Formulation and Evaluation of Flurbiprofen Oral Film

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Abstract

Fast dissolving film can be defined as a dosage form, which when placed in the oral cavity. It will rapidly disintegrate and dissolves to release the medication for oral mucosal absorption or allow for the gastrointestinal absorption to be achieved when swallowed.

Flurbiprofen is non-steroidal anti-inflammatory agent with antipyretic and analgesic properties and can be used in low doses 8.75 mg as analgesic and anti inflammatory agent in sore throat infection. This study aims to formulate flurbiprofen as oral dissolving films, to improve the effective relief of pain with severe sore throats with little or no adverse effect.

Nine formulas were prepared using solvent-casting method, and the effect of different formulation variables on the physical and mechanical properties of the prepared films, besides to the drug release behavior was evaluated.

It was found that, the prepared oral film of flurbiprofen that contains hydroxypropyl methylcellulose alone showed the fastest in- vivo disintegration time (30 sec.) Among other investigated polymers. The drug release rates was also observed

The prepared formula F1 which contains HPMC in concentration of (54% w/w), PEG 400 (16% w/w) showed the fastest disintegration time 30seconds, Drug release was 77.5% within 2minutes with satisfactory mechanical properties.

The overall results suggested that the prepared formula of flurbiprofen can be conveniently administered orally in the form of an oral film for sore throat infection.

Keyword:Oral strip, fluriprofen, HPMC polymer.

تصييغ وتقييم الفلوربابروفين كشرائط فموية

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الخلاصة

يمكن تعريف الشرائح سريعة الذوبان بأنها شكل دوائي حديث يعطى فمويا او عن طريق الفم والتي ما إن يتم وضعها فأنها تتفكك وتذوب لتحرير الدواء ليتم امتصاصها عن طريق الغشاء المخاطي الفموي أو يسمح لها بالأمتصاص عن طريق الجهاز الهضمي والذي يتحقق عند بلعه.

فلوربايبروفين ,هو مضاد للالتهابات اللاستيروديه مع خصائص خافضه للحراره ومسكنه للالام ,ويمكن أستخدامه في جرعات منخفضة ٨,٧٥ مللي غرام في معالجة الآلام وكمضاد للالتهاب في عدوى التهاب الحلق والبلعوم .ومن المعروف أن الأعراض الجانبية للفلوربايبروفين يمكن أن تكون مرتبطه بالجرعه الدوائية وبالتالي من المتوقع أن إعطاء الفلوبايبروفين بشكل شرائح ذائبة بالفم تعمل على تقليل الالام في التهاب الحلق بحد أدنى او بدون أعراض جانبية.

تم تحضير تسعة صيغ دوائية بطريقة القشط كما تم دراسة المتغيرات المختلفة و الخواص الفيزياوية و الميكانيكية للشرائط المحضرة إضافة إلى دراسة تحرر الدواء. لقد وجد ان الشرائط المحضرة المحتوية على هيدروكسي بروبيل مثيل سليلوز وحده أظهرت أسرع زمن تفكك ٣٠ ثانية كذلك ضمن مجموعة من البوليمرات تم دراسة تحرر الدواء ايضا.

لقد أظهرت النتائج أن الصيغة المحضرة الأولى ف١ (F1) التي تحتوي على هيدروكسي بروبيل مثيل سليلوز بتركيز ٥٤% (w/w) وبروبيل اثيل كلايكول بتركيز ١٦% (w/w) هي الافضل بين الصيغ الاخرى من ناحية زمن التفكك في الجسم ٣٠ ثانيه ونسبه تحرر الدواء خلال دقيقتان يكون ٧٧% وكذلك أظهرت خواص ميكانيكيه مقبولة . أجمالي النتائج تشير إلى أمكانية استخدام الفلوربايبروفين والتي تعطى فمويا كشرائح سريعة الذوبان لالتهابات الفم .

الكلمات المفتاحية:الشرائط الفموية ،فلوربايبروفين ، HPMC بوليمر .

Introduction

Oral drug delivery has been known for decades as the most widely utilized route of administrated among all other routes that have been employed for systemic delivery of a drug via various pharmaceutical products of different dosage forms [(1)].

Drug delivery through the oral cavity offers many advantages, the oral mucosa is conveniently and easily accessible and therefore allows uncomplicated application of dosage form, furthermore the oral mucosa is hurt against local stress or any damage and show fast cellular recovery after such incident[(2)].

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Fast dissolving films (FDF) is a type of oral drug delivery system for the oral delivery was developed based on the technology of the monolithic transdermal patches. This delivery system consists of a thin film which is simply placed on the patients tongue or mucosal tissue of cheek [3].

A film or strip can be defined as a dosage form that employs a water-dissolving polymer (generally a hydrocolloid, which may be a bioadhesive polymer), which allows the dosage form to quickly hydrate adheres, and dissolves when placed on the tongue or in the oral cavity.

These oral thin films or strips which are flexible one similar in size, shape and thickness to a postage stamp (2x3 cm) and can be packaged in multi dose containers or individually pouched [4].

Flurbiprofen is a non-steroidal anti-inflammatory drug, the structural formula are shown in figure 1[5].

Flurbiprofen is a drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of flurbiprofen, like that of other non-steroidal anti-inflammatory drugs, is not completely understood but may be related to prostaglandin synthetase inhibition [5].

The present study is undertaken to prepare flurbiprofen oral dissolving films of (8.75 mg), to improve patient compliance, reduce the frequency of administration and to obtain greater therapeutic efficacy.

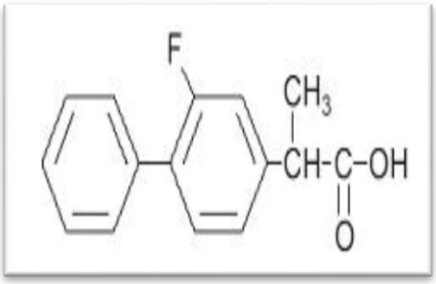

Figure 1: The chemical structure of Flurbiprofen

Experimental Work

Materials

Flubiprofen FDC limited , India, Citric acid Panreac , Barcelona, Espana, Gelatin Medichem Enterprise(Shanghais) co. Limited, China, Glycerin Searle company, England, Hydroxy propyl methylcellulose (HPMC E-15) Sodium carboxymethyl cellulose (CMC Na) Sigma-Aldrich, USA, Mannitol Riedel-De-Haen , Germany, Polyethylene glycol 400 (PEG400) J.T Baker,China, Poly oxyethylene sorbitan Monooleate (Tween 80) SinopHarm chemical reagent Co.,Ltd, Potassium dihydrogen Ortho pHospHate, KH_2PO_4 Sd fine-Chem. Limited,Mumbai.

Each film area = 2×2 = 4 cm^2

Methods

Characterization of Flubiprofen

Determination of Melting Point

The melting point of flurbiprofen was determined according to the method stated by USP [6] a compact column of flurbiprofen powder was prepared by inserting a small quantity of the powder into a one side sealed capillary glass tube. The tube was moderately tapped on a solid surface to form column of powder in the bottom of the tube, which is then positioned in electrical melting point apparatus and monitored until complete melting of the powder where the temperature reading was recorded.

Determination of λ max

Accurately weighed 10mg of pure flurbiprofen was transferred to 100ml volumetric flask. The drug then dissolved and diluted with phosphate buffer pH 6.8 to get concentration of 100µg/ ml of stock solution [7].

From stock solution aliquot was prepared to get concentration of 10 µg /ml and scanned over the wavelength range 200-400 nm against phosphate buffer 6.8 using spectrophotometer .the spectrum of absorbance versus wavelength was recorded using UV-spectrophotometer and analyzed for the absorbance maximum (of λ max)-the wavelength at which the highest absorbance was observed.

Construction of calibration curves

From stock solution 0.1 mg/ml aliquots were prepared 2, 4, 6, 8, 10, 14, 16 ml and transferred to 100ml volumetric flasks and diluted to get concentration of 2, 4, 6, 8, 10, 14 ,16 µg /ml, respectively . The absorbance of solution was measured at 247 nm using UV-visible Spectrophotometer against phosphate buffer pH6.8 as a blank. The plot of absorbance versus concentration µg /ml is plotted& data was subjected to linear regression analysis.

Preparation of flurbiprofen oral films method of preparation of rapidly dissolving films

Nine formulas were prepared (F1-F9)with their composition shown in table (8), using solvent casting method, each film with surface area approximately 4 cm^2 is loaded with 8.75 mg flurbiprofen which is equivalent to about as a base. The area and number of films prepared for each batch can be calculated as follow [8]:

Total area of Petri dish was 154 cm^2

Number of films in batch =154/4 =38.5

Total drug load = 8.75×38.5 = 341.25 mg (flurbiprofen)

An aqueous dispersion(solution 1) of film forming polymer was prepared by dissolving 1.053 gm HPMC in 50 ml distilled water ,then add on it 39mg citric acid , 39mg mannitol, and 312mg of PEG. Then the dispersion allowed to stir for 3 hours &kept at room temperature for 20 hour to remove all air bubble entrapped and then solution 2 is prepared by dissolving 341.25mg flurbiprofen in 50 ml ethanol and 78 mg of tween 80 (surfactant) were added with a a constant stirring for 45 min. both solution (1 & 2) stirred for 1hour , and were used after at least 24 hours in the refrigerator to rest and remove all the air bubbles entrapped, then was cast onto 14 cm –diameter Petri dish and was dried in the oven at 40 ºC for 24 hours. The films were carefully removed from the Petri dish, checked for any imperfections and cut into the required size (2 x 2 cm^2) to deliver the equivalent dose per strip. The samples were stored in glass container until further analysis. Film samples with air bubbles, cuts or imperfections were excluded from the study.

Table(1) Composition of the prepared flurbiprfen oral films formulas.

Formula No.	HPMC	CMC	HPMC +CMC 50: 50	Gelatin	PEG 400	Citric acid	Glycerin	Flurbiprofen	Tween 80	Mannitol
1	27 mg				8mg	1 mg		8.75mg	2mg	3.25 mg
2		mg27			8 mg	mg 1		8.75 mg	2 mg	3.25mg
3	21 mg				8 mg	1 mg		8.75 mg	2 mg	3.25 mg
4		21mg			8 mg	1mg		8.75 mg	2mg	3.25 mg
5				27 mg	8mg	1mg		8.75mg	2mg	3.25mg
6				21 mg	8mg	1mg		8.75mg	2mg	3.25mg
7			21mg		8mg	1mg		8.75mg	2mg	3.25mg
8			21mg			1mg	8mg	8.75mg	2mg	3.25 mg
9			21mg			1mg	10mg	8.75mg	2mg	3.25mg

Characterization of flurbiprofen oral films drug content uniformity

Five films unit of each formulation were taken in separate 100ml of volumetric flasks, 100m of pH 6.8 phosphate buffer was added and continuously stirred for 24 hr using water bath shaker. The solutions were filtered, diluted suitably and analyzed at 247 nm in a UV-spectrophotometer. The average of flurbiprofen was calculated.

Visual inspection

Properties such as homogeneity, color, transparency and surface of the oral films were evaluated for all the prepared formulas visually [(9)].

Weight variation

The weight variation of the Flurbiprofen oral film was done by weighting twenty films individually and the average weight was calculated. For the film to be accepted, the weight of not more than two films deviate from the average weight by no more than 7.5% and no film deviates by more than 15% [(10)].

Thickness measurements

The thickness of each film was measured at five different locations (centre and four corners) using vernier caliper micrometer .The data are represented as a mean±SD of three replicate determinations. [(11)]

Folding endurance

The folding endurance of randomly selected films was determined by repeatedly folding one film at the same place till it break or folded maximum 250 times [(12)]. The data are represented as a mean of three replicate determinations.

Surface pH measurement

The surface pH of oral film was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH, may cause irritation to the oral mucosa. Oral film was slightly wet with the help of water. Then the pH was measured by pH paper [(13)]. The data are represented as a mean of three replicate determinations.

In-vivo disintegration study

The time required for complete disintegration in the oral cavity was collected from three healthy volunteers. The volunteers were told about the purpose of the test. Before the test, the mouth cavity was rinsed with a cup of water [48]. The film was placed on the tongue and subsequently the tongue was gently moved. The time required for disintegration in mouth was measured with a stopwatch and recorded as a disintegration time [14]. The data are represented as a mean of three replicate determinations.

In-vitro dissolution study

The in vitro dissolution test was carried out for all formulas in a USP basket dissolution apparatus type 1 [15].A 4-cm^2 sample of film was exactly weighed. The dissolution medium was 900 mL of phosphate buffer pH 6.8[51]. The rotation speed was 100 rpm at 37±0.5°C.10 ml aliquot of the dissolution medium was withdrawn at specific time intervals, and replaced with 10 ml of the phosphate buffer. The drug release was analyzed spectrophotometrically at λ max 247 nm. One film was placed into each vessel. The data are represented as a mean of three replicate determinations.

Result and Discussion

Characterization of flurbiprofen

Determination of melting point

The melting point of flurbiprofen measured was 115 ^{0}C; this result is the same as reported [16] which indicates the purity of the drug powder.

Determination of λ max

Scanning the diluted solutions of Flurbiprofen in phosphate buffers (pH 6.8) by UV spectrophotometer at 200- 400 nm gave the λ max found was 247 nm as reported [16].

Construction of calibration curve

Calibration curve of Flurbiprofen in phosphate buffers (pH 6.8) are represented in figure2.

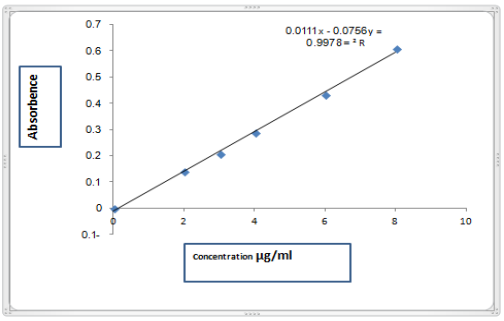

Figure 2: Calibration curve of Flurbiprofen in phosphate buffer (pH 6.8) and 37 °C.

Evaluation of flurbiprofen oral films

drug content uniformity

All the prepared films were found to contain a uniform quantity of the drug. The preparations met the criteria of British Pharmacopeia content uniformity (85- 115) % of the label claim. On this basis, it was found that the drug was dispersed uniformly throughout the film [17].

Visual inspection

HPMC films were transparent, colorless, thin and soft, and those prepared from sodium carboxy methyl cellulose (Na CMC) were opaque, white and combination of HPMC and Na CMC have semi-transparent appearance as shown in figure 3, while gelatin films were excluded from visual inspection because of rough surface , aggregation appearance ,and very poor film forming capacity.

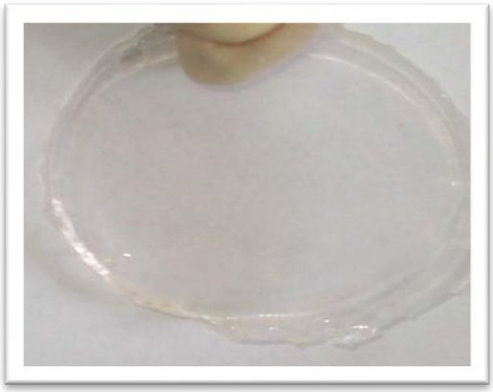

Figure 3: Formula F1 containing HPMC (hydroxy propyl methyl cellulose) polymer

Weight variation

The results reveal that: the average weights for all the prepared formulas were uniform and comply with the referred values as showed in the table 2.

Thickness measurements

Table 2 gives the average thickness value of 3 films for each formula. A very low standard deviation value is indicating that the method used for the formulation of films is reproducible and give films of uniform thickness and hence dosage accuracy in each film can be ensured [18].

Surface pH study

The surface pH of all films was found between (6.2 -7.4) which is within the range of salivary pH.6.2 -7.4. No significant difference was found in surface pH of different films, and no mucosal irritation [19].

Folding Endurance

The results were reported in table 2 were the folding endurance was found to be higher in F1(>300) due to the flexibility

nature and the concentration of the polymer formula F9(180) was due to change of plasticizer from PEG400 to Glycerol and increase the concentration of plasticizer[20].

Disintegration time in - vivo

The results table 2 showed that both changing the plasticizer types and concentration had non-significant difference (HPMC), while in formula F8(298) was, on the mouth disintegration time of oral films. This because the two plasticizers are water soluble and will diffuse out of polymeric films in aqueous media generating void spaces in the film through which diffusion of fluid occurs, facilitating film disintegration[21] .

Table(2)The physicochemical parameters of the prepared flurbiprofen oral films

Formula code	Thickness (mm)	Surface pH	*In- vivo* DT (sec)	Weight variation (mg)	% Drug relase within 2min.	Folding endurance
F1	0.1±0.01*	6.91	30.0	47±2*	77.5	>300
F2	0.1±0.03*	6.73	92.32	45±2*	26.3	1
F3	0.15±0.05*	6.913	32	44±4*	34.04	70
F4	0.1±0.03*	6.86	90	48±2*	36	4
F5	---	---	---	---	---	---
F6	---	---	---	---	---	---
F7	0.14±0.007*	6.66	50	36±1*	32	2
F8	0.13±0.012*	6.78	65	34±3*	22.16	298
F9	0.14±0.012*	6.75	60	41±5*	52	180

*** Standard deviation from mean n=3**

In - vitro Dissolution

In - vitro release was carried out in USP basket type dissolution apparatus .F1 Formulation showed that the drug was rapidly released 77.5% with in 2 minute and Formulation F3 release 34.04% with in 2 minute as shown in Figure 4 and this is because increasing the concentration of HPMC E-15 may increased the release due to the leakage of the soluble part of the film during dissolution which left pores for drug release[22]. On other hand F2 Formula has low release which is 26.6% when compared with formula F4 which is 36% which is drug release within 2 minute so increase CMC concentration increases the viscosity of the gel surrounding the film upon hydration and leads to the formation of a gel layer with longer diffusional path therefore decrease drug release [23].

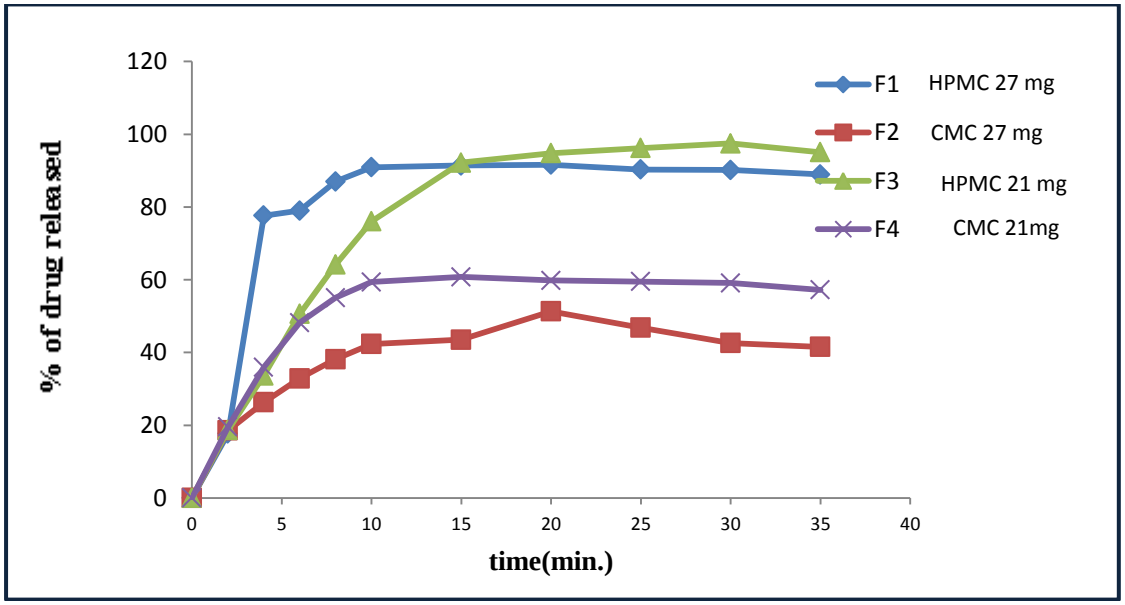

Figure4: Effect of polymer type and concentration on the release profile of Flurbiprofen in F1, F2, F3, and F4 phosphate buffer pH 6.8 and 37 °C.

The combination of HPMC and Na CMC show more retardation in the release from Formula F8, which is 22.6% within two minutes as shown in figure 5.

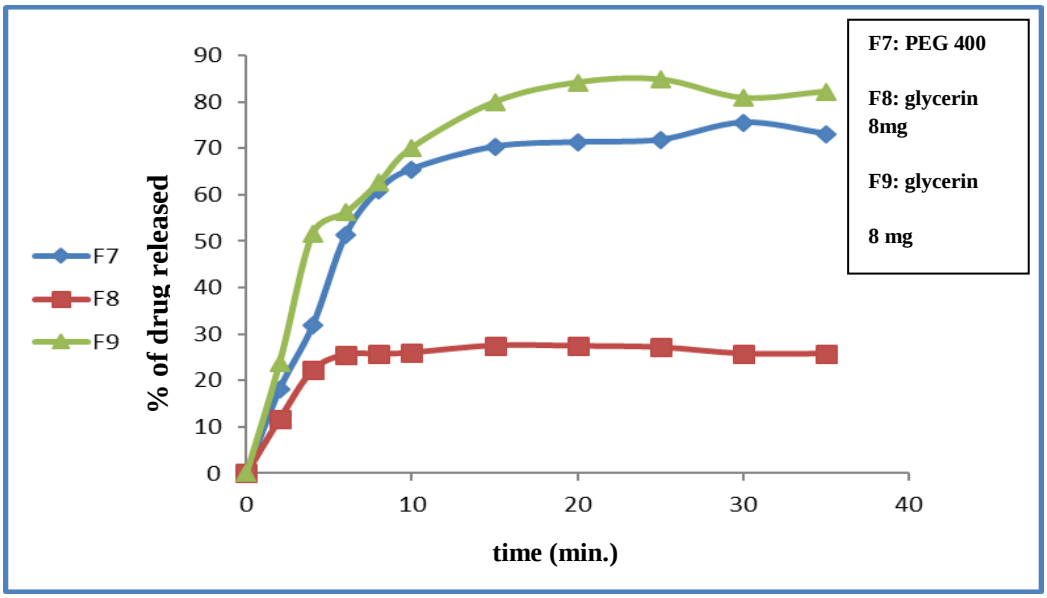

Figure 5: Effect of plasticizer type and concentration on the release profile of Flurbiprofen in F7, F8and F9 phosphate buffer pH 6.8 and 37 °C.

Conclusion

On the basis of the results obtained; hydroxy propyl methyl cellulose showed the fastest in vivo disintegration time. In addition, an acceptable mechanical properties and dissolution behavior were achieved. Also glycerin was the best plasticizer as it showed an improvement in mechanical and physical characteristics of the flurbiprofen oral film.

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