BUCCOADHESIVE TABLETS OF TRIFLOUPERAZINE: FORMULATION, EVALUATION AND EFFECT OF FORMULATION PARAMETERS

*** Ashti M. H. Saeed**
Address: Mustansiriyah University, college of pharmacy- Baghdad - Iraq
phashti@gmail.com
009647702560198

Ebtihal A. Dakhil
Address: Mustansiriyah University, college of pharmacy- Baghdad - Iraq

Maryam H. Alaayedi
Address: Kerbala University, college of pharmacy- Kerbala- Iraq

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ABSTRACT

Buccal drug delivery has become one of the popular delivery systems due to its comparable and significant advantages over the conventional dosage form. Trifluoperazine is an antipsychotic which is a phenothiazine compound. It is mainly used for schizophrenia. This work presents different formulations of trifluoperazine HCl as a mucoadhesive tablet by using various polymers in order to avoid the effect of 1st pass metabolism; hence, improve the drug bioavailability as well as to obtain better patient compliance. The tablets compressed by direct compression and designed to provide the release of drug from one side and using ethyl cellulose (EC) to cover the other side. Various polymers were employed such as carbapol 934 (CP 934), chitosan, guar gum, sodium carboxymethylcellulose (SCMC), hydroxypropyl methylcellulose K4M (HPMC K4M) and others. The formulations (F1-F12) were undergoing different evaluations as *ex vivo* and *in vitro* methods and statically analyzed the bioadhesion, swelling index and *in-vitro* release of drug. The results showed that F6 which included SCMC in addition to CP 934 was giving the optimum release of 91.95%, swelling index of 87 after 6 hours and mucoadhesive strength equal to 20.12 g.

تصنيع وتقييم حبوب لاصقة ببطانة الفم ودراسة تاثير عوامل مختلفة عليها

اشتي محمد حسين سعيد*، ابتهال عبد الكاظم داخل*، مريم حسين العايدي**

*كلية الصيدلة/ الجامعة المستنصرية

**كلية الصيدلة/ جامعة كربلاء

الخلاصة

توصيل الدواء من خلال بطانة الخد تعتير ولحدة من اهم طرق اعطاء الدواء بسبب الفوائد العديدة بالمقارنة بطرق اعطاء (توصيل) الدواء المعروفة.ترايفلوبيرازين هو مركب فينوثيزايد يستخدم للاضطرابات النفسية مثل انفصام الشخصية. في هذا

البحث عدد من تشكيلات لحبة الدواء الي مصممه لتلصق في بطانة الخد قد هيأت باستخدام بوليمرات مختلفة من اجل تحسين تواجد الدواء في جسم الانسان وتجنب ايض الدواء في الكبد. الحبات شكلت بطريقة الكبس المباشر وقد صممت بشكل تحرر الدواء بجانب واحد من خلال استخدام الاثل سيليلوز. البوليمرات المستخدمة تشمل كاربوبول 934 وجيتوسان و كواركم وصوديوم كاربوكسي مثل سيليلوز وهايدروكسي بروبل مثل سيليلوز. جميع الحبات المصنوعه خضعت للعديد من الاختبارات التقيمية متضمنه معامل انتفاخ الحبة، قوة الاتصاق بباطن الخد وواختبار تحرر الدواء من الحبة وغيرها. النتائج وضحت ان F6 التي تحتوي على صويوم كاربوكسي مثل سيليوز بالاضافة الى الكاربوبول اعطت افضل نتيجة بتحرير 91.95% من الدواء ومعامل انتفاخ 87 بعد مرور 6 ساعات و قوة التصاق باغشاء باطن الخد مقاربة ل 20.12 غم.

كلمات مفتاحية: حبة لاصقة لبطانة الخد، ترايفلوبيرازين، دلالة الانتفاخ، اختبار تحلل الحبة.

1. INTRODUCTION

Oral delivery system is the preferred route of drug administration since it has number of advantages due to its ease of administration, lower cost and enhances patients' compliance. However, the gastrointestinal tract acidity and enzymatic activity as well as extensive hepatic metabolism are the major drawbacks of oral drug uptake. Transmucosal delivery can be considered as a potential strategy for drug administration since it can avoid most of the oral administration problems.[1,2] Oral mucosa can be used for systemic drug delivery due to its unique physiological characteristics either via sublingual or buccal mucosa. The later comprises of multiple layers of different cell types. Buccal mucosa has a non-keratinized stratified squamous epithelium with approximately 40-50 cell layers, 500- 600 µm thickness and 50.2 ± 2.9 cm^2 surface area. The epithelial layers locate on an elastic and thin lamina properia and submucosa.[2,3] Lamina properia is the basement membrane that separates between epithelium and supporting connective tissue and it is highly nourished with blood vessels which end with jugular vein.[4]

Buccal drug delivery has become one of the popular delivery systems due to its comparable and significant advantages over the conventional dosage form. The buccal mucosa has several advantages as a route of delivery. The oral cavity has lower enzymatic activity than gastrointestinal tract as well as it averts the first pass metabolism in liver.[1,5,6] In addition, buccal mucosa has excellent systemic accessibility, immobile, self-placement possibility for the dosage form and highly nourished with blood supply. Furthermore, the applied dosage forms can be removed at any time. Finally, patients' compliance and acceptance will be enhanced with this route since it is non-invasive.[7]

In order to develop a buccal delivery system for a drug, mucosal adhesion of the drug dosage system is a key element. Buccoadhesive dosage form of a drug is an interaction between a drug carrier polymer (and other excepients) and the mucin in the buccal mucosa surface. These substances can be wetted by the mucous and fluidity which allow an optimum adsorption of polymer and penetration of the carried drug passively.[8,9,10]

Trifluoperazine is an antipsychotic which is a phenothiazine compound. It is mainly used for schizophrenia. It is indicated for use in severe nausea and vomiting, agitation and patients with behavioural problems, as well as severe anxiety. Trifluoperazine extensively metabolized in the liver; therefore it is one of the candidate medicaments for buccoadhesive formulation since it avoids the first pass metabolism in liver and increases bioavailability, minimizes the dose, reduces

the side effects, and improves patient compliance.[11] The aim of this study is to formulate trifluoperazine HCl as a mucoadhesive tablet using different polymers in order to improve the drug bioavailability.

2. MATERIALS AND METHODS

2.1. Materials

Carpabol 934 (CP 934), polyvinylpyrrolidone (PVP) K30, and sodium carboxymethyl cellulose (SCMC) were bought from Wuhan Senwayer Century Chemical Co., Ltd. (China). Trifluoperazine HCl, ethyl cellulose (EC), lactose, talc, magnesium stearate, hydroxypropyl methyl cellulose (HPMC) K4M, chitosan and guar gum were purchased from Baoji Guokang Bio-Technology Co.,Ltd. (China). Sodium alginate was supplied from SD fine-chem limited (Mumbai-India). All other reagents used were of analytical grade.

2.1. Methods

2.1.1. Formulation of mucoadhesive bilayer tablets

Twelve formulas of Trifluoperazine HCl mucoadhesive tablets were prepared, as shown in Table 1. All tablets were prepared by direct compression methods. The tablet core ingredients were accurately weighted and blended in a mortar with a pestle in order to obtain homogenous mixture then compressed with tablet machine. After the compressing the, EC was added and again compressed to obtain bilayer mucoadhesive tablet.[12,13]

Table 1: Different formulations of Trifluoperazine HCl mucoadhesive tablets

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
TFP	10	10	10	10	10	10	10	10	10	10	10	10
Carpabol	5	10	5	10	20	5	10	20	30	10	30	10
Na alginate	40	30	-	-	-	-	-	-	-	-	-	-
HPMC K4M	-	-	40	30	20	-	-	-	-	-	-	-
SCMC	-	-	-	-	-	40	30	20	-	-	-	-
Guar gum	-	-	-	-	-	-	-	-	-	-	10	30
Chitosan	-	-	-	-	-	-	-	-	10	40	-	-
Na saccharin	1	1	1	1	1	1	1	1	1	1	1	1
EC	20	20	20	20	20	20	20	20	20	20	20	20
Lactose	81	86	81	86	81	86	86	86	86	76	86	86
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Mg stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight	160	160	160	160	160	160	160	160	160	160	160	160

4.1.1. Evaluation the flow properties for the pre-compressed tablet powder

4.1.1.1. Angle of repose

This test was performed using funnel and petri dish method. The physical mixture of each formula was poured into the fixed funnel to be allowed for flowing over a known diameter petri dish, the angle of repose of the powder was calculated according to the equation below:

$$\text{Tan } Ø = h/r$$

Where *Tan Ø* is the tan of the angle, *h* is the resulted con height after pouring, *r* is the fixed petri dish radius.[14]

2.1.1.2. Compressibility index (Carr's index)

A powder sample of each formula was poured into graduated cylinder of 10 ml capacity to measure the initial bulk volume (V_0), then the cylinder subjected to constant tapping until a constant volume of the powder was achieved (V_t). Carr's index was calculated as following: [14]

$$\text{Compressibility Index} = [(V_0 - V_t)/ V_0] * 100$$

2.1.2. Evaluation of Trifluoperazine buccoadhesive tablet

2.1.2.1. Hardness of tablet

Hardness of three mucoadhesive tablets of each formula was measured using manual hardness tester (Vanguard, USA).

2.1.2.2. Friability of tablet

Friability test was performed using tablet friability test apparatus ((Vanguard, USA). Twenty pre-weighed tablets were rotated at 25 rpm for 4 min, and then the tablets were de-dusted with piece of cloth and reweighed. The percentage friability was measured using following equation.

$$\% \text{ Friability} = (W_0 – W)/ W_0 \times 100.$$

Where W_0 is the weight of the tablets before test, W is the weight of the tablet after test.[14]

2.1.2.3. Thickness of tablet

Thickness of three tablets selected randomly of each formula was measured using digital micrometre calliper.

2.1.2.4. Surface pH of the tablet

The surface pH of the tablets was determined using a combined glass electrode (Ohaus, USA). Tablet was left to swell by keeping it in contact with 1 ml of the buffer (pH=6.8) for 2 hours at room temperature. The pH was measured with the electrode.[14]

2.1.2.5. Weight variation

This test was performed by weighing 20 tablets individually which selected randomly from each formula. The average weight and standard deviation of 20 tablets were calculated.[14]

2.1.2.6. Content uniformity

Five tablets from each formula were grinded in a mortar with pestle and amount from the powder equivalent to 10 mg of the drug was taken and extracted with 60% methanol in conical flask by vigorous shaking. The resulted mixture was filtered, then the filtrate diluted with the buffer to make 10 mcg/ml concentrations and the concentration was measured at 256 nm with UV spectroscopy and the validated calibration curve equation used as mentioned above.[14]

2.1.2.7. Swelling study for the tablet

This test was performed by putting the tablet on glass cover slide and its weight was recorded. The tablets with the stacked glass slide were put into petri dish filled with 15 ml phosphate buffer solution (pH 6.8). The swelled tablet with the cover slide glass was removed from the petri dish and weighted frequently over regular time intervals (1, 2, 4 and 6 hours). The swelling index was calculated according to the equation below:

$$\text{Swelling Index} = (W_1\text{-}W_0)/W_0 * 100$$

Where W_1 is the weight of the swelled tablet and W_0 is for the tablet before the test.[8]

2.1.2.8. Mucoadhesive strength study

The ex vivo bioadhesion strength of the tablet was determined by using especially designed balance. Fresh sheep intestine was used since the intestine provide flat and uniform surface.[15] The membrane was tied to the vial which was fitted into a beaker filled with pH 6.8 phosphate buffer which touched the mucosal surface. The tablet stacked to the lower part of a stopper. Then, 5g weight on the right-hand pan was used to keep the balance two sides equal before the study. The used weight was removed from the right-hand pan that was lowered the pan along with the tablet over the mucosa. A force was applied on the left pan side by adding water drop wise until complete detachment of the tablet, after leaving the balance was kept in the previous position for 2 minutes contact time. The mucoadhesive strength represents the amount of water added (in grams) minus the weight of the preload, and the mucoadhesive force was calculated from the following equation:[16]

$$\text{Mucoadhesive force (N)} = \text{Mucoadhesive strength X } 0.0098$$

2.1.2.9. Determination of *ex vivo* residence time

The ex vivo residence time of the tablet was measured using fresh sheep intestine mucosa. The mucosa attached in the internal side of a beaker and a side of the tablet wetted with 1 ml of the phosphate buffer, then attached to the fixed mucosa. The beaker was filled with 800 ml of the buffer. A stirring rate of 150 rpm was applied after 120 seconds to simulate the normal buccal movement. Time recorded and tablet behaviour was monitored till complete detachment of tablet occurred.[17]

2.1.2.10. *In vitro* drug release study

Trifluoperazine release from the buccoadhesive tablets was performed using USP type II (paddle type) dissolution test apparatus (Pharma Test, 63512 Hainburg-Germany). The tablets were formulated to release the drug from one side only using EC as impermeable backing membrane on the other side. Therefore, the tablet was fixed on 2X2 cm glass slide with an adhesive solution of cyanoacrylate. The tablet with the glass slide was placed into the dissolution apparatus which

containing 900 ml of phosphate buffer (pH 6.8) and the paddle was rotated at 50 rpm at 37°C. Samples of 5 ml were drawn at regular time interval during 6 hours study and replaced with the same amount of fresh buffer, then analyzed spectroscopically.[18, 19]

2.1.3. Drug-excipients interaction

The compatibility between pure trifluoperazine and all excepients were determined used FTIR. The drug and the excipients were mixed with potassium bromide (IR grade). The resulted pellets were scanned over 4000-400 cm^{-1} wavelength.

2.1.4. Statistical analysis

Statistical analysis was performed using One-way ANOVA (GraphPad Prism 7.00, USA).The difference is considered statistically significant when ($P < 0.05$).

3. RESULTS AND DISCUSSION

3.1. Angle of repose and Carr's index

The tests results in Table 2 which showed that the powder blends of the formulas had acceptable flow characters and tablets could be obtained by direct compression method.[14]

3.2. Evaluation of the mucoadhesive tablets

3.2.2. Tablet hardness, friability, surface pH, thickness, content uniformity and weight variation

In this study, Trifluoperazine buccoadhesive tablet was prepared using different amount of polymers including CP 934, HPMC, SCMC, PVP, PEG, guar gum and chitosan. EC was utilized as backing layer. The physicochemical evaluations of the buccoadhesive tabet formulas, as shown in Table 2, indicate that the tablets hardness was within range of 4.99 ± 0.05 to 6.5 ± 0.02 kg/cm^2 and thickness of 3.3 ± 0.3 to 3.34 ± 0.2 mm. The drug weight uniformity and the content analysis of the prepared formulations have shown that the process adopted for punching tablets in this investigation is capable of giving films with a minimum intra-batch variability and uniform drug content. The percentage friability of the prepared formulations was within acceptable range, <1%.[14,18] The surface pH of the tablets demonstrates their safety since it was within the pH of the buccal cavity range of 5.8-7.4 and which cannot cause mucosal irritation.[20]

The surface pH of the tablets was determined in order to investigate the possibility of any side effects, as shown in Table 2, as the acidic or the alkaline pH may cause irritation to the buccal mucosa. All formulations exhibited surface pH within satisfactory limits (5.8-7.4).[21]

Table 2. Rheology characteristics of the formulas powder blend

Formula No.	Angle of repose	Carr's index	Flow property
F1	25	15.9	Excellent/Good
F2	24.2	15.3	Good
F3	31	21	Good/Fair
F4	32	19.3	Good/Fair

F5	32.4	18	Good/Fair
F6	24	15	Good
F7	23.7	14.1	Good
F8	23	13.5	Good
F9	25	17	Excellent/Good
F10	26.8	19	Excellent/Fair
F11	22	16.9	Fair
F12	25	18	Excellent/Fair

Table 2. Physico-chemical parameters of different formulations of Trifluoperazine buccoadhesive tablet, all results represent mean ± SD (*n* = 3).

Formulations	Surface pH	Thickness (mm ± SD)	Weight variation (g ± SD)	Friability (% ± SD)	Hardness (kg/cm^2 ±SD)	Drug content (% ±SD)
F1	6.01 ± 0.21	3.32 ± 0.24	0.161 ± 0.003	0.044 ± 0.002	6.2 ± 0.02	98.96 ± 0.43
F2	6.2 ± 0.22	3.3 ± 0.3	0.162 ± 0.004	0.021 ± 0.003	5.5 ± 0.03	99.1 ± 0.32
F3	6.08 ± 0.36	3.31 ± 0.19	0.160 ± 0.002	0.054 ± 0.007	5.12 ± 0.12	99 ± 0.14
F4	5.83 ± 0.15	3.32 ± 0.22	0.159 ± 0.006	0.114 ± 0.003	6.5 ± 0.02	97.9 ± 0.23
F5	5.96 ± 0.19	3.31 ± 0.13	0.159 ± 0.009	0.024 ± 0.004	6.02 ± 0.03	97.96 ± 0.7
F6	6.29 ± 0.31	3.32 ± 0.25	0.162 ± 0.005	0.014 ± 0.005	5.33 ± 0.04	98.88 ± 0.65
F7	6.03 ± 0.18	3.33 ± 0.31	0.16 ± 0.004	0.032 ± 0.002	4.99 ± 0.05	98.73 ± 0.3
F8	5.87 ± 0.21	3.34 ± 0.2	0.161 ± 0.002	0.064 ± 0.003	5.11 ± 0.03	98.12 ± 0.65
F9	6.13 ± 0.2	3.31 ± 0.11	0.16 ± 0.008	0.034 ± 0.003	6.24 ± 0.07	99.13 ± 0.42
F10	5.79 ± 0.24	3.31 ± 0.14	0.158 ± 0.009	0.052 ± 0.005	6.18 ± 0.06	97.91 ± 0.34
F11	6.11 ± 0.28	3.32 ± 0.18	0.159 ± 0.004	0.04 ± 0.004	5.81 ± 0.03	98.6 ± 0.22
F12	5.93 ± 0.32	3.31 ± 0.17	0.16 ± 0.001	0.047 ± 0.002	6.3 ± 0.05	98.74 ± 0.18

3.2.3. Swelling study

This test is essential to study the swelling, adhesion and release of the drug from the tablet. The results demonstrated that the amount and nature of the used polymer significantly affect the swelling of the tablet. All the obtained results represent in Table 3. It has been found that the amount of the CP 934 did not affect the swelling index because the carboxylic acid group of the CP 934 ionized at high pH resulting in ionic repulsion of the polymer molecules. Another theory suggests that increasing the amount of CP 934 could help increase the swelling index by enhance the repulsion with the ionic polymer. Sodium alginate and SCMC easily wetted by water therefore adding these polymers to CP 934 significantly help increase swelling of the tablet. The tablets containing SCMC polymer in different proportion showed that they provided better swelling index,

F6 with highest index of 87 ± 1.16, then F8 85 ± 2.01 and F7 82 ± 1.94 and increasing the amount of the polymer significantly improved swelling. The formulations containing combination of CP 934 and HPMC demonstrated good swelling which resulted from increasing the repulsion between molecules and then swelling.[20,22,23,24]

3.2.4. Mucoadhesive strength and time study

Mucoadhesive study for all formulas were conducted and the results shown in Table 4 and Figure 1. The formulations containing increasing amount of CP 934 significantly has high mucosal adhesion strength due to the ability of the polymer to form mucobioahesion bonds with the mucin which increasing tablet swelling and drug release.[25,26] These hydrogen secondary bonds which considered as the main factor that enhances the tablet adhesion because of its carboxylic groups and this also recorded with Na alginate, HPMC and SCMC. However, chitosan and guar gum, had lowest strength due to the ionic interaction between the anionic natural polymers and cationic CP 934 which prevents some of hydrogen bonds to form.[20,27,28,29]

The adhesion time is the time required for complete detachment of the tablet from the buccal mucosa surface. The results are between 4 ± 0.3 and 10 ± 0.5, as illustrated in Table 4, and that is occurred due to the different in the polymer combination between the formulas. Mucoadhesion resident time was found to be increased with increasing concentration of CP 934 because of CP 934 high mucoadhesive nature.[8,20,26,30]

Table 3. Swelling index of Trifluoperazine formulations, all results represent mean ± SD (*n* = 3).

Formula No.	Time (hr)			
	1	2	3	6
F1	19 ± 0.98	23 ± 0.83	29 ± 0.92	64 ± 1.05
F2	16 ± 0.65	22 ± 0.42	28 ± 0.36	57 ± 0.68
F3	25 ± 1.34	29 ± 2.03	35 ± 1.89	53 ± 1.75
F4	28 ± 1.45	32 ± 2.06	35.9 ± 2.14	59 ± 2.58
F5	29 ± 0.85	33 ± 0.99	41 ± 0.47	62 ± 0.79
F6	29 ± 1.54	40 ± 2.01	58 ± 1.94	87 ± 1.01
F7	33.47 ± 2.42	35 ± 2.49	50 ± 0.3	82 ± 1.16
F8	28 ± 2.12	36 ± 3.02	48 ± 3.57	85 ± 2.94
F9	6 ± 1.05	7 ± 0.67	9 ± 0.58	14 ± 1.77
F10	7.57 ± 0.49	9 ± 0.58	12 ± 0.89	17 ± 1.18
F11	5.1 ± 0.34	7.6 ± 0.53	7.91 ± 0.42	11.73 ± 1.3
F12	4.56 ± 0.26	6.84 ± 0.42	7.5 ± 0.45	10.47 2.3

Table 4. Measurements of bioadhesive strength of Trifluperazine different formulations, all results represent mean ± SD (*n* = 3).

Formulation	Mucoadhesive strength (g)	Mucoadhesive strength (N)	Mucoadhesive residence time (hr)
F1	14.6 ± 0.3	0.143	6.25 ± 0.3
F2	16.4 ± 0.2	0.161	6.5 ± 0.2

F3	15 ± 0.77	0.147	6 ± 0.14
F4	16.7 ± 0.34	0.164	6.5 ± 0.32
F5	18.7 ± 0.62	0.183	7.25 ± 0.6
F6	20.1 ± 0.74	0.197	10 ± 0.5
F7	19.2 ± 0.42	0.188	8.75 ± 0.25
F8	17.5 ± 0.25	0.172	9.5 ± 0.5
F9	10.1 ± 0.4	0.099	5.6 ± 0.3
F10	12 ± 0.5	0.118	6.2 ± 0.2
F11	10.5 ± 0.5	0.103	4.5 ± 0.15
F12	9.6 ± 0.4	0.094	4 ± 0.3

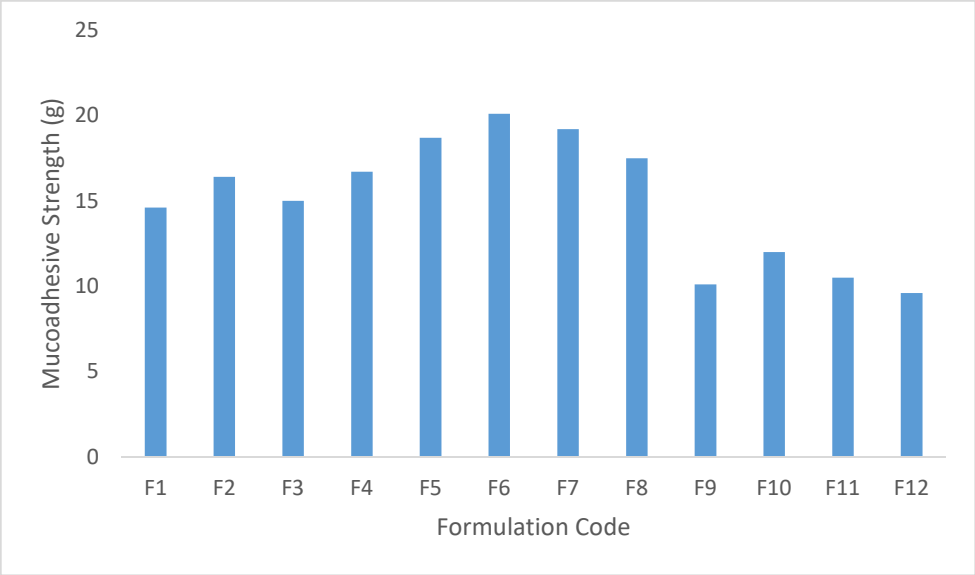

Figure 1. Buccoadhesive Strength of trifluoperazine tablet formulas.

3.2.5. *In-vitro* drug release studies

Triflouperazine tablets release study, as illustrated in Figure 2, showed that F6 has the highest release of drug with 91.95%. The formulations containing SCMC and HPMC in addition to CP 934 in a proportion of 3:1 (F6) and 2:2 (F5) had a highest release of the drug of 91.95 ± 3.1% and 88.12 ± 2.93%, respectively. It was concluded that the percent of the drug release from the tablets was found to be increased with increasing the concentration of CP 934 accompanied with decreasing the concentration of SCMC. This could be due to increased hydration and swelling of CP with increasing concentration and due to SCMC low viscosity which facilitate the dissolution media penetration within the highly CP 934 viscous gel layer leading to Trifluoperazine release. Formulas containing HPMC in addition to CP 934 had lower percent of drug release compared with SCMC formulas which is because of the synergistic increase in the viscosity resulting from competent water uptake of CP 934 and HPMC leading to the strong gel layer formation and consequently lower drug dissolution. A Trifluoperazine release was decreased with increasing HPMC K4M concentration. It could be resulted from the interaction between two oppositely charged bioadhesive polymers of CP 934 (anionic) and HPMC K4M in formulations F3 to F5. The formulations with chitosan and guar gum had lower drug release than others because of their

nature and their ability to interact with CP 934 to form complex that negatively affected the trifluoperazine release from the tablet.[20,31,32,33]

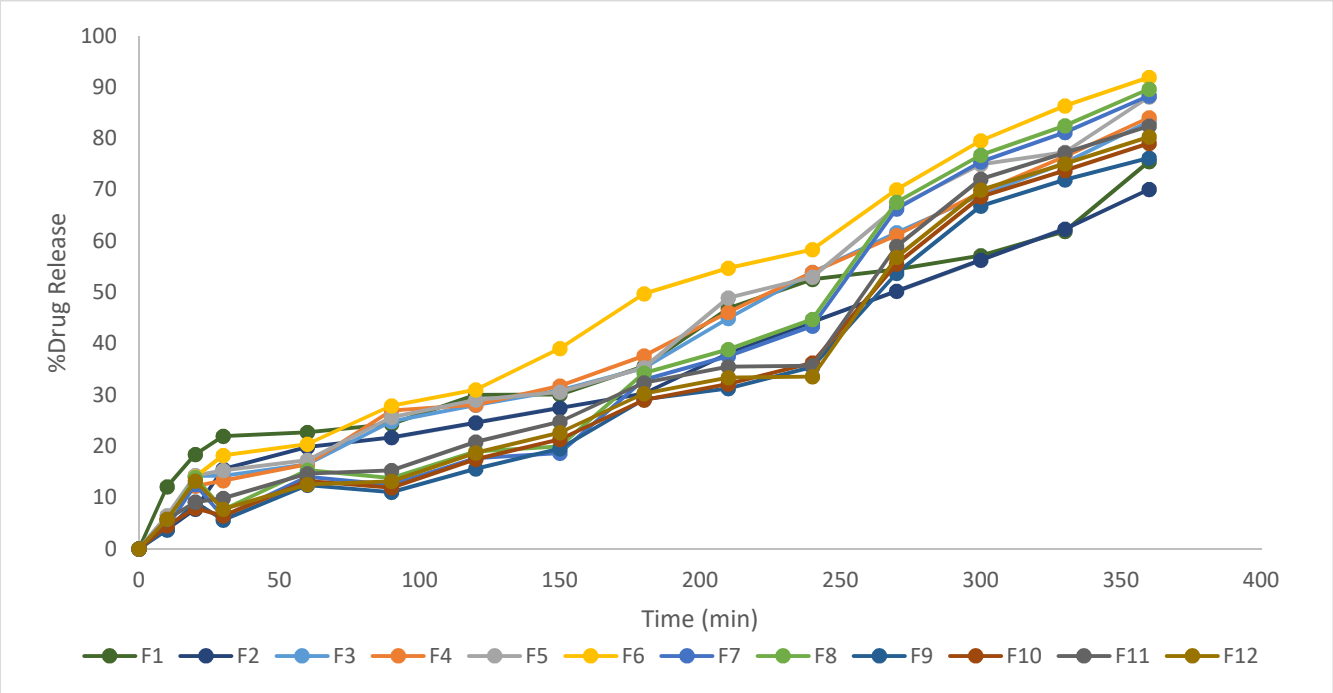

Figure 2. Percent of drug release of different trifluoperazine formulas.

3.3. Trifluoperazine excipients study

FTIR spectra for the pure drug alone, its combination with other excipients and the optimum formula had been obtained. The spectra indicated that there is no interaction between trifluoperazine and the additives since the drug identification peaks were present.

4. CONCLUSION

The triflouperazine HCl buccoadhesive tablets had been successfully prepared using different natural and synthetic polymers. However, not all the formulations provided the promising results. Formulas include HPMC K4M and SCMC with adding the carbapol 934 revealed the optimum results and could reduce the dose needed and the frequency of drug, consequently, improve the bioavailability.

5. REFERENCES

1. Patel VF, Liu F and Brown MB, Advances in oral transmucosal drug delivery, Journal of Controlled Release, 2011, 153(2), 106-16.
2. Iyire A, Alaayedi M and Mohammed AR, Pre-formulation and systematic evaluation of amino acid assisted permeability of insulin across in vitro buccal cell layers, Nature journal; Scientific reports, 2016, 6(32498), 1-14.
3. Hao J and Heng PW, Buccal delivery systems, Drug Development and Industrial Pharmacy, 2003, 29(8), 821-832.
4. Sudhakar Y, Kuotsu K and Bandyopadhyay AK, Buccal bioadhesive drug delivery-a promising option for orally less efficient drugs, Journal of Control Release, 2006, 114(1), 15-40.

5. Khafagy el-S, Morishita M, Onuki Y and Takayama K, Current challenges in non-invasive insulin delivery systems: a comparative review, Advanced Drug Delivery Reviews, 2007, 59(15), 1521-46.
6. Kumria R and Goomber G, Emerging trends in insulin delivery: Buccal route, Journal of Diabetology, 2011, 2(1), 1-9.
7. Heinemann L and Jacques Y, Oral Insulin and Buccal Insulin: A Critical Reappraisal, Journal of Diabetes Science and Technology, 2009, 3(3), 568–584.
8. Jaffar IS and Maraie NK, Formulation and In vitro Evaluation of Buccal Mucoadhesive Tablets of Promethazine HCl, Int. J. Pharm. Sci. Rev. Res., 2014, 24(1), 61-69.
9. Divani MJ, Patel KR, Patel NM, Review on mucoadhesive drug delivery system. International Journal of Universal Pharmacy and Bio Sciences, 2013, 2(1), 35-48.
10. Shaikh AA, Pawar YD, Kumbhar ST, Effect of Chitosan and Sodium Alginate on mucoadhesion and drug release of Itraconazole tablets, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2012, 3(1), 293-297.
11. Asperheim MK and Favaro J, Introduction to Pharmacology, Elsevier: Saunders, 2012.
12. Arun Prasanth B, Sankaranand R, Venugopal V, Sathvika P, Pranitha R and Ashritha M, Formulation and evaluation of bucco-adhesive tablets of insulin using locust bean gum, International journal of research in pharmacy and chemistry, 2011, 1(2), 172-178.
13. Miyazaki S, Kawasaki N, Nakamura T, Iwatsu M, Hayashi T, Hou W M, Attwood D, Oral mucosal bioadhesive tablets of pectin and HPMC: in vitro and in vivo evaluation, Int. J. Pharm, 2000, 204, 127–132.
14. The United State Pharmacopeia (USP) 30, NF28, 2010, USA: The United State Pharmacopia Convention Inc.
15. Nafee NA, IsmailF A, Boraie NA, Mortada LM, Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing, Int. J. Pharm, 2003, 264, 1–14.
16. Patel AA, Patel K, Patel M, Patel N, Formulation and evaluation of mucoadhesive buccal Adhesive tablets of venlafaxine HCl, American Journal Of Pharmatech Research, 2012, 2(3), 1081-1100.
17. Perioli L, Ambrogi V, Rubini D, Giovagnoli S, Ricci M, Blasi P, Rossi C, Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease, J. Control. Release, 2004, 95, 521– 533.
18. Vidya S, Archana P, Vandana P and Prafulla S, Characterization of natural polymers from jackfruit pulp, calendulaflowers and tara seeds as mucoadhesive and controlled release components in buccal tablets, International Journal of Biological Macromolecules, 2017, 95, 321-330.
19. Reddy KA, Venugopal K, Formulation and in vitro evaluation of buccal tablets of piroxicam, Int. J. Chem. Sci, 2012, 10(1), 399-412.
20. Raju KN, Velmurugan S, Deepika B, Vinushitha S, formulation and in-vitro evaluation of buccal tablets of metoprolol tartarate, International Journal of Pharmacy and Pharmaceutical Sciences, 2011, 3(2), 239-246.
21. Parth S, Patel Ashish M, Parmar Nilang S, Doshi Hardik V, Patel Raxit R, Patel Chetan Nayee, Buccal Drug Delivery System: A Review, International Journal of Drug Development and Research, 2013, 5(3), 35-48.

22. Bakde BV, Chandewar AV, Kshirsagar MD, Design, development and in vitro characterization of deltiazem buccoadhesive tablet, International Journal of Pharmaceutical Research And Development, 2011, 3(11), 83-92.
23. Perioli L, Ambrogi V, Rubini D, Giovagnoli S, Ricci M, Blasi P, Rossi C, Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease, J. Control. Release, 2004, 95, 521– 533.
24. Khan GM, Zhu JB, Studies on drug release kinetics from ibuprofen–carbomer hydrophilic matrix tablets: influence of co-excipients on release rate, J. Control. Release, 1999, 57, 197–203.
25. John AS, Sathesh BPR, Divakar G, Jangid MK, Purohit KK, Development and evaluation of buccoadhesive drug delivery system for atorvastatin calcium, Journal of Current Pharmaceutical Research, 2010, 1, 31-38.
26. Pathak K, Sharma V, Akhtar N, Rastogi P, Localization of fluconazole in oral cavity by preferential coating of buccoadhesive tablet for treatment of oral thrush, International Journal of Pharmaceutical Investigation, 2016, 6(2), 106-115.
27. Wadageri GV, Raju SA, Shirsand SB, P Vijay, Reddy PVP, Design and evaluation of mucoadhesive bilayer buccal tablets of Atenolol, Int. J. Novel Drug Deliv. Tech, 2012, 2(1), 256-264.
28. Singh S, Govind M, Bothara SB, A Review on in vitro - in vivo mucoadhesive strength assessment, PharmaTech Medica, 2013, 2(1), 211-229.
29. Russo E, Selmin F, Baldassari S, Gennari CGM, Caviglioli G, Cilurzo F, Minghetti P, Parodi B, A focus on mucoadhesive polymers and their application in buccal dosage forms Journal of Drug Delivery Science and Technology, 2016, 32, 113-125.
30. Prasanth VV, Mudiyala S, Mathew ST, Kamalakkannan V, Mathappan R, Mucoadhesive tablets of lisinopril for buccal drug delivery: Development and characterization, Drug Invention Today, 2011, 3(5), 49-51.
31. Patel MC and Patil CC, Formulation and Evaluation of Mucoadhesive Buccal Tablets of Repaglinide, RGUHS J Pharm Sci, 2014, 4(4), 156-165.
32. Singh I, Kumar P, Kumar S, Rana V, Formulation and development of matrix tablet of tramadole using katira gum as release modifier, Yakugaku Zasshi, 2010, 130(9), 1225-1231.
33. Prasanna RI, Anitha P and Madhusudhana Chetty, C, Formulation and Evaluation of Bucco-Adhesive Tablets of Sumatriptan Succinate, Int J Pharm Investig 2011, 1(3), 182-191.