CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187

Available online at: http://www.iajps.com *Research Article*

ENHANCEMENT OF SOLUBILITY AND FORMULATION OF FAST DISSOLVING SUBLINGUAL WAFERS OF FLURBIPROFEN FOR EFFECTIVE TREATMENT OF DENTAL PAIN

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Article Received: October 2022 **Accepted:** November 2022 **Published:** December 2022

Abstract:

The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of the drug development. Among the different methods of dissolution enhancement, Solid dispersion technology was found to be more successful with number of drugs. Solid dispersion of Flurbiprofen with PVP K-90 by physical mixture method were prepared. Further fast dissolving oral film of Flurbiprofen were conveniently formulated by solvent casting method. The In vitro dissolution studies showed that Flurbiprofen fast dissolving films formulation F3 showed maximum 98.78±0.25% over a period of 15min. Overall the results of the dissolution rate studies indicated greater dissolution rate of Flurbiprofen from fast dissolving oral film. Fast dissolving oral film containing Flurbiprofen were prepared using solvent casting method. Total six formulations were prepared using varying amount of Sodium Starch glycolate and Croscarmellose sodium. The prepared films were further evaluated for Thickness, Uniformity of Weight, Folding endurance, Disintegrating time, Tensile strength, Percentage Moisture Content, % Assay and In-vitro Release Studies. Percentage assay of different formulation was determined by UV-Vis Spectroscopy. The percentage assay of different formulation was in range of 97.14±0.41 to 99.45±0.36%.

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Please cite this article in press Vivek Gupta et al, ***Enhancement Of Solubility And Formulation Of Fast Dissolving Sublingual Wafers Of Flurbiprofen For Effective Treatment Of Dental Pain..,*** *Indo Am. J. P. Sci, 2022; 09(12).*

INTRODUCTION:

Fast dissolving wafers are a new arising oral dosage forms used by patients world widely. These dosage forms can be used even in acute condition for getting instant relief. Fast dissolving wafers have gained vast attention on the market because of its various advantages along with an extended shelf life of 2-3 years. These oral sublingual wafers are nothing but a thin oral strip which when place in the sublingual cavity dissolves immediately due to presence of saliva in the mouth by releasing medicament within short span of time. Sublingual wafers seem to be highly advantageous dosage form during travelling as it does not need water for engulfment. Even rapid onset of action is achieved as this dosage form is highly efficient in avoiding first pass metabolism [1].

Wafers are administered sublingually to improve the onset of action, lower the dose and enhance efficacy of the medicament, it is more stable, durable and quicker dissolving than other conventional dosage forms, an oral wafer helps to enhance bioavailability of the drug, improves dosing accuracy i.e., single unit dosage form, has the potential to allow the use of bitter tasting drug into the formulation and improves patient compliance.

Benign prostatic hyperplasia is a condition in which there is enlargement of prostate gland without malignancy. The bladder wall thickens and loses the ability to empty completely. Tamsulosin hydrochloride causes relaxation of smooth muscles of prostate and bladder neck to improve urine flow and to reduce bladder outlet obstruction. This disorder is seen mainly at the age of 40-45 years in the patient since time immemorial, oral drug administration has been one of the most convenient and widely accepted routes of delivery for most therapeutic agents. Traditionally, oral dosage forms refer to tablets, capsules, and liquid preparations taken orally, swallowed and transiting the gastrointestinal tract for post buccal absorption [2].

To be effective, the drug must be delivered to the site of action. Hence patient compliance is the major factor; because when patient does not take the medication, there can be no delivery of drug to its active site. Compliance has become a major problem, particularly for children and elderly patients. In certain instances, particularly where constant blood levels are not essential, the need for patient friendly dosage form may be satisfied by a fast dissolving intraoral tablet that has a pleasant taste and mouth feel [3].

Solid dispersions (SDs) are molecular dispersions of drug in the carriers and they were formulated by different methods, important are solvent evaporation and fusion (melt) method. Solid dispersions is a technique, in which drug is obtained as fine particles by dissolving the carriers in an aqueous fluids. It is a simple and flexible formulation process of obtaining solid dispersions without using toxic substances and enhances solubility and dissolution rate of drug. Flurbiprofen is non-steroidal anti-inflammatory drug that belongs to BCS class II because of its poor water solubility [4].

Rapid or fast dissolving oral wafers is becoming an increasingly popular drug delivery system because of its wide and varied benefits. On contact with saliva, it dissolves within a few seconds, without the need of water, making them particularly suitable for paediatric and geriatric patients. As most of the polymers used in mouth dissolving wafers are amorphous, dispersion of drug in polymer matrix aids rapid dissolution. These advantages enhance the patient compliance and make pharmaceutical manufacturer invest money in change of the existing products in the market to fast dissolving oral wafers [5]. Flurbiprofen also be used to treat other painful conditions such as toothache, pain after operations, period pain and migraine. The aim of present work to enhance solubility of Flurbiprofen and development of fast dissolving oral wafers using Different molecular weights of polyethylene glycols using solvent evaporation method.

MATERIAL AND METHODS:

Preparation of solid dispersions:

Optimization of Drug: Polymer Ratio:

In order to optimize the drug is to polymer ratio, we have prepared the matrices by both i.e. physical mixture method and solid dispersion method.

Physical mixture method:

All the ingredients were weighed accurately and passed through sieve no. 85 in order to obtain powder of fine particle size with narrow size distribution. The physical mixtures of drug with carrier PEG 4000 and PVP K-90 was prepared in different concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: PEG 4000 and drug: PVP K-90 ratio which was taken as 1:1, 1:2, and 1:3 respectively. Then the resultant powder was passed through sieve no 85 and was stored in desiccator for 2-6 hrs to carry out further analysis. The prepared physical mixture was subjected to spectrophotometric method [6].

Preparation of solid dispersion of Flurbiprofen

For the preparation of Flurbiprofen-PEG 4000 and Flurbiprofen-PVP K-90 solid dispersion by conventional method, PEG 4000 and PVP K-90 was weighed and melted at 58°C (±1°C) and a measured amount of Flurbiprofen was added and stirred. After solidification at room temperature, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. 10mg of Flurbiprofen - PVP K-90 powder (containing 50mg of Flurbiprofen and 150mg of PVP K-90) and was used for further investigations.

Evaluation of dispersion dispersion:

Percentage drug content:

For the determination of Flurbiprofen content, dispersion equivalent to 10 mg of Flurbiprofen, were weighed and extracted with 10 ml of methanol by mechanical mixing for 5min followed by centrifugation at 10,000 rpm for 5 min on a centrifuge. The supernant was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for Flurbiprofen at 244nm using a validated UV spectrophotometric method.

Formulation of oral film of Flurbiprofen:

Casting process of fast disintegrating oral film:

Various methods are available for casting of oral films. This is fast disintegrating oral film hence on the laboratory scale solvent casting technique was adopted for formulation of films.

Solvent casting technique:

Flurbiprofen containing fast dissolving films were fabricated by the solvent casting method. The optimized amount of HPMC was dissolved in 5ml of water and stirrered continuously for 1 hour, optimized amount of plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2ml of water and kept in sonicator for proper dispersion. Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm^2 10 films area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use [7].

Table 1: Selection and Optimization of Film Forming Agents

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6
API Equivalent to 50 mg	200	200	200	200	200	200
HPMC	300	400	500	300	400	500
Glycerin	-	-	-	-	-	-
PEG-400	100	100	100	100	100	100
SSG	100	150	200	-	-	-
CCS	-	-	-	100	150	200
Aspartame	25	25	25	25	25	25
Citric acid	10	10	10	10	10	10
DM water qs to (ml)	30	30	30	30	30	30

HPMC=Hydroxypropyl methylcellulose, PEG 400= Polyethylene glycol 400, SSG= Sodium starch glycolate, CCS =Croscarmellose sodium.

Dose calculations:

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm^2 films present whole plate = 12
- Each film contains 25 mg of drug.
- 12 no. of films contains mg of drug = 25×12 = 300mg
- The amount of drug added in each plate was approximately equal to 300mg.

Evaluation of prepared film [8-10]:

Thickness:

The thickness of films was measured at three different places using a vernier caliper.

Weight uniformity:

For each formulation, three randomly selected films were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Folding endurance:

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage moisture content:

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

Drug Content Analysis:

The films (n=3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 244nm.

Disintegrating time:

The objective of present work is that films should be dissolved within few seconds. Three super disintegrating agent were selected for minimizing the disintegration time.

***In vitro* dissolution study:**

The *in vitro* dissolution test was performed using the USP dissolution apparatus II (Paddle with sinker). The dissolution studies were carried out at 37±0.5°C; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Film size required for dose delivery (2.5×2.5 cm^2) was used. Five ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved Flurbiprofen was determined using UV-Visible spectrophotometer at 244nm. The results were presented as an average of three such concentrations.

RESULTS AND DISCUSSION:

On the basis of % Enhancement of solubility, it was concluded that solid dispersion is better option in spite of pure drug. In solid dispersion it was found that in Drug: PVP K-90 **(**1:3) % Solubility Enhancement was found 365.33%. Therefore 1:3 ratios were found to be superior and were used for further formulation development.

Fast dissolving oral film containing Flurbiprofen were prepared using solvent casting method. Total six formulations were prepared using varying amount of Sodium Starch glycolate and Croscarmellose sodium. The prepared films were further evaluated for Thickness, Uniformity of Weight, Folding endurance, Disintegrating time, Tensile strength, Percentage Moisture Content, % Assay and *In-vitro* Release Studies. Percentage assay of different formulation was determined by UV-Vis Spectroscopy. The percentage assay of different formulation was in range of 97.14±0.41 to 99.45±0.36%.

The maximum percentage assay (99.45±0.36%) and less disintegration time were found for formulation F3. The optimized formulation of batch F3 subjected to further *In vitro* drug release.

The *In vitro* drug release study of the enhanced detailing was subjected to integrity of fit test. The concentration of the dissolved Flurbiprofen was determined using UV-Visible spectrophotometer at 224nm. The results were presented as an average of three such concentrations.

Table 2: Percentage cumulative drug release of physical mixture

S. No.	% solubility Enhancement						
	Drug: PEG 400			Drug: PVP K-90			
	1:1	1:2	1:3	1:1	1:2	1:3	Pure Drug
Absorbance	0.125	0.142	0.215	0.165	0.198	0.274	0.075
% Solubility Enhancement	166.67	189.33	286.67	220.00	264.00	365.33	----

Table 3: Results of drug content

Formulation	Label claim	Amount found*	Label claim (%)
Physical mixture	10mg	9.95	99.50±0.15

Table 4: Results of Evaluation of prepared Film

Formulation code	General Appearance	Thickness (µm)	Weight (mg)
F1	Translucent	98±5	115±2
F2	Translucent	102±6	125±5
F3	Translucent	105±4	132±6
F4	Translucent	95±6	132±4
F5	Translucent	97±5	145±2
F6	Translucent	103±2	152±3

Table 5: Result of folding endurance, disintegration time, tensile strength moisture content and assay

Formulation code	Folding endurance	Disintegration time (min.)	Tensile strength (kg/cm^2)	Moisture Content (%)	Assay (%)
F1	185±3	2.36±0.25	0.98±0.05	1.45±0.25	98.85±0.45
F2	192±5	2.15±0.15	0.78±0.06	1.35±0.35	98.45±0.25
F3	235±6	1.45±0.32	0.85±0.3	1.24±0.25	99.45±0.36
F4	178±4	2.65±0.17	0.68±0.08	1.65±0.14	97.87±0.41
F5	195±5	2.32±0.26	0.74±0.07	1.47±0.15	96.65±0.32
F6	205±8	2.74±0.24	0.68±0.05	1.74±0.22	97.14±0.41

Table 6: Results of *In-Vitro* release study of optimized formulation F3

S. No.	Time (Min.)	Cumulative % Drug release
1.	1	45.65±0.35
2.	2	65.58±0.25
3.	5	73.32±0.36
4.	10	85.65±0.14
5.	15	98.78±0.25

CONCLUSION:

Flurbiprofen is a nonsteroidal anti-inflammatory agent (NSAID) that is effective as an anti-inflammatory agent, an analgesic for mild to moderate pain and antipyretic. Flurbiprofen is classified as a nonsteroidal anti-inflammatory drug belonging to the arylpropionic group of compounds (other members include ibuprofen, naproxen, and ketoprofen). The enhancement of dissolution rate and oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of the drug development. Among the different methods of dissolution enhancement, Solid dispersion technology was found to be more successful with number of drugs. Solid dispersion of Flurbiprofen with PVP K-90 by physical mixture method were prepared. Further fast dissolving oral film of Flurbiprofen were conveniently formulated by solvent casting method. The *In vitro* dissolution studies showed that Flurbiprofen fast dissolving films formulation F3 showed maximum 98.78±0.25% over a period of 15min. Overall the results of the dissolution rate studies indicated greater dissolution rate of Flurbiprofen from fast dissolving oral film.

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