesive potential and drug release profiles.

Investigating differential scanning calorimetry (DSC) thermograms, it is evident that the DSC curves of all formulations are almost the same which displays that the isosorbide dinitrate (ISDN) may spread or be solved in the polymeric matrix through film preparation.

About 84.17% of the ISDN was released in 5 minutes from the films of the F1 formulation. This formulation demonstrated high hydration (19.04%) indicating the rapid water uptake and thus faster drug release. The bound polymer molecules in these formulations were easily corroded, which permitted the simple release of ISDN. Finally, the release was known to be 100% in the films after 8 hours (Figure 3, Table 3).

The highest flux and apparent permeation for the F_1 film was 5×10^{-4} mg/cm^2.min and 2.23×10^{-6}, respectively. Based on the results of several studies, the release of the drug is markedly influenced by the erosion of the film. Additionally, the degradation rate of the film relies on the plasticizer.[2] The drug should be released from the delivery system at an optimum rate in order to penetrate into the biological membrane. In addition, assessing the drug release from the film is essential since it is the rate-determining step in the process of absorption.

Conclusion

In general, the sublingual ISDN film has the potential to improve the onset in a small dose and increase the effect and safety profile of the medicine. The thin film is firmer instead of being stable and rapidly dissolves compared to the other popular dosage forms. Further, the thin strip certifies more precise administration of drugs and may develop compliance due to the known nature of the dosage form and its inherent simple administration. The above-mentioned characteristics are mainly useful for pediatric, geriatric, and neurodegenerative patients for whom proper and perfect dosing may be difficult. Finally, the ability of the thin film to quickly dissolve without a need for water provides an option for patients with swallowing disorders.

Conflict of interests

The authors disclose no conflict of interests regarding the publication of this study.

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Table 1. Isosorbide Dinitrate Films Prepared by Solvent Casting Method With Different Drug to Polymer Ratios

Formulation code	Drug to polymer ratio	[a] ISDN (mg)	[b] HPMC (mg)	[c] DCM (mL)	Ethanol (mL)	[d] PG (g)	Aceton (mL)	Water (mL)
F_1	1:5	20	100	2.5	2.5	0.3	1.7	0.3
F_2	1:7.5	20	150	2.5	2.5	0.3	1.7	0.3
F_3	1:10	20	200	2.5	2.5	0.3	1.7	0.3

Note. [a]Isosorbide dinitrate; [b]Hydroxypropyl methylcellulose; [c]Dichloromethane; [d]Propylene glycol.

Table 2. The Effect of the Drug to Polymer Ratio on Physicomechanical Characteristics and Mucoadhesive Films

Variables	**Formulation Code**		
	F_1	**F_2**	**F_3**
Drug to polymer ratio	1:5	1:7.5	1:10
Weight variation (mg ± SD)	0.52±6.56	9.72±0.67	11.14±0.77
Thickness (mm± SD)	0.69 ± 0.008	0.84±0.003	0.93±0.008
Folding endurance (n±SD)	>200	<200	<200
Drug content (1×1 cm^2) (mg/cm^2±SD)	0.14±0.03	0.23±0.08	0.31±0.01
Content drug (Total) (%±SD)	3.73±1.80	4.64±0.13	6.22±0.15
Production Yield (%±SD)	85.86±1.98	95.39±7.59	87.13±5.23
Absorbed moisture (% ±SD)	18.5±4.21	5.78±0.73	6.08±0.31
Lost moisture (% ± SD)	5.26±0.67	4.88±0.65	3.49±2.39
Surface pH (n±SD)	7.80±0.08	7.83±0.09	7.82±0.003
Swelling index (%±SD)	19.05±8.24	11.91±4.13	16.67±4.12
Mucoadhesive strength (N/cm^2±SD)	12.85±0.66	14.97±0.64	18.05±0.92
Residence time (Sec±SD)	24.3±4.02	36±3.01	45±0.52

Table 3. The Comparison of Various Release Characteristics of the Isosorbide Dinitrate From Different Film Formulations, Commercial® Tablet and Isosorbide Powder

Formulation code	[a]Rel_5 (%±SD)	[b]Rel_{480} (%±SD)	[c]DE (%)	[d]MDT (min)	[e]f_1	Flux (mg/cm^2min)*10^{-4}	Papp (cm/sec)*10^{-6}
F_1	84.17±3.07	101.36±11.65	100.13	5.84	32.63	5	2.23
F_2	54.31±1.65	101.08±18.34	94.31	32.16	17	4	1.44
F_3	43.09±10.79	100.42±2.58	91.50	42.65	15.27	3	0.084
Commercial Tablet®	4.13±1.50	86.78±1.30	79.61	39.67	0	-	-
Untreated ISDN powder	-	-	-	-	-	7	1.17

Note. [a] Rel5: The amount of drug release after 5 minutes; [b]Rel480: The amount of drug release after 480 minutes; [c]DE: Dissolution efficiency; [d]MDT: Mean dissolution time; [e]f1: Differential factor (0<f1<15).

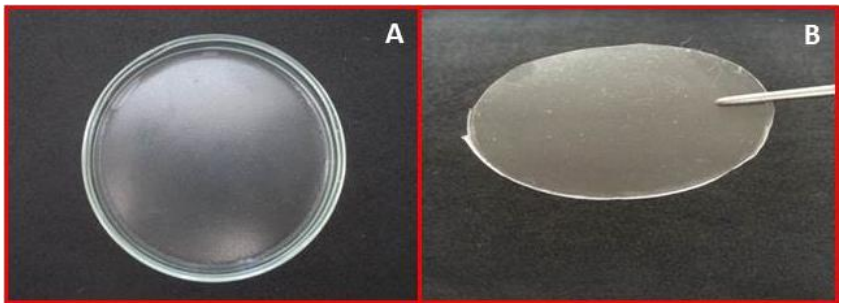

Figure 1. The optical microscopic photograph of the sublingual film of the isosorbide dinitrate.
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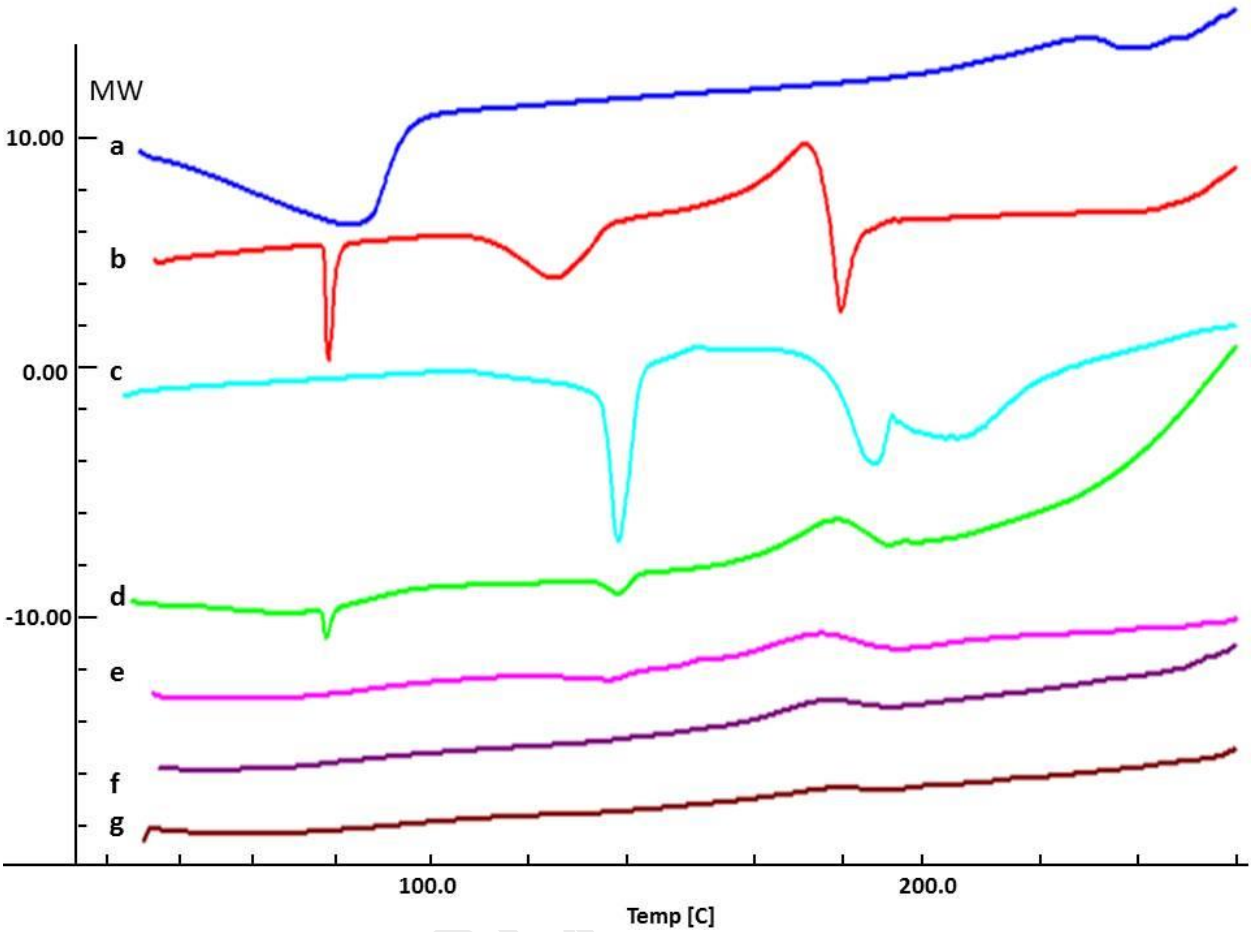

Figure 2. Differential scanning calorimetry thermogram of hydroxypropyl methylcellulose (a), isosorbide dinitrate (b), lactose monohydrate (c), the physical mixture of F1 (d), F1 (e), F2 (f), and F3 (g).

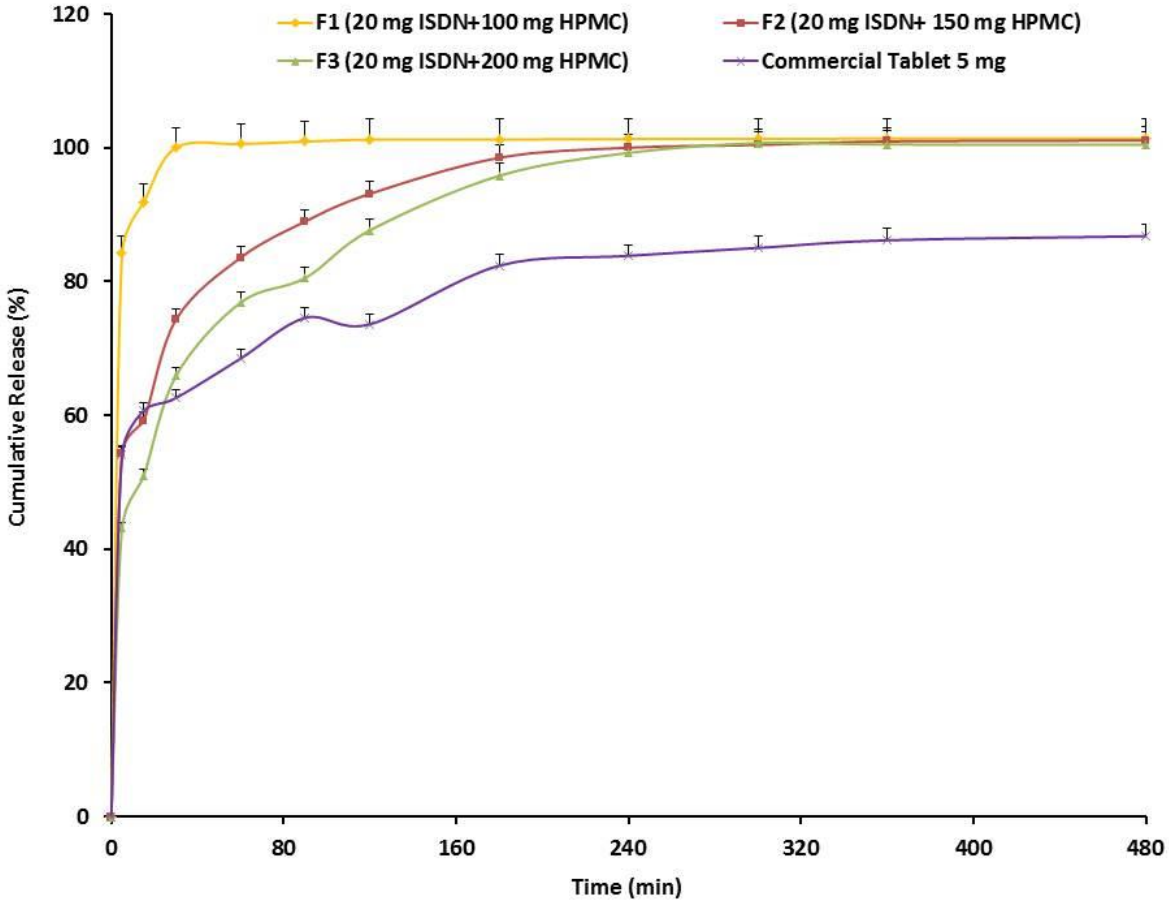

Figure 3. The cumulative release of the isosorbide dinitrate from the films prepared with a different drug to polymer ratios and ISDN tablet commercial.