Formulation and evaluation of Acyclovir compressed lozenges

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Abstract:

Lozenges are formulations of solid dosage form which tend to liquefy in mouth or pharynx. They could be consisting of one or more drugs in a flavored and sweetened base. They are recommended to treat local mouth or pharynx irritation or infection, or they may be used also for systemic combination of two drugs (Acyclovir and Lidocaine) by pressed coated tablet lozenges. Thus, the lozenges will have both antiviral and local anesthetic effects suitable for the treatment of virus that infects oral cavity.

In this study, nine formulations of acyclovir compressed tablet lozenges were prepared to investigate the effects of type and concentration of binders (gelatin, acacia, and tragacanth) on physical appearance, weight variation, hardness, thickness, friability, dissolving , drug content and in vitro released of drug. Compressed tablet lozenges formula F4 contening (Acacia 10%) as binder was successfully prepared and has been selected as optimum formula since it released 98% of drug after 45 min, as compared to other formulas.

Key words: Compressed tablet lozenges, Acyclovir, effect of binders.

تحضير وتقييم اقراص المص المكبوسه للاسايكلوفير

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الخلاصة:

اقراص المص(المستحلبات) عبارة عن تركيبات من الجرعات الصلبة تميل إلى التسييل في الفم أو البلعوم. يمكن أن تتكون من دواء واحد أو أكثر في قاعدة منكهة ومحلاة. يوصى باستخدامها لعلاج تهيج أو عدوى الفم أو البلعوم المحلي ، أو يمكن استخدامها أيضًا للامتصاص الجهازي للدواء. تم اقتراح الهدف من هذه الدراسة لتحضير توليفة جديدة من عقارين (Acyclovir و Lidocaine) بواسطة أقراص استحلاب مضغوطة مغلفة. وبالتالي ، فإن المستحلبات سيكون لها تأثير مضاد للفيروسات ومخدر موضعي مناسب لعلاج الفيروس الذي يصيب تجويف الفم.

في هذه الدراسة ، تم تحضير تسع تركيبات من أقراص استحلاب الأسيكلوفير المضغوطة لفحص تأثير نوع وتركيز المواد الرابطة (الجيلاتين ، والسنط ، والكراكانث) على المظهر الجسدي ، وتغير الوزن ، والصلابة ، والسمك ، والتفتت ، والذوبان ، ومحتوى الدواء وفي صدر المختبر من المخدرات. تم تحضير معينات الأقراص المضغوطة بتركيبة F4 (أكاسيا ١٠٪) كمادة رابطة بنجاح وتم اختيارها كصيغة مثلى منذ أن أطلقت ٩٨٪ من الدواء بعد ٤٥ دقيقة ، مقارنة بالصيغ الأخرى....

الكلمات المفتاحية: اقراص المص المكبوسه الاسايكلوفير ، تاثير ماده التماسك

Introduction

Lozenges are solid dosage form formulations that are planned to melt in mouth or pharynx. They may possibly consist of one or more drugs in a flavored and sweetened base. These are recommended for treating local mouth or pharynx pain or Infection, and may also be used for systemi c drug absorption(cetirizine lozenges) (1).

Generally, lozenge used to relive minor sore throat pain and irritation, and was also widely used to deliver topical antibacterial and anesthetics. Nowadays lozenges encompass diverse class of remedy as follows: [2]

Analgesics, anesthetics, antimicrobials, antiseptics, antitussives, astringents, decongestants, demulcents, other classes of and drug combinations.

Sore throats, sores, as well as other mouth and pharynx irritations are common conditions which can cause pain. Although there are a number of pharmaceuticals available to treat pain for both prescription and over the-counter, these medications can sometimes be difficult to prescribe to patients who are reluctant and/or unable to take traditional oral medications. For instance, children and adults may have trouble in swallowing tablets or capsules. Patients may resist taking medication in liquid form due to the unpleasant taste or texture of drug or difficulty in swallowing[3].

Lozenges types :[4]

Chewable Lozenges, Hard Lozenges, Soft Lozenges, Compressed lozenges.

(ACV) is a nucleoside guanosine analogue with a selective affinity to thymidine kinase (TK), necessary for activating of acyclovir, in virus-infected cells. Acyclovir is an effective inhibitor of viral DNA synthesis and therefore finally stops viral replication.

the oral bioavailability of ACV is significantly small (around 15–30%) as a consequence of its low lipophilicity (around 0.2%, 25°C) and short half-life (around 2.5 h) (6). This categorizes ACV as a class III or IV Bio pharmaceutics classification system (BCS) with low permeability and high solubility or very low solubility and permeability (7). The absorption of ACV is extremely variable and dose dependent (6). The phenomenon of absorption was called narrow absorption window through a small part of the GIT. As a result, ACV must be taken five times a day at an oral dose of 200 mg, which cause compliance complications to patients. Recurrently administration of high doses; result in irregular nausea, diarrhea, rash and headache.

Materials and Methods

Material

Acyclovir powder obtained from Wuxi Hexia, Chemical Company - China.

Formulation of Compressed Lozenges

Formulation of Acyclovir compressed lozenges

Different formulas (F1-F9) were prepared by wet granulation method as shown in Table 1(A, B, C). These formulas were used to investigate the effect of different type and concentration of binders. Accurately weighted quantities of active ingredient Acyclovir (ACV), binders (Gelatin, Acacia and tragacanth), and (sucrose) which was used as sweeting agent and diluent. The weighted amount of (ACV) 200 mg was mixed with 790 mg of sucrose thoroughly as illustrated in table 1(A, B, C). The mixture was granulated using different concentrations of binder solution (gelatin, acacia and tragacanth). The resultant granules then were sieved via sieve of a mesh size 16 to be then dried in an oven for 2hr and the temperature of oven was adjusted at 50°C. The granules were dried and left on the sieve no.18, together were mixed with lubricant (Magnesium stearate) and glidant (talc) and were subjected to compression in tablet machine with compression force 13 kg to achieve a squeezed plane surface lozenges with weight 1000mg. Flavoring and coloring(orange flavor) are add to the binder solution in sufficient quantities (q.s).

Table (1-A): the composition of formulas (F1, F2, and F3) with using Gelatin as Binder

Ingredient	F1	F2	F3
Sucrose	790 mg	790 mg	790 mg
Drug	200 mg	200 mg	200 mg
Gelatin solution (concentratio (n, w/v	5%	10%	15%
Talc	5mg	5 mg	5 mg
Magnesium stearate	5mg	5 mg	5 mg
Flavor	q.s	q.s	q.s
Color	q.s	q.s	q.s

Table (1-B): The composition of formulas (F5, F6 and F7) with using Acacia as Binder

Ingredient	F4	F5	F6
Sucrose	790 mg	790 mg	790 mg
Drug	200 mg	200 mg	200 mg
Conc. of Acacia solution	10%	15%	25%
Talc	5mg	5 mg	5 mg
Magnesium stearate	5mg	5 mg	5 mg
Flavor	q.s	q.s	q.s
Color	q.s	q.s	q.s

Table (1-C): The composition of formulas (F7,F8 and F9) with using Tragacanth as Binder

Ingredient	F7	F8	F9
Sucrose	790 mg	790 mg	790 mg
Drug	200 mg	200 mg	200 mg
Concentration of tragacanth solution	10%	15%	25%
Talc	5mg	5mg	5mg
Magnesium stearate	5mg	5mg	5mg
Flavor	q.s	q.s	q.s
Color	q.s	q.s	q.s

Evaluation of the Prepared Compressed Lozenge

Organoleptic properties test [5]

Organoleptic properties are a significant factor to be estimated; for example, alteration in outer appearance or color like staining or surface coarseness is sign that the formulations were unstable.

Weight Variation Test[6]

From each batch of the formulation 20 tableted lozenges have been randomly chosen and weighed together after that the tablets were weighed separately. For the group of the formulas to passes the weight variation test is that "if not higher than two of the distinct lozenge weight differs from the mean weight by further than the percentage according to IP limits" shown in table 2.

Table (2): Weight variation limit according to IP(7)

Average Weight of Tablet (Mg)	% Deviation
Less than 80	10
80-250	7.5
More than 250	5

Tablet Friability[7]

The Determination of tablets' Friability had been performed by using Roche friabilator. Ten tableted lozenges were weight before placing in the friabilator and subject to 100 revolutions 25 rmp. Tablets clean from the dust by using a smooth muslin cloth and weight again. Percentage friability was determined using equation (1) shown below.

$$Friability\ \%= Initial\ weight - Final\ weight\ /\ Intial\ weight \times 100 \ldots Eq.1$$

Tablet Hardness [8]

The determination of lozenges hardness was through using Monsanto Hardness tester. The force applied to breakdown each lozenge was recorded. The hardness of lozenges was obtained in terms of (kg/cm^2).

Tablet thickness and Diameter [8]

The tableted lozenges thickness and diameter were verified by using vernier callipers. Three compressed tablet lozenges from each set were selected for these measurements and an average value was determined.

Drug content [5]

Lozenges were pulverized and initially dispersed in 5mL of methanol then complete the volume up to 50 ml with pH 6.8 buffer. From this solution 1 mL taken and diluted to 50 ml with pH 6.8 phosphate buffer following this, solution was sonicated for about 30 min and filtered through a filter paper. UV absorbance of this solution was measured at 254 nm For determination amount of ACV available in lozenges.

In-vitro dissolving time [9]

The Dissolving time is the time interval during which the whole lozenges disappear from disintegration media or solution. Dissolving time determination of the prepared tablets was achieved according to that stated in USP, using a disintegration tester (Erweka, Germany) via the disintegration medium of phosphate buffer with pH 6.8 maintained at 37 ± 0.5°C.

In vitro Drug Dissolution Test [10, 11]

In vitro dissolution test was done by using apparatus II (paddle type) dissolution apparatus to determine the dissolution profile of drug from the prepared ACV compressed tablet lozenge. The dissolution media used was 250 ml of phosphate buffer (PH 6.8) at 37 ºC with stirring speed of 50 rpm for 1 hr. every 5 min 5 ml of samples were withdrawn and replaced by 5ml of dissolution medium at predetermined time intervals for 60 min. Samples were then analyzed

spectrophotometric ally at the λ max 254 nm.

Results and discussion

The evaluation data of formulas F1-F9 are utilized to study the effect of different binder types (gelatin , acacia and tragacanth) with different concentration (5% ,10% and 15%) for gelatin and (10%, 15% ,25%) for acacia and tragacanth on the physical properties of prepared Acv compressed lozenges .

Results obtained are shown in Table 3. According to the ingredients composition in Table1 A, B and C , weight of the tablet should be 1000 mg, experimental average weight of a tablet obtained for formulation F1-F9 was in the range (980-995) mg according to the Table (3). it is clear that the all tablet samples obeys with the standard as the individual weight does not deviate from the mean (average value) more than permitted in terms of percentage (5%) for tablet weight more than 250 mg as per the British Pharmacopoeia (BP). This is because granules of tablet formulation possessed free following property result out from wet granulation method[12], so that tablets formed were of uniform weight with acceptable weight variation due to uniform die fill. Thickness (5.57 to 5.79 mm) of tablets was not greatly influenced by different binders[13].

Tablet hardness of all batch of formulation was shown in Table (3). It seems that with the increasing concentration of the binder, resulted in increasing the hardness of the tablet. Increasing the amount of binder resulted in a gradual decrease in tablet porosity as more of the inter particulate spaces were filled with binder [14]. It was detected that tablets hardness for all formulation was ranged from (5 ±0.055 to 7.3 ±0.0706) except formula F1 tablets fail the hardness test may be due to type of binder and concentration. Hardness of tablets depends on the amount of the binder and the compression force. The higher hardness of the tablet with the binder can be related to its film formation ability and its cohesive strength to make solid bonds between particles. As a consequence, the binder is forced into the inter particulate voids causing more solid bond between granules[15].Tableted lozenges manufactured using gelatin as a binder has a hardness that is no different from the tablet hardness that uses Acacia and Tragacanth as a binder This result proposes that the compressibility and compatibility of granules produced good enough to be compressed into a tablet since the bonding between the particles has good bond strength[16].

Friability of tableted lozenges showed the lowest percentage of weight loss, so that indicating higher inter- granular forces between the granules due to presences of binder in the formulas.

Dissolving times obtained for prepared formulas (F1-F9) was from 16 - 79± S.D 0.35 min, the dissolving time of the tablet formulations was significantly affected by the type of binder and concentration used during formulation. Dissolving time increased as the concentration of the binder increased[17] ,Figure (1) displays dissolving values of the lozenge tableted formulations. The dissolving rate was directly propositional to the dissolution rate. The dissolving rate was influenced by the rate of influx of water into the tablets which is correspondingly dependent on the porosity of the tablets. While the porosity is high, dissolving is just influenced by tablet formulation or else dissolving will be affected by the excipients[18] .The formulation content acacia has lower dissolving time due to that acacia demonstrated less binding properties than gelatin and tragacanth.

Table (3): the Effect of Type and Concentration of Binder on Post compression Parameter of ACV Compressed Lozenges

Formula code	Weight Variation (mg) n=10	Thickness (mm) n=15	Hardness (Kg/ cm^2) ± S.D. * n=3	Friability (%) n=10	In Vitro Dissolving Time (min) ±S.D.* n=2	Drug content
F1	993	5.79	3.5 ±0.0513	0.82	20 ±0.25	95%
F2	980	5.70	5.7 ±0.0611	0.46	30 ±0.2	95.5%
F3	987	5.78	7 ±0.0805	0.45	59 ±0.5	92.5%
F4	995	5.70	5.5 ± 0.0502	0.43	16 ±0	98.9%
F5	988	5.72	6.4 ±0.0604	0.53	21±0.2	98.5%
F6	987	5.66	7.3 ±0.0706	0.41	25±0.2	98.5%
F7	991	5.76	5 ±0.055	0.4	59±0.125	98%
F8	991	5.75	5.7± 0.0501	o.47	75±0	98%
F9	994	5.57	5.6±0.0801	0.43	79±0.35	98%

*S.D. Stander deviation for mean n

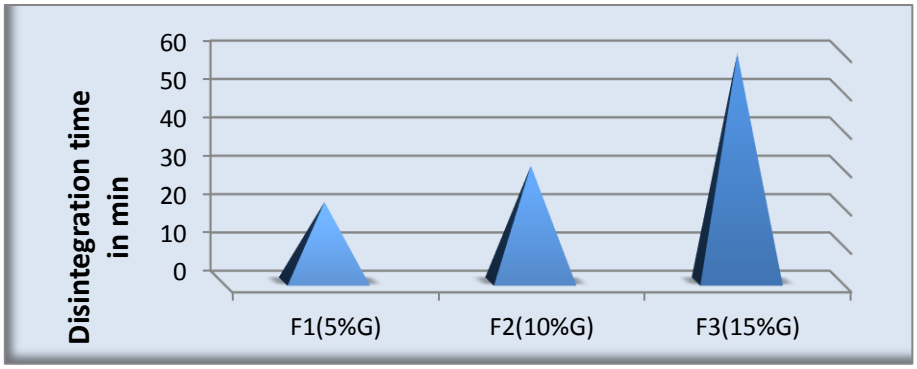

Figure (1A): Effect of different concentrations of the binder (gelatin) on dissolving time of ACV lozenges .

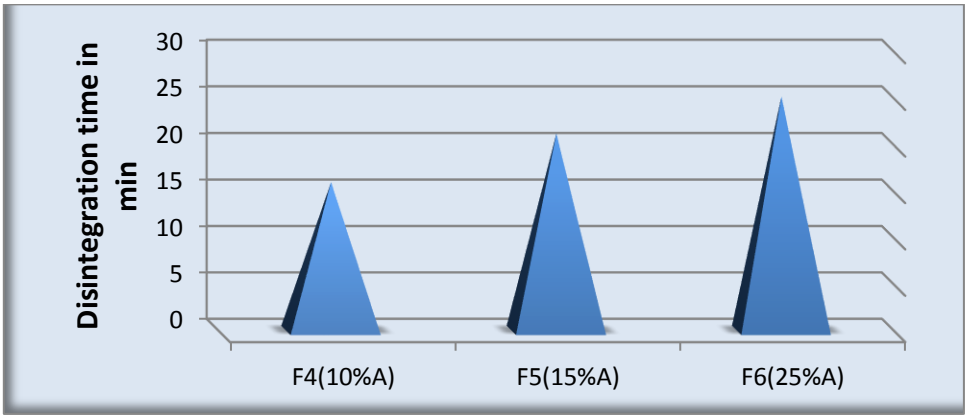

Figure (1B): Effect of different concentrations of the binder (Acacia) on dissolving time of ACV lozenges .

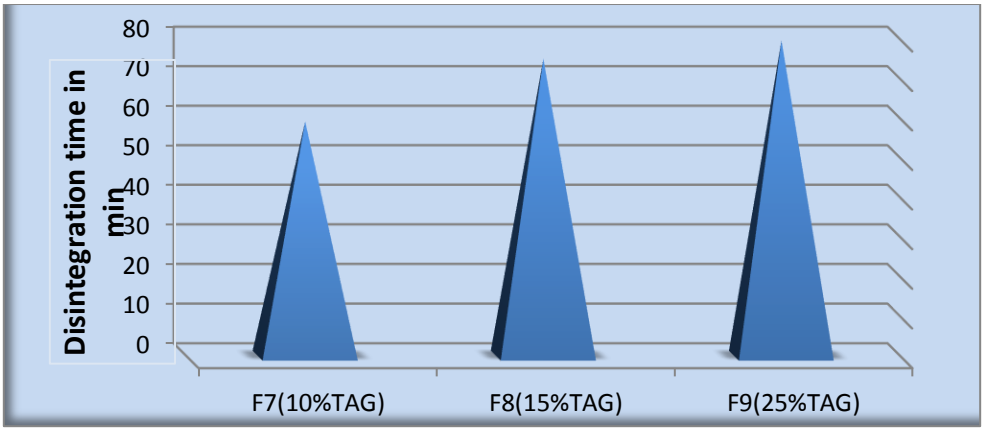

Figure (1C): Effect of different concentrations of the binder solution (tragacanth) on dissolving time of ACV lozenges

The release profile of prepared ACV compressed tablet lozenges of all formulas (F1-F9) were tested using phosphate buffer (pH 6.8) which represent the media of mouth where the dissolution of prepared ACV compressed tablet lozenges may occurs. The dissolution profiles of the prepared ACV compressed tablet lozenges of all formulas are shown in figures (2, 3, and 4).

It was no difference in percentage of released of acyclovir from formulation (F1, F2.F3) since (f_2 >50). It was observed that there was different between (F4 and F5) and (F4 and F6) in percentage of Acyclovir released from formulation since (f_2 <50) the order of released Acacia formulation was F5 (98.5%) after 55 min > F4 (98%) after 45 min >F6 (97.3%) after 55 min. it was observed that there was different between (F7 andF8) and (F7 and F9) in percentage of acyclovir released from formulation since (f_2 <50),the order of released tragacanth from formulation was F7 (96.2%) >F8 (94%) >F9 (90%) after 65 min .

The binder used has significant influence on the tablet qualities(friability ,hardness) and dissolution rate of ACV from the compressed tablet lozenges.it was observed that there was different between (F1 and F4) and (F4 and F7) and (F1 and F7) in percentage of released of Acyclovir from formulation since (f_2 <50),the order of release from the formulations with different binder and lower concentration after 45 min was found F4 (98%) >F1(80.6%) >F7(50%), so that the order

of binders based on decreasing dissolution rate was tragacanth > gelatin > acacia. When the dissolution rate and extent are compared for ACV Acacia based formulations showed significantly faster and more complete dissolution of the ACV as compared to other binders. Fastest dissolution of the drug is achieved at 10% acacia level. The criteria for dissolution of ACV dissolution show dependency on the type and concentration of binder used Acacia gum can swell ,yet has low viscosity due to water absorption and easily eroded so that can release of drug faster than other binder[19].

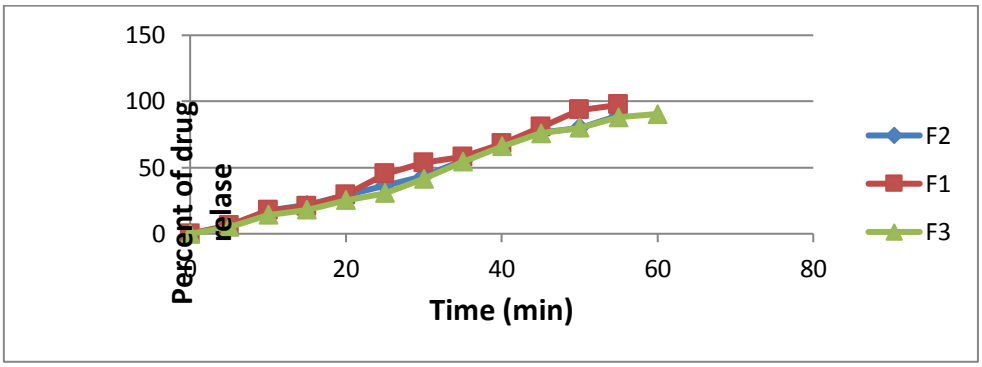

Figure (2) : The dissolution profile of prepared ACV Compressed tablet lozenges (F1 ,F2 and F3) in phosphate buffer (pH 6.8) at 37ºC ±0.5 ºC

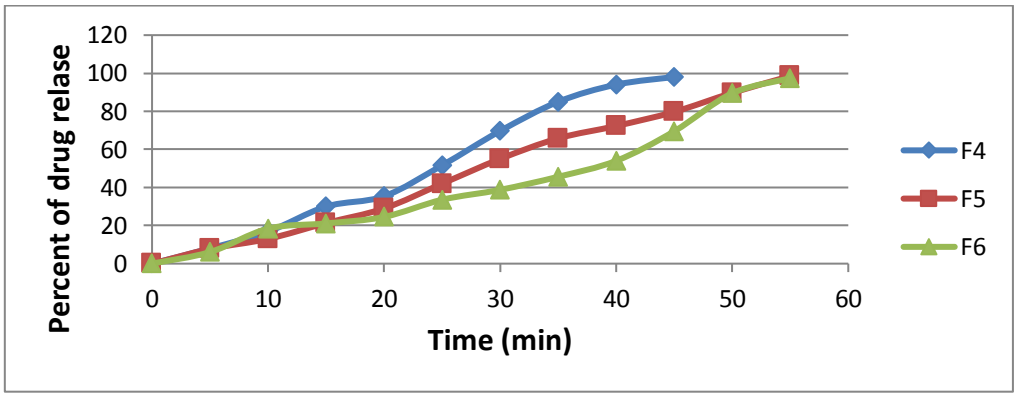

Figure (3): the dissolution profile of prepared ACV compressed tablet lozenges (F4, F5 and F6) in phosphate buffer (pH 6.8) at at 37ºC ±0.5 ºC and 50 r.p.m.

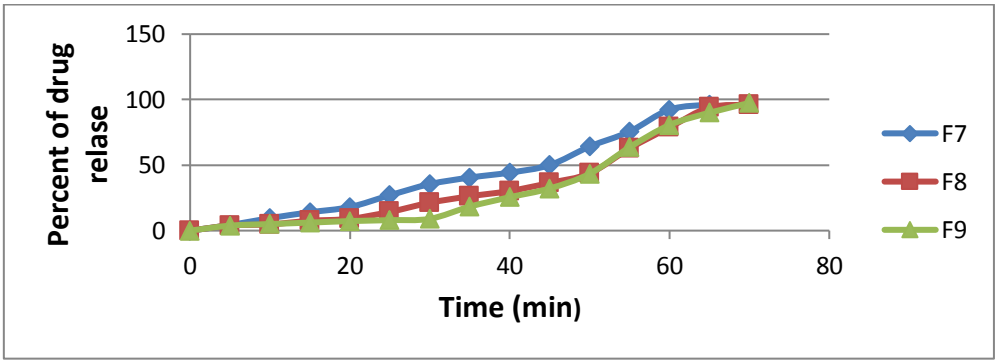

Figure (4): the dissolution profile of prepared ACV compressed tablet lozenges (F7, F8 and F9) in phosphate buffer (PH 6.8) at at 37ºC ±0.5 ºC and 50 r.p.m.

Conclusion

Compressed tablet lozenges formula F4 containing (Acacia 10%) as binder was successfully prepared and has been selected as optimum formula since it released 98% of drug after 45 min, as compared to other formulas.

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