

Formulation of nicotine mucoadhesive tablet for smoking cessation and evaluation of its pharmaceuticals properties

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Abstract

Background: Nicotine replacement therapy (NRT) with gradual decreasing of nicotine is one of the smoking cessation methods. Mucoadhesive formulations are among the novel drug delivery systems that are available in the form of tablets and films, and can be used for NRT. Mucoadhesive nicotine tablets when placed in the upper gum will attach to the buccal mucosa and release nicotine content in a controlled manner. This will meet the immediate and long-term need of the individual to the nicotine, such that the person can decrease his/her dependency on smoking.^[1]

Materials and Methods: In this study, the tablets were prepared using different conventional bioadhesive polymers such as Hydroxypropyl Methycellulose (HPMC) 50cps, sodium carboxy methyl cellulose (NaCMC), and carbapol 934 (CP934) in singular or mixture form. Magnesium hydroxide were used as the pH increasing agent; magnesium stearate as the lubricant; and lactose as the excipient. Nicotine hydrogen bitartrate, more stable than the liquid, was used in different formulations. Pharmaceutics characteristics such as adhesion degree and drug release rate were evaluated.

Results: Increasing of HPMC 50cps in the formulations decrease speed release of nicotine. The carbapol in formulations beget slow releasing of nicotine. With increasing the percent of lactose, the rate of release in formulations was increased. Formulations, which have HPMC 50cps has best adhesiveness and the formulations contains carbapol had not suitable adhesiveness. Formulations contains NaCMC were very fast release and had not suitable adhesiveness.

Conclusion: The formulation contains mixture of HPMC50cps and CP934 was the best because of suitable adhesiveness and minimum swing in release.

Key Words: Mucoadhesive tablet, nicotine, smoking cessation

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INTRODUCTION

The number of cigarette smokers is increasing, and consequently the rate of the diseases resulting from smoking, such as cardiovascular diseases, respiratory diseases, and different types of cancer, especially, head and neck, and lung cancers is growing. These lead to different problems for the smokers and community's

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health system. Therefore, it is reasonable to find ways to decrease these problems and help the smokers quit smoking. It was demonstrated in different studies that willingness to quit smoking is high in individuals who became aware of their disease in the early stages of head and neck and lung cancers. Therefore, pharmacotherapy for smoking cessation may be helpful in these patients.^[2] Smoking cessation is a very hard process, and the most important element in the process is the actual willingness of the smoker. The consultations and medical prescription provided by medical care providers can help the smokers who are willing to quit smoking. One of the methods of smoking cessation is Nicotine Replacement Therapy (NRT), in which maintenance of the individual's daily need to nicotine would facilitate the smoking cessation process. Using the method, the cessation symptoms will decrease and also the desire for the cigarette smoking would be less.^[3]

Nicotine is an alkaloid medicine, present in the leaves of *Nicotiana tabacum*. The substance has different effects on the central and autonomous nervous system. Nicotine is agonist of cholinergic receptors and leads to increased secretion of saliva, and increased gastric movements and acid secretion. Moreover, it causes catecholamine release, heart stimulation, and contraction of peripheral vasculars. Nicotine is a nervous system stimulant, which leads to increased consciousness, concentration, and attention; as well as decreased appetite. Frequent use of nicotine is associated with tolerance and dependency.^[3,4]

Various formulations of nicotine including, gums, skin patches, oral and nasal sprays, lozenges, tablets, and mucoadhesive films have been evaluated in NRT for smoking cessation. Nicotine gums, skin patches, lozenges, nasal sprays, and oral sprays are currently on market throughout the world. The mucoadhesive drug delivery systems are among the novel systems in pharmacy, which have attracted great attention in recent years owing to their ability to adhere to and remain on mucosal surfaces, and their continuous and slow drug release. These formulations can potentially be used in smoking cessation. Since the formulations adhere to the oral mucosa, its nicotine content can be released in controllable manner that meets the immediate and long-term nicotine need of the individual, and thus reduces the individual's dependency on smoking.^[4,5]

Some advantages of mucoadhesive tablets are the ease of production, simple use, the low-cost production process, and appropriate primary release. The complications of nicotine gums include local side-effects of excessive and sudden release of nicotine in the mouth; development of oral, gingival,

and mandibular lesions; tooth decay, tooth damages resulted from gum chewing; jaw pain due to slow and continuous chewing of the gum throughout the day; and peptic ulcer. Mucoadhesive nicotine tablets reduce the occurrence of these complications.^[1,6]

The drug formulation is prepared with a matrix consisted of nicotine hydrogen bitartrate, which is more stable than nicotine, and mucoadhesive polymers such as sodium carboxy methyl cellulose (NaCMC), hydroxyl propyl methyl cellulose (HPMC), and carbapol. Furthermore, magnesium hydroxide is added to formulate on to enhance the absorption of nicotine hydrogen bitartrate from oral mucosa.

MATERIALS AND METHODS

Material

Nicotine hydrogen bitartrate powder (Sigma), HPMC 50cps (Daru Pakhsh Co.), NaCMC powder (Merck), Carbapol 934 NF (Daru Pakhsh Co.), magnesium stearate powder (Merck), magnesium hydroxide powder (Daru Pakhsh Co.), lactose powder (Merck).

Apparatus

Dissolution testers (6 vessels) (Erweka, Germany), double-punch tablet press AR400 (Erweka, Germany), Ultra Violet/Visible double-beam spectrophotometer (UV-1650 PC, Shimadzu, Japan), Sartorius Portable Balance (PT 120, USA), tablet adhesion measurement instrument designed in Shiraz Faculty of Pharmacy, friability measurement instrument (Iran), Erweka-Apparatebau Tablet Hardness Tester (Germany).

General method of nicotine hydrogen bitartrate preparation

First, the calculations required for preparation of 30 tablets for each formulation was performed. The required powders for each formulation were picked, and then the powders were completely mixed. Then, the double-punch and matrix with the diameter of 9 mm was installed on the tablet press instrument, and the desired weight and hardness was manually set on the instrument. The tablets' weight was determined to be 120 mg. Then, the tablet of each formulation was prepared manually with the direct pressing method and the amount of weight variation was calculated and kept in the range of $\pm 3\%$. Furthermore, content uniformity was calculated. The hardness of all tablets was set at 4-6 kg.

General method of measurement of tablets' dissolution

Dissolution tester was used to measure the rate of drug release from the prepared matrixes. In all the six vessels of the dissolution tester 500 ml of phosphate buffer with pH 6.8 was poured. After starting the tester, its temperature was set at $37 \pm 0.5^\circ\text{C}$. Considering

the weight light of the tablets and the probability of floatation on the solvent surface, basket method was used and tablets were kept in the depth of 25 ± 2 mm from the bottom of the vessel. The rotation of stirrers was set at 100 ± 2 rpm. For each formulation, 30 tablets were prepared, from which six tablets were randomly selected for each formulation. The weights of tablets were precisely measured and put in the vessels, inside the solvent. Since the instrument was automatic, there was no need to manually set the distance to the bottom of the vessels. Sampling was carried out in minutes 15, 30, 60, 120, and 180. In each sampling, 5 ml of the solution was picked with a pipette and was replaced by 5 ml of phosphate buffer. The picked samples were transparent and there was no need to sieve them. The absorbance of the solutions against the control phosphate buffered was determined using spectrophotometer.^[7,8]

Preparation of nicotine hydrogen bitartrate formulations from with different polymers

To evaluate the effect of each of polymers, HPMC 50cps, CP934 and NaCMC on release of nicotine hydrogen bitartrate, three sample of each of them were prepared. The ingredients of each formulation are provided in Table 1. Furthermore, to evaluate the effect of mixture of HPMC 50cps, CP934, and NaCMC on release and level of adhesion in tablets, some formulations with different amounts of these polymers, with or without of Lactose were prepared. These formulations are presented in Table 2. In all of formulations magnesium hydroxide with certain amount 19.8 mg is added to the formulation to enhance the absorption of nicotine hydrogen bitartrate from oral mucosa. Furthermore, magnesium stearate was used with certain amount 2.2 mg in formulations. Amount of nicotine hydrogen bitartrate was measured 5.7 mg in formulations with single polymer.

Measurement of the level of adhesion of nicotine hydrogen bitartrate tablets

There are several methods for determination of the level of adhesion of mucoadhesive products, most of which are based upon measurement of the force required for detachment of the product from a smooth surface. To this end, an instrument used that designed in Shiraz Faculty of Pharmacy [Figure 1]. The instrument consists of a fixed column, an elevator, a digital balance attached to a metal frame, and two pieces of smooth glass, between which the product is placed. When the product is placed between the glasses, a shear stress between the two surfaces is developed by twisting a screw and lowering of the mobile part. The value of the stress is measured by the digital balance. The tablets are firstly placed in distilled water for 15 min and then after absorption of water, swelling, and becoming mucilaginous, the tablets were tested by

Table 1: Ingredients of formulations prepared by each of hydroxypropyl methylcellulose 50cps, carbapol 934 and sodium carboxy methyl cellulose

Formulation's code	HPMC (mg)	CP934 (mg)	NaCMC (mg)	Lactose (mg)
F1	70	-	-	2.2
F2	50	-	-	22.2
F3	30	-	-	42.3
F4	-	70	-	2.2
F5	-	50	-	22.2
F6	-	30	-	42.3
F7	-	-	70	2.2
F8	-	-	50	22.2
F9	-	-	30	42.3

CP934: Carbapol 934, HPMC: Hydroxypropyl methylcellulose, NaCMC: Sodium carboxy methyl cellulose

Table 2: Ingredients of formulations prepared by mixture of hydroxypropyl methylcellulose 50cps, carbapol 934 and sodium carboxy methyl cellulose

Formulation's code	NHT (mg)	HPMC (mg)	CP934 (mg)	NaCMC (mg)	Lactose (mg)
F10	5.7	20	30	-	-
F11	5.7	20	50	-	-
F12	5.7	20	20	-	-
F13	5.7	15	20	-	-
F14	5.7	-	20	20	-
F15	5.7	-	25	15	-
F16	5.7	-	15	25	-
F17	5.7	50	-	20	-
F18	5.7	30	-	20	-
F19	5.7	40	-	20	-
F20	5.7	30	20	-	22.3
F21	5.7	30	20	-	-
F22	11.4	20	50	-	2.1
F23	11.4	30	30	-	2.1

NHT: Nicotine hydrogen tartrate, CP934: Carbapol 934, HPMC: Hydroxypropyl methylcellulose, NaCMC: Sodium carboxy methyl cellulose

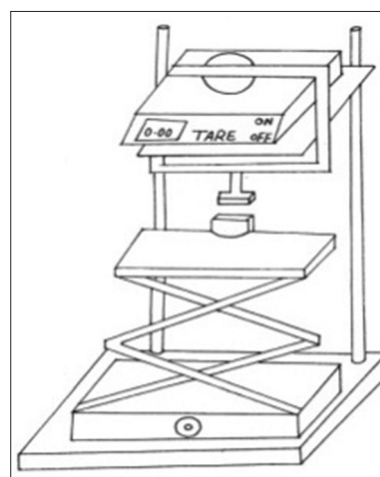


Figure 1: The instrument used for adhesion measurement of tablets

the instrument. Each product is evaluated three times and the average value was reported.

Measurement of hardness of nicotine hydrogen bitartrate tablets

Tablets should have a reasonable level of hardness to be able to bear the strokes during production, packing, and transportation, as well as the mechanical pressures applied by the consumers (for instance, placing the tablets in their bag, pocket, or a box). Tablet hardness is defined as the force required for crushing the tablet in the diagonal axis with a compressive force. To this end, the tablets were placed between the two anvils of the hardness measurement instrument and then were crushed by applying pressure on the anvils in a diagonal direction. The required force for the process was recorded. In this step of the study, for each formulation, five tablets were selected and their hardness was measured.^[1,8]

Measurement of dissolution efficiency (DE) and mean dissolution time (MDT)

DE% and MDT parameters was used to compare the drug release from the formulations.

$$DE \% = \left(\int_0^t y dt / Y_{100} \times t \right) \times 100$$

$$MDT = \left(\sum_{i=1}^n t_{mid} \times \Delta M / \sum_{i=1}^n \Delta M \right)$$

Y_{100} : Total drug loaded

T_{mid} : Average of two consecutive time's t_1 and t_2

ΔM : Drug released between two consecutive times

Measurement of friability of nicotine hydrogen bitartrate tablets

Friction and strokes are the factors that lead to erosion, friability, and crushing of tablets. The level of friability can be measured by friability test. The instrument is composed of a plastic container, which rotates at 25 rpm, and in each rotation, the tablets are dropped from a 15-cm height. To measure the friability of the

tablets, the weight of tablets was firstly recorded, and then the tablets were rotated in the instrument for 4 min (100 rounds). Then, the dust attached to the tablets was removed and the weight of tablets was again measured. If the weight decrease of tablets was 0.5-1%, the tablets were considered to be appropriate for packing. In this step, from each formulation, 10 tablets were selected and after precise measurement of their weight, the friability test was performed. Then, the weight of the tablets was again measured.^[7,9]

RESULTS

Results of nicotine hydrogen bitartrate release from tablets

To evaluate the percentage of nicotine hydrogen bitartrate released from tablets with HPMC 50cps matrix, six tablets were tested from each formulation, and the percentage of nicotine release was determined. The mean and standard deviation of each formulation was determined. The curves of nicotine release for each sample is depicted in Figure 2. As can be observed in the figure, an increase in the amount of HPMC 50cps in the formulation decreased the rate of nicotine release. Furthermore, the formulations have a low fluctuation in the rate of drug release, and release the drug in a short period of time. Furthermore, results of nicotine hydrogen bitartrate release from tablets prepared by CP934 and NaCMC are depicted respectively in Figures 3 and 4.

Results of nicotine hydrogen bitartrate release from tablets prepared by combination of HPMC 50cps and CP934 is depicted in Figure 5. In this formulation, drug released occurs with some delay and when the overall percentage of the polymers increased, the drug release percentage decreased. Results of nicotine hydrogen bitartrate release from tablets prepared by combination of NaCMC and CP934 is depicted in Figure 6. When the overall percentage of polymer

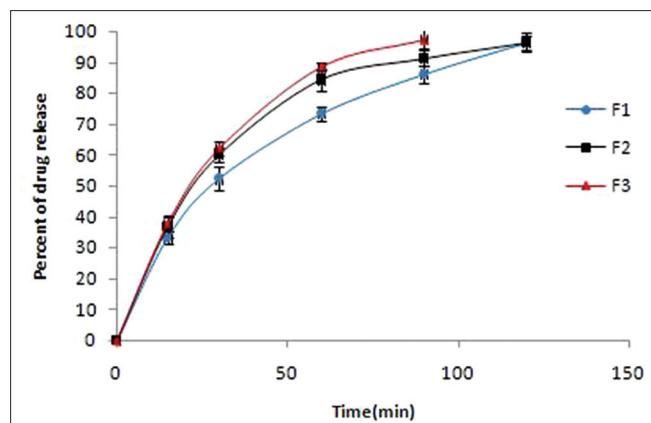


Figure 2: Effect of different ratios of hydroxypropyl methycellulose 50cps in the nicotine hydrogen tartrate release pattern

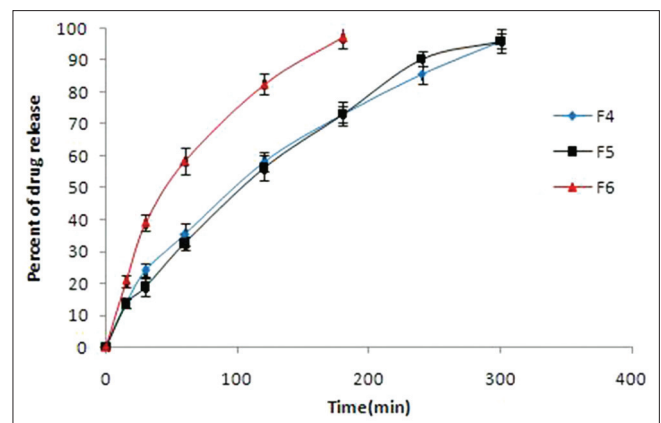


Figure 3: Effect of different ratios of carbapol 934 in the nicotine hydrogen tartrate release pattern

increased in the formulation, the ratio of CP934 to NaCMC is effective in the rate of drug release in a specific time interval.

Results of nicotine hydrogen bitartrate release from tablets prepared by combination of NaCMC and HPMC 50cps is depicted in Figure 7. When the overall percentage of polymer increased in the formulation, the ratio of HPMC 50cps to NaCMC is effective in the rate of drug release in a specific time interval. Results of nicotine hydrogen bitartrate release from tablets prepared by combination of CP934 and HPMC 50cps with and without lactose and results of formulations prepared by combination of CP934 and HPMC 50cps containing 4 mg of nicotine are depicted respectively in Figures 8 and 9.

Results of mucoadhesion test of products prepared from nicotine hydrogen bitartrate

Evaluation and comparison of adhesion of products prepared from mucoadhesive polymers was carried

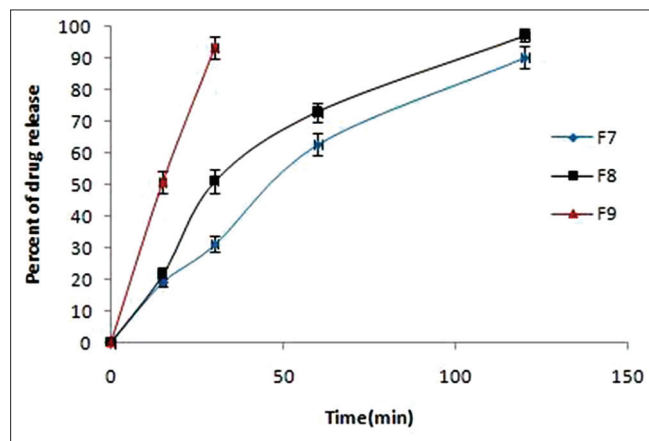


Figure 4: Effect of different ratios of sodium carboxy methyl cellulose in the nicotine hydrogen tartrate release pattern

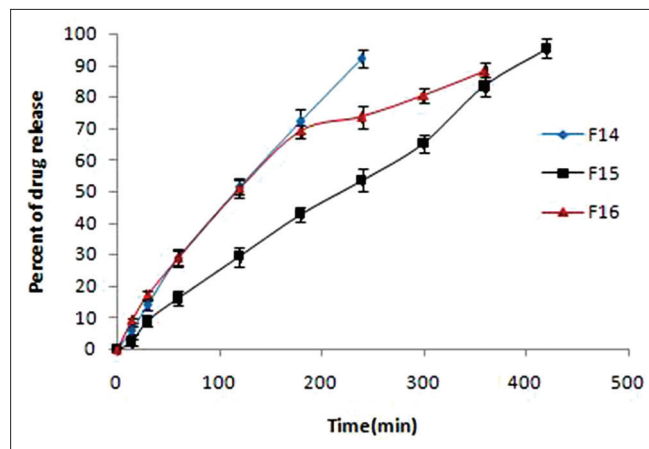


Figure 6: Effect of different ratios of the combination of sodium carboxy methyl cellulose and carbapol 934 in the nicotine hydrogen tartrate release pattern

out using the shear stress mechanism [Figure 1]. The results obtained are presented in Table 3 in g/cm^2 . In all cases, when the tablet was detached from the adhesion tester, the value on the balance was recorded.

Results of measurement of DE and mean dissolution time

The results of the calculation of kinetic parameters (DE and MDT) are followed in the Table 4.

The amount R^2 in all of the formulations was between 0.913 and 0.991.

Results of fitting regression coefficient of release data to different kinetic models

The values of regression coefficient of release data fitted to different kinetic models mentioned in a Table 5 for comparison of different kinetic models for each formulation.

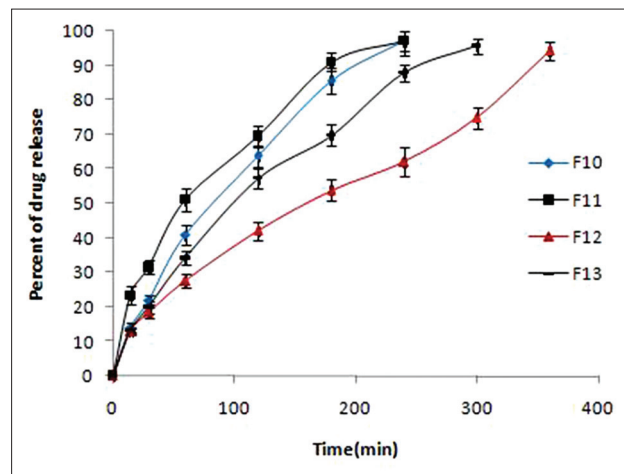


Figure 5: Effect of different ratios of the combination of hydroxypropyl methylcellulose 50cps and carbapol 934 in the nicotine hydrogen tartrate release pattern

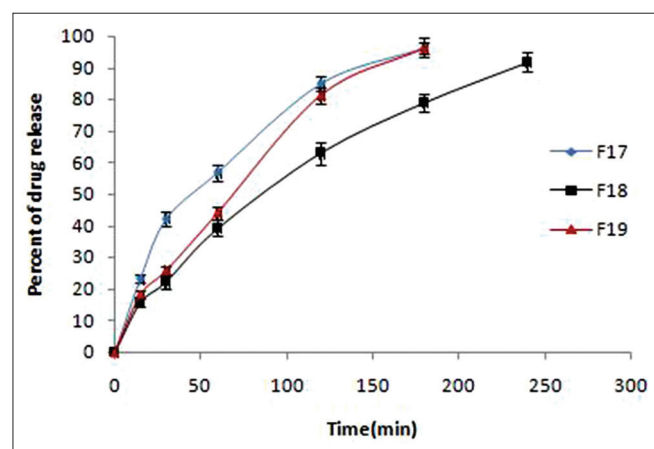


Figure 7: Effect of different ratios of the combination of sodium carboxy methyl cellulose and hydroxypropyl methylcellulose 50cps in the nicotine hydrogen tartrate release pattern

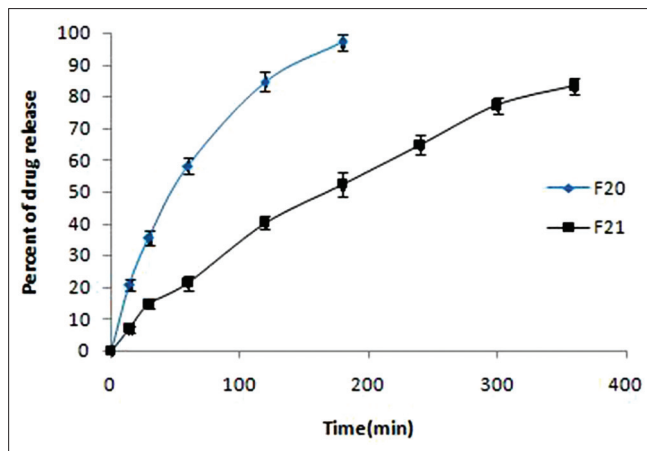


Figure 8: Effect of different ratios of lactose in the nicotine hydrogen tartrate release pattern

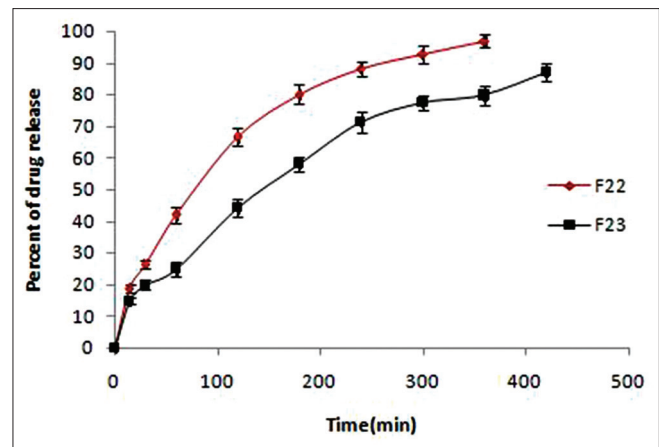


Figure 9: Effect of different ratios of the combination of carbopol 934 and hydroxypropyl methylcellulose 50cps in the nicotine hydrogen tartrate release pattern

Table 3: Results of adhesion of products prepared from mucoadhesive polymers

Formulation's code	Mean of mucoadhesion (g/cm ²)	SD	CV (%)
F1	65.4	1.67	2.56
F2	59.6	1.52	2.54
F3	54.4	2.3	4.23
F4	45.4	4.34	9.55
F5	32.2	1.48	4.61
F6	19.2	2.59	13.48
F7	20	1.22	6.12
F8	18.4	1.14	6.2
F9	14.8	1.64	11.1
F10	82	3.08	3.76
F11	108.6	3.21	2.96
F12	88.8	7.4	8.33
F13	67.4	1.95	2.89
F14	44.4	2.74	6.22
F15	78.4	4.16	5.31
F16	59.6	1.95	3.27
F17	58.4	2.7	4.63
F18	48.8	2	4.08
F19	51.2	1.79	3.49
F20	56.2	2.39	4.25
F21	21.2	3.96	3.27
F22	111	2.74	2.47
F23	118	5.24	4.44

CV: Coefficient of variation, SD: Standard deviation

Table 4: Results of calculation dissolution efficiency % and mean dissolution time of all formulations

No.	DE %	MDT (min)	SD
F1	74.38	41.82	1.23
F2	79.62	36.42	1.06
F3	81.23	33.09	2.11
F4	66.32	102.35	0.98
F5	65.28	105.69	1.46
F6	71.67	69.38	2.44
F7	67.80	47.12	1.81
F8	71.24	33.25	1.39
F9	75.37	14.89	0.74
F10	69.55	82.64	1.80
F11	67.02	69.08	1.38
F12	61.28	126.54	2.41
F13	62.94	101.33	2.58
F14	63.14	108.17	1.68
F15	58.62	179.02	1.97
F16	61.86	122.31	3.12
F17	71.29	41.98	2.11
F18	63.22	63.41	1.25
F19	68.40	54.07	0.92
F20	65.38	62.51	1.61
F21	60.28	129.63	2.05
F22	67.68	89.35	1.47
F23	64.30	119.08	1.22

DE: Dissolution efficiency, MDT: Mean dissolution time, SD: Standard deviation

Results of hardness and friability test of products prepared from nicotine hydrogen bitartrate

For Measurement of hardness of nicotine hydrogen bitartrate tablets, in each formulation, five tablets were selected and their hardness was measured and the required force was recorded. The amount of hardness in all of the formulations was suitable and between 43.29 N and 69.48 N.

After primary measurement of the weights of ten tablets, which was in general 12171 mg, the test was performed

and the dusts attached to the tablets were removed. The secondary weight was 12135 mg and thus 36 mg was decreased and hence, the weight decrease was less than 0.5-1%. Regarding this, the tablets were appropriate for packing. In all formulations, weight decrease was in an ideal range and the tablets were packable.

DISCUSSION

According to what was introduced, NRT was the most important way of smoke cessation in recent years, that

Table 5: Results of fitting regression coefficient of release data to different kinetic models

Formulation's code	R ² regression coefficient to zero order model	R ² regression coefficient to Higuchi's model	R ² regression coefficient to first order model	n calculated with Peppas equation
F1	0.880	0.996	0.953	0.991
F2	0.797	0.965	0.995	1.006
F3	0.773	0.955	0.971	1.011
F4	0.962	0.990	0.782	0.796
F5	0.971	0.975	0.914	0.803
F6	0.912	0.991	0.948	0.895
F7	0.960	0.962	0.983	0.966
F8	0.903	0.977	0.959	0.995
F9	0.997	0.967	0.937	0.961
F10	0.969	0.980	0.809	0.844
F11	0.929	0.997	0.905	0.823
F12	0.974	0.977	0.805	0.742
F13	0.968	0.986	0.921	0.794
F14	0.995	0.950	0.930	0.843
F15	0.998	0.945	0.881	0.804
F16	0.937	0.985	0.986	0.771
F17	0.906	0.992	0.921	0.892
F18	0.962	0.985	0.977	0.830
F19	0.970	0.970	0.877	0.891
F20	0.933	0.990	0.932	0.897
F21	0.983	0.975	0.984	0.767
F22	0.883	0.983	0.985	0.760
F23	0.950	0.988	0.996	0.737

reduce gradually the need for nicotine, which were provided various forms of nicotine as the gum, skin patches, oral sprays, nasal spray, and Lozenge. Wern and Shiffman, *et al.* studies show how these forms were reduced the dependence on smoking.^[2,10] Furthermore, noted that mucoadhesive drug delivery systems were new forms of drug delivery, that in the form of tablets, gel, and film are available. These systems have been considered in recent years because of ability to stick to the mucus and ease of use and retention on mucosal surfaces and slowly and consistently release of drug. Kumar *et al.* studies, including studies that express standards of mucoadhesive films.^[11]

Bio-adhesive polymers in comprehensive studies for the preparation of mucoadhesive products with using of many drugs such as miconazole, dextrometorphan, pioglitazone, and phenytoin, have been evaluated and published in numerous articles. Miller *et al.* studies completely described the mucoadhesive polymers.^[12] In this study with using of nicotine hydrogen bitartrate (nicotine stable form), and with mucoadhesive polymers, mucoadhesive tablets were prepared that person can decrease his/her dependency on smoking.

According to Peppas equation, from the formulations containing HPMC 50cps, F1 follows Higuchi's model, and F2 and F3 follows first degree model.^[13] Since HPMC 50cps is a water-soluble hydrophilic polymer,

it creates matrixes, from which the drug is released according to Higuchi's or first degree models. As the percentage of the polymer increased in formulations F1, F2, and F3, viscosity of the tablet increased, while the porosity decreased, which leads to decreased drug release. Because of having high percentage of HPMC, formulation F1 had the lowest rate of drug release, followed by F2 and F3. Moreover, the level of drug released increased from F1 to F3. Formulations, F1, F2, and F3 released the drug more rapidly than the formulations containing HPMC and CP934 or NaCMC and CP934. Fluctuation in drug release was very low in formulations F1 to F3, and the drug was released very rapidly. As it was expected, as the percentage of HPMC increased, the rate of drug release decreased. Noha *et al.* studies show similar results.^[6]

The formulations containing carbapol (F4, F5, and F6) had lower rate of drug release. Formulation F6 had the lowest amount of carbapol and the highest rate of drug release, while formulation F4 had the highest percentage of carbapol and the lowest rate of drug release and released the drug in a longer period of time (5 h). From among formulations F4, F5, and F6, formulations F4 and F6 were closer to Higuchi's model. With regard to some characteristics such as the ability to highly swell and also its high hydrophilic property, carbapol changes the kinetic of drug release in all formulations. Development of inter-polymer complexes and alteration of system viscosity are also

other effects of carbapol on the process of drug release. The percentage of NaCMC was lower in formulation F9, in which more than 90% of the drug was released in 30 min, while in formulation F7 with a higher percentage of NaCMC, almost 30% of the drug was released in the same period of time. This can be due to the decreased porosity of the system and increased viscosity.

Formulations F10, F11, F12, and F13 contain the combination of HPMC 50cps and CP 934, among which F11 follows the Higuchi's model. In these formulations, as the percentage of the polymers increased, the rate of drug release decreased. The formulations, with a combination of these two polymers have slow drug release, such that 90% of the drug was released in 4-6 h. Because of the higher ratio of CP934 to NaCMC in formulation F15, the rate of drug release was very slow (almost 7 h), since when the ratio of CP934 to NaCMC increases, the system viscosity increases and the rate of drug release decreases. Formulations F14 and F15 obey the zero order model. This group of formulations showed a considerable level of fluctuation in drug release process, which can be due to the high sensitivity of combination of the two polymers to compression pressure. Tiwari and Rajabi-Siahboomi studies completely described the Modulation of drug release from hydrophilic polymers.^[14]

In formulations with combination of NaCMC and HPMC 50cps, it was expected that F17, which had the highest percentage of HPMC 50cps (50%), releases the drug at the lowest rate, but it did not occur. In contrast, in formulation F18, which had a lower percentage of HPMC 50cps (30%), the drug was released in the longest period of time. This can be due to the sensitivity of the two polymers to pressure; such that when pressure increases, the rate of release decreases and vice versa and hence, there was a considerable level of fluctuation in drug release. The effect of lactose on the rate of drug release was evaluated in formulations F20 and F21, which had the same type and percentage of polymers with and without lactose. It seems that as the amount of lactose is higher, the porosity of the tablets after complete resolution lactose and also the rate of diffusion are higher. Formulation F23 with higher amount of CP 934, released the drug more slowly. In all formulations, the reaction kinetic is determined up to 60% of drug release, and in higher levels the reaction kinetic may change. Shaila *et al.* studies show similar results.^[15]

In evaluation and comparison of adhesion of products prepared from mucoadhesive polymers, in formulations prepared from HPMC 50cps, because of the high

viscosity, adhesion is high (Adhesion: F1>F2>F3, drug release: F3>F2>F1). The formulations containing carbapol had a low level of adhesion. The formulations prepared from HPMC 50cps and CP934 had the highest value of adhesion per area and other formulations had a medium level of adhesion, according to the percentage of the polymer. Formulation F11 with the highest percentage of F11 had the highest level of adhesion, which is due to the increased number of contact points of the tissue and increased level of adhesion (F11>F12>F10>F13). Development of inter-molecular complexes among the polymers can be a main cause of increased level of adhesion. In formulations prepared from HPMC 50cps and NaCMC, formulation F17 had the highest percentage of polymer, and thus, had higher adhesion in comparison with F18 and F19.

CONCLUSION

In general, because of appropriate adhesion and low-fluctuation in drug release, formulations prepared from the combination of CP934 and HPMC 50cps, particularly F12, and F21, were selected as the desirable formulations.

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