

Preparation and Evaluation of Sodium Fluoride Orodispersible Tablets Shaimaa N. Abd Al Hammid

Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

Email:shaimaa_alsamarrai@yahoo.com

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ABSTRACT

Fluoride is used to prevent dental caries. Administration of fluoride tablet is an acceptable way for compensating the need for fluoride. The purpose of this study was to prepare orodispersible tablets of sodium fluoride and evaluation its physical properties as weight variation, hardness, disintegration, friability and release study. Different formulas of fast dissolving sodium fluoride tablets were prepared using direct compression method to enhance patient compliance using three different types of super disintegrants (sodium starch glycolate (SSG), croscarmellose (CC), and crospovidone (CP). Directly compressible mannitol was used as a diluent to enhance the mouth feel and compressibility, in addition to that, the prepared formulas were evaluated for hardness, friability, disintegration, dissolution time and content uniformity. Crospovidone was the best superdisintegrant used among croscarmellose sodium and sodium starch glycolate since crospovidone showed the fastest disintegration time (16 ± 0.5 , 15 ± 0.5), and wettability (7 ± 0.5 , 9 ± 1) in F3, and F4 respectively, between croscarmellose sodium and sodium starch glycolate in addition to the acceptable hardness (4 ± 0.3), friability (0.962%) and taste also with dissolution time within 20 minutes and 55% drug release within 10 minutes for the selected formula F6. It was concluded that sodium fluoride can be prepared as orodispersible tablet using crospovidone as a superdisintegrant, manitol as a diluents and 15% sodium saccharine as a sweetener.

تصنيع و تقييم حبة فلوريد الصوديوم المشتتة فمويا

شيماء نزار عبدالحميد صالح

العراق, بغداد, جامعة بغداد, كلية الصيدلة, فرع الصيدلانيات

المخلص:

الفلورايد يستعمل لمنع تنخر الاسنان لذلك اعطاء اقراص الفلورايد هي طريقة مقبولة لتعويض الحاجة للفلورايد. الغرض من هذه الدراسة كان تحضير حبوب فلوريد الصوديوم المشتتة فمويا و دراسة خواصها الفيزيائية: اختلاف الوزن و قسوة و تفكك و هشاشة الحبة و تحرر الدواء. حضرت حبوب سريعة التفكك في الفم باستخدام طريقة الكبس المباشر لزيادة تقبل المريض للعلاج. الحبوب حضرت باستخدام عدة مواد مفككة و هي (صوديوم ستارج كلايكوليت, كروسكارميلوز صوديوم, و كروسبوفيدون) كما ان مادة المانيتول مباشرة الكبس قد استخدمت كمادة مخففة و لتحسين طعم الحبة في الفم. تم تقييم الحبوب عن طريق قياس قوة الصلابة, نسبة الهشاشة, وقت التحلل, وكمية الدواء. وقد وجد ان الحبة التي تحتوي على كروسبوفيدون قد اعطت نسبة هشاشة مقبولة و أقل وقت تحلل بين صوديوم ستارج كلايكوليت و كروسكارميلوز صوديوم. كروسبوفيدون اعطى اسرع وقت تحلل (16 ± 0.5 , 15 ± 0.5) و اسرع وقت تبلل (7 ± 0.5 , 9 ± 1) في الصيغ الدوائية الثالثة F3 و السادسة F6 على التوالي. بالاضافة الى القسوة المقبولة (4 ± 0.3) و الهشاشة (0.962%) و الطعم المقبول مع وقت تحرر للدواء خلال 20 دقيقة مع تحرر 55% من الدواء في 10 دقائق للصيغة المختارة رقم 6 (F6). تم الاستنتاج حول امكانية تحضير حبوب فلوريد الصوديوم المشتتة فمويا باستعمال الكروسبوفيدون بتركيز 15% و استعمال المانيتول كمادة مخففة و استعمال السكرين 15% كمادة محليه للطعم.

INTRODUCTION

The beneficial effects of fluoride on reducing dental caries are well documented. Administration of fluoride tablet is an acceptable way for compensating the need for fluoride. Sodium fluoride acts systemically and topically by increasing tooth resistance to acid dissolution, by promoting remineralization, and by inhibiting the cariogenic microbial process.⁽¹⁾

The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow.⁽²⁾ Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of the motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention.⁽³⁾

Orodispersible tablets (ODT) are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue.⁽⁴⁾ The aim of this study is to prepare orodispersible tablets of sodium fluoride and study its physical properties: weight variation, hardness, disintegration, friability and release study.

MATERIALS AND METHODS

MATERIALS

Sodium fluoride powder, sodium starch glycolate, microcrystalline cellulose (avecil Ph 102), aspartame, and croscarmellose (Samara Drug Industry, Iraq), crospovidone (pharmaceutical Wuhan international Co. Ltd, China), mannitol, and magnesium stearate, (Riedel-De-Haen AG Seelze, Germany).

METHOD

Preparation of Sodium Fluoride Tablets

Each formula (F1, F2, F3, F4, F5 and F6) were formulated by mixing all the ingredients (except the lubricant) for 15 minutes after which the lubricant was added and blended for another 1 minute. The final mixture was compressed using a 7 mm single- punch tablet machine to get tablets of 150 mg weight as shown in table 1.

Before tablets preparation, the mixture blends of all the formulation were subjected for pre compression parameter like bulk density, tapped density, and angle of repose.

Evaluation of Tablets

Micromeritic Properties (pre compression)

Angle of Repose (θ)

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} (h/r)$$

Where, θ is the angle of repose, h is height of pile and r is radius of the base of pile. The angle of repose is determined by fixed funnel method. The powder mass is allowed to flow through the funnel kept on a stand at a fixed height. The powders are carefully poured through the funnel on the Petri dish until the apex of conical pile just reached the tip of the funnel. The height of the pile and radius of the conical pile is noted and the angle of repose is calculated by the above equation ⁽⁵⁾.

Bulk Density and Taped Density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another ⁽⁶⁾.

LBD = Weight of the powder /Volume of the packing

TBD = Weight of the powder /Tapped volume of packing

Carr's Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index ⁽⁶⁾.

$$\text{Carr's Index (\%)} = (TBD - LBD) / TBD \times 100$$

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. If the Hausner's ratio of the powder is near to 1.25 indicates better powder flow. It is calculated by the following formula ⁽⁵⁾.

Hausner's ratio=tapped density/bulk density

< 1.25-good flow.

> 1.25-poor flow.

These results of angle of Repose, Carr's index, and Hausner's ratio are shown in table2.

Post-Compression Parameters

Hardness

Hardness of tablet (or tablet crushing strength) is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to abrasion or breakage under condition of storage, transformation, and handling before usage depends on its hardness.

Three tablets were randomly selected from each formula and hardness of tablets was determined by using Monsanto Hardness Tester. The mean values and standard deviation for each batch were calculated. The hardness was measured in terms of Kg/cm² ⁽⁸⁾.

Friability

Friability indicates the ability of a tablet to withstand mechanical shocks while handling. Friability of tablets were determined using Roche Friabilator and is expressed in percentage

(%). The friabilator consists of a plastic-chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. Ten tablets were initially weighed ($W_{initial}$) and placed into the friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions and then the tablets were de-dusted ,weighed again(W_{final}).The loss in tablet weight due to abrasion or fracture was the measure of tablet friability. Percent friability (%f) was calculated by using the following formula ⁽⁸⁾:

$$\text{Percent friability} = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

% friability of less than 1 % is considered acceptable.

Twenty pre-weighed tablets were rotated at 25 rpm for 4 min and then the tablets were dedusted and reweighed. The weight loss (%) was calculated ⁽⁹⁾.

Wetting Time and Water Absorption Ratio

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A piece of tissue paper folded double was placed in a Petri plate containing 6ml of water.

The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds ^(10, 11).

$$\text{Water absorption ratio} = (W_a - W_b) / W_b$$

Where,

W_b = weight of tablet before absorption of water

W_a = weight of tablet after absorption of water.

Weight Variation

Weight variation test is done by weighing 20 tablets individually on a digital weighing balance, calculating the average weight and comparing the individual weight to the average. The deviation from the average weight of the tablet should not exceed ± 7.5 % (according to the USP limitations of weight variation test). ⁽¹²⁾.

In-Vitro Disintegration Time:

The disintegration time for all formulations was carried out using USP disintegration apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed.

The phosphate buffer pH 6.8 was maintained at a temperature of $37^{\circ} \pm 0.5^{\circ}C$ and time (in seconds) taken for the entire tablet to disintegrate completely was noted. ^(13, 14).

In-Vivo Disintegration Time

The time required for complete disintegration in the oral cavity was collected from five healthy volunteers. All volunteers were told about the purpose of the test. Before the test, the mouth cavity was rinsed with a cup of water. The tablet was placed on the tongue and

subsequently the tongue was gently moved. The time required for the elimination of any residue or fragment of the tablet was measured with a stopwatch and recorded as a disintegration time ⁽¹⁵⁾.

Fluoride Measurement:

Fluoride was analyzed by the direct method, using a fluoride specific electrode Fluoride (201 E. HANNA instrument, China) and an ion analyzer (201 E. HANNA instrument, China). Prior to the samples analysis, a set of standards (ranging between 0.025-3.2 ppm F) was prepared in triplicate, using serial dilution from a 100 ppm NaF stock solution (E. Merck, Darmstadt, Germany). The milli voltage potentials were converted to µg F using a standard curve ⁽¹⁶⁾.

Drug Content

Weigh and powder 20 tablets. An amount of the powder equivalent to 1mg of sodium fluoride was dissolved in 100ml of pH 6.8 buffer, filtered, and analyzed for drug content ⁽⁸⁾.

In-vitro Drug Release Study

In-vitro dissolution of the designed sodium fluoride orodispersible is studied using USP XXIII type-II dissolution apparatus (Copley dissolution 8000, Copley Scientific, U.K.) using a paddle stirrer at 50 rpm. The prepared phosphate buffer (250 ml) is added and the temperature at $37\pm 0.5^{\circ}\text{C}$ as dissolution medium. For every test one tablet is used and the studies are run in triplicate (n=3). Aliquot of sample (5 mL) is taken periodically and evaluated for drug-content. Aliquot of sample (5 mL) is taken periodically and evaluated for drug-content measurement. The volume of sample withdrawn at each time interval is replaced immediately with equal amount of newer dissolution medium and the cumulative percent of drug released is calculated. This release pattern and then plotted against time ^(17, 18).

RESULTS AND DISCUSSION

Flow-compression characters of these formulas gave good compression parameters, Carr's index (10.01-13.88) and Hausner's ratio below 1.25 which considered being in the acceptable range ⁽⁷⁾. While angle of Repose range is (32-34) which indicate that the powder mixture has good flow character ⁽⁷⁾.

Evaluation of the Prepared Sodium Fluoride Orodispersible Tablets

Hardness

Three tablets were randomly selected from each formula and hardness of tablets was determined by using Monsanto Hardness Tester. The hardness of all the prepared orodispersible tablets was kept constant at (3.5-6 kg/cm²), which is satisfactory range for orodispersible tablet to study the effect of other factors in constant hardness ⁽¹⁹⁾. The results are shown in table 3. Formulas containing crospovidone as a super disintegrant showed the lowest hardness (F3, and F6).

Friability Test

Friability of sodium fluoride tablets were determined using Roche Friabilator and is expressed in percentage (%) as shown in table 4. Formulas containing crospovidone as a super disintegrant showed the highest friability within the accepted limits 0.9921% and 0.962% for

F3 and F6 respectively. On the other hand formulas containing croscarmellose showed the lowest friability 0.04113% and 0.0115% for formulas F2 and F5.

Wetting Time

Crospovidone showed the fastest wetting properties among the other two disintegrants; 7 and, 9 seconds in F3, and F6 respectively, as shown in table 5. While formulas containing croscarmellose as a superdisintegrant showed the slowest wetting time 40 seconds as in F5.

In-vitro Disintegration Time

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Crospovidone showed the fastest disintegration time between croscarramelose sodium and sodium starch glycolate; 14 and, 16 seconds in F3, and F6 respectively, as shown in table 5.

Disintegration time for crospovidone is faster than that of both croscarramelose sodium and sodium starch glycolate as mentioned and this may be due to the tendency of croscarramelose sodium and sodium starch glycolate to swell with gel formation which make a viscous layer on the surface of the tablet and prevent water penetration to the tablet and delay swelling. While crospovidone has no tendency to form a gel layer, so it's swelling and wicking will be faster⁽²⁰⁾.

Weight Variation

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The weight variation test would be satisfactory method of determining the drug content uniformity of tablet⁽⁸⁾. All the tablets were found to pass the weight variation test ($150 \pm 7.5\%$).

Content Uniformity

The content uniformity of the prepared Sodium flouride orodispersible tablet was complied with BP criteria. No tablet from ten tablets lies out of the range of 85-115% of the label claim. These results indicated that the dosage form had uniform distribution and proper dose of the active ingredient⁽⁸⁾.

In-Vivo Disintegration Time

Crospovidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth (F3, and F6). Unlike other superdisintegrants, which rely principally on swelling for disintegration. Crospovidone as a superdisintegrant use a combination of swelling and wicking.

When examined under a scanning electron microscope, crospovidone particles appear granular and highly porous. This unique, porous particle morphology facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Due to its high crosslink density, crospovidone swells rapidly in water without gelling. Other superdisintegrants have a lower crosslink density and, as a result, form gels when fully hydrated.

Although crospovidone polymers swell by 95% to 120% upon contact with water, swelling is not the only mechanism for tablet disintegration. Swelling or swell volume is mainly a

measure of the change in volume of the disintegrant after it is introduced to an aqueous solution and the system has reached equilibrium. However, swell volume does not measure the rate at which a disintegrant absorbs water and swells or the pressure generated by swelling. Crospovidone polymers, with their porous particle morphology rapidly absorb water (wicking) via capillary action. As the deformed crospovidone particles come in contact with water that is wicked into the tablet, the crospovidone particles recover their normal structure and then swell, resulting in rapid volume expansion and high hydrostatic pressures that cause tablet disintegration⁽²¹⁾.

In term of overall parameters, formula F6 was considered as the selected best formula, thus it was subjected to stability study, the short term stability study show no changes in tablet hardness, friability, drug content, in vivo disintegration time and dissolution rate at the end of the stability study period.

In-vitro Drug Release Study

Choosing the most appropriate and fast disintegration time formula F6 for mouth-feel since it is critical in orodispersible tablets, and patients should receive a product that feels pleasant therefore one tablet from F3, and F6 was tested for the sensation by placing the tablet on the tongue on healthy human volunteers and F6 was the best therefore selected for further in vitro release study as shown in figure 1. The results showed fast release of the drug in the oral cavity within 20 minutes with 55% release within the first 10 minutes.

Conclusion

Based on the results of this study, the followings may be concluded: crospovidone was the best superdisintegrant used among croscarramelose sodium and sodium starch glycolate since crospovidone showed the fastest disintegration time, and wettability between croscarramelose sodium and sodium starch glycolate in addition to the acceptable hardness, friability and taste. The overall results of this study indicate the possibility of utilizing the selected best formula (F₆) in the preparation of Sodium fluoride orodispersible tablet.

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Table 1: Composition of the Sodium Fluoride Orodispersible Formulas

Composition Formula Number	Sodium Fluoride (mg)	sodium starch glycolate (mg)	Cros Carmelose (mg)	Cros Povi done (mg)	Sodium Saccharine (mg)	Mannitol (mg)	Magnesium Stearate (mg)	Total weight
F1	1	15			5	127.5	1.5	150
F2	1		15		5	127.5	1.5	150
F3	1			15	5	127.5	1.5	150
F4	1	15			10	122.5	1.5	150
F5	1		15		10	122.5	1.5	150
F6	1			15	10	122.5	1.5	150

Table 2: Flow-Compression Character ⁽⁷⁾

Type of Flow	Compressibility Index	Hausner's ratio	Angle of Repose (θ)
Excelent	1-10	1-1.1	25-30
Good	11-15	1.12-1.18	31-35
Fair	16-20	1.19-1.25	36-40
Passable	21-25	1.26-1.34	41-45
Poor	26-31	1.35-1.45	46-55
Very poor	32-37	1.46-1.59	56-65
Extremely poor	>38	>1.6	>66

Table 3: Hardness of the Prepared Sodium Fluoride Tablets

Formula No.	F1	F2	F3	F4	F5	F6
Hardness Kg/cm ²	4.5± 0.2	5± 0.35	3.5± 0.23	4± 0.38	6± 0.20	4± 0.3

Table 4: Friability of the Prepared Sodium Fluoride Tablets

Tablets Weight (gm) Formula No.	W initial (g)	W final (g)	% Friability
F1	1.4195	1.4093	0.7185%
F2	1.4586	1.458	0.04113%
F3	1.4615	1.4470	0.9921%
F4	1.4509	1.4400	0.751%
F5	1.4882	1.4711	0.0115%
F6	1.4763	1.4621	0.962%

Table 5: Wetting Time and Disintegration Time in seconds for the Prepared Sodium Fluoride Tablets

Formula number	Wetting Time (second)	Disintegration Time (seconds)
F1	36±2	40±3.2
F2	28±1	22±1.7
F3	7±0.5	16±0.5
F4	32±2	37±1.8
F5	40±3	20±1.4
F6	9±1	15±0.5

Table 6: Weight Variation Specification as per USP⁽⁸⁾

Average Weight of	Max. % Deviation
130 or less	±10
130-324	±7.5
More than 324	±5

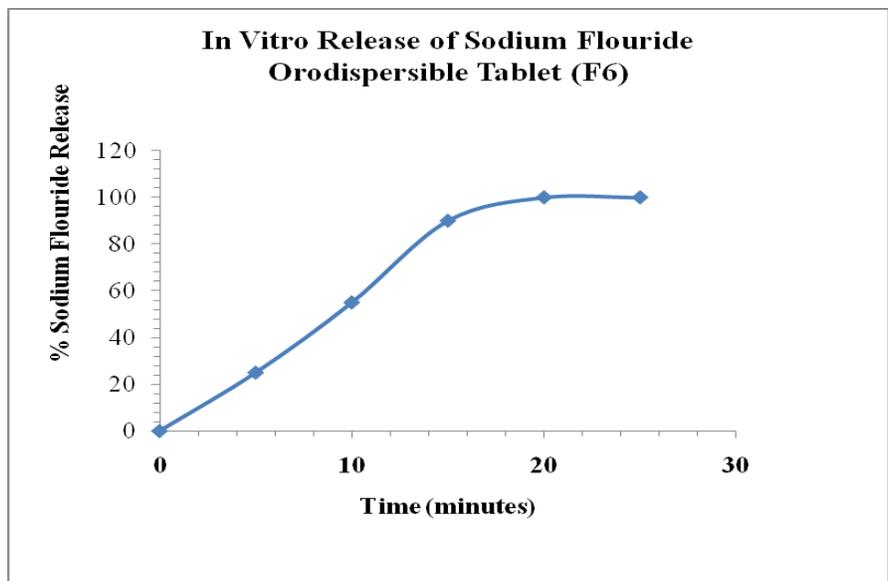


Figure 1: In-vitro drug release study of selected sodium fluoride orodispersible tablet in phosphate buffer pH6.8 at 37°C±0.5°C and 50 RPM