International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.4, pp 26-38, 2017

Formulation and *In Vitro* Evaluation of Fast Dissolving Film of Metoclopramide Hydrochloride

Iman Sabah Jaafar*

Department of Pharmaceutics, College of Pharmacy, Al-Mustansiriyah University, Baghdad, Iraq.

Abstract : Objective: The goal of this study was to formulate and *In vitro* evaluate fast dissolving oral film of metoclopramide hydrochloride (MCP HCl) in order to supply valuable and acceptable dosage form for patients who are suffering from difficulties in swallowing like children and geriatric patient or patients who are unable to swallow like unconscious patients.
Methods: Solvent casting method was used to prepare MTC HCl fast dissolving films using different types of film forming polymers including hydroxy ethyl cellulose (HEC), hydroxy propyl methyl cellulose 15 cp (HPMC 15 cp) and sodium carboxy methyl cellulose (SCMC) in different concentration .Different types of plasticizer are employed including glycerin (Gly), polyethylene glycol 400 (PEG 400) and propylene glycol (PG) to enhance the film forming properties of polymer.
Results: The prepared films were evaluated for visual homogeneity, thickness, weight variation, surface pH, drug content, folding endurance, *In vitro* disintegration time (DT) and *In vitro* release profile. The optimized formula was subjected to comparison in release profile with marketed product as well as Fourier Transform Infrared Spectroscopy(FTIR).Among the prepared formulations, F12 which was prepared using 54% (w/w) SCMC and 20% (w/w) Gly showed satisfactory physicochemical parameters, disintegration time (DT) 14 seconds, and the highest dissolution rate as 68.3 % of drug released in 2 minutes and 80% of drug is released in 4 minutes.
Conclusion: The results reveled that fast dissolving film of MTC HCl can be prepared successfully and to be considered as a encouraging drug delivery system.
Keywords: Fast dissolving film, Metoclopramide HCl,Sodium carboxy methyl cellulose, Glycerin.

Introduction

One of the most crucial routes of administrating a drug with high credit to obtain a systemic effect is the oral administration for its simplicity, comfortability by producing no pain compared with the systemic administration and other remarkable benefits over the other routes [1].However, it also comes with disadvantages in case of certain dosage forms as capsules and tablets, as problems of swallowing especially for children and infants and for elders leading to incompliance and disadherence to the treatment [2]. This was proved by evidence that approximately 35% of the population showed dysphagia and troubles with swallowing as an example, people with sea/ motion sickness, hiccups, gagging and obstruction of the esophagus pathway will be force to search for other alternatives which favor the systemic drug delivery such as fast dissolving medication [3]. One of the fast dissolving dosage forms is oral thin films which are an ultra-thin film that relay on an efflorescent and highly adherible hydrophilic polymer over placement on the tongue or inside the buccal cavity, those films have

high tendency of disintegration and/or dissolution in few seconds releasing the active ingredients with no aids of chewing nor swallowing [4]. Using such dosage forms have quite privileges such as rapid onset, with immediate bioavailability to the active constituent because of the anatomical composition of buccal cavity, that provides a high blood flow to the area as well as the high preamable nature of the buccal mucosa[5].

Metoclopramide HCl is a drug that employed for increasing the gastroinsestinal tract motility for conditions such as GERD (gastroesophageal reflux disorder), dyspepsia, nausea and vomiting as well as gastroparesis, also it is used for disorders other than that affecting the GIT, as for management migraine, sometimes after surgery, or with cancer therapy also to enhance gastric emptying process during radiographic procedures.

As a drug, MTCHCl, shows a rapid and approximately of complete absorption from the GIT following the oral administration, however the absorption is reduced after certain conditions as in vomiting or obstructed gastric tract [6]. The problem with oral route is that majority of medication given through the oral routs with be consumed via the fisrt-pass effect and this is variable for the drugs though , giving a noticeable variations in the bioavailability to range from 60 – 90% [7,8] therefore, MTC HClis highly recommended to be formulated as fast dissolving films since this will results in enhancing the pharmacokinetic characteristics of drug by improving the absorption rate and overcome first pass effect of the liver ,development of an pleasing and successful dosage form for children and geriatric patient , patient with nausea and vomiting ,unconscious patient as well as those with dysphagia .

Materials and Methods

Material

Metoclopramide HCl (MCP HCl) and Hydroxyl propyl methyl cellulose 15 cp (HPMC 15cp) (Provizer Pharma, India). Sodium carboxy methyl cellulose (Na CMC) (low viscosity), hydroxyl ethyl cellulose (HEC), glycerin (Gly) and Meclodin®tablets (Samara Drug Industry, Iraq). Sodium saccharine (Na sach) (Avonchem limited). Poly ethylene glycol 400 (PEG 400) (Sinopharm Chemical Reagent Co, Ltd). Citric acid (Panreac AAG, Spain.China).

Methods

Preparation of fast dissolving films

1. Calculation of drug loaded in the film:

The petri dish diameter is 8.8 cm.
Total surface area of petri dish was 60.79 cm^2 .
Each film surface area = 2×2 = 4 cm^2 .
Number of films in batch = 60.79/4 = 15.1 approximately 15 films.
The amount of drug in each patch is 15 ×5 = 75mg. [9]

2. Formulation of fast dissolving oral films

Twelve formulas with different composition as shown in table 1 were prepared using solvent casting method. Polymer solution desired percentage was prepared by dispersion of the polymer in its powder form into distilled water with constant continuous stirring using magnetic stirrer**.** Then after, the resultant solution was left with no agitations nor does stirring for about 3-4 hours to expel the air bubble within the solution. In a separate beaker precisely weighed amount of drug, plasticizer and other excipients were dissolved in distilled water. When the complete hydration of polymer with water was obtained, drug-plasticizer and all excipient solutions were added and mixed thoroughly, and the volume completed with distilled water up to 10mL. The resultant solution was poured into a petridish with defined surface area then left to dry using an oven supplying 40 ^oC. The resultant films were stored into aluminum foil[10].

Table (1): Composition of MCP HCl fast dissolving film in each formula

Ingredient (mg)	Formula Code											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
MCP HCl	5	5	5	5	5	5	5	5	5	5	5	5
HEC	27	29	31									
HPMC 15 cp				27	29	31						
SCMC							27	29	31			
Glycerin	8	8	8	8	8	8	8	8	8			10
PEG 400										8		
PG											8	
Citric acid	1	1	1	1	1	1	1	1	1	1	1	1
Na sacharine	2	2	2	2	2	2	2	2	2	2	2	2
Tween 80	3	3	3	3	3	3	3	3	3	3	3	3
Mannitol	4	2		4	2		4	2		4	4	2
Total weight	50	50	50	50	50	50	50	50	50	50	50	50

Evaluation of oral fast dissolving film

Visual inspection of film

Homogeneity, transparency, integrity and color of the produced film was inspected visually[11].

Weight variation

For the film not to be rejected, the weight of no more than two films should be within ±7.5 % of the total average and no film out of the ±15% of the average of the films,, therefore the MTC HCL oral film was subjected to this test and five films were weighed individually after being cut out the cast film at different places and the average weight of the five films was calculated [12].

Thickness:

The thickness of film was measured by vernier caliper micrometer at different locations (five locations; centre & four corners) and mean thickness was calculated. This is crucial to determine the film thickness uniformity as this is directly correlated to the dose accuracyin the film [13].

Drug content

To determine the MCP HCl content percent in the films, in 100 ml phosphate buffer (pH 6.8), a 4 cm^2 film that contains 5 mg of the drug, was dissolved in a volumetric flask with the aids of ultrasonicator for 3 hours, then it was left undisturbed at room temperature for 24 hours, then after the solution was filtered via filter paper and examined by UV spectrophotometer at wavelength of 273 nm,, the procedure was repeated in triplicate and the average was calculated[14].

Surface pH measurement

The pH of the surface of the films was investigated to determine the probable side effects, since that incompatible alkaline or acidic pH may irritate the mucosa of the mouth. The pH meter was employed to measure the surface pH of the film by bringing the electrode in contact with a swollen yet intact film after exposure to 1 mL of distilled water for 1 min at the room temperature, the pH was recorded after direct contact between the electrodes with the surface to equilibrate for 1 minute [15].

Folding endurance

The number of folds i.e. how many times the film being folded at same place that required to disrupt the film sample or developing a noticeable cracks, this is known as folding endurance. This term provide an

indication of film brittleness, that a strip has been subjected to this test through film folding at same point repeatedly for many times until a noticeable crack was detected, the values are stated [16].

***In-vitro* disintegration time**

The disintegration time is measured by modified disintegration procedure, that the product (film) was placed in a petridish that hold 10 ml of specified buffer (pH 6.8 phosphate buffer); the time when the film is completely disintegrated was documented as disintegration time [17].

***In-vitro* drug dissolution study**

The dissolution test of the film was established with the aids of paddle apparatus, the jars were filled with 500 ml of dissolution media with phosphate buffer pH 6.8 at 37 ± 0.5 °C, and 50 rpm stirring speed, during 40 minutes, and at constant and defined interval, with constant volumes of both of sample withdrawal and media replacement (5 mL of each), finally the absorbance was taken for each sample by UV spectrophotometer at wavelength equals to 273 nm[18].In addition, the dissolution test was also carried out for conventional tablets (Meclodin®SDI) as reference tablets for comparison with the optimized formula for release profile.

Fourier Transform Infrared Spectroscopy(FT-IR)

FT-IR spectroscopy was done to determine the drug polymer interaction. Sample of both pure drug and selected formula were grinded carefully with potassium bromide, the Infrared spectra for both of thesamples were determined using a disk of KBr which prepared via a hydraulic press. The range of the spectral width used in this study was laying between 400–4,000 cm^{-1}[19].

Statistical analysis

ANOVA test (one way analysis of the variance) and student t-test were employed for statistical analysis. When ($p < 0.05$) then there would be a significant statistical differences.

Results and Discussion

Physicochemical parameters of MCP HCl fast dissolving films

The organoleptic appearance of the prepared films was evaluated. All the films prepared with different polymer concentrations were found to be flexible, smooth, transparent, and homogeneous figure 1 shows the physical appearance of the prepared films. The results show uniformity among the prepared formula regarding the average weights, which were all within specified values

Fig. 1: Prepared casted film of MCP HCl

The thickness of the prepared formulas were variable ranging from (0.049 to 0.133 mm). Minor standard deviation value would validate a study to be reproducible, therefore, the employed method can come with films of uniform thicknesses, resulting in content uniformity of the desired does .The results also showed that as the concentration of the used polymer increased the thickness of the prepared film increased. This may

be attributed to the viscosity differences of polymeric solutions. These results are convenient if compared to the results obtained by preparation of zolpidem fast dissolving films [20].

The surface of each film has underdo a pH investigations to determine side effects likely to occur after administration of such films, which may happen as a result pH changes while *in vivo*, that improper pH (acidic or alkaline) will cause buccal mucosa irritations.5.95 to 6.86 was the range of the surface pH. From these results it is clear that all films have pH value closer to the neutral PH , which indicates films doesn't cause any buccal mucosa irritations.

Assay of drug content proved a uniform distribution of the drug through outeach film; this distribution was laying within the specified standards of the US pharmacopia, i.e., within 90-110 % (USP). Nevertheless, every film mimic the other films in the quantity of MTC, which represent how highly reproducible this technique is.

Brittleness of the film was determined via the folding endurance. It measures the ability of the film to withstand rupture [21]. Any formulated filmhas a folding endurance value, a value more than 300 indicates an acceptable results. Table 2 shows the physicochemical parameters of MTC HCl fast dissolving films.

Table 2: Physicochemical parameters of MCP HCl fast dissolving films

Formula code	Thickness (mm)	Drug content	pH	Folding endurance
F1	0.058±0.001	92.4±0.6	6.07	>300
F2	0.099± 0.000577	95.93±1.171893	6.12	>300
F3	0.133±0.003055	97.47±0.723418	5.95	>300
F4	0.049±0.002309	97.7±1.457166	6.87	>300
F5	0.058±0.005774	93.63±0.70946	6.87	>300
F6	0.12±0.004	95.27±0.378594	6.85	>300
F7	0.072± 0.003464	98.5±0.360555	6.86	>300
F8	0.107±0.003055	96.63±0.61101	6.82	>300
F9	0.067±0.003055	94.03±0.873689	6.87	>300
F10	0.064±0.001	95.6±0.793725	6.83	>300
F11	0.068±0.001002	97.97±0.450925	6.81	>300
F12	0.068±0.000577	97.4±0.4	6.84	>300

In vitro disintegration time

Since the limited volume of human saliva within the mouth, which is estimated to be less than 6 mL , therefore a 900 mL conventional disintegration tester won't be realistic nor represent the real environment within the buccal cavity , accordingly a modified procedure was conducted that employs a petridish having a diameter of 6.5 cm to evaluate the actual disintegration time *in vivo*, this technique is comparable to the diameter of the sublingual area which is about 3-4 cm. moreover, the small volume of the media solution resemble the volume of the saliva as well as the lack of agitation maintained through the test mimic the static conditions within the buccal cavity[22].

The test come to show that the formula disintegrate *in- vitro* within one minute. According to the polymer type, the results showed that the disintegration time was (27, 14 and 12) sec for formulas F1,F4 and F7 which contain fixed concentration (54% w/w) of HEC ,HPMC and SCMC respectively. Significant decline ($p<0.05$)in DT was observed when HEC was replaced by same concentration of either HPMC or SCMC since both polymers (HPMC and SCMC) are highly hydrophilic with low viscosity. As a result, high solubility of formulas containing these polymers in polar solvents, therefore such formula will show direct and rapid

disintegration without forming gel residues, and ensuring fast matrix disintegration [23]. In the presence of the same polymer , the disintegration time was increased significantly ($p<0.05$) by increasing the concentration of the polymer within the film as it was (27,34 and 39) sec for HEC (F1,F2 and F3) ,(14,19and 26) sec for HPMC (F4,F5 and F6) and (12,16and 21) sec for SCMC (F7,F8 and F9) when their concentrations are 54,58 and 62% (w/w) respectively.This can be explained as the higher concentration of the polymer, the thicker gel will produce upon contact with the media, which require longer time to disintegrate [24], this result come with agreement of the study of formulation and evaluation of fluoxetine HCL in fast dissolving buccal films [25]. Figure 2 showed the effect of type and concentration of polymer on disintegration time.

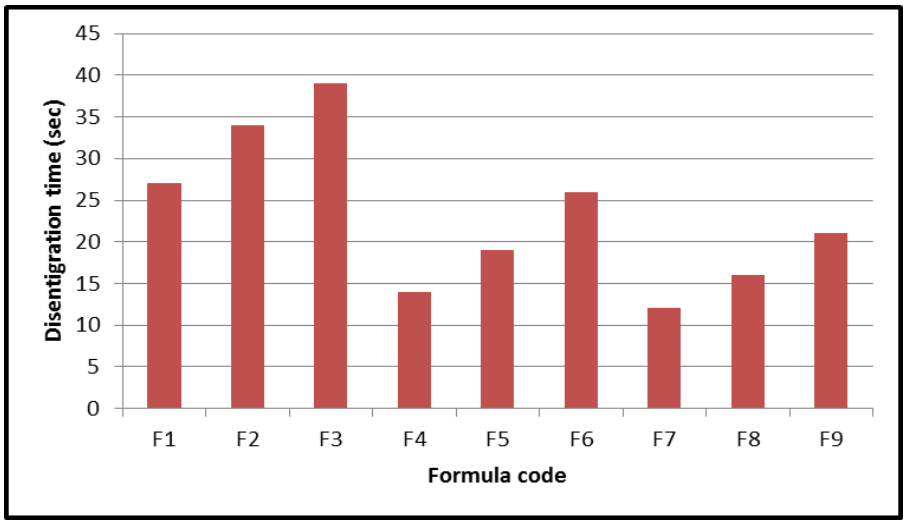


Fig. 2: Influenceof polymer type and concentration on *In vitro* disintegration time.

In respect to plasticizer type, the result showed that DT increased significantly ($p<0.05$)as glycerin (F5) was replaced by PG in F11 while non-significant increase ($p>0.05$)in DT was observed when glycerin was replaced by PEG 400 in F10 where the DT was (12, 15 and 18) sec for F5, F10 and F 11 respectively. Such results were proven in another study of characterization and optimization of formulations of orodisersible mosapride film[26].

It was also found that F10 which contain 16 % (w/w) PEG 400 has shorter DT (15) sec comparing to F11 which contain same concentration of PG, (18) sec and as shown in figure 3.This is may be attributed to the weakening effect of both Gly and PEG 400 on the film resistance to solubility[27]. When they immersed in dissolution media they could leach out from the film, this will result in increased the penetration of dissolution media due to the loss of plasticizer and cause fast disintegration time[28].

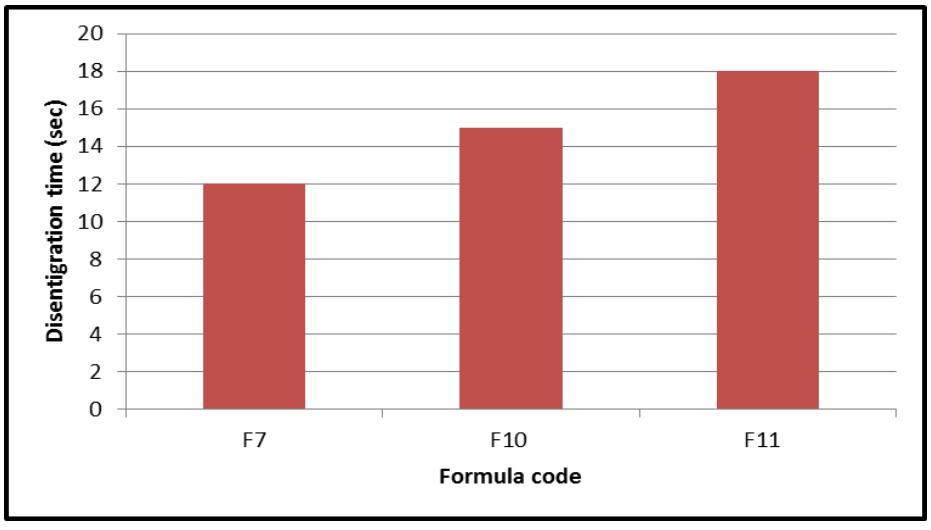


Fig. 3: Influence of plasticizer type on *In vitro* disintegration time.

By using different concentration of Gly with a fixed concentration of SCMC (54% w/w) .It was noticed that increasing the concentration of glycerin from 16% (w/w) in F7 to 20% (w/w) in F12 led to non-significant increase ($p>0.05$) in DT where DT was 12 & 14 sec for F7 and F12 respectively as illustrated in fig.4, this can be attributed toblooming phenomenon as well as stickiness resulted when more than 18%w/w concentration of a plasticizer from the total dry weight is used[29].

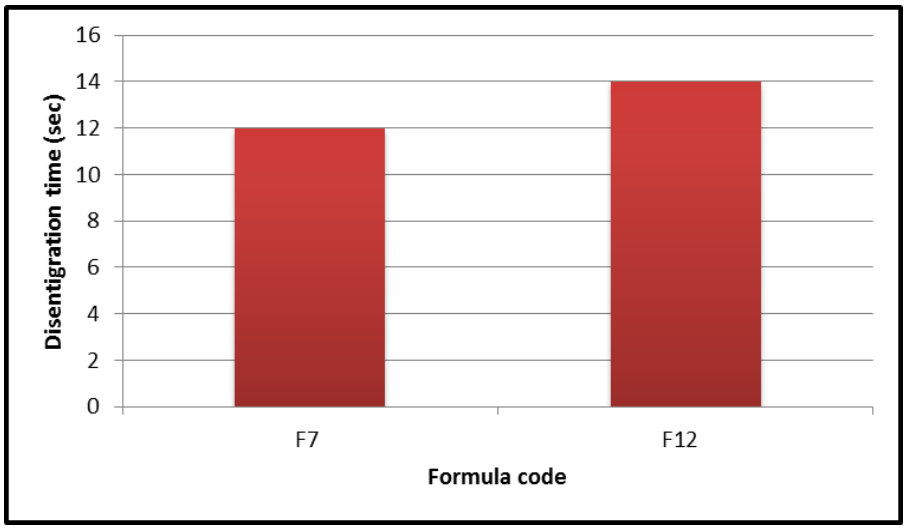


Fig. 4: Influence of glycerine concentration on *In vitro* disintegration time.

***In vitro* release evaluation**

Dissolution study was performed as an *In vitro* evaluation by employing USP paddle type apparatus utilizing half liter phosphate buffer (pH 6.8). Table 2 shows the percentage of drug being dissolved in through 2 minutes (D_2 min) as well as the required time for releasing 80% of the drug (T80%).The percent drug dissolved in 2 minutes (D_2 min) was employed for comparison purpose due to the value of rapid drug release in case of fast dissolving films preparation.

Table 2: ***In-vitro* dissolution parameters in phosphate buffer (pH6.8)at 37°C**

	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
D_2 min	18.49	11.52	8.1	51.56	43.8	38.5	63.6	51.56	48.6	56	50	68.3
T80%	35.18	40.78	49.32	10.18	15	20.1	5.17	9.81	14.8	9.9	19.75	4

Comparing the three investigated polymers ,the value of D_2 min for F7 (SCMC),F4 (HPMC)and F1(HEC) containing fixed concentration (54% w/w) of polymer was 63.6 %, 51.56% and 18.49% respectively and as shown in figure 5. Formula 1 prepared with HEC showed a significant decrease ($P<0.05$) in drug release, this may be attributed to the high viscosity of HEC and formation of high viscous gel layer that act as barrier for the diffusion of drug by retarding the solvent passage into the film and reduce the drug release [30].

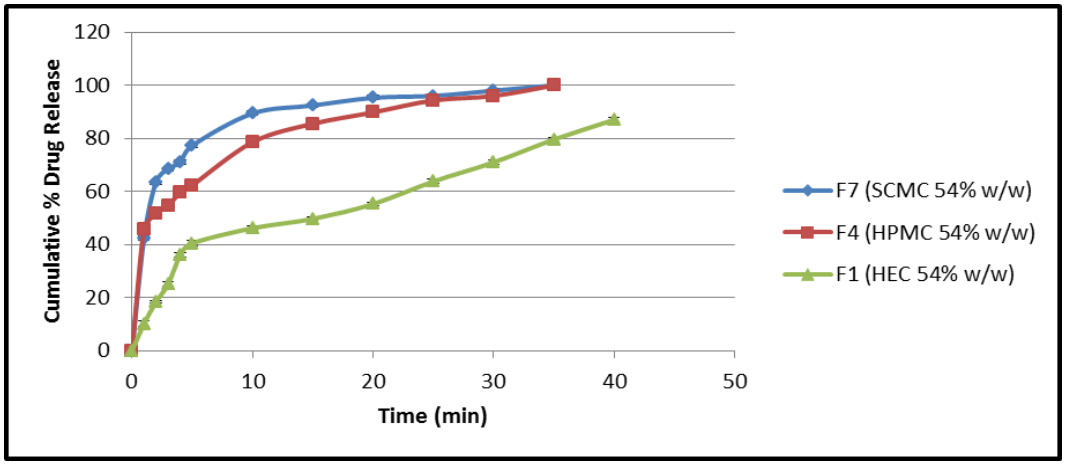
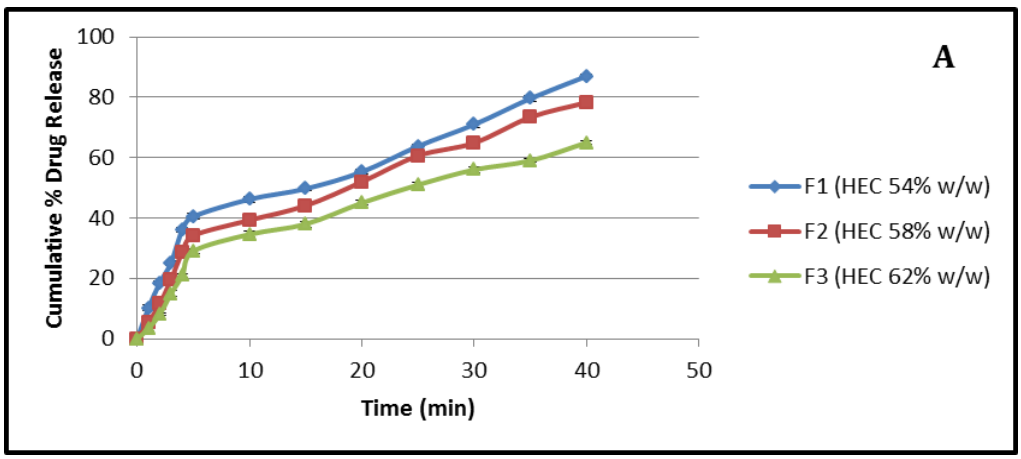
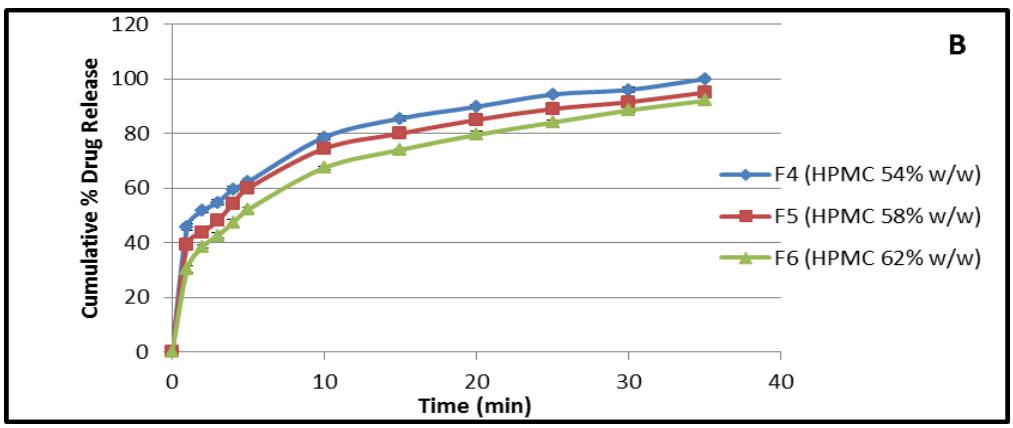


Figure5: Influence of polymer type on *In vitro* release profile in phosphate buffer pH 6.8 at 37±0.5°C (n=3) (mean±SD)

The results also indicate that increasing the polymer concentration from 54 % (w/w) to 62% (w/w) consequences in significant decline($p<0.05$) in drug release from the prepared film as the D_2 min was 18.49%, 11.52 % and 8.1 % for formulas F1, F2 and F3 which contain HEC and as shown in figure 6 A, 51.56%, 43.8% and 38.5% for formulas F4, F5 and F6 as shown in figure 6 B in which HPMC is the film forming polymer and 63.6%, 51.56% and 48.6% when SCMC is used in formulas F7, F8 and F 9 which is illustrated in figure 6 C .This decrease in drug release correlated to the increment of film thickness in consequence of increasing polymer concentration. So more time is needed for the dissolution media to infiltrate into polymer chain situated through film's depth resulting in an rise in the time essential for the drug molecules implanted in the polymer matrices to come into solution[31].Similar results were observed in levocitirizine dihydrochloride fast dissolving films preparation and evaluation [32].





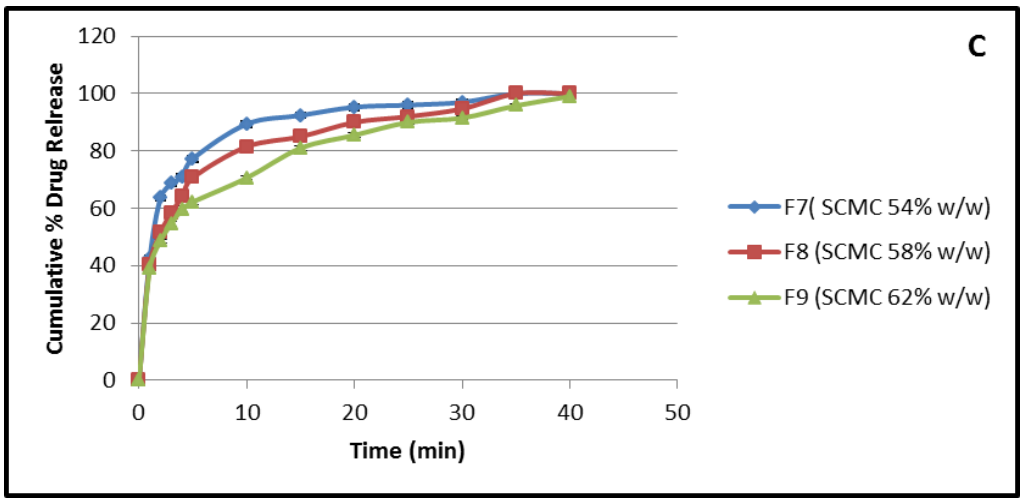


Figure6 (A, B and C): Influence of polymer concentration on *In vitro* release profile in phosphate buffer pH 6.8 at 37±0.5°C (n=3) (mean±SD)

According to the type of plasticizers used and as shown in figure 7, significant improvement ($p<0.05$) in drug release was observed with F4 (16 % w/w glycerin) comparing to F10 (16% w/w PEG400) and F11 (16% w/w PG) where D_2 min was (63.6%, 56% and 50%) respectively. This is may be due to hygroscopic nature of glycerin which leads to increase the absorption of more humidity by the film resulting in increasing the hydrophilic properties of the film, enlarging the internal spaces in the molecular structure of the polymer by reducing the internal hydrogen bonds between the polymer chains[33].

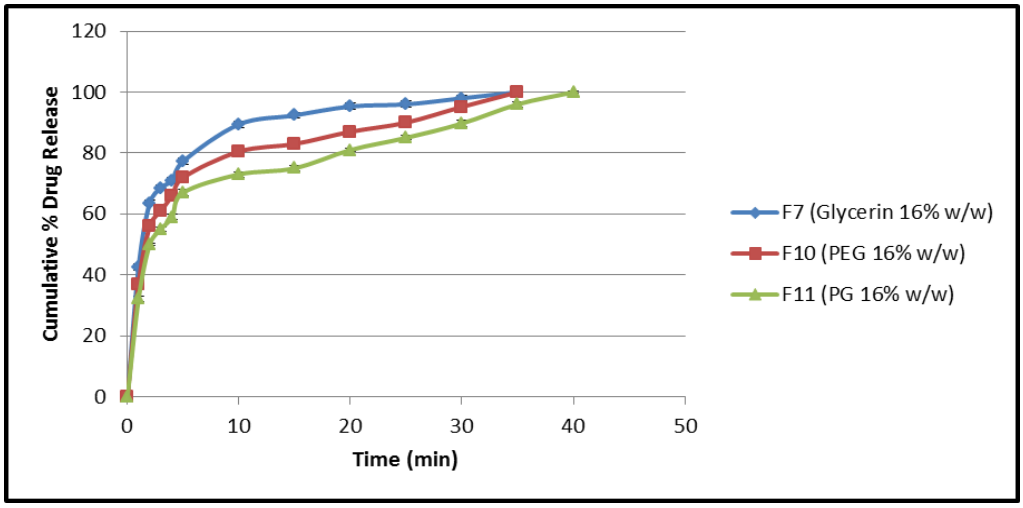


Figure7: Influence of plasticizer type on *In vitro* release profile in phosphate buffer pH 6.8 at 37±0.5°C (n=3) (mean±SD)

Increasing glycerin concentration from 16% w/w (F4) to 20% w/w (F12) resulted in non-significant enhancement ($p<0.05$) in drug release as shown in figure 8were 63.6 % and 68.3 % of drug was released at 2 min respectively. This increase is due to the solubility of glycerin in water [34]; it will generate void spaces in the film through which diffusion occurs more by diffusing out of the polymeric film[35].

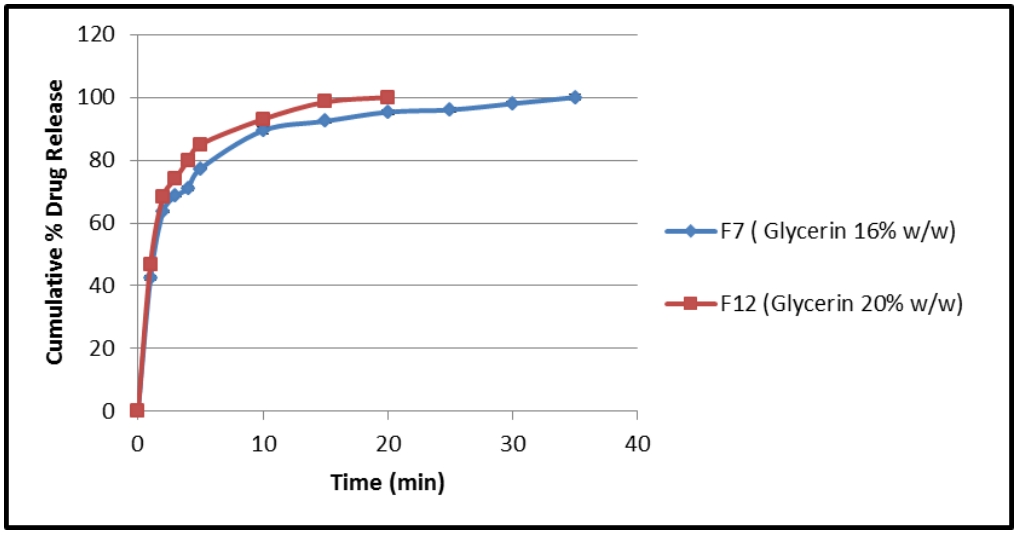


Figure8: Influence of glycerin concentration on *In vitro* release profile in phosphate buffer pH 6.8 at 37±0.5°C (n=3) (mean±SD)

For all prepared film the improvement in the rate of dissolution was followed similar model as enhancing the disintegration time as earlier reported which approved that there is a straight relationship between these parameters except in F12.

Comparison of selected formula F12 with marketed tablet (Meclodin®) for drug release profile in phosphate buffer pH 6.8 as dissolution medium is shown in table 3.

The results illustrated in figure 9 indicated a significant difference ($p<0.05$) in the percent of drug released in phosphate buffer pH 6.8 (at 37^0C) between prepared formula (F12) and conventional tablet, these results showed that higher D_2 min (68.3 %) was observed with the selected formula (F12) in comparison to Meclodin®tablet (26.3 %)., indicating that F12gave fastest dissolution rate compared with traditional tablets, Meclodin ®.

Table 3: ***In-vitro* dissolution parameters of optimized formula and marketed tablet (Meclodin®) in phosphate buffer (pH6.8)at 37°C**

	F12	**Meclodin®**
D_2min	68.3	26.3
T80%	4	9

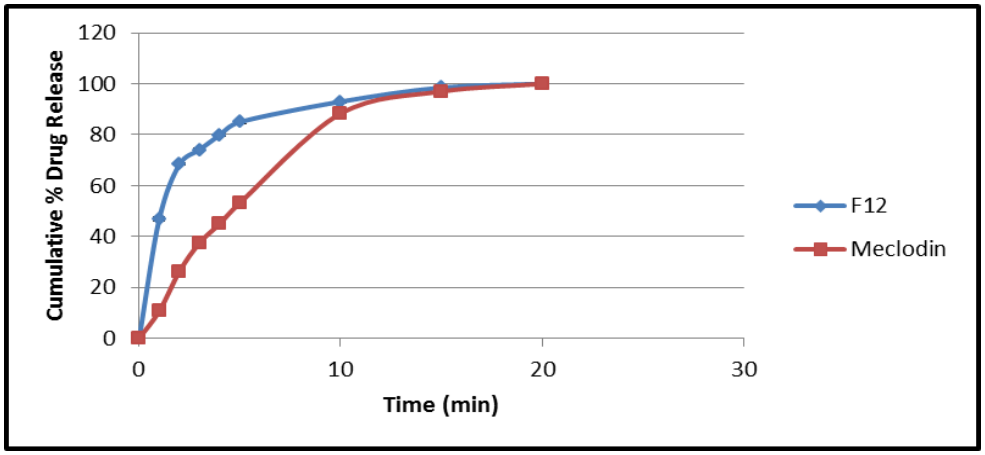


Figure 9:Drug release profile of F12 and marketed tablet (Meclodin®) in phosphate buffer pH 6.8 at 37±0.5°C (n=3) (mean±SD)

Fourier Transform Infrared Spectroscopy

Table 4 shows the characteristic peaks of pure MCP HCl, and the optimized formula (F12). The results demonstrate that there is no significant change in the FT-IR spectra of F 12 in comparison with pure MCP HCl as shown in fig. 10 and 11 respectively which indicates that there is no interaction between the drug and additives.

Table 4: FT-IR spectral for pure MCP HCl and optimum formula F12.

Characteristic groups	Pure drug	F12
O-H stretch	3392	3394
N-H and N-H amide stretch	3192.3	3196.15
C-H stretch	2985.91/2941.54/ 2871.93	2985.91/2943.47/2875.96
C=O amide vibration	1629.9	1629.9
N-H amide bend	1537.32	1539.25
C-O-C vibration	1267.23	1269.2

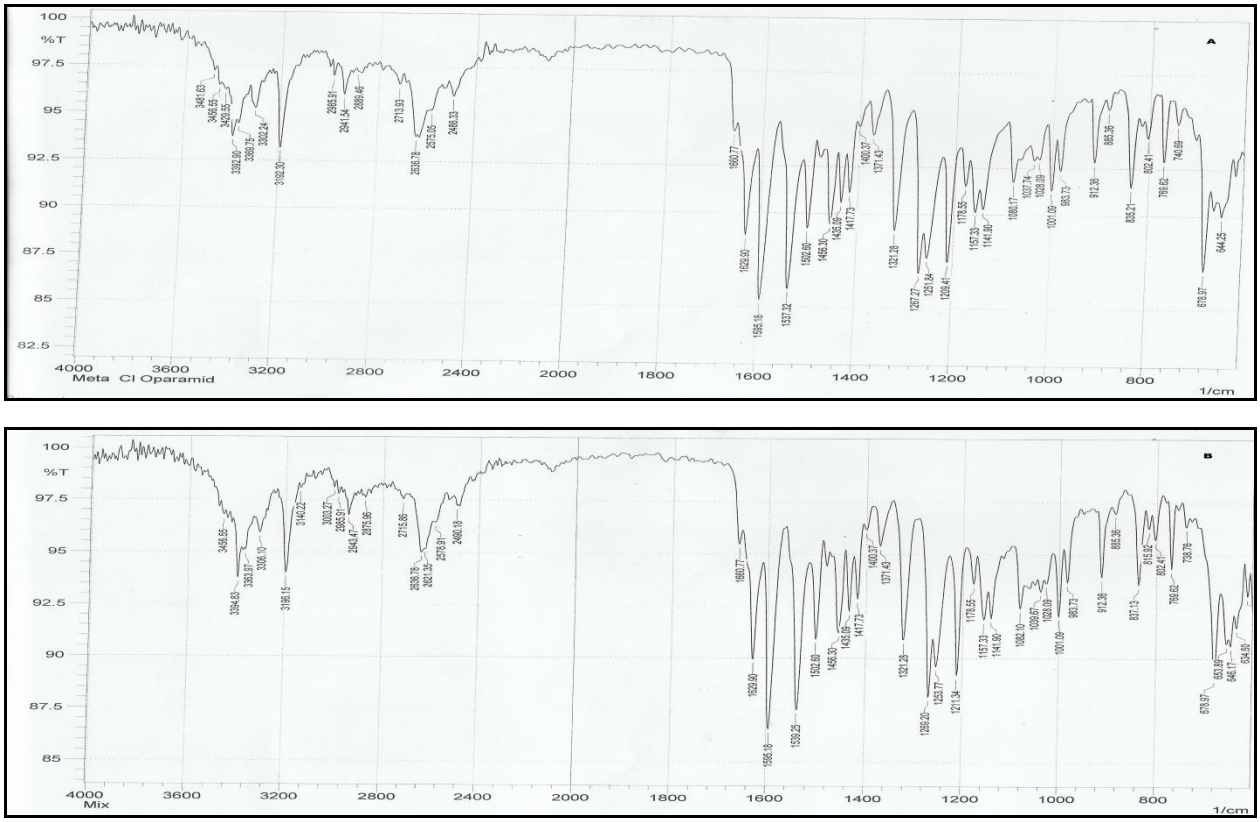


Figure 10 (A and B):FTIR spectrum of MCP HCl pure drug and optimized formula (F12)

Conclusion

In the present study twelve formulas were prepared using different types and concentration of film forming polymers (HEC,HPMC 15 cp and SCMC) and different plasticizers (Gly ,PEG 400 and PG) by employing solvent casting method.

Among the twelve formulas, formula 12 which is prepared using SCMC (54% w/w), Gly (20% w/w) and Tween 80 (6% w/w); stand for low DT with the highest rate of drug dissolution and acceptable physicochemical characteristics was selected as optimized formula.

Acknowledgment

The author would like to express gratitude to Al-Mustansiriyah University (www.uomustansiriyh.edu.iq) Baghdad-Iraq for its support in the present work. The author also would like also to show appreciation to assistant lecturer Ameera A Radhi, assistant lecturer Nora Z Yousif and assistant lecturer Zahraa A Abdulhussain from the department of pharmaceutics, college of pharmacy, Al-Mustansiriyah University, Baghdad-Iraq for their support during the course of this study.

References

1. Patel D, Patel M, Upadhyay P, Shah N, Shah S, A Review on Mouth Dissolving Film. JPSBR, 2015, 5; 266-273.
2. Konar S, Mukhopadhyay A. Fast Dissolving Drug Delivery System: A Novel Approach. IJPBS, 2014, 1; 1-10.
3. Nair V, Saudagar RB, Gondkar SB. A Review on Fast Dissolving Sublingual Films for Systemic Drug Delivery. WJPPS, 2015, 4; 342-361.
4. Joshua JM, Hari R, Jyothish FK, Surendran SA, Fast Dissolving Oral Thin Films: An Effective Dosage Form for Quick Releases, Int. J. Pharm. Sci. Rev. Res., 2016, 38; 282-289.
5. Banarjee T, Ansari VA, Singh S, Mahmood T , Akhtar J, A Review on Fast Dissolving Films for Buccal Delivery of Low Doses Drugs. IJLSR, 2015, 1; 117-123.
6. Sweetman SS, Martindale: The Complete drug reference. 36th ed., London; Pharmaceutical Press, 2009; 589.
7. Jackson JV, Moss MS, Widdp B. Clark's isolation and identification of drugs. Second ed., London; The pharmaceutical press, 1986; 776.
8. Stosik AG, Junginger HE, Kopp S, Midaha KK, Shah VP, Stavchansky S, Dressman JB et al. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Metoclopramide Hydrochloride. J. Pharm. Sci., 2008, 97; 3700- 3708.
9. Goutam K, Garg R, Sharma A, Singh A,Sharma P,Kaushal S. Formulation and Evaluation of Oral Fast Dissolving Films of Promethazine Theoclate. IAJPR, 2015, 5; 2536-2544.
10. Bais PV, Upadhye KP, Dixit G. Formulation and Evaluation of Fast Dissolving Oral Melt in Mouth of Lorazepam for Sublingual. WJPPS, 2016, 5; 763-775.
11. Nair SS , Padmanabhan R, Sreena K. Development and Evaluation of Fast Dissolving Oral Thin Film Containing Prochlorperazine Maleate. EJPMR, 2016, 3; 379-384.
12. SABAR MH. Formulation and In –Vitro Evaluation of Fast Dissolving Film Containing Amlodipine Besylate Solid Dispersion. Int J Pharm Pharm Sci, 2013, 5; 419-428.
13. Poluri K, Mulpur E, Puttugunta SB, Govada. Formulation Development and Evaluation of Novel Oral Soluble Films of Ziprasidone Hydrochloride in the Treatment of Schizophrenia. Int J Pharm Pharm Sci, 2013, 5; 619-627.
14. Swamy NGN, Kumar SS. Formulation and Evaluation of Fast Dissolving Oral Films of Palonosetron Hydrochloride Using HPMC-E5. IJCPS, 2014, 3; 145-150.
15. Vijaya Sri K, Rohini P, Reddy G. Mntelukast Sodium Oral Thin Films: Formulation and In Vitro Evaluation. Asian J Pharm Clin Res, 2012,5;266-270.
16. Hirpara F, Debnath KS, Saisivam S. Optimization and Screening of Different Film Forming Polymers and Plasticizer in Fast Dissolving Sublingual. Int J Pharm Pharm Sci, 2013, 6; 41-42.
17. Kaur M, Bala I, Kamboj A, Jain UK. Formulation and Evaluation of Fast Dissolving Oral Films of Fluvastatine Sodium by Using Taste Technique. JBPRAU, 2016,5; 62-70.
18. Koland M, Sandeep VP, Charyulu NR. Fast Dissolving Sublingual Films of Ondansetron Hydrochloride: Effect of Additives on in vitro Drug Release and Mucosal Permeation. J Yong Pharm, 2010, 2; 216-222.
19. Liew KB, Fung Tan YT, Kok Khiang Peh KK. Characterization of Oral Disintegrating Film Containing Donepezil for Alzheimer Disease.AAPS PharmSciTech. , 2012, 13; 134–142.
20. Nirmala D, Nandhini S, Sudhakar M. Design and Evaluation of Fast Dissolving Oral Films of Zolpidem by Solvent Casting Method. Asian J. Pharm. Res., 2016, 6; 67-71
21. Chinnala KM, Panigrahy RN, Bantu R, Sravanthi B. Formulation and Evaluation of Mouth Dissolving Films Containing Tizanidine Hydrochloride.IJPRHS, 2015, 3; 621-629.

22. Shukla D, Chakraborty S, Singh S, Mishra B. Mouth Dissolving Tablets II: an Overview of Evaluation Techniques. Sci Pharm., 2009, 77; 327–341.
23. Vidyadhara S, Balakrishna T, Sasidhar RLC, Babu CS, Harika DL**.** Formulation and Evaluation of Zolmitriptan Fast Dissolving Buccal Films. Scholar Research Library, 2013, 5; 145-152.
24. Chauhan SS, Lin S, Madan PL. Preparation and Evaluation of Nicotine Hydrogen Tartrate Fast Dissolving Films for Smoking Cessation. Asian Journal of Pharmaceutical Sciences, 2012, 7; 181-192.
25. Devi AS, Jyothi PN, Raju PC, Kumar PK, Prasad KA, Sultana SM. Formulation and Evaluation of Fast Dissolving Oral Films of Fluoxetine Hydrochloride. J Global Trends Pharm Sci, 2016, 7; 3394 – 3400.
26. El MeshadAN, El Hagrasy AS.Characterization and Optimization of Orodispersible Mosapride Film Formulations.AAPS PharmSciTech., 2011, 12; 1384–1392.
27. 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, 2005,18;25-38.
28. Bharkatiya M , Nema RK, Bhatnagar M. Designing and Characterization of Drug Free Patches for Transdermal Application, Int J Pharma Sci Drug Res , 2010, 2; 35-9.
29. Zerbe H.G, Guo J, Serino A. Water Soluble Film for Oral Administration with Instant Wettability**.** U.S. Patent 6177096 2001.
30. Thomas L M .Formulation of floating in situ gel of metronidazol .Int J Pharm Pharm Sci, 2014, 6; 265-269.
31. Scott R.A., Park K., Panitch A., Water Soluble Polymer Films for Intravascular Drug Delivery of Antithrombotic Biomolecules. Eur J Pharm Biopharm, 2013, 84; 125-31.
32. Prabhu P, Malli R, Koland M, Vijaynarayana K, D'Souza U, Harish NM et al. Formulation and Evaluation of Fast Dissolving Films of Levocitirizine Dihydrochloride.Int J Pharm Investig. , 2011, 1; 99–104.
33. Salman ZD, Maraie NK, Alabbassi MG, Mowafaq M. GhareebMM. In Vitro/In Vivo Evaluation and Bioavailability Study of Amitriptyline Hydrochloride from the Optimized Oral Fast Dissolving Films.UKJPB, 2014, 2; 32-42.
34. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. Sixth edition. London: Pharmaceutical press.2009; P.283–285.
35. Radhi A.A, KamalB.A.Formulation and In- vitro Evaluation of Ketotifen Fumarate Oral Strips.IJST, 2012, 7; 53-63.

*****