ORIGINAL ARTICLE

Preparation and evaluation of oral soft chewable jelly containing flurbiprofen

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ABSTRACT

Oral jelly is a semisolid preparation that could resolve problem associated with dosage form's swallowing, especially in pediatric and elderly ones. This work aimed to prepare oral flurbiprofen (FBP) jelly to improve patient compliance. Heating and congealing method was used to prepare FBP jelly using three different polymers (pectin, sodium carboxymethyl cellulose, and hydroxypropyl methylcellulose). The effect of different concentrations of pectin and sucrose on jelly properties was studied. The results revealed that both pectin and sodium carboxymethyl cellulose polymers gave acceptable jelly appearance and consistency. It was also observed that the increase of pectin or sucrose concentration had a significant impact on jelly viscosity. All pectin jellies except formula containing 5.5% pectin and 50% weight by volume (w/v) sucrose exhibited more than 50% and 85% of FBP releasing within 15 and 30 min, respectively. The formula (FP2) consisting of 4.5% pectin and 40% w/v sucrose was selected as optimum formula which had a high percent dissolution efficiency (78.95%) and better consistency during handling. This work succeeded in the preparation of new FBP oral jelly, which can be considered a promising dosage form for enhancement of patient compliance and drug solubility.

Key words: Dysphagia, easily swallowing, flurbiprofen, oral jelly, pectin

INTRODUCTION

The oral route is the most common route of drug administration. Till today, it is still a widely preferred and acceptable route among patients owing to its advantages, such as ease of administration, safeness, noninvasiveness, and convenience for self-administration.[1]

However, one of the obstacles to oral drug delivery experienced by many patients, particularly pediatric and geriatric population, is dysphagia. Dysphagia causes difficulties in swallowing conventional solid oral medicines and the risk of choking by liquid preparations. Consequently, patients usually try to crush hard tablets or open capsules and mix them with food or water to become swallowing easily. Such behavior can result in dosing inaccuracy and changing of drug release and absorption, as well as undesirable drug taste palatability.[2,3]

Today, one of the appropriate potential alternative oral dosage forms is jelly, similar to gelatinous food and confection. The jellies can address swallowing problems, ensure patient safety, and ease of handle and taken without water. Thus, jellies can improve patient compliance in addition to their flavoring taste and esthetic pleasant appearance. Jellies have advantages of both solid and liquid preparations.[4]

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Jellies intended for oral administration mean "nonflowable gelatinous preparations of definite size and shape" and must meet the requirements of dissolution and content uniformity according to the *Japanese pharmacopeia*.[5] Recently, several drugs have been marketed as medicated oral jelly, such as tadalafil (Apcalis®, Ajanta), alendronate (Bonalon®, Teijin Pharma Limited), and donepezil (Aricept®, Eisai). In addition, numerous research studies to improve patient acceptance and/or enhance drug bioavailability have been published.[6,7]

The main excipients of jellies are a gelling agent, stabilizer, preservative, and flavoring and sweetening agents. Jellies act as a vehicle for a drug which presents either as dissolved or dispersed/suspended form that can release and mix with saliva to be absorbed through gastrointestinal tract mucosa. By choosing the right gelling agent, which can be either natural or synthetic hydrophilic polymers at a suitable concentration, the drug can release immediately or sustained from the jelly vehicle.[8]

Flurbiprofen (FBP) is one of the widely used nonsteroidal anti-inflammatory drugs. FBP acts as a potent pain reliever. Recent reports suggest its potential topical and systemic use in the inhibition of colon tumor and platelet aggregation.[9] FBP is also considered a promising medicine for the management of Alzheimer's disease.[10] However, Food and Drug Administration (FDA) approval oral formulations of FBP are only as tablets of different strengths and capsules.

The objective of this study was to prepare an oral FBP jelly to be easily swallowed by geriatric and pediatric patients. To achieve our aim, the effect of three gelling agents; pectin, hydroxypropyl methylcellulose K100 (HPMC K100), and sodium carboxymethyl cellulose (SodCMC), on physicochemical properties include appearance, texture, and *in vitro* release profile of the prepared jellies were evaluated to select the optimum formula.

MATERIALS AND METHODS

FBP and HPMC K100 were purchased from (Hangzhou Hyper Chemicals Limited, Zhejiang, China). Pectin was purchased from (Cargill,Redon, France), SodCMC, and Tween 80 were from (Alpha Chemika,India). Polyethylene glycol (PEG400) was from (J.T Baker, China). Citric acid, methylparaben, and propylparaben were purchased from (Fluka Chemical AG, Switzerland).

Methods

Preformulation studies

The drug–polymer compatibility study was carried out after incubation of the pure drug and a 1:1 ratio physical mixture of FBP and each gelling agent in the oven at 40°C for 2 weeks by comparing Fourier-transform infrared (FTIR) spectra (4000-400 cm^{-1}) using (FTIR-Shimadzu, Japan).[11]

Preparation of flurbiprofen jelly

Several jelly formulations were prepared using heating and congealing method.[12] Three gelling agents (pectin, HPMC K100, and SodCMC) were used [Table 1]. Each of the polymers was dispersed in a small volume of warm distilled water and stirred using a magnetic stirrer to facilitate the hydration of hydrophilic polymer. Then, the required amount of sucrose will add to the polymer solution with continuous stirring; after that, FBP and all the remaining excipients are added under stirring. The final weight was adjusted to 25 g with distilled water. Then was poured into molds to be stored as separate unit doses (the weight of each dose is 2.5 g and contains 50 mg FBP) and allowed to cold at room temperature.

Characterization of flurbiprofen jelly

Determination of physical appearance and pH

All prepared FBP jellies were inspected visually for appearances such as color, transparency, homogeneity, and consistency. Grittiness and stickiness were evaluated by mild rubbing of the prepared jellies between the thumb and index fingers.[13] One gram of each prepared FBP jelly was weighed and dispersed in 100 mL of distilled water and pH was examined.

Weight variation, drug content uniformity, and syneresis

For each formulation, ten jellies were taken and their individual weight was determined. The average weight percent was calculated. Furthermore, three jelly units of each formulation were taken in a separate volumetric flask. The phosphate buffer (pH 7.2) was added and continuously stirred to dissolve FBP. Then, the solution was filtered and diluted suitably to analyze at 247 nm by ultraviolet spectrophotometer.[14] Syneresis was performed by visual inspection for any change in jelly consistency or size shrinkage after 48 h storage at room temperature. Hence, jellies that undergo syneresis would be excluded from further evaluation tests.[15]

Viscosity

The viscosity of jellies was measured using (VR 3000 MYR Viscometers) with spindle number 7 at 25°C. Viscosity spindle was inserted in 50 g of prepared sample and rotated at speeds that were 10 rpm.[13]

Table 1: The components of different formulations of oral flurbiprofen jelly

Ingredients*	FP1	FHP1	FSC1	FP2	FP3	FP4	FP5
Pectin (mg)	875			1125	1375	1125	1125
HPMC K100 (mg)		875					
SodCMC (mg)			875				
Sucrose (g)	10	10	10	10	12.5	7.5	12.5
Water up to (g)	25	25	25	25	25	25	25

*In addition, each formula contained FBP 500 mg, saccharine 50 mg, PEG400 750 mg, Tween 80 250 mg, citric acid 250 mg, methylparaben 45 mg, and propylparaben 5 mg. HPMC K100: Hydroxypropyl methylcellulose K100, SodCMC: Sodium carboxymethyl cellulose, PEG400: Polyethylene glycol 400, FBP: Flurbiprofen

Texture analysis

The textural description of jelly, as its mouthfeel in terms of firmness, was determined using the (TA. XT Plus-Stable Micro Systems) texture analyzer. Using compression analysis, the texture profile analysis was performed using probe P100 and set with a trigger of 5 g, deformation of 1.2 mm, and a speed of 1.0 mm/s. The maximum force value on the graph is a measure of firmness.[16]

In vitro flurbiprofen dissolution

The dissolution test was carried out using the paddle method (apparatus II with a stirring rate of 50 rpm at 37°C and phosphate buffer medium pH 7.2). A volume of 5 mL of the dissolution medium was taken at the time points of 5, 10, 15, 20, 30, 45, and 60 min, filtered, diluted, and analyzed at λ_{max} 247 as listed in the USP Pharmacopeia 11th edition. The drug release performances of prepared jellies have been compared using cumulative percent release at 15 min, the dissolution efficiency (% DE), and mean dissolution time (MDT) at the end of 60 min. For quantitative kinetic analysis of FBP release profile from optimum jelly formulation, DDSolver software was applied to investigate the best data fit to order.[17]

Statistical analysis

All experiments were done in triplicate for each sample; the results were presented as mean ± standard deviation. One-way analysis of variance analysis was employed to identify significant differences between data. Data were analyzed by omitting the insignificant term with probability value (P) ≤0.05.

RESULTS AND DISCUSSION

Preformulation studies

The FTIR spectral of FBP powder showed two characteristic peaks; carbonyl stretching band donated at 1696.02 cm^{-1} and broad peak of O-H stretching of the carboxylic acid group at 2500–3300 cm^{-1} were investigated. The other characteristic peak was C-F stretching at 1217.83 cm^{-1} [Figure 1a]. The results were inconsistent with Sohail *et al.* findings.[18] For the physical mixture of drug and polymer, there is no significant deviation in three characteristic FBP peaks [Figure 1b-d], meaning that there was no considerable impact of polymer existence on the integrity of FBP peaks and confirmed compatibility.

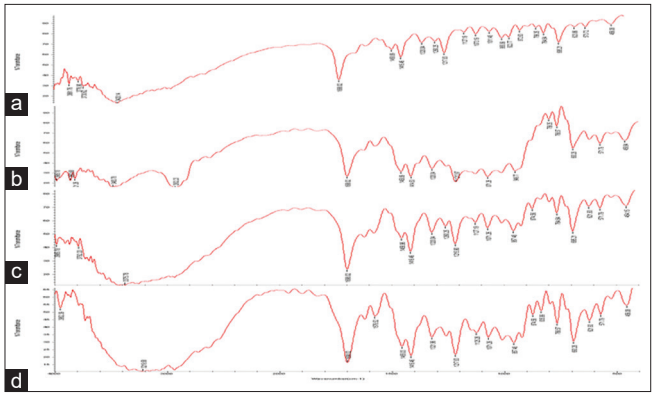

Figure 1: FTIR spectrum of (a) pure flurbiprofen, the physical mixture of flurbiprofen with (b) HPMC K100, (c) SodCMC, and (d) pectin. FTIR: Fourier-transform infrared

Preparation of flurbiprofen jelly

Based on the earlier study, PEG400 and Tween 80 were used as cosolvent and surfactant, respectively, to enhance FBP solubility based on published studies.[14,19] Sucrose is selected as sweeteners to improve the taste and viscosity of the formulation.

PEG 400 at a concentration higher than 3% weight by volume (w/v) was found to affect the consistency of jellies. Increasing the concentration of HPMC and SodCMC above 3.5% w/v resulted in a very viscous gel that was difficult to be poured into molds.

Characterization of flurbiprofen jelly

All prepared FBP jellies had a pleasant odor with bright yellow color for pectin formulations (FP1-FP5), whereas SodCMC formula had white color as shown in Figure 2. Table 2 summarizes the appearance parameters. All formulations showed good homogeneity without significant stickiness during holding except the formula (FHP1) containing HPMC K100. Hence, the formula FHP1 was excluded from further tests.

The pH value of oral jelly formulations as shown in Table 3 was found to be in the range of 3.58–4.19. This is considered to be slightly acidic due to citric acid incorporation as pH modifier to enhance the gelling ability of pectin and stabilize it.[5] Pectin is a natural polysaccharide with a negatively charged carboxylic group of galacturonic acid units which interfere with pectin gelation. When the pH increased, pectin gelation decreased as a result of higher charge density with higher electrostatic repulsion among

Figure 2: The appearance color of SodCMC formula FSC1 (middle) and pectin formulas (FP1 – left and FP2 – right)

Table 2: The result parameters of the physical appearance of flurbiprofen oral jelly

Formulas code	Transparency	Consistency	Grittiness	Stickiness
FP1	Translucent	Smooth and acceptable	No grittiness	Slightly sticky
FHP1	Slight cloudy	Too soft and thick	Grittiness	Sticky
FSC1	Cloudy	Slightly hard breakable	Slightly gritty	Nonsticky
FP2	Translucent	Smooth and acceptable	No grittiness	Nonsticky
FP3	Translucent	Smooth and acceptable	No grittiness	Nonsticky
FP4	Translucent	Smooth and slight too soft	No grittiness	Nonsticky
FP5	Translucent	Smooth and acceptable	No grittiness	Slightly sticky

Table 3: The results of evaluated parameters for flurbiprofen oral jelly formulations

Formula code	pH±SD	Percentage drug content±SD	Viscosity (poise)±SD
FP1	3.71±0.05	98.81±0.302	283.3±11.93
FSC1	4.19±0.032	98.28±0.41	-
FP2	3.59±0.083	99.29±0.621	324.7±10.07
FP3	3.58±0.046	97.95±0.380	340.0±2.65
FP4	4.03±0.07	99.58±0.24	246.0±6.56
FP5	3.68±0.064	98.78±0.49	686.0±25.16

SD: Standard deviation

the pectin molecules, thus preventing the cross-linking and formation of a three-dimension triple helix network.[20] While at the pH range of 3.5–4.2, hydrophobic interactions formed between methyl ester groups and hydrogen bonding occurred between undissociated carboxyl groups, leading to form elastic and stable gel.[21]

The weight variations of all prepared formulas were ranged between 2.75% ± 0.161% and 3.78% ± 0.207% [Table 3]. The jelly content of FBP in the tested formulations was within the acceptable pharmacopeia limit and ranged between 97.950 and 99.58%; there was no statistically significant difference, indicating the uniform distribution of FBF.

All formulations contain pectin as the gelling agent did not show any syneresis due to immobilization of free water by sucrose at prepared pH.[22] Meanwhile, the formula (FSC1) showed syneresis, so it was excluded from further evaluation.

The viscosity of the evaluated jellies was illustrated in Table 3. The increase in percent w/v of pectin would significantly ($P \leq 0.05$) increase viscosity. These results are attributed to improve intermolecular interactions between pectin molecules and reduce intermolecular distance.[23] From this data, it was suggested that pectin concentration directly influenced the gel strength and viscosity, a similar finding was reported by Prakash.[13]

In addition, it was observed that at constant pectin concentration, the increase in sucrose concentration had a significant impact on jelly viscosity due to sucrose would stabilize the junction zone through the addition of more hydrogen bonding during pectin gelation, so increase gel strength.[21,23]

Texture properties play an important role in swallowing physiology and hence consumer palatability and acceptance. Soft jelly, which has a low firmness value, is more chewable and easily swallowed with a low risk of aspiration.[24] Data demonstrated that both pectin polymer and sucrose had a significant ($P \leq 0.05$) effect on the firmness. It was observed when increasing pectin concentrations from 3.5% to 4.5% and 5.5 w/v percent, the firmness increased from 153.8 ± 13.9 to 188.65 ± 10.38 and 391.01 ± 30.7 g, respectively. In addition, there was a direct correlation observed between sucrose concentration and firmness at constant pectin.

In vitro flurbiprofen dissolution

As illustrated in Figure 3, increasing pectin percent from 3.5% to 4.5% w/v percent had a nonsignificant ($P > 0.05$) impact on FBP releasing during the first 30 min. On the contrary, FBP percent released had revealed a significant ($P \leq 0.05$) decrease with an increase in pectin content up to 5.5% w/v. On the other hand, at a constant pectin percent of 4.5% w/v, there was a significant decrease in FBP percent released with increasing sucrose percentage [Figure 4]. This can be explained by the influence of the interstices fluid viscosity of jelly matrix on the dissolution rate which it decreased with increasing polymer or sucrose concentration.[25]

Regardless of the difference in the percent of the components between the prepared formulations, all pectin jellies except formula FP5 showed more than 50% and 85% of FBP released within the first 15 and 30 min, respectively [Table 4]. These dissolution results were satisfying with immediate release dosage requirements; such fast dissolution may be explained by hydrophilic pectin nature which has the ability to easily disintegrate and dissolve in a basic medium and hence causes faster drug release.[26]

Table 4 shows the lowest $MDT_{60\ min}$ and highest percent DE values indicated faster FBP released from jelly formulations. Although the formula (FP4) showed the highest percent DE and lowest $MDT_{60\ min}$, the formula FP2 was selected as optimum formula which also had a high percent DE (78.95%) and better consistency and handling compared to formula FP4.

Table 4: The dissolution parameters of flurbiprofen oral jelly

Formula code	Cumulative percentage FBP released at 15 min	Cumulative percentage FBP released at 30 min	Percentage DE	MDT 60 min
FP1	65.666±4.10	94.181±0.34	78.19	13.72
FP2	69.34±1.34	96.64±1.22	78.95	12.56
FP3	52.68±1.54	84.296±3.09	68.88	16.82
FP4	94.995±3.13	100.37±0.23	89.03	6.78
FP5	33.593±1.83	64.315±2.2	53.73	23.36

FBP: Flurbiprofen, DE: Dissolution efficiency, MDT: Mean dissolution time

Table 5: The determination coefficients of different mathematical models of formula FP2

Parameter	Zero-order	First-order	Higuchi	Korsmeyer-Peppas
R^2	0.3943	0.9784	0.8905	0.9761
n				0.687

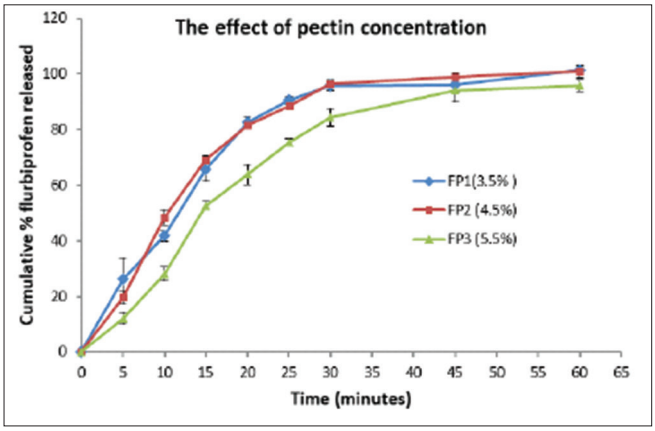

Figure 3: Comparative flurbiprofen dissolution profile from prepared jellies at different pectin concentrations

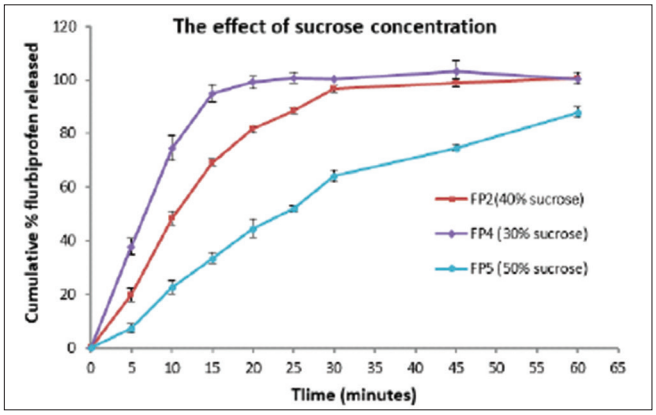

Figure 4: Comparative flurbiprofen dissolution profile from prepared jellies at constant pectin concentration (4.5% w/v) with different sucrose concentration

The results of FBP release kinetics from formula (FP2) revealed that a higher coefficient of determination value (R^2 = 0.9784) was for first-order kinetic [Table 5]. While the fitting of the drug released data on Korsmeyer–Peppas model showed nonfickain mechanism of drug transport (n value between 0.5 and 1) that assumed the drug releasing depends on both diffusion and polymer swelling with the time.[17]

CONCULSION

One of the strategies for enhancing oral FBP solid dosage acceptance by pediatric, geriatric, and patients with swallowing difficulties is to formulate the drug as soft jelly. Both type and concentration of polymer had an impact on jelly consistency. Increasing pectin concentration would increase jelly viscosity and hardness. The formula (FP2) consisting of 4.5% pectin and 40% w/v sucrose was selected as optimum formula which had a high percent DE (78.95%) and better consistency during handling with acceptable jelly characteristics.

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Conflicts of interest
There are no conflicts of interest.

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