تحضير أقراص سلفات سالبوتامول متفتتة في الفم باستخدام زوج فوار ضعيف وتقييمها في الزجاج

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الملخص

هدف البحث إلى تحضير أقراص من مادة سلفات السالبوتامول تتفتت في الفم من خلال استخدام زوج فوار ضعيف (كربونات الكالسيوم مع حمض الليمون) كعامل مفتت، ومقارنة النتائج عند استخدام مواد مفتتة قوية مثل كروس كارميلوز الصودي وكروس بوفيدون. تم التأكد من توافق المادة الدوائية مع الزوج الفوار من خلال اختبار المسح الحراري التفاضلي، حُضّرت الأقراص بطريقة الضغط المباشر، وقيّمت الأقراص المحضرة كلّها بإجراء فحص تجانس الوزن، الهشاشة، زمن التفتت، وزمن التبلل، فضلاً عن حساب كمية الدواء المتحررة. أعطت الصيغة F2 الحاوية على زوج فوار بنسب 10% زمن تفتت 12 ثانية وزمن تبلل 20 ثانية، وكان تحرر الدواء منها سريعاً ومنتظماً خلال 20 دقيقة، في حين ازداد زمن التفتت وزمن التبلل في الصيغ الحاوية على كروس كارميلوز أو الحاوية على كروس بوفيدون بنسبة 10%، واختيرت الصيغة F2 أفضل صيغة.

الكلمات المفتاحية: سلفات السالبوتامول، كربونات الكالسيوم، المفتتات القوية، زمن التبلل، الأقراص المتفتتة في الفم.

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Preparation and in Vitro Evaluation of Oral Disintegrating Salbutamol Sulfate Tablets Using Weak Effervescent Base

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Abstract

The purpose of this research was to prepare orally disintegrating tablets (ODTs) of Salbutamol Sulfate by using weak effervescent base (calcium carbonate plus citric acid) as a disintegrating agent, the results were compared with the results of Crosspovidone cl (CPcl), and Crosscarmellose sodium (CCs) as superdisintegrants in ODTs. Differential scanning calorimetric studies did not indicate any excipients incompatibility. Tablets were prepared by direct compression method. F2 showed disintegration time of 12 sec, and the wetting time was 20 sec. F2 was achieved faster and regularly released of drug within 20 minutes, while the disintegrating and wetting times were increased in tablets containing Crosspovidone cl or Crosscarmellose sodium. Orally disintegrating tablets of Salbutamol Sulfate with temporal disintegration and less wetting times were achieved via using weak effervescent base at 10% concentration.

Keywords: Salbutamol sulfate, calcium carbonate,, superdisintegrants , wetting time, orally disintegrating tablets.

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Introdution:

The oral route is the most preferred route for administration of therapeutic agents because of accurate dose, easy administration, and patient compliance. So tablets and capsules are most preferred dosage forms for oral route. But these dosage forms are difficult to administer by children and geriatrics. Hence, oral disintegrating tablets(ODT), are favored for administration and improvement in therapeutic efficacy of dosage form [1,2]. Other names for ODTs are: orodispersible tablets, mouth dissolving tablets (MDT) , quick disintegrating tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, or porous tablets [3-4].

European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily within 3 min in mouth before swallowing.[4] United States Food and Drug Administration (FDA) defined orally disintegrating tablet as "a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for orally disintegrating tablets generally ranges from several seconds to about a minute**.** These products are designed to disintegrate or dissolve rapidly on contact with saliva, thus eliminating the need to chew the tablet, swallow an intact tablet, or take the tablet with liquids. This mode of administration was initially expected to be beneficial to pediatric and geriatric patients, also for people with conditions related to impaired swallowing, and for treatment of patients when compliance may be difficult (e.g., for psychiatric disorders)

The saliva plays an important role in disintegration of orally disintegrating tablets and primarily secreted in the oral cavity by sublingual glands, and also by numerous minor glands. Saliva is mainly constituted by water (99.5% w/v). The principal components of saliva are inorganic electrolytes (0.2% w/v), gases The accepted range of normal salivary flow ranges from about 0.1 to 0.2 ml /min and reaches 7 ml/min upon stimulation[5]

Salbutamol sulfate is a sympathomimetic agent selectively acting on the β2 adrenergic receptor. It is used as a bronchodilator in the management of disorders such as reversible airways obstruction and chronic obstruction pulmonary diseases.[6] It shows site-specific absorption in the stomach and in the upper part of the small intestine.[7] The maximum plasma concentration occurs within 2.5 h and the plasma half-life ranges from 2.7 to 7.0 h. It is given orally at a dose of 2–4 mg, three to four times a day.[8] The oral bioavailability of Salbutamol sulfate is ~40% because of extensive sulfonation in the gut and degradation in the colon.[9]. Salbutamol sulfate is awater soluble drug and its formulation into an orodispersible tablet form would lead to rapid disintegration and result is rapid absorption and relieving asthma attacks without any lag time.

Materials:

Salbutamol sulphate (Litaka Pharmaceutical Ltd. Pune, India), Crospovidone (CPcL), Croscarmellose Sodium (CCs),Sodium Stearyl Fumarate (SSF), Scharine, (Welable healthcare, Mehsana, India) ,Manitol, Microcrystalline cellulose PH102 (Hyderabad, India) Citric acid, Calcium carbonate (Nitika, India), Aerosil 200 (BASF, Germany)) Potassium phosphate monobasic (Sigma-Aldrich Germany)Sodium Hydroxide(Avon chem UK).

Instruments:

Electronic balance 0.001g (Shimadzu auw220d dualrange semi-micro).

Spectrophotometer (Shimadzu UV-1601 UV/Vis double beam).

DSC apparatus (METTLER TOLEDO, OH, USA).

Microprocessor pH Meter (HANNA instruments pH 211, USA).

USP dissolution testing apparatus 2 (Erweka, tupe DT 800, Germany).

Pharmacopoeial sieves 60 mesh (CISA, UK).

Hardness and diameter tester (Erweka TBH 300S, GmbH, Germany).

Friability tester (ErwekaTAR20, GmbH Roche, Germany).

filter 0.45 micron (Whatman, Germany).

Compression single machine (Erweka EK-0, Motor Drive AR 402, Heusenstamm, Germany).

Methods:

1- Drug scanning

Salbutamol sulphate (SS) dissolved in phosphate buffer (pH= 6.8) was scanned by spectrophotometer with wavelength 200-400 nm to determine the maximum absorption.

2- linear coefficient (R^2) :

A series of normative material concentrations of 2 mcg / ml to 14 mcg / ml and measurement of this series at the wavelength of 225 nm .

Validation of the calibration method according to the USP 34 was done , there are compatible in terms of linear and accuracy. [10]

3- Testing the mixture of powders prepared for compression

The mixture prepared for compression was tested by measuring angle repose, bulk density, tapped density, Carr's index, and Hausner's ratio. These aspects were measured to determine the mixture flow ability inside the compression machine [11, 12]

4- ODT tablets preparation

Ten formulas of ODT Salbutamol sulphate were prepared (table 1) using Salbutamol sulphate and different excipients. These tablets were prepared by direct compression (DC) **using compression single machine (Erweka EK-0, Motor Drive AR 402, Heusenstamm, Germany).**

All amounts of substances were weighed accurately and passed through sieve 60 mesh (particles size 250 µm). Salbutamol sulphate was blended with Aerosil to improve drug flow ability and mixed with other powders for 15 minutes, Sodium stearyl fomarate was added as a lubricant and blended for 5 minutes. Materials mixtures were compressed by 8 mm punches, at 20 °c and RH 28%.Each tablet contain 4 mg Salbutamol sulphate , final weight 200mg.

This work achieved at laboratory of Pharmacy College- Damascus University.

Table (1) ODTs Formulas for Salbutamol Sulphate

Effervascent Base	**Crosspovidone**				**Crosscarmelose**					
	5%	**10%**	**15%**	**20%**	**5%**	**10%**	**15%**	**5%**	**10%**	**15%**
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Salbutamol sulfate	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Cellulose microcrystalline	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**	**30**
Citric acid	**4.35**	**8.7**	**13.05**	**17.4**	**-**	**-**	**-**	**-**	**-**	**-**
Calcium carbonate	**5.65**	**11.3**	**16.95**	**22.6**	**-**	**-**	**-**	**-**	**-**	**-**
Crosspovidone	**-**	**-**	**-**	**-**	**10**	**20**	**30**	**-**	**-**	**-**
Crosscarmelos e	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**10**	**20**	**30**
Aerosil 200	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Sodium saccharin	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Sodium steryl fomarate	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Manitol (for all formulas)	**----------**		**Qs To 200 mg**							

Total Weight = 200 mg for each tablet .

5-Compatibility of (SS) with excipients:

Deferential scanning calometric studies were achieved for (SS) and other excipients using DSC apparatus.

6- EVALUATION OF Tablets:

6-1- Weight Variation

Twenty tablets were randomly selected from each formulation and weighed The mean SD values were calculated.[13]

6-2- Hardness and Friability

a- Hardness or crushing strength of the tested orally disintegrating tablet formulations were measured using the dial hardness and diameter tester(Erweka TBH 300S, GmbH).

b- Friability of a sample of 20 orally disintegrating tablets was measured utilizing a Friability tester (ErwekaTAR20, GmbH Roche, Germany) and calculating as the following :

Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then de-dusted and reweighed, then percentage weight loss (friability) was calculated. [14,15]

$$\textit{100\% Friability} = \frac{w0 - w}{W0}$$

W○= initial weight of 20 tablets

W= weight of 20 tablets after 100 revolutions

6- 3- Wetting Time:

Five circular tissue papers were placed in a Petri dish of 10cm diameter.Ten milliliters of water containing a water-soluble dye (methylene blue), were added to the petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petridish at 25°C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. . Wetting time was recorded using a stopwatch. [16]

6-4- In Vitro Disintegration Time

In vitro disintegration time (DT) of the orally disintegrating tablets was

determined following the procedure described by (Gohel et all 2004) 10 mL of water at 25°C was placed in a petri dish of 10 cm diameter. The tablet was then carefully positioned in the center of the petri dish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in replicates of six tablet (n=6) and mean SD values were recorded. [17, 18, 19] .

6-5- In Vitro Dissolution Studies

Release rate of Salbutamol sulphate from ODT tablets (n = 6) was determined using Dissolution Testing Apparatus 2 (paddle). The dissolution test was performed using 500 mL of phosphate buffer(pH= 6.8) at 37 ± 0.5°C and 50 rpm. A sample (10 mL) of the solution was withdrawn from the dissolution apparatus after (1, 2, 3, 4, 5, 6, 7, 8, 10, 15, 20,25) minutes, and the samples were replaced with fresh dissolution medium. The samples were filtered through filter paper (0.45M) and the absorbance of these solutions was measured at 225 nm . The quantities released were calculated from the standard curve plotted between concentrations and absorbance at wavelength 225 nm. the relations between Q% and time were achieved.

Results:

I- DSC TEST:

1- In DSC apparatus, Salbutamol sulphate showed peak at : 201,98 ° as shown in Figure (1).

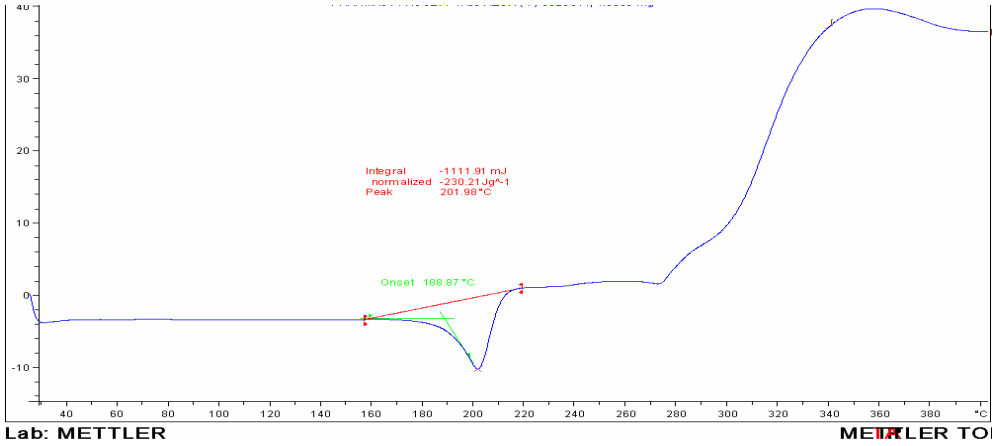


Figure (1)) DSC For Salbutamol sulphate (peak= 201.98)

2- DSC for citric acid appeared peak at: 152.7C°,and for calcium carbonate peak appeared at 174.7 C° Fig 2

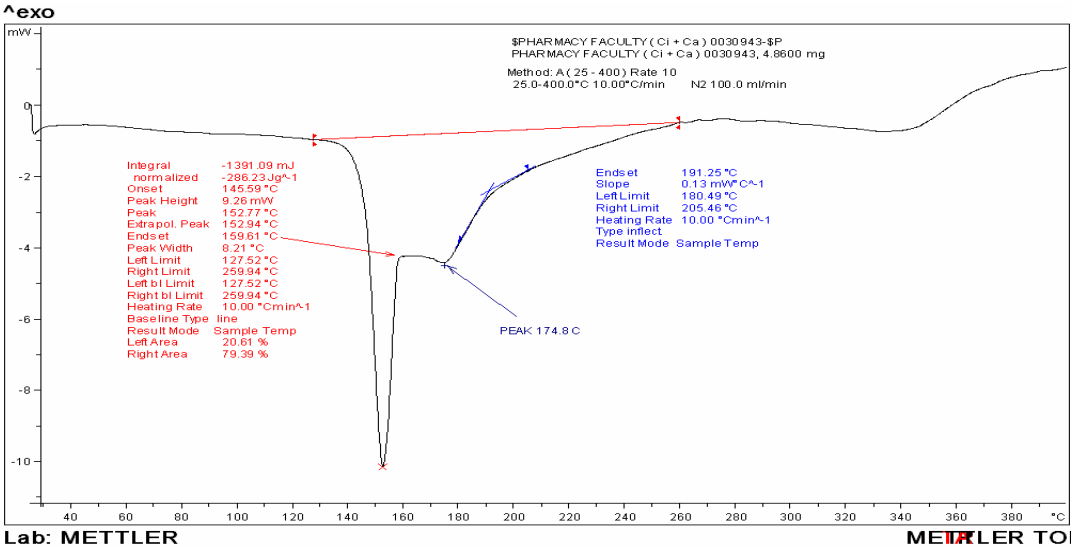


Fig (2)
DSC For (citric acid :152.7, calcium carbonate: 174.7)

3- DSC for mixing Salbutamol sulphate with citric acid and calcium carbonate showed that there was compatibility between the API and effervescent base.

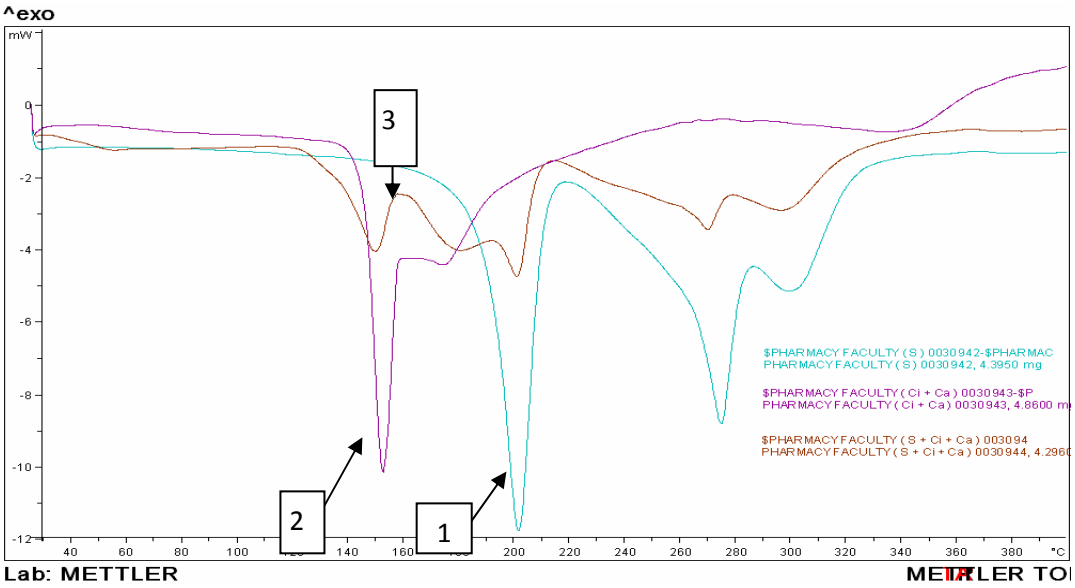


Fig (3) : (1 - Salbutamol sulphate)
(2- Effervescent Base (citric acid ,calcium carbonate)
(3- Salbutamol sulphate & Effervescent Base

II- **Salbutamol sulphate absorption**

Maximum absorption for : (SS) was at 225 nm as shown in Figure (4).

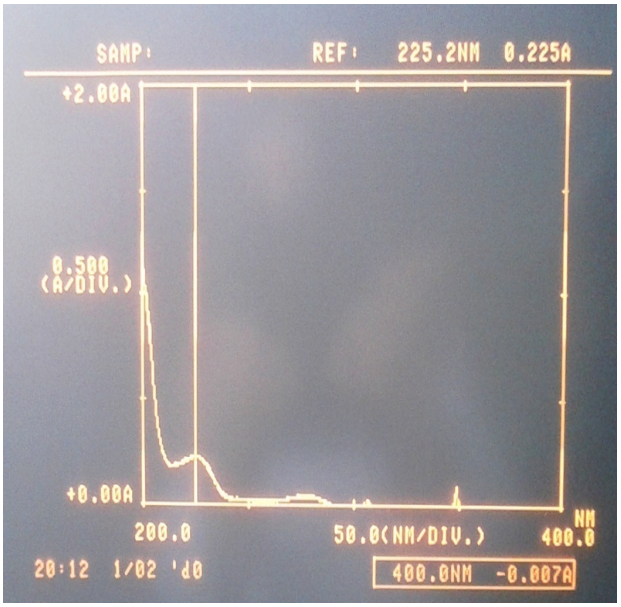


Fig (4)
Peak of maximum absorption for Salbutamol sulphate

III- linear coefficient:

Validation of the calibration method according to the USP 34, $R^2 = 0.999$ was done , there are compatible in terms of linear and accuracy. Fig 5

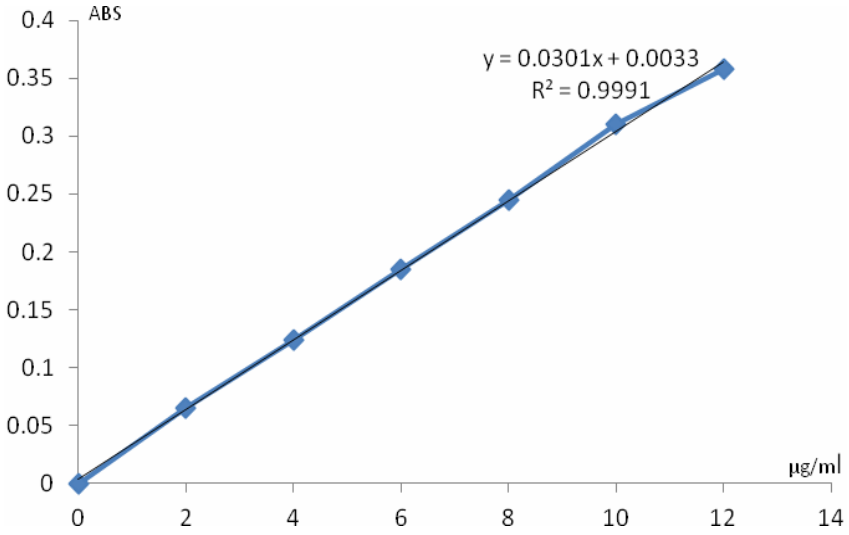


Figure (5)

IV- Evaluation parameters::

IV:1- For ODTs with Effervescent Base as disintegrants :

Weight Variation, Friability, hardness, Disintegrating time(s), - Wetting time(S) Drug content,. For all Studied formulas and all of them were acceptable .Table (2) and table (3).

(Table 3) evaluation parameters for F1,F2,F3,F4

	F1(5%)	`F2(10)	F3(15%)	F4(20)
1 - Weight Variation	201.1±2	200.47±3.8	199.9±2.4	199.8±2.2
2- Friability(%)	0.56	0.54	0.66	0.69
3- hardness(Kg/cm^2)	2.85±1.2	2.9±1.3	2.95±1.45	2. 75±1.25
4- Disintegrating time(s)	16±2.2	12±2.4	15±2.8	14±1.8
5- Wetting time(S)	24±1.5	20±2.4	20±1.3	18±2.3
6- Drug content(%)	98%	96.5%	97.8	98.3%

According to these results all formulas showed rapidly disintegrating time and short wetting time,F1 showed wetting time relatively longer than others, F2 (10%) had shown short disintegrating time without effervescent action, which makes it more suitable when it takes place on the tongue . But F3 and F4 showed effervescent directly when contact with water for the tablet so these tablet may hurt the tongue and the patient cannot use it.

IV: 2- For ODTs with Crosspovidoncl and Crosscarmelose Na as disintegrants

Table (4)) evaluation parameters for: F5, F6,F7,F8,F9,F10

	F5	`F6	F7	F8	F9	F10
	(5%)	(10%)	(15%)	(5%)	(10%)	(15)
1-Weight Variation	200.5±1.8	199.8±3	204±1.5	199.9±2.4	200.4±2.3	200.7±1.6
2- Friability(%)	0.56	0.58	0.55	0.59	0.58	0,64
3- hardness(Kg/cm^2)	2.8±2.2	2.9±1.8	3.2±1,5	2.85±1.2	2.8±2.4	2.75±1.8
4- Disintegrating time(s)	23±2.4	21±1.9	20±1.75	27±2.3	25±1.6	21±1.7
5- Wetting time (s)	58±1.5	55±1.2	48±2.4	56±1.6	52±2.3	45±2.8
6- Drug content(%)	98%	96.5%	97.8%	96%	97.9%	98%

V-Disintegration time and wetting time:

Disintegration time and wetting time for all formula were acceptable , Fig (6)and (7), shape of wetting for F2 and F3 showed in Fig (8)

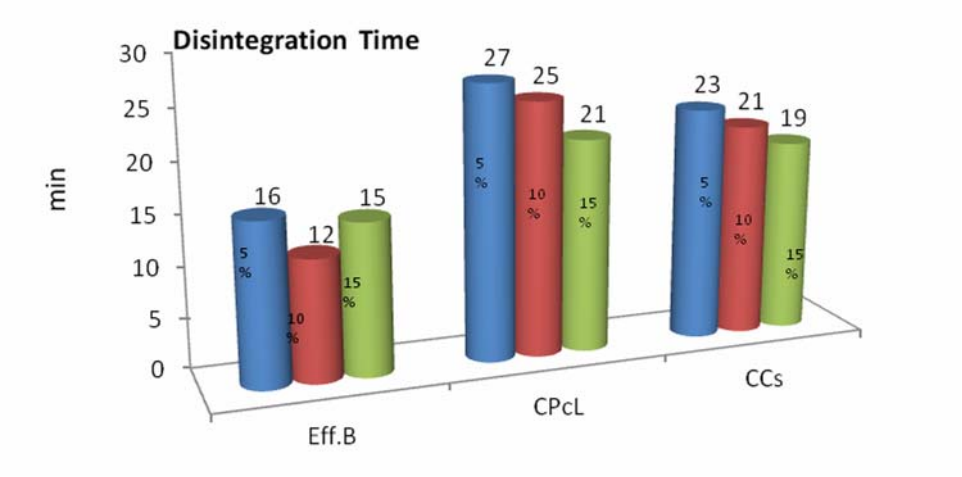


Fig (6). Disintegration time test for (SS)ODT with different disintegrants

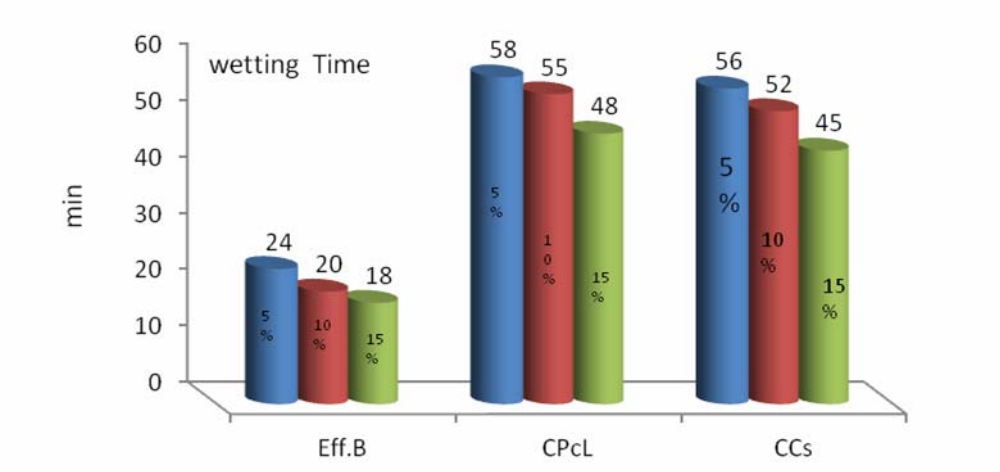
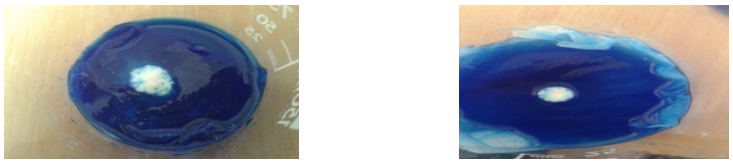


Fig (7) Wetting time (s) for (SS)ODT with different disintegrants



A B

Fig (8): Shape of wetting

A: Wetting test ODT tab with 15% effervescent base(F3)
B: Wetting test ODT tab with 10% effervescent base(F2)

VI- Dissolution test:

Quantity of Salbutamol sulphate released from all formula of ODT tablets (n = 6) was determined using Dissolution Testing Apparatus 2 (paddle). The dissolution test was performed using 500 ml of phosphate buffer(pH= 6.8) at 37 ± 0.5°C and 50 rpm. and quantity released of (SS) was calculated. Fig (9) Fig(10 Fig (11)) and Fig (12).

Quantity of (SS) released from effervescent base: F1: showed a slow drug released, F2 showed fast and regular release of Salbutamol sulphate without any effervescent action and this result is compatible with short disintegrating and short wetting time for F2. In F3 and F4 a very fast released of drug were achieved because of relatively cleared effervescent action showed in dissolution medium which will be not desirable when tablet take place on the tongue . Fig (9)

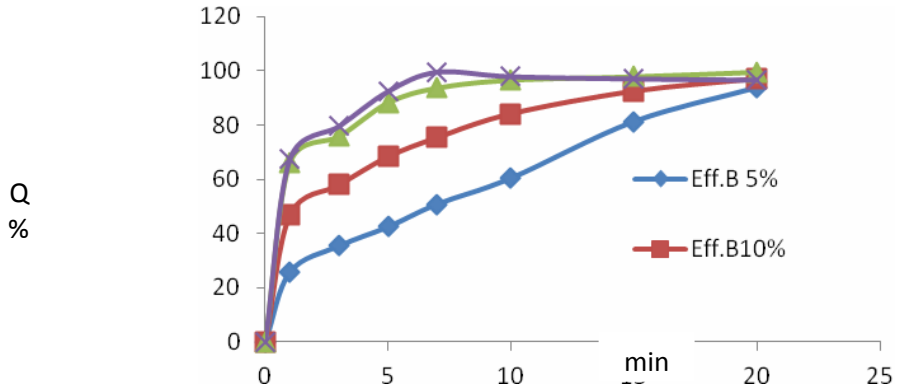


Fig (9) Q% Of (SS) from Tablets with different concentrations of weak Effervescent base(Eff.B)

ODTs with cosspovidon cl in different concentration as supper disintegrent gave different quantity released of (SS) .Fig(10)

Quantity released of (SS) from ODTs using Cross carmelose Na as disintegrent in different concentration were different due to percentage of CCs which effect on uptake of water hence the time of disintegration. Fig (11)

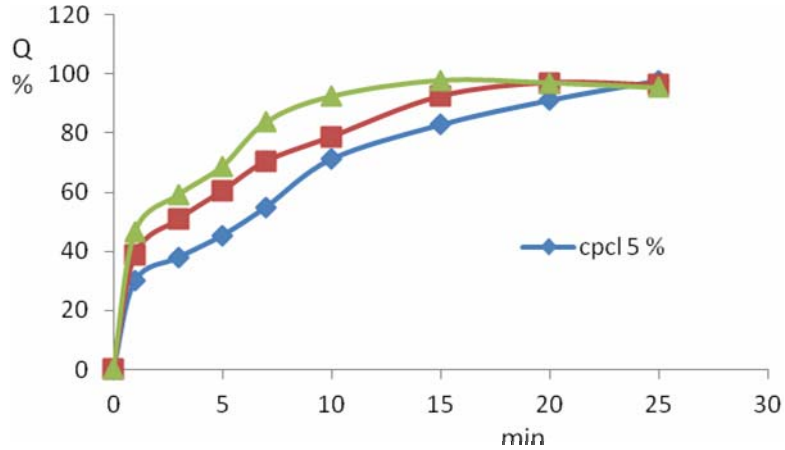


Fig (10) Q% Of (SS) from Tablets with different concentrations of Crosspovidon CPcl (F5,f6 and F7)

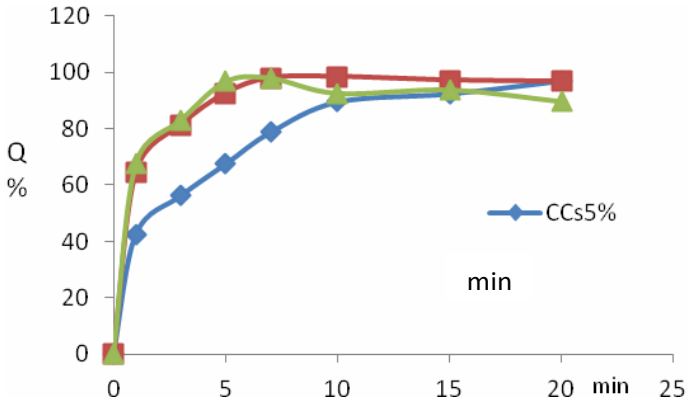


Fig (11) Q% Of (SS) from Tablets with different concentrations of Cross carmelose Na (F8,F9,F10)

Compairing the effect of three types of disintegrets on Salbutamol sulphate released cleared in Fig(12). All of them have showed a rapid release for drug during 20 minutes, and in concentration 10% Effervescent base, 10% CCs ,and 10% CPcl , Quantities of SS released Were closed to each other but F2 had shown the largest percent of release since the first minute.

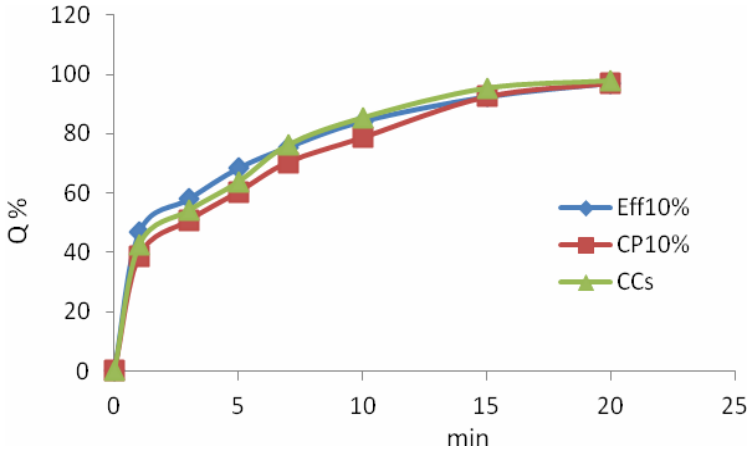


Fig (12)Q% Of (SS) from Tablets with Effervescent base10%, Cross carmelose 10%, Cross povidone CL 10%

Discussion:

All formulas prepared have given acceptable hardness arranged between 2.75 and 3.2, low friability less than 1 in all preparation tablets and short disintegration time less than one minute in all tablets. F2 (10%) effervescent showed disintegrating time 12 second, compared to 21 second in CP cl (10%), and 25sec in CCs 10%. The wetting time was 20 sec in F2 , but it was 55 sec with CPcl 10% and 52 sec with CCs 10%. F3 and F4 were avoided because they showed clear effervescent action which may hurt the tongue. All Formulas have more than 96% of drug according to drug uniformity test, and there weight were acceptable about 200 mg with low standard deviation. Results of dissolution studies showed that using 10% of effervescent base gave good and regular released for drug more than 46% at the first minute of dissolution test and 97% released after 20 minute, while using of 15% , 20% of effervescent base in tablets showed clear effervescent which not desirable when the tablet take place on the tongue. F1 showed acceptable disintegrating and wetting time but drug released was relatively slow . ODTs of Salbutamol sulfate were prepared successfully by using an effervescent base as a superdisintegrants agent with suitable concentration.

Formulas with CCs showed fast release of drug and acceptable disintegrating and wetting time due to hydrophilic properties of Crosscarmellose which Swells 4-8 folds during less than 10 seconds which make the tablets disintegrate in two ways : Swelling and wicking both.

Formulas with Crosspovidone CL as superdisintegrants showed more wetting time, This is due to the capillarity nature of Crosspovidone due to Swells 7-12 folds in less than 30 seconds , thus lead tablets Swells and disintegrating act by capillary action, so that's why the quantity released of (SS) from tablets with (CCs) a little more than tablets with (CPcl).

Conclusion:

Oral disintegrating tablets of Salbutamol sulphate were prepared successfully by decreasing the disintegration time which enhances drug dissolution rate and disperse ODTs into the primary particles by using 10% of weak effervescent base (calcium carbonate plus citric acid). The rapid dissolving of Salbutamol sulphate could be great importance in relieving acute asthmatic attacks. Tablets were prepared by direct compression and had acceptable hardness and low friability.

Orally disintegrating tablets have better patient acceptance and compliance and offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. ODT products developed to overcome the difficulty in swallowing conventional tablets among pediatric, geriatric, and psychiatric patients with dysphasia.

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