Development of a Novel Ketorolac Tromethamine Sublingual Film

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Abstract: Ketorolac Tromethamine (KT) is a non-steroidal anti-inflammatory drug (NSAID). All NSAIDs can disturb gastric mucosa and lead to ulcers. Fast dissolving oral films (FDOFs) gained great interest as an alternative to conventional tablets to improve patient compliance. The aim of this study was to enhance sublingual permeability of KT and to formulate KT sublingual FDOFs to provide fast relieve of pain with minimum local gastric side effects. Different concentrations of sodium lauryl sulphate (SLS) and sodium tarucholate (STC) were used to enhance KT permeability. KT sublingual FDOFs were prepared by solvent-casting method using methocel (E5 and E50, 1% and 2% w/v) as film-forming agent, propylene glycol (PG) or polyethylene glycol 400 (PEG 400) as plasticizers and SLS as permeation enhancer. The prepared formulae were evaluated for their *in vitro* dissolution characteristics, *in vitro* disintegration time, and physico-mechanical properties. The optimized formula was subjected to stability study.SLS (1% w/w of KT weight) improved KT permeation parameters with PER of 218.6%. The optimized formula composed mainly of methocel E5, PEG 400 and SLS had the highest drug dissolution rate ($T_{100\%}$= 2min) with the least disintegration time (16sec) and suitable physico-mechanical properties with absence of any signs of instability. These results provide a rational to subject KT sublingual FDOF for further clinical studies.
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Key words: Fast-dissolving oral films; permeability enhancement; solvent-casting method; ketorelac tromethamine.

1. Introduction:

Fast dissolving oral delivery systems (FDODSs) are widely gaining interest in the pharmaceutical industry. These systems either dissolve or disintegrate generally within a minute when placed on the mouse without drinking or chewing (Cilurzo *et al.,* 2010). FDODSs added the advantages of conventional tablets (accurate dose, self administration) to those of liquid dosage forms (easy swallowing, quick bioavailability) (Siddiqu *et al.,* 2011). They are preferred by patients suffering from dysphasia, motion sickness, repeated emesis and mental disorders since they are unable to drink large amounts of water (Lakshmi *et al.,* 2011). Absorption of therapeutic agents from the oral cavity provides a direct entry of such agents into the systemic circulation, thereby avoiding the first-pass hepatic metabolism, gastrointestinal degradation and local gastric side effects of these agents (Desai and Kumar, 2004).

Fast dissolving oral films (FDOFs) are the most advanced form of FDODSs. They are gaining interest as an alternative of fast dissolving tablets to definitely eliminate patients' fear of chocking and overcome patent impediments. FDOF is very thin oral strip which was developed based on the technology of the transdermal patch and are generally constituted of plasticized hydrophilic polymers or blends made thereof that rapidly dissolves on or under the tongue or buccal cavity (Kumar *et al.,*2010; Saini *et al.,*2011).

Ketorolac tromethamine (KT) is a water soluble non-steroidal, anti-inflammatory drug (NSAID), which possess potent analgesic and moderate anti-inflammatory activity. KT administration rate is frequent as it has short plasma half-life 3-6 h. The frequent intake of NSAIDS like KT leads to gastric ulceration, bleeding and other gastric complications. The parenteral formulation is used intra-muscularly (IM) or intravenously (IV) to reduce gastric side effects and for the treatment of moderate to moderately severe pain in postoperative and emergency pain control. Sublingual FDOFs of KT can be used as an alternative to parenteral formulation with comparable analgesia when no need for IV line and to avoid discomfort of IM injection (Moffat *et al.,* 2004; Vemula and Veerareddy, 2011; Bacon *et al.,* 2012).

Although KT is class I drug according to Biopharmaceutical Classification System (BCS) where it is highly soluble and highly permeable; trial was done hoping to increase sublingual permeability of KT than its high level by the use of penetration enhancers through rabbit sublingual mucosa than the drug alone. This hopeful trial was done on the light of (Al-Ghananeem, 2009) who prepared KT sublingual spray and study the sublingual permeability enhancement in presence of permeation enhancers from different groups at different concentrations to assist in the speed of efficiency and bioavailability.

The term "permeation enhancer" or "penetration enhancer" refers to an agent that improves the rate of transport of a pharmacologically active agent across the sublingual mucosal surface. Typically, a penetration enhancer increases the permeability of mucosal tissue to a pharmacologically active agent. The effective amount of permeation means an amount that will provide a desired increase in mucosal membranes permeability to provide, for example, the desired depth of penetration of a selected compound, rate of administration of the compound and amount of compound delivered (Al-Ghananeem, 2009).

The present investigation was undertaken with the objective of enhancing sublingual permeability and formulating sublingual FDOFs of KT to be potentially useful for treatment of acute pain and to enhance the convenience and compliance by the elderly and pediatric patients with decrease in gastric side effects of NSAIDs by avoiding direct contact with the gastric mucosa.

2. Materials and Methods:

Materials:

KT was kindly supplied from Amriya Pharm. Ind. Co., Alex., Egypt. Sodium lauryl sulphate (SLS) and Sodium taurocholate (STC) were purchased from sigma Aldrich (UK). Hypromellose (HPMC, Methocel E5 and E50 premium LV, Sigma-Aldrich, Chemi, GmbH, Germany). Propylene glycol (PG: El-Nasr Pharmaceutical Chemicals Co., Cairo, Egypt). Polyethylene Glycol 400 (PEG 400: Oxford Laboratory, Mumbai, India).Aspartame was provided as a gift from Amoun Pharmaceutical Co., Cairo, Egypt.

Methods:

Selection of Optimum Permeation Enhancer (PE):

In vitro permeation study of KT through rabbit sublingual mucosa was performed according to a method previously described by many researchers (Veuillez *et al.,* 2002; Desai and Kumar, 2004; Yamagar *et al.,* 2010) using Franz diffusion cell (Hanson Research Corporation, HRC, USA) with permeation area 1.77 cm^2, receiver compartment capacity of 7.5 ml and temperature adjusted at 37±0.5 ^oC .

The experiment protocol was approved by the Animal Ethics Committee of the Faculty of Pharmacy, Cairo University, Egypt. Albino male rabbits weighting 2-2.5 kg were humanly scarified and their sublingual tissues were removed. The sublingual mucosa was separated by removing the underlying connective tissue using surgical scissors making sure that the basal membrane was still present. Care was taken to avoid any damaged sections of the mucosa and any glandular openings. The separated sublingual tissues were rinsed with phosphate buffer and stored in ice-cold buffer till experiment setup (Chetty *et al.,* 2001; Attia *et al.,* 2004; Dhiman *et al.,* 2009). The sublingual membrane was clamped between donor chamber (mimics the site of drug delivery) and the receiver chamber (mimics the general circulation). After an equilibrium period of one hour with phosphate buffer (pH 7.4 in the receiver chamber and pH 6.8 in the donor chamber), the buffer in the donor chamber was replaced with 500µl of KT solution (20mg/ml) in phosphate buffer pH 6.8 (Padula *et al.,* 2013). The solution in the receiver compartment was continuously stirred at 400 rpm. At predetermined time intervals, aliquots of three ml volume were withdrawn from the receiver chamber, replaced by the same volume of phosphate buffer and analyzed spectrophotometrically (Shimadzu, model UV 1601, Japan) at λmax 323 for their KT content after filtration and appropriate dilution.

For selection of superior PE for KT through rabbit sublingual mucosa, the experiment was repeated in presence of two permeation enhancers in three different concentrations. The investigated permeation enhancers were SLS in concentrations 0.1, 0.5 and 1% w/w, and STC in concentrations 1, 2 and 3% w/w (permeation enhancer/KT) (Martin *et al.,* 2001).

The cumulative amounts of KT permeated per unit area were calculated as mean values of three measurements and plotted versus time. The resultant curves were used to calculate different permeation parameters as steady state efflux (Jss =slope of the linear portion of the curve) and permeability coefficient (Kp = Jss/ Cv), where Cv is the total donor concentration of drug (Bayrak *et al.,* 2011).

For permeation profiles of KT in presence of PE, permeation enhancement ratios (PERs) were also calculated. Where (PER= Kp of KT with enhancer / Kp of KT without enhancer).KT drug solution without enhancers was assigned to the value of 100 for PER (Rai *et al.,* 2011).Data obtained after calculation of enhancement ratio from different enhancers at different concentrations were subjected to statistical analysis using non-paired, two tailed Student's t-test (Microsoft excel 2007) at p level≤ 0.05 to test the significance between results.

Preparation of KT sublingual FDOFs:

HPMC as film forming polymer was used in two grades (Methocel E5 and Methocel E50; Premium LV), PG or PEG 400 as plasticizers, aspartame as sweetener and SLS as PE. The detailed composition of the prepared films is presented in table I.

The films were prepared by solvent casting method (Morales and McConville, 2011).HPMC was dissolved in distilled water preheated at 80ºC with the aid of magnetic stirrer (Thermolyne Co., USA) at 200 rpm until it reach room temperature. After that,

plasticizer, sweetener, PE and KT were added to the polymeric solution and stirred again using the magnetic stirrer at 200 rpm until all ingredients dissolved to get clear solution followed by 15 minutes on ultrasonicator (Ultrasonic crest sonicator, Trenton. U.S.A) to remove incorporated air bubbles (Jug *et al.,* 2012). A defined volume of the formed solution was poured in cups of 3.7 cm diameter cup and left to dry in oven (Fisher isotemp oven, 200 series, model 230F, USA) at 75 ºC for 30 min followed by 50ºC overnight. The resultant film was cut into small squares of 1cm × 1cm in size, in which 10 mg KT was included.

Thickness Measurements:

The thickness of each film was measured at five different locations (centre and four corners) using micrometer (Mitutoyo co., Kanagawa, Japan). Data were represented as a mean ± SD of five replicate determinations.

Determination of Moisture Uptake:

The prepared films were cut into squares of unit area and their initial weights were recorded. The films (n=3) were then transferred to a dessicator containing saturated NaCl solution (relative humidity 75%) at 25 ± 2°C for one week (Ammar *et al.,*2009). Percent moisture uptake was calculated according to the following equation (Rajasekaran *et al.,* 2010):

% moisture uptake = [(Final weight-Initial weight)/ initial weight] ×100

For each formula, the mean value of percent moisture uptake of three films as well as the standard deviation was calculated.

***In vitro* Disintegration Time (DT):**

Disintegration time (DT) was measured using the modified method previously described by many researchers (Gohel *et al.,* 2004; Rawas-Qalaji *et al.,* 2006; Hirani *et al.,* 2009). The film size required for dose delivery (1×1 cm) was placed on a glass Petri dish containing 10 ml of distilled water. Disintegration time is the time when an oral film starts breaking when brought in contact with water. The test was done in triplicates and the mean values were subjected to statistical analysis using non-paired, two tailed Student's t-test (Microsoft excel 2007) at p level ≤ 0.05 to test the significance between results.

Drug Content Uniformity Determination:

One square centimeter samples representing five different regions (center and four corners) within the film were cut. Each film was placed in 100 ml volumetric flask and dissolved in phosphate buffer pH 6.8. After filtration and suitable dilution, the drug content was determined spectrophotometerically (Shimadzu, model UV 1601, Japan) as before (Lakshmi *et al.,* 2011).

For each prepared formula, a plain (non-medicated) film was prepared. It contained the same amount of all ingredients of the corresponding medicated formula, however it lacked the drug. The prepared non-medicated films were subjected to the same test and the resultant solutions were used as blanks for the corresponding medicated formulae during spectrophotometric determination of the drug content. The drug content was expressed as mean ± SD.

Surface pH Determination:

Previously reported method (Parejiya *et al.,* 2013) was used to determine surface pH of the film. The film to be tested was cut into strip of 2×2 cm and was placed in a Petri dish then it was moistened with 1 ml of distilled water and kept for 1 minute. The surface pH was measured using a pH meter (G 820 Schott- Gerate, W. Germany) by keeping the electrode in contact with the surface of the film and allowing it to equilibrate for one minute before recording the pH value .Test was performed in triplicate (n = 3).

***In-Vitro* Dissolution Study:**

The *in-vitro* drug dissolution study was carried out in 600 ml of phosphate buffer pH 6.8 at 37.0±0.5°C, using the dissolution apparatus I (Basket) (Hanson Research Test, USA) at a stirring speed of 100 rpm (Yehia *et al.,* 2008; Mahendar and Ramakrisha, 2012).

The film size required for dose delivery (1×1 cm) was used. Three ml samples were withdrawn every minute for a period of ten minutes and replaced with an equal volume of dissolution medium preheated at 37.0±0.5°C. The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved KT was determined spectrophotometerically as before (Shimadzu, model UV 1601, Japan). Plain films were subjected to dissolution test as mentioned before and the collected samples were used as blanks for the corresponding medicated formulae.

The test was done in triplicates and the mean values were subjected to statistical analysis using non-paired, two tailed Student's t-test (Microsoft excel 2007) at p level ≤ 0.05 to test the significance between results.

Mechanical Properties Determination:

The tensile strength (TS) of the prepared films as well as their percent elongation (%E) and modulus of elasticity (EM) at rupture point were determined using a tensile strength tester (H1Ks, USA). Rectangular, 1 x 3 cm- samples of the tested films were cut and hanged without any stretch between the 2 clamps of the apparatus. The load applied to the sample was automatically increased at specified rate until its rupture. The rupture force (N), elongation (mm), and % elongation (% E) were recorded. Measurements were run in triplicates for each film formula but results of those samples which ruptured at –rather than between- the clamps, were not considered.

TS of film samples were calculated according to the following equation (Schroeder *et al.,* 2007):
TS =Maximum rupture force (N) /Cross sectional area of the film

EM was calculated from the following equation (Alanazi *et al.,* 2007):
EM=TS/ [film length after elongation (Ls)/ original film length (Lo)]

Folding endurance of the film was measured by repeatedly folding a small strip of the film (2×2 cm) at the same place till it broke. The number of times, the film could be folded at the same place without breaking, gave the value of folding endurance (Mamatha *et al.,* 2010). The experiment was repeated three times for each formula and the results were expressed as mean values ± SD.

The % E and EM are the most important variables for assessing ductility/flexibility of film formulation. Mean values of % E and EM were subjected to statistical analysis using non-paired, two tailed Student's t-test (Microsoft excel 2007) at P level ≤ 0.05 to test the significance between results. Where, TS is the maximum force applied (N/cm^2) to the FDOF until it tears. Elongation at break is defined as the elongation of the FDOF when force is applied and EM defines the stiffness of the FDOF (Peh and Wong, 1999; Dixit and Puthli, 2009; Morales and McConville, 2011). Folding endurance can be described as an inconvenient stress-test (Preis *et al.,* 2013).

Stability Study:

Sublingual FDOFs of formula F3 were stored in a butter paper followed by aluminum package at laboratory ambient conditions and under accelerated stability conditions by storage in a chamber controlled at 40ºC and 75% relative humidity using saturated NaCl solution (Nishimura *et al.,* 2009).

The films were visually inspected for any physical changes, the results of films disintegration time, drug content and mechanical properties were compared before and after storage. The dissolution testing was also performed for the stored films in the same manner as done for freshly prepared ones; where the percent drug dissolved after 2 minutes were compared.

For films stored at ambient conditions, the examination done after 3-, 6- and 12-month storage. While those stored under accelerated conditions were examined after 1-, 2- and 3-month storage .The mean results (n=3) before and after storage were compared statistically using paired t-test (Microsoft excel 2007) at *p* level ≤ 0.05 to test the significance between results.

3. Results and Discussion:

Selection of Optimum Permeation Enhancer (PE):

Human buccal mucosa rarely available and if obtained by donation, the size of the tissue available from one donor is not sufficient to perform adequate number of *in-vitro* experiments. Therefore, recent research efforts relied on the use of isolated animal buccal tissues in buccal absorption studies with respect to differences in physiology and anatomy of buccal tissue between species. The rabbit is the only laboratory animal with non-keratinized surface layer of buccal tissue similar to human and suitable for permeation study (Obradovic and Hidalgo , 2008).

SLS is an anionic surfactant which enhances sublingual permeability by pertub the entire membrane composition affecting both protein and lipid structures. Expansion of intercellular spaces and insertion of SLS molecules into the lipid structure has also been observed (Dodla and Velmurugan, 2013). STC is trihydroxy bile salt. The sublingual drug permeability enhancement in the presence of bile salts is believed to happen by a complex process. Some of the proposed mechanisms of the bile salts include solubilization and micellar entrapment of intracellular lipids, denaturation and extraction of proteins, enzyme inactivation and tissue swelling (Mahalingam *et al.,* 2007).

The *in-vitro* permeation profiles of KT in presence and absence of different enhancers are illustrated in (Fig. I a and b). Table II represents the permeation parameters.

Concerning SLS, The increase in SLS concentration from 0.1 % to 0.5 % w/w resulted in non-significant increase in the mean PER, while increase concentration from 0.5 to 1% w/w resulted in highly significant increase in PER .On the other hand, there was non-significant difference in the mean PER between all concentrations of STC. Comparing the two investigated enhancer, the mean PER calculated for 1% SLS significantly exceeded that of 1% STC.

KT is classified to class I according to BCS (highly soluble and highly permeable). The trial done hoping to increase sublingual permeability of KT was actually succeeded. 1% SLS has significantly the highest PER of KT through rabbit sublingual mucosa over others. Also 1% SLS significantly increased KT sublingual permeation compared to KT solution alone.

These results highly agreed with (Whitehead *et al.,*2008) who studied the enhancement potential and toxicity potential of different PEs on the oral mucosal membrane and concluded that ionic surfactant (specially SLS) are more effective and more safe than bile salts. They mentioned that SLS is one of the top ten chemical PEs in terms of the highest overall potential value which is the difference between enhancement potential and toxicity potential that have been previously analyzed for oral delivery. Depending on the results obtained by (Narkar *et al.,*2008) who

found that the local effect of SLS on the morphology and swelling of the oral mucosa is reversible and temporary, 1% SLS was chosen to be incorporated in the formulation of KT sublingual films to add more enhancement to KT sublingual permeability.

Preparation of KT sublingual FDOFs:

Solvent casting was the method of choice for preparation of sublingual FDOFs according to the results of (Cilurzo *et al.,* 2008) who compared maltodextrins films prepared with hot-melt extrusion method to those prepared with solvent casting method. Where films prepared with solvent casting method exhibited the highest patients' compliance and best performances in terms of *in vitro* and *in vivo* disintegration time over those prepared with hot-melt extrusion.

Plasticized HPMC E50 or E5 seems to have appropriate qualities to prepare FDOFs. These polymers have an added advantage that they are non-ionic, dissolve in water with no sharp solubility limit and act as surfactants in aqueous solutions. The prepared solutions using these polymers were easily pourable and its viscosity did not appear to change during pouring of solution, and the solution spread over the entire base of the used cup with uniform distribution and can be removed easily after drying (Garima *et al.,* 2013).

Different homogenous KT sublingual FDOFs were prepared; the films were faint yellow, thin and soft, and with no spot found on the films. The prepared films were evaluated in terms of physico-mechanical properties and the results are given in Tables III and IV.

Physico-mechamical Characterization of KT Sublingual FDOFs:

Thickness:

The average thickness of the films ranged from 0.06–0.18 mm. It is essential to ascertain uniformity in the thickness of film as this is directly related to accuracy of dose distribution in the film. The increased thickness of films is attributed to the increase in the amount of HPMC.

Moisture Uptake:

Presence of moisture in films protects them from becoming dry and brittle due to plasticizing effect of water; all FDOFs lose water in dry conditions and pick moisture over 60% RH (Arora and Mukherjee, 2002). Percentage moisture uptake was found to be moderate for all films and ranges from 3.91- 9.10 % w/w.

From the results it is clear that moisture absorbing capacities of HPMC films plasticized with PEG 400 were higher than that of PG plasticized films for the same polymer type and concentration. PEG 400 has a number of hydroxyl groups, so that they are capable of forming more hydrogen bonds with diffusing water molecules, thereby increasing the moisture permeability of HPMC films (Johnson *et al.,*1991).Bourtoom (2008) explained the high moisture uptake observed with PEG 400 plasticized biodegradable blend films from rice starch-chitosan to its flexible structure with low TS values observed. These results were similar to (Bharkatiya *et al.,* 2010) who concluded that moisture uptake of HPMC K4M: Polyvinyl alcohol patches plasticized with PEG 400 was higher than that of PG plasticized patches.

For films prepared using the same HPMC grade E5 or E50 it was observed that; as the concentration of hypromellose increased the moisture uptake increased. HPMC is propylene glycol ether of methylcellulose. Generally, all cellulose ethers are hygroscopic. HPMC is known to be moderately hygroscopic based on the classification by (Callahan *et al.,*1982); therefore it will absorb moisture and logically the moisture uptake increases as the concentration of HPMC increases (Akbari *et al.,* 2011).The results also demonstrated the effect of viscosity of used methocel on the moisture uptake value of the casted films; the films prepared with the lower viscosity HPMC E5 showed lower moisture uptake values than the films casted with higher viscosity HPMC E50. This may related to the higher molecular weight (MWT) of methocel E50 compared to E5; where HPMC viscosity is directly proportional to its MWT (Tahara *et al.,* 1995). These results come in accordance with (Akbari *et al.,* 2011) who observed the increase in the moisture uptake of HPMC polymer with the increase in MWT.

***In –Vitro* Disintegration Time (DT):**

The volume of saliva in the human buccal cavity is less than 6 ml and so the conventional disintegration tester that uses 500 ml of solution will not be representative of actual disintegration rate in vivo. Therefore, a small Petri dish filled with 10 ml of distilled water was used in this method to evaluate the *in-vitro* disintegration rate, which is comparable to that of the sublingual area with a diameter of approximately 3–4 cm. Furthermore, the small volume of water used as well as the relatively low agitation employed during the test closely resembles the volume of saliva and the relatively static environment in the buccal cavity, respectively (ElMeshad and El Hagrasy, 2011).

In vitro DT was within 60 seconds for all prepared sublingual FDOFs films. From the results it was clear that; the DT determined for methocel films (at the same grade and concentration) plasticized with PEG 400 had been lower than that for HPMC FDOFs plasticized with PG. This may be due to , PEG 400 weakened HPMC films resistance to solubility (Saringat *et al.,*2005);where PEG 400 could leach out from the films when immersed in distilled water, the loss of plasticizer from the films made it more

penetrable to the water molecule; this caused rapid film dissolution and lower DT (Bharkatiya *et al.,* 2010). These results agree strongly with (Choudhary *et al.,* 2011) who concluded that DT for plasticized methocel films was higher for PG films than PEG 400 films.

In the presence of the same plasticizer; Methocel E5 FDOFs had shorter DT at the same concentration as E50, this may be related to its lower viscosity (Garima *et al.,* 2013). *In vitro* DT was found to be increased with the increase in the amount of polymer used. This coincides with (Saber , 2013) who made amlodipine fast dissolving films and his results showed that as the concentration of sodium carboxymethylcellulose increases the DT increases.

Generally, FDODSs dissolve or disintegrate within a minute; while the actual DT the patient can experience ranges from 5-30 seconds (Hirani *et al.,* 2009).Formulae F1 ,F3 and F7 had DT of 21.6, 16 and 30 seconds, respectively. The DT for F3 was significantly shorter than of F1 and F7. However, the difference in DT between F1 and F7 was non-significant.

Drug Content:

Assay of drug content at five different places in each film showed that the drug was uniformly distributed throughout the films; and were also within the required compendial specifications, i.e., within 98.5–101.8% (B.P., 2014). In addition, all films were found to contain an almost uniform quantity of drug indicating reproducibility of technique.

Surface pH:

The surface pH of the prepared KT sublingual FDOFs was determined to evaluate the possible irritation effects on the oral mucosa. Attempts were made to keep the surface pH as close to salivary pH as possible, by the proper selection of polymer for developing FDOFs. The surface pH was found to be in the range of 6.38-6.89 .The almost neutral pH reflected; that FDOFs will be non-irritant to oral mucosa (Auda *et al.,* 2014).

***In-vitro* Dissolution:**

The *in-vitro* dissolution profiles of KT films are given in Fig. (II).It was noticed that the films got hydrated rapidly and began to dissolute the drug within minutes. All the films dissolved completely within 10 minutes except F6; where only 92.86% was dissolved in 10 min. This may be due to the water solubility of the drug and the polymer (El-Setouhy and Abd El-Malak, 2010).Also, the release profiles had shown that using HPMC reveals a steady dissolution (Shimoda *et al.,* 2009).

Although it was stated by (Prior *et al.*,2010) that in case of more than 85% of the active substance dissolved in less than 15 minutes, the dissolution profiles of different formulations are considered similar without further mathematical calculations. We performed statistical analysis of data of percent dissolved after 2 minutes for reason of comparison. For methocel E5 films, decreasing E5 concentration from 2 % (F2) to 1% (F1) in presence of PG or from 2% (F4) to 1% (F3) in presence of PEG 400 resulted in significant increase in percent drug release. On the other hand, percent drug released of formula F3 (PEG 400) significantly increased than F1 (PG). Concerning E50 films, decreasing concentration of E50 plasticized with PG from 2% (F6) to 1% (F5) and from 2% (F8) to 1% (F7) in presence of PEG 400 significantly increased the cumulative percent of drug released. Formula F7 (PEG 400) has significantly higher cumulative percent released than F5 (PG).

The significant decrease in the mean cumulative amount released by increasing polymer concentration could be related to the increase in thickness of the film with the increase of HPMC concentration. Thus, the time required for dissolution medium to penetrate into the polymer chains located through the depth of the film increases and this leads to an increase in the time required for the dissolution of drug molecules embedded in the polymer matrices (Scott *et al.,* 2013).

Comparing the two investigated polymers, the mean cumulative percent of drug released from formula F3 (1% E5) significantly exceeded that of F7 (1% E50). This was similar to that observed by (Prabhu *et al.,* 2011) where the lower the viscosity of HPMC the faster the drug release determined.

PEG 400 weakened the resistance of HPMC films to solubility; this could explain the higher significant release rate of methocel films plasticized with PEG 400 over those plasticized with PG at the same HPMC grade and concentration (Saringat *et al.,* 2005).

For all films the enhancement in dissolution rate was followed the same pattern as enhancing the DT as previous reports provided that there where a direct correlation between these two parameters (enhance dissolution rate and fast DT) (Perissutti *et al.,* 2002; Leonardi *et al.,* 2007).

Mechanical Properties:

The presence of plasticizer generally lowers the TS of HPMC film and this could be attributed to increased crystallinity and segmental chain mobility of HPMC (Saringat *et al.,* 2005).The mechanical behavior of prepared FDOFs is shown in table IV.

The % E and EM are the most important variables for assessing ductility/flexibility of film formulation. For methocel E5 films, Increasing E5 concentration from 1 %(F1) to 2% (F2) in presence of PG resulted in significant increase in % E and significant decrease in EM, while % E was non-significantly increased and EM was non-significantly decreased when the concentration of E5 increased

from 1% (F3) to 2% (F4) in presence of PEG 400. On the other hand, % E of formula F3 significantly increased than F2 and EM was significantly decreased. Concerning E50 films, Increasing concentration of E50 plasticized with PG from 1% (F5) to 2% (F6) significantly increased % E and significantly decreased EM, while % E was not significantly increased and EM was non-significantly decreased when we increased concentration of E50 plasticized with PEG 400 from 1% (F7) to 2% (F8).Formula F7 have significantly higher % E than F6 and non-significantly lower EM. Comparing the two investigated polymers, the mean % E of formula F6 doesn't significantly exceeded than that of F3 while mean EM of F3 significantly decreased than that of F7.

Visually, PG plasticized HPMC films exhibited good plasticizing effect in comparison to PEG 400 as the total number of molecules of the low molecular weight PG in the film solution is greater than those of the higher molecular weight PEG 400 which allows it to be more readily inserted between the polymer chains, and consequently exert more plasticizing effect (Bourtoom, 2008). On the other hand PG plasticized methocel films were patchy in appearance and consequently showed poor mechanical properties, while films plasticized with PEG 400 showed good mechanical properties. These observations are in accordance with (Choudhary *et al.,* 2011). The predominant effect of PEG 400 over PG on the mechanical properties was also determined by (Bharkatiya *et al.,* 2010) who observed that the % E of Eudragit RL100: Eudragit RS100 patches containing PG as plasticizer were higher than PEG 400 plasticized patches. Bourtoom(2008) found that PEG 400 plasticized biodegradable blend films from rice starch-chitosan had a flexible structure.

The mechanical properties results indicated that on increasing the concentration of HPMC E5 or E50 from 1% to 2%; % E increased and EM decreased. This is quietly in accordance with the results of (Pandey *et al.,* 2013) who prepare FDOFs using different hypomellose concentrations. HPMC films plasticized with PEG 400 were excluded from this observation which may be due to the pronounced effect of plasticizer on % E and EM at the least polymer concentration.

Folding endurance gives an indication of brittleness of the film to ensure that the film can be handled and administered (Bhikshapathi *et al.,* 2014). There is no reference, which minimum folding time needs to be achieved to assume damage-free handling (Preis *et al.,* 2013). It was ranged from 262.66 to 300.39 times. Results shown that as the concentration of polymer increased, folding endurance of sublingual FDOFs increased. This was similar to (Kiran Kumar *et al.,* 2011) who observed that higher concentration of HPMC E5 LV scores higher folding endurance.

Orodispersible film should possess moderate TS, high % E, low EM, low DT, and high percent of drug release (El-Setouhy and Abd El-Malak, 2010). The formula F3 composed of methocel E5 (1%), PEG 400 (20%) and 1% SLS; previously representing the lowest significant DT with the highest significant drug dissolution rate; appears to had moderate TS (1.98 N/cm^2), significantly the lowest EM (1.99), and highest significant % E (80.4%) with moderate moisture uptake.

Based on the above results the sublingual FDOF of formula F3 was chosen to be subjected to both compatibility and stability study mentioned before. These results were in a good agreement with (Dinge and Nagarsenker, 2008) who indicated that amongst various grades of HPMC, Methocel E5 Premium LV gave films with the most desired properties. Also, this comes in accordance with (Heinämäki *et al.,* 1994) who concluded that concerning the moisture permeability and mechanical properties, HPMC film are most effectively plasticized with PEG 400 at a concentration in the range from 10-20%.

Stability:

One of the major disadvantages of FDOFs is their instability due to its hygroscopic nature. Special packaging is needed to protect the product, which increases the production cost. Development of a stable formulation would help to reduce the packaging cost (Liew *et al.,* 2012). Generally, when the drug is freely soluble in the polymer then the film should have excellent stability (Gaisford *et al.,* 2009).

Visual inspection of the stored films revealed that they preserve their color and shape on the storage at accelerated storage conditions or under long term stability conditions. The mean values of disintegration time, drug content and mechanical properties [TS, % E, EM and folding endurance] were not statistically affected by storage at accelerated stability conditions. In addition, the mean values of % drug dissolved after 2 minutes for stored films were statistically non-significantly different from freshly prepared ones indicating the stability of prepared sublingual FDOF (F3) at these conditions. These results are in a good agreement with (Daud *et al.,* 2011) who reported the high stability of HPMC FDOFs under accelerated stability conditions

In addition, when the prepared films were stored at room temperature for one year, the mean values of disintegration time, drug content and mechanical properties as well as % drug dissolved after 2 minutes were non-significantly affected.

Table I: Composition of Different Sublingual FDOFs Containing KT

Ingredients % [a]	Formulae							
	F1	F2	F3	F4	F5	F6	F7	F8
Methocel E5	1	2	1	2				
Methocel E50					1	2	1	2
Propylene glycol [b]	20	20			20	20		
Polyethylene glycol 400 [c]			20	20			20	20
Aspartame	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Sodium lauryl sulphate[d]	1	1	1	1	1	1	1	1

The concentration of KT in formulae was 2.15 % w/v. [a]The ingredients are represented as % w/v.
[b]Propylene glycol weight was calculated as %w/w of the dry methocel weight.
[c]Polyethylene Glycol 400 was weighted as %w/w of the dry methocel weight.
[d]Sodium lauryl sulphate weight was calculated as % w/w of the dry drug weight.

Table II: Permeation Parameters of KT With and Without Permeation Enhancers through Rabbit Sublingual Mucosa

Permeation enhancer		Permeation parameters		
Type	Conc. (%w/w)[a]	Jss (μg/cm^2 .min)	Kp(cm/min)	PER
No enhancer		36.5±0.0003	0.006461±0.0001	100±0.001
SLS	0.1%	47.3±0.007	0.008365±0.0001	129.5±0.97
	0.5%	57.2±0.005	0.009651±0.00004	149.4±0.98
	1%	79.8±0.01	0.014123±0.00009	218.6±0.63
STC	1%	38.6±0.008	0.006807±0.0002	105.4±1.42
	2%	46.9±0.07	0.008301±0.00007	128.5±0.21
	3%	52.9±0.09	0.00905±0.00001	140.1±0.79

SLS Sodium lauryl sulphate, *STC* Sodium taurocholate ,*Jss* Steady state efflux, *Kp* Permeability coefficient, *PER* Permeation enhancement ratio. [a]SLS and STC were calculated as % w/w of the dry drug weight.

Table III: Physicomechanical Properties of Different KT sublingual FDOFs

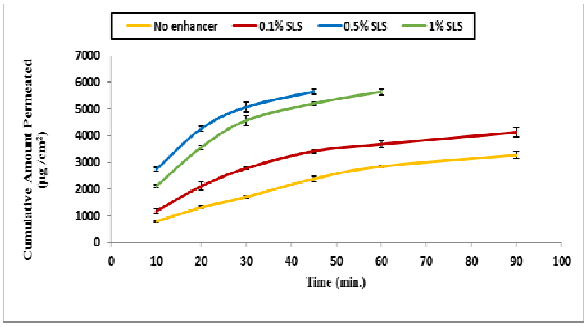
Formula	Thickness (mm) [a]	% Moisture Uptake [b]	DT (Sec)[b]	% Drug content [a]	Surface pH [b]
F 1	0.06±0.0039	3.91±0.06	21.6±2.08	99.5±1.02	6.56±0.12
F 2	0.12±0.011	4.42±0.12	40±1.52	99.98±0.98	6.8±0.12
F 3	0.07±0.0015	4.28±0.06	16±1	100.12±0.20	6.38±0.134
F 4	0.18±0.0092	6.09±0.19	32±4.33	101.06±0.32	6.76±0.153
F 5	0.06±0.0031	5.51±0.05	44±3.5	100.8±0.19	6.47±0.111
F 6	0.15±0.057	7.61±0.79	60±5.13	100.04±0.08	6.89±0.128
F 7	0.09±0.012	6.08±0.14	30±2.51	98.98±1.53	6.63±0.154
F 8	0.18±0.0025	9.10±0.11	49±1.52	100.43±0.24	6.7±0.178

DT Disintegration time [a] Values are expressed as mean ± SD; n=5 [b] Values are expressed as mean ± SD; n=3

Table IV: Phsicomechanical Properties of Different KT sublingual FDOFs

Formula	TS (N/cm^2)	% E (cm %)	EM	Folding Endurance
F1	1.42±0.03	62.50±3.2	3.05±0.15	257.45±0.99
F2	2.07±0.25	71.09±5.32	2.11±0.27	270.41±3.5
F3	1.98±0.13	80.4±2.39	1.85±0.34	272.3±1.15
F4	2.65±0.48	85.97±2.44	1.84±0.14	287.7±155
F5	1.52±0.33	77.54±3.25	2.73±0.58	262.66±2.51
F6	2.11±0.28	82.46±3.11	2.09±0.09	290.06±2.01
F7	2.67±0.09	85.12±5.09	2.27±0.46	285.24±0.57
F8	2.98±0.56	90.51±1.76	2.09±0.04	300.39±1

TS tensile strength, *EM* modulus of elasticity, *%E* % elongation Values are expressed as mean ± SD; n=3



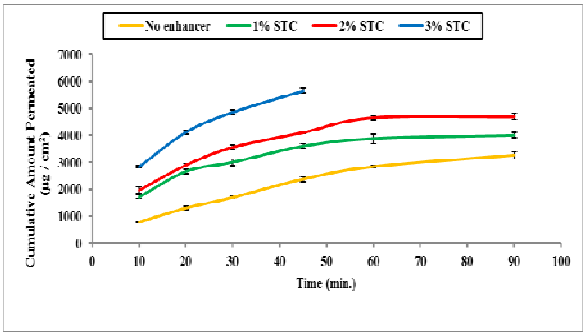


Fig. I (a and b): Permeation Profiles of KT through Rabbit Sublingual Mucosa with and Without Permeation Enhancers.

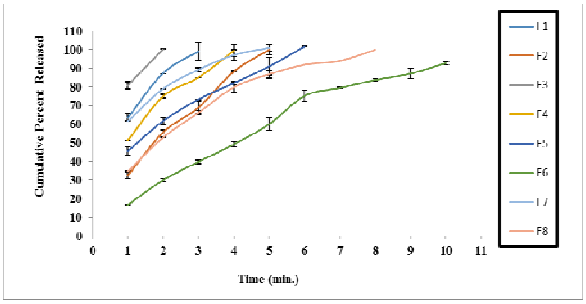


Fig II: *In-vitro* Dissolution Profiles of KT from Different Sublingual FDOFs

4. Conclusion:

The FDOFs of KT prepared using HPMC by the solvent-casting method showed satisfactory drug dissolution and acceptable physico-mechanical characteristics.

Amongst eight formulae, the film composed of methocel E5 (1%), PEG 400 (20%) and 1% SLS (F3); representing the lowest significant DT with the highest significant drug dissolution rate and satisfactory physic-mechanical properties. These results provide a rational to subject KT sublingual FDOF (F3) for further clinical studies compared to commercially available KT tablets.

References:

1. Akbari J., Enayatifard R., Saeedi M., Saghafi M., Influence of hydroxypropyl methylcellulose molecularweight grade on water uptake, erosion and drug release properties of diclofenac sodium matrixtablets, Trop J Pharm Res, 10:535-41, (2011).
2. Alanazi F.K., Abdel Rahman A.A., Mahrous G.M., Alsarra I.A., Formulation and physicochemical characterization of buccoadhesive films containing Ketorolac, J Drug Del Sci, 17:183-92, (2007).
3. Al-Ghananeem A.M., ketorolac sublingual spray for the treatment of pain, US Patent 2009/0246273 A1, (2009).
4. Ammar H.O., Ghorab M., El-Nahhas S.A., Kamel R., Polymeric matrix system for prolonged delivery of tramadol hydrochloride, part I: Physicochemical evaluation, AAPS PharmSciTech, 10:7-19, (2009).
5. Arora P., Mukherjee B., Design, development, physicochemical, and *in-vitro* and *in-vivo* evaluation of transdermal patches containing diclofenac diethylammonium salt, J Pharm Sci, 91:2076–89, (2002).
6. Attia M.A., El-Gibaly I., Shaltout S.E., Fetih G.N., Transbuccal permeation, anti-inflammatory activity and clinical efficacy of piroxicam formulated in different gels, Int J Pharm., 276:11-28, (2004).
7. Auda S.H., El-badry M., Ibrahim M.A., Design, formulation and characterization of fast dissolving films containing dextromethorphan, Digest J Nanomaterials Biostructures, 9:133-41, (2014).
8. Bacon R., Newman S., Rankin L., Pitcairn G., Whiting R., Pulmonary and nasal deposition of ketorolac tromethamine solution (SPRIX) following intranasal administration, Int J Pharm., 431:39– 44, (2012).
9. Bayrak Z., Tas C., Tasdemir U., Erol H., Ozkan C.K., Savaser A., Ozkan Y., Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: *In vitro* and *in vivo* evaluation, Eur J Pharm Biopharm., 78:499-505, (2011).
10. Bharkatiya M., Nema R.K., Bhatnagar M., Designing and characterization of drug free patches for transdermal application, Int J Pharma Sci Drug Res, 2: 35-9, (2010).
11. Bhikshapathi D.V.R.N., Madhuri V.D., Rajesham V.V., Suthakaran R.,Preparation and evaluation of fast dissolving oral film containing NaratriptanHCl, Am J PharmTech Res, 4:799-812, (2014).
12. Bourtoom T., Plasticizer effect on the properties of biodegradable blend film from rice starch-chitosan, Songklanakarin J Sci Technol, 30:149-65, (2008).
13. British Pharmacopoeia (B.P.), The Stationary Office, London, UK, Volume II, pp II-(54-55), (2014).
14. Callahan J.C., Cleary G.W., Elefant M., Kaplan G., Kensler T., Nash R.A., Equilibrium moisture content of pharmaceutical excipients., Drug Dev Ind Pharm, 8:355–69, (1982).
15. Chetty D.J., Chen L.L., Chien Y.W., Characterization of captopril sublingual permeation: determination of preferred routes and mechanisms, J Pharm Sci, 90:1868-77, (2001).
16. Choudhary D.R., Patel V.A., Chhalotiya U.K., Patel H.V., Kundawala A.J., Formulation and evaluation of fast dissolving film of levocetirizine dihydrochloride using different grades of methocel, J Pharmacy Res, 4:2919-24,(2011).

17. Cilurzo F., Cupone I.E., Minghetti P., Buratti S., Selmin F., Gennari C.G., Montanari L., Nicotine fast dissolving films made of maltodextrins: a feasibility study, AAPS PharmSciTech, 11:1511-7, (2010).
18. Cilurzo F., Cupone I.E., Minghetti P., Selmin F., Montanari L., Fast dissolving films made of maltodextrins, Eur J Pharm Biopharm., 70: 895–900,(2008).
19. Daud A.S., Sapkal N.P., Bonde M.N., Development of Zingiberofficinale in oral dissolving films: Effect of polymers on *in vitro*, *in vivo* parameters and clinical efficacy, Asian J Pharm, 5:183-9,(2011).
20. Desai K.G.H, Kumar T.M.P, Preparation and evaluation of a novel buccal adhesive system, AAPS PharmSciTech, 5:1-9, (2004).
21. Dhiman M.K., Dhiman A., Sawant K.K., Transbuccal delivery of 5-fluorouracil: permeation enhancement and pharmacokinetic study, AAPS PharmSciTech. , 10:258-65, (2009).
22. Dinge A., Nagarsenker M., Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity, AAPS PharmSciTech, 9:349-56, (2008).
23. Dixit R.P., Puthli S.P., Oral strip technology: overview and future potential. ,J Control Rel, 139: 94–107, (2009).
24. Dodla S., Velmurugan S., Buccal penetration enhancers-an overview, Asian J Pharm Clin Res., 6 :39-47, (2013).
25. El Meshad A.N., El Hagrasy A.S., Characterization and optimization of orodispersible mosapride film formulations, AAPS PharmSciTech., 12:1384-92, (2011).
26. El-Setouhy D.A., Abd El-Malak N.S., Formulation of a novel tianeptine sodium orodispersible film, AAPS PharmSciTech, 11:1018-25, (2010).
27. Gaisford S., Verma A., Saunders M., Royall P.G., Monitoring crystallisation of drugs from fast-dissolving oral films with isothermal calorimetry, Int J Pharm, 380: 105–111, (2009).
28. Garima B., Vipin G., Siddiqui N., Investigation of polymers alone and in combination for the development of oral thin film , Int J Inv Pharm Sci,1:231-5, (2013).
29. Gohel M., Patel M., Amin A., Agrawal R., Dave R., Bariya N., Formulation, design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique, AAPS PharmSciTech, 5:1-6, (2004).
30. Heinämäki J.T., Lehtola V-M., Nikupaavo P., Yliruusi J.K., The mechanical and moisture permeability properties of aqueous-based hydroxypropyl methylcellulose coating systems plasticized with polyethylene glycol, Int J Pharm, 112:191-6, (1994).
31. Hirani J.J., Rathod D.A., Vadalia K.R., Orally disintegrating tablets: a review, Trop J Pharma Res, 8: 161-72, (2009).
32. Johnson K., Hathaway R., Leung P., Franz R., Effect of triacetin and polyethylene glycol 400 on some physical properties of hydroxypropyl methylcellulose free films, Int J Pharm, 73:197-208,(1991).
33. Jug M., Maestrelli F., Mura P., Native and polymeric b-cyclodextrins in performance improvement of chitosan films aimed for buccal delivery of poorly soluble drugs, J Incl Phenom Macrocycl Chem, 74:87–97, (2012).
34. Kiran Kumar S., Senthil Kumar S., Sundaramoorthy K., Shanmugam S., Vetrichelvan T., Formulation and *In-vitro* evaluation of rizatriptan benzoate rapimelt tablets and oral thin films – A novel approach, Res J Phar, Biolo Chem Sci(RJPBCS), 2:106-20,(2011) .
35. Kumar S.V., Gavaskar B., Sharan G., Rao Y.M., Overview on fast dissolving films, Int J Pharmacy Pharm Sci, 2:29-33, (2010).
36. Lakshmi P.K., Sreekanth J., Sridharan A., Formulation development of fast releasing oral thin films of levocetrizine dihydrochloride with Eudragit® Epo and optimization through Taguchi orthogonal experimental design, Asian J Pharm, 5:84-92,(2011).
37. Leonardi D., Barrera M.G., Lamas M.C., Salomón C.J., Development of prednisone: polyethylene glycol 6000 fast-release tablets from solid dispersions: solid-state characterization, dissolution behavior, and formulation parameters, AAPS PharmSciTech , 8:E1-8, (2007).
38. Liew K.B., Tan Y.T., Peh K.K., Characterization of oral disintegrating film containing donepezil for Alzheimer disease, AAPS PharmSciTech. 13:134-42, (2012).
39. Mahalingam R., Ravivarapu H., Redkar S., Li X., Jasti B.R., Transbuccal delivery of 5-Aza-2´-Deoxycytidine: effects of drug concentration, buffer solution, and bile salts on permeation, AAPS Pharm Sci Tech, 8:E1-6, (2007).
40. Mahendar R., Ramakrisha K., Formulation and evaluation of fast dissolving films of amlodipine by solvent casting method, PHARMANEST, 3:294-300, (2012).
41. Mamatha T., Venkateswara R.J., Mukkanti K., Ramesh G., Development of matrix type transdermal patches of lercanidipine hydrochloride: physicochemical and in-vitro characterization, DARU, 18: 9-16, (2010).
42. Martin A., Swarbrick J., Cammmarata A., Physical Pharmacy, 3rd Edition, New Delhi: Lippincott Williams &Wilkins: p 303, (2001).
43. Moffat A.C., Osselton M.D., Widdop B., Clarke's analysis of drugs and poisons, Vol. 2:1157-8, 3rd Edition, Pharmaceutical Press: London (2004).
44. Morales J.O., McConville J.T., Manufacture and characterization of mucoadhesive buccal films, Eur J Pharm Biopharm, 77: 187–99, (2011).
45. Narkar Y., Burnette R., Bleher R., Albrecht R., Kandela A., Robinson J.R., Evaluation of mucosal damage and recovery in the gastrointestinal tract of rats by a penetration enhancer, Pharma Res, 25: 25-38, (2008).
46. Nishimura M., Matsuura K., Tsukioka T., Yamashita H., Inagaki N., Sugiyama T., Yoshinori Itoh Y., *In vitro* and *in vivo* characteristics of prochlorperazine oral disintegrating film, Int J Pharm,. 368:98–102, (2009).
47. Obradovic T., Hidalgo I.J., *In vitro* models for investigations of buccal drug permeation and

metabolism, drug absorption studies, Biotechnology: Pharma Aspects, VII: 167-81, (2008).
48. Padula C., Pozzetti L., Traversone V., Nicoli S., Santi P., In vitro evaluation of mucoadhesive films for gingival administration of lidocaine, AAPS Pharm Sci Tech, 14:1279-83, (2013).
49. Pandey G.S., Kumar R., Sharma R., Singh Y., Teotia U.V.S, Development and optimization of oral fast dissolving film of salbutamol sulphate by design of experiment, Am J PharmTech Res, 3:1-17, (2013).
50. Parejiya P.B., Patel R.C., Mehta D.M., Shelat P.K., Barot B.S., Quick dissolving films of nebivolol hydrochloride: formulation and optimization by a simplex lattice design, J Pharm Investigation, 43:343–51,(2013).
51. Peh K.K., Wong C.F., Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties, J Pharm Pharmaceut Sci, 2: 53–61, (1999).
52. Perissutti B., Newton J.M., Podczeck F., Rubessa F., Preparation of extruded carbamazepine and PEG 4000 as a potential rapid release dosage form, Eur J Pharm Biopharm,53:125-32, (2002).
53. Prabhu P., Malli R., Koland M., Vijaynarayana K., D'Souza U., Harish N., Shastry C., Charyulu R., Formulation and evaluation of fast dissolving films of levocitirizine dihydrochloride, Int J Pharm Investig, 1: 99-104 , (2011).
54. Preis M., Woertz C., Kleinebudde P., Breitkreutz J., Oromucosal film preparations: classification and characterization methods, Expert Opin Drug Deliv, 10:1-15, (2013).
55. Prior A., Frutos P., Correa C.P., Comparison of dissolution profiles: current guidelines, Doncencia, 507-509, (2010).
56. Rai V., Tan H.S., Michniak-Kohn B., Effect of surfactants and pH on naltrexone (NTX) permeation across buccal mucosa, Int J Pharm, 411: 92–7,(2011).
57. Rajasekaran A., Sivakumar V., Karthika K., Preetha J.P., Abirami T., Design and evaluation of polymeric controlled release natamycin ocularinserts, Kathmandu Univer J Science, Engineering Techn, 6: 108-15, (2010).
58. Rawas-Qalaji M.M., Simons F.E., Simons K.J., Fast-disintegrating sublingual tablets: effect of epinephrine load on tablet characteristics, AAPS PharmSciTech, 7:E1–7, (2006).
59. Saber M.H., Formulation and *in-vitro* evaluation of fast dissolving film containing amlodipine besylate solid dispersion, Int J Pharmacy Pharm Sci., 5:419-28, (2013).
60. Saini S., Nanda A., Dhari J., Formulation, development & evaluation of oral fast dissolving anti-allergic film of levocetrizine dihydrochloride, J Pharm Sci Res, 3:1322-5, (2011).
61. Saringat H.B., Alfadol K.I., Khan G.M., The influence of different plasticizers on some physical and mechanical properties of hydroxypropyl methylcellulose free films, Pak J Pharm Sci,18:25-38, (2005).
62. Schroeder I.Z., Franke P., Schaefer U.F, Lehr C., Development and characterization of film forming polymeric solutions for skin drug delivery, Eur J Pharm Biopharm, 65: 111–21, (2007).
63. Scott R.A., Park K., Panitch A., Water soluble polymer films for intravascular drug delivery of antithrombotic biomolecules, Eur J Pharm Biopharm, 84:125-31, (2013).
64. Shimoda H., Taniguchi K., Nishimura M., Matsuura K., Tsukioka T., Yamashita H., Inagaki N., Hirano K., Yamamoto M., Kinosada Y., Itoh Y., Preparation of a fast dissolving oral thin film containing dexamethasone: a possible application to antiemesis during cancer chemotherapy, Eur J Pharm Biopharm, 73:361-5, (2009).
65. Siddiqui N., Garg G., Sharma P.K., A short review on "A novel approach in oral fast dissolving drug delivery system and their patents", Adv Biological Res , 5:291-303, (2011).
66. Tahara K., Yamamoto K., Nishihata T., Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910, J Control Rel, 35:59-66, (1995).
67. Vemula S.K., Veerareddy P.R., Formulation and evaluation of Ketorolac tromethamine tablets for time and pH dependent colon specific delivery, J Current Pharm Res, 8: 31-9, (2011).
68. Veuillez F., Rieg F.F., Guy R.H., Deshusses J., Buri P., Permeation of a myristoylated dipeptide across the buccal mucosa: topological distribution and evaluation of tissue integrity , Int J Pharm., 231:1–9, (2002).
69. Whitehead K., Karr N., Mitragotri S., Safe and effective permeation enhancers for oral drug delivery, Pharma Res, 25:1782-8, (2008).
70. Yamagar M., Kadam V., Hirlekar R., Design and evaluation of buccoadhesive drug delivery system of metoprololtartrate, Int J PharmTech Res, 2: 453-62, (2010).
71. Yehia S.A., El-Gazayerly O.N., Basalious E.B., Design and *in vitro*/*in vivo* evaluation of novel mucoadhesive buccal discs of an antifungal drug: relationship between swelling, erosion, and drug release, AAPS Pharm Sci Tech, 9:1207-17, (2008).

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