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FORMULATION AND EVALUATION OF ORAL SOLUBLE FILM OF DAPAGLIFLOZIN USING PERMEATION ENHANCER

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ABSTRACT:

The aim of this study was to develop Oral soluble film of Dapagliflozin using permeation enhancer. The oral soluble films are more beneficial in comparison to the tablets and capsules because oral films tend to dissolve within a minutes after placing on tongue. Dapagliflozin is a drug of choice used in the treatment of diabeties. Administering the drug by oral soluble route enhances the bioavailability and oral films bypasses the first pass metabolism of the drug. Oral soluble films are the advancement in the solid dosage forms and having more patient compliance. Films were prepared by using solvent casting method. As Dapagliflozin is BCS class III drug , Dimethyl sulphoxide plays important role in formulation as it used as permeation enhancer. Poly ethylene glycol 400 was used as plasticizer and HPMC used as Polymer. Sodium saccharine was used to mask the bitter taste of the drug. Film was evaluated for drug content, disintegration time, dissolution, thickness, tensile strength, folding endurance and surface pH. The optimized formulation F4 exhibited acceptable folding endurance (120), disintegration time

(67 sec) and drug release of 99.92% in 300 sec. It can be concluded from the study that the oral soluble films of Dapagliflozin can be a potential novel drug dosage form.

KEYWORDS: Dapagliflozin, Oral Soluble Film, Dimethyl Sulphoxide, Franz diffusion Cell method.

INTRODUCTION[1,2,3]:

Oral disintegrating/dissolving or soluble films or strips can be defined as follows: "These are drug delivery systems that they are quickly releasing the drug by dissolving or adhering in the mucosa with saliva within a few seconds due to it contains water-soluble polymers when it placed in the mouth cavity or on the tongue". The sublingual mucosa has high membrane permeability due to its thin membrane structure and high vascularization. Due to this rapid blood supply, it offers very good bioavailability. Enhanced systemic bioavailability is owing to skipping the first-pass effect and better permeability is owing to high blood flow and lymphatic circulation. In addition, the oral mucosa is a very effective and selective route of systemic drug delivery because of the large surface area and ease of application for absorption. In general, OSF are characterized as a thin and flexible polymer layer, with or without plasticizers in their content. They can be said to be less disturbing and more acceptable to patients, as they are thin and flexible in their natural structure. Thin films are polymeric systems that provide many of the requirements expected of a drug delivery system. In studies, thin films have shown their abilities such as improving the initial effect of the drug and duration of this effect, decreasing the frequency of dosing, and increasing the effectiveness of the drug. With thin-film technology, it can be beneficial to eliminate the side effects of drugs and reduce common metabolism procured by proteolytic enzymes. Ideal thin films should possess the desired properties of a drug delivery system, such as a suitable drug loading capacity, rapid dispersion/dissolution, or prolonged application and reasonable formulation stability. Also, they must be nontoxic, biodegradable and biocompatible. some patients, especially paediatrics and geriatrics have difficulties in swallowing or chewing some oral solid dosage forms like tablets and hard gelatine capsules. Because of the fear of choking, they are unable to take these dosage forms. In order to overcome this, several fast dissolving drug delivery systems (FDDDS) came into existence. Research in the oral drug delivery system has led to the advancement of dosage forms from simple conventional

tablets/capsules to modified release tablets/capsules to oral disintegrating tablet to wafer to the recent development of oral soluble films.

MATERIALS AND METHODS[4]:

Materials

All the chemicals used in this research were of standard pharmaceutical grade. Dapagliflozin was received from Indiamart. HPMC, Polyethylene Glycol 400, Dimethyl sulfoxide, Citric Acid, Sod. Saccharine, Glycerin, Methanol from SD Fine chemicals, Mumbai.

Methods

Oral soluble film of Dapagliflozin was prepared by solvent casting method. HPMC, Polyethylene Glycol 400, Dimethyl sulfoxide, Citric Acid, Sod. Saccharine, Glycerin, Methanol was used to oral soluble film.

PREPARATION OF ORAL SOLUBLE FILM[4,5]:

Films were prepared by solvent casting method . The specified amount of polymer was weighed and dissolved in a specified amount of water and methanol . Drug, sodium Saccharine, citric acid, DMSO, was dissolved in water and Methanol. The drug solution was added to the polymer solution and mixed using mechanical stirrer for 1 hour. The resulting solution was degassed to remove the bubbles formed. The bubble free solution was cast on to a dish mounted with aluminum foil in surface area of 16.59 cm2 . It was dried for 2 hours in tray dryer. The film was removed from the dish and observed for any imperfections. Further studies were conducted for the selected formulations. Films of area 4 cm2 (1cm ×1cm) were cut and stored in a desiccator.

Table no.1: Formulation of oral soluble film

Ingredients	F01	F02	F03	F04	F05	F06	F07
Dapagliflozin(mg)	79.85	79.85	79.85	79.85	79.85	79.85	79.85
HPMC (mg)	60	60	300	662.08	662.08	662.08	662.08
PEG 400 (ml)	40	40	40	0.04	0.04	0.04	0.04
Sod. Starch Glycolate (mg)	40	40	40	-	-	-	-
Sod. Saccharin (mg)	20	20	20	24.82	24.82	24.82	24.82
Citric Acid (mg)	-	-	-	33.104	33.104	33.104	33.104
DMSO (ml)	0.4	0.4	0.4	0.04	0.04	0.04	0.04
Glycerin (ml)	-	-	-	0.015	0.015	0.015	0.015

Water (ml)	10.5	4.5	4.5	5	5	5	5
Methanol (ml)	4.5	10.5	10.5	11.58	11.58	11.58	11.58

Fig 01: Batch 01

Fig 02: Batch 02

Fig 03: Batch 03

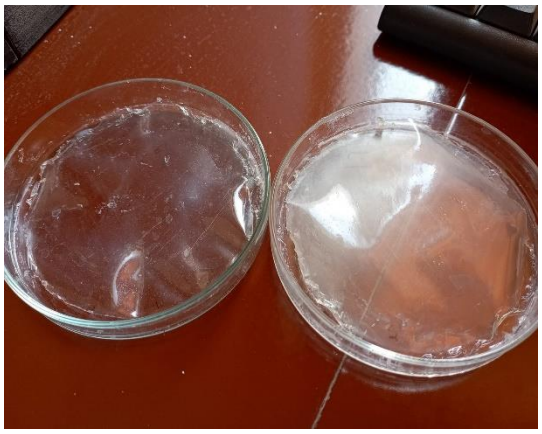


Fig 04: Batch 04 (Optimized batch)

EVALUATION AND CHARACTERIZATION:

Weight variation of the film[8]: 4 cm^2 films was cut at five different places in the cast film. The weight of each film strip was taken and the average weight was calculated**.**

Thickness of the film[8]: The thickness of the patch was measured using digital Vernier Calipers with a least count of 0.01mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken.

Surface pH[8]: The surface pH of Film was determined to investigate the possibility of any side effects in in vivo studies. As an acidic or alkaline pH may cause irritation to the oral mucosa, it was ensured to keep the surface pH as close to pH 6.8 (oral cavity pH). The pH of an oral film was usually determined by putting the film in Test tube and film solution was made with distilled water and noting pH by a pH meter.

Tensile strength[8]: Tensile testing was conducted using a texture analyzer AG/MC1 (Acquati, Italy), equipped with a 5 N load cell. The film was cut into 2×2cm strips. Tensile test was performed according to ASTM International Test Method for Thin Plastic Sheeting . Each test strip was placed in a tensile grip on the texture analyzer. The test was consider concluded when the film breaks. Tensile strength, was computed with the help of load require to break the film and cross sectional area to evaluate tensile properties of the films. (8,9,10)

Tensile Strength = Force at break (N) / Cross sectional area (mm^2)

Folding endurance[8,9]**:** Folding endurance to determine mechanical properties of film and was measured by repeatedly folding of the film at the same place to the extent where film breaks. The number of times the film is folded without breaking is calculated as the folding endurance value.This parameter was checked simply by visual inspection of films.

Disintegration time[10]**:** Disintegration test was performed according to specification of oral dispersible tablet reported in European Pharmacopeia by USP disintegration apparatus on samples of area 2 cm × 2 cm. The disintegration time is the time when the film starts to break or disintegrates completely, normally disintegration time for oral films s within 2 min.15

In-vitro Dissolution studies[10]: Dissolution study was carried out using USP type I (basket apparatus) with 300 ml of 6.8 pH Phosphate buffer as the dissolution medium, maintained at 37 ± 0.5°C. Medium was stirred at 50 rpm for a period of 10 minutes. Samples were withdrawn at 1, 2, 4 ,5 min interval, replacing the same amount with the fresh medium. Samples were suitably diluted with 6.8 pH phosphate buffer and analyzed for drug released at 223nm.

Diffusion Study[10]: In-vitro diffusion study of prepared Oral soluble film by Franz diffusion Cell method. Franz diffusion cell was employed for the in vitro characterization of oral soluble film formulations. The receptor compartment of the diffusion cell was filled with 30.0 ml of phosphate buffered saline (pH 6.8), and in vitro drug release studies were carried out using Chicken skin. The prepared formulations were placed on to the membrane in the donor compartment and were uniformly spread onto Chicken skin membrane. The assembly was constantly maintained at 37.0 ± 5.0 °C. Samples (1.0 ml aliquots) were then withdrawn at suitable time intervals (0, 5, 10, 15, 20, 30 Min) and replenished with an amount of medium to maintain the receptor phase volume to 30 ml. The samples were analysed spectrophotometrically at 223nm.

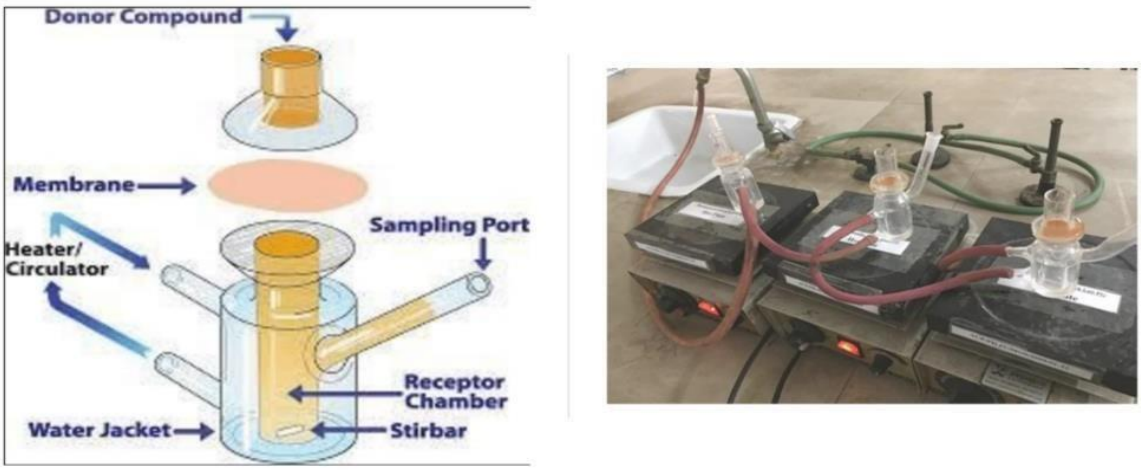


Fig 05: Franz diffusion cell assembly

Drug Content[11]: A film of size 2cm × 2cm was cut and kept in 10 ml of volumetric flask containing methanol as solvent. Then the volume was makeup upto the 10ml with methanol to acquire a concentration of 1000 µg/mL. The working standard solution of 10 µg/mL was prepared by appropriate dilution of the stock solution with distilled water. The drug content was determined spectroscopically after appropriate dilution and measured at 223 nm

RESULTS AND DISCUSSION:

The present work efforts have been made to Prepare Oral soluble film of Dapagliflozin, using HPMC, Polyethylene glycol 400 as a plasticizer by solvent casting technique. The selection of polymer produces clear, smooth, uniform, substantive, flexible and desired thickness for film. The prepared formulation were evaluated for different physical & chemical characteristics such

as thickness, weight variation, folding endurance, tensile strength, surface pH, drug content, disintegration time, drug release and drug permeation characteristics of the formulation were studied in vitro conditions. In vitro drug release studies were carried out in phosphate buffer (PH 6.8) for 5 Mins.

Calibration Curve of Dapagliflozine:

The standard stock solution was prepared by dissolving 10.0 mg of Dapagliflozin in 10.0 mL of methanol to acquire a concentration of 1000 µg/mL. The working standard solution of 10 µg/mL was prepared by appropriate dilution of the stock solution with distilled water.

Selection of appropriate wavelengths for analysis for Dapagliflozin Method I (Zero order): The working standard solution of 10 µg/mL was prepared and scanned in the UV range 400–200 nm; Dapagliflozin shows a maximum absorbane at 223nm

Preparation of Calibration Curve: Appropriate dilutions of standard stock solution were made to get final concentration in the range of 0.2-4 µg/mL. Absorbance were measured of each prepared solution at above selected wavelengths. The calibration curve was plotted between concentration vs. absorbance, having correlation coefficient 0.995.

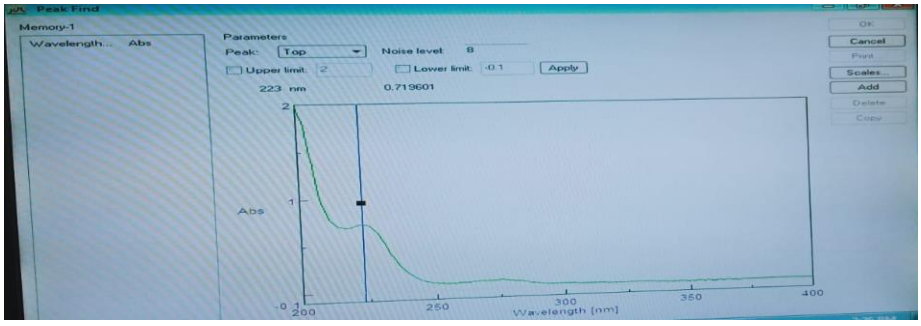


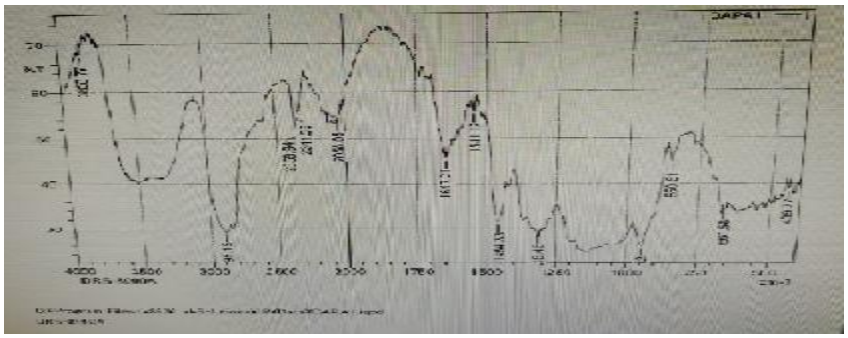
Fig :06 UV Spectra of Dapagliflozin

Table No:02 Absorbance of Dapagliflozin at various conc.

Concentration	Absorbance
0.5	0.1546
1	0.2171
1.5	0.3447
2	0.4319
2.5	0.5521
3	0.621
3.5	0.7681
4	0.8412

Fig :07 Calibration Curve of Dapagliflozin

Drug-Excipient Compatibility Study: (Dapagliflozin and HPMC)



Trial Batches observation:

F1: Film was not prepared

F2: Film was sticked to petridish

F3: Film was sticked to petridish

F4: Film results glossy, transparent, good plasticity.

F5: Film results glossy, transparent, good plasticity.

F6: Film results glossy, transparent, good plasticity.

F7: Film results glossy, transparent, good plasticity.

Table no 03: Results of evaluated batches from F 04- F 07

Parameter	**F4**	**F5**	**F6**	**F7**
		Batches To Check Reproducibility		
Physical Appearance and surface texture	Glossy Transparent and Smooth	Glossy Transparent and Smooth	Glossy Transparent and Smooth	Glossy Transparent and Smooth
Average Weight (mg)	0.34 ±0.023	0.36 ±0.031	0.34 ±0.022	0.38 ±0.042
Thickness (mm)	0.11 ±0.01	0.11 ±0.01	0.12 ±0.02	0.14 ±0.021
Folding Endurance	60 ±1	65 ±1	62 ±1	62 ±1
Surface pH of Film	6.06±0.051	6.08 ±0.056	6.12 ±0.062	6.08 ±0.0641
Tensile Strength	34.11 ±1	32.96 ±1.2	33.13 ±1.1	32.86 ±1.2
Disintegration Time (Sec)	67 ±1	77 ±1.2	75 ±1	73 ±1.3
Drug Content (%)	95.12±0.015	96.22±0.014	95.19±0.015	94.75 ±0.012

Data are represented as mean ± S.D (n=3).

Table no 4: % Drug release of F04-F07 Formulations of Oral soluble film

Formulation Batch no.	**Drug release (%)**
F04	99.92 ± 0.956
F05	96.41 ± 0.947
F06	96.18 ± 1.098
F07	98.52 ± 0.998

Data are represented as mean ± S.D (n=3).

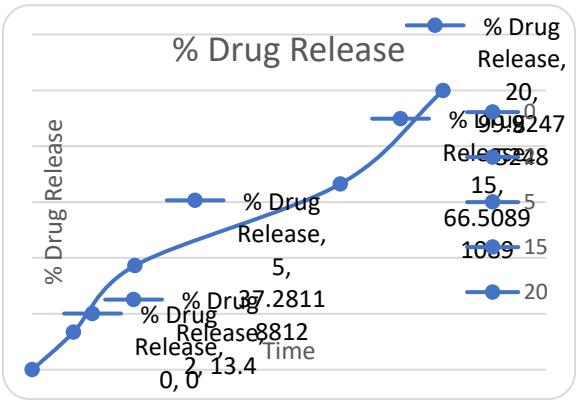


Fig 08: F 04

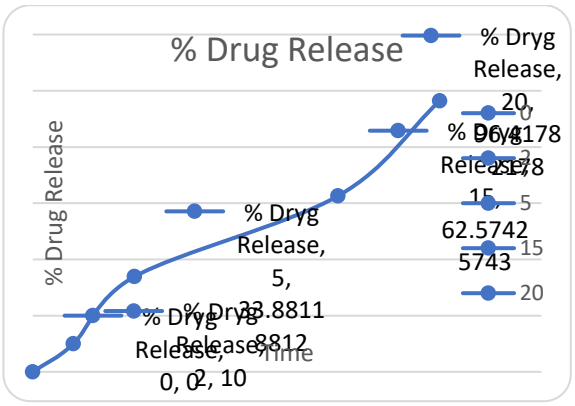


Fig 09: F 05

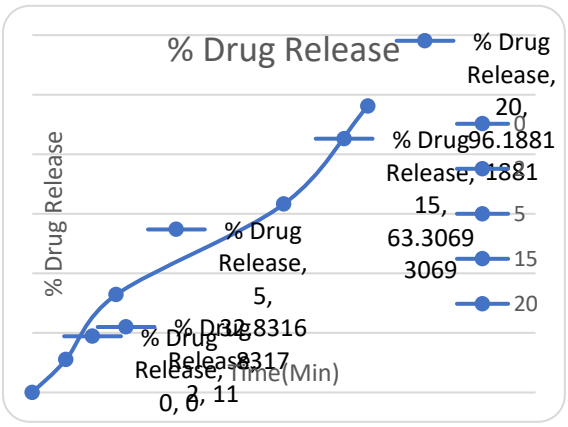


Fig 10: F 06

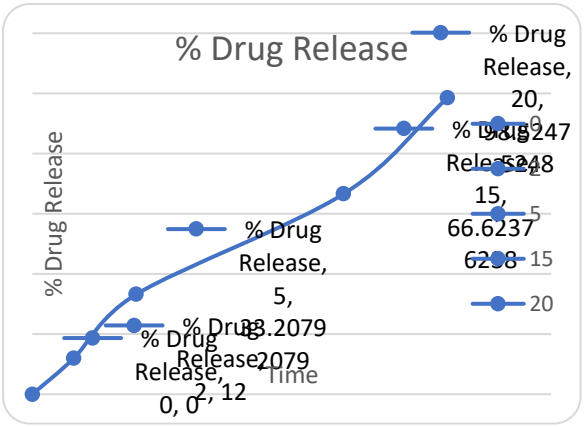


Fig 11: F 07

In-vitro drug release study of optimized batch of Oral soluble film by Franz diffusion Cell method:

Table no 5: In-vitro drug permeation of Dapagliflozin oral soluble film by Franz diffusion cell

Time (Min)	Absrbance	Concentration (µg/mL)	Dilution Factor	Concentrtion in 900ml(mg)	Cumulative release(mg)	% Drug Release
2	0.008±0.002	0.039	0.396	0.356	0.35	7
5	0.013±0.004	0.0643	0.643	0.579	0.929	18.584
15	0.021±0.010	0.103	1.039	0.935	1.864	37.297

20	0.029±0.031	0.143	1.435	1.292	3.156	63.138

Data are represented as mean ± S.D (n=3)

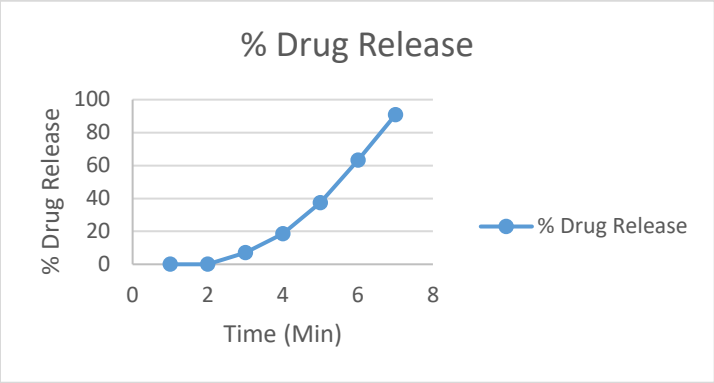


Fig 12: Drug Permeation of F 04 batch prepared without DMSO

Table no 6: In-vitro drug permeation of Dapagliflozin oral soluble film with DMSO by Franz diffusion cell

Time (Min)	Absorbance	Concentration (µg/mL)	Dilution factor	Concentrtion in 900ml(mg)	Cumulative release(mg)	% Drug Release
2	0.011±0.002	0.058	0.584	0.525	0.52	10.4
5	0.024±0.006	0.123	1.232	1.109	1.629	32.588
15	0.031±0.012	0.156	1.564	1.407	3.037	60.746
20	0.038±0.028	0.190	1.900	1.710	4.748	94.964

Data are represented as mean ± S.D (n=3)

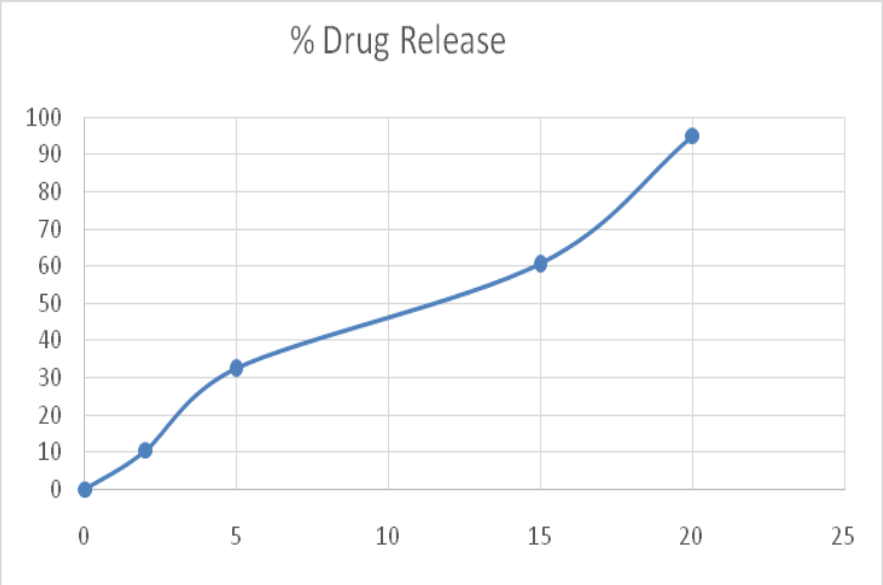


Fig 13: Drug Permeation of F 04 batch prepared with DMSO

Stability studies: Stability studies of the optimized batch F4 were carried out at 40°C/75%RH, 25°C/60%RH and 25°C/40%RH. Films stored at 40°C/75%RH were highly unstable within 1 month storage. Films stored at 25°C/60%RH were unstable after 2 months period by developing color change (slightly yellow) and becoming sticky in appearance. Films stored at 25°C/40%RH were found to be stable for 3 months. The batch was found acceptable visually and mechanically, with slight change in in-vitro disintegration time. The above observations indicate that temperature and humidity plays a critical role in the stability of the oral soluble films containing HPM as the film-forming polymer. Therefore, selection of appropriate packaging plays a crucial role in the stability of oral thin films.

Table no 03: Stability Study

Temp and Humidity condition	Time	Stability Condition
40°C/75%RH	1 Month	Highly unstable
25°C/60%RH	2 Month	Unstable (Slightly Yellow)
25°C/40%RH	3Months	Stable

CONCLUSION:

In present work oral soluble film of Dapagliflozin with DMSO can meet the ideal requirements for fast release intra-oral devices, which can be a good way to bypass the extensive hepatic first pass metabolism and increase bioavailability. Dapagliflozin can be conveniently administered

orally in the form of films. The prepared Oral soluble film using different polymer and plasticizer such as HPMC and PEG 400 had shown good promising results for all the evaluated parameters. DMSO was used as permeability enhancer and F 04 shown 94.96 % drug permeation in 20 mins hence It was concluded that DMSO can enhance permeability of Dapagliflozin. F 04 was disintegrated in 67 Sec and released 99.92% of drug Dapagliflozin within 05 Min and was considered as the optimized formulation.

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